A 24-Week, Open-Label Extension Study to Investigate the Long-Term Safety, Tolerability, and Efficacy of 13.3 mg/24 h Rivastigmine Patch in Patients with Severe Alzheimer's Disease

Martin R. Farlow, MD,[1] George T. Grossberg, MD,[2] Carl H. Sadowsky, MD,[3] Xiangyi Meng, PhD,[4] Drew M. Velting, PhD[4]

[1]Department of Neurology, Indiana University School of Medicine, Indianapolis, IN, USA; [2]Department of Neurology and Psychiatry, St Louis University School of Medicine, St Louis, MO, USA; [3]Division of Neurology, Nova Southeastern University, Fort Lauderdale, FL, USA; [4]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

Corresponding author:

Martin R. Farlow, MD, Indiana University School of Medicine, Department of Neurology, 355 W. 16th Street, Suite 4700, Indianapolis, IN 46202, USA.

Phone: +1 (317) 963-7402; Fax: +1 (317) 963-7533; E-mail: mfarlow@iupui.edu

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The long-term safety, tolerability and efficacy of high-dose 13.3 mg/24 h rivastigmine patch in severe Alzheimer's disease was evaluated in a 24-week, open-label extension to the double-blind (DB) ACTION study. Safety and tolerability, and efficacy on the Alzheimer's Disease Cooperative Study–Activities of Daily Living scale–Severe Impairment Version (ADCS-ADL-SIV), Severe Impairment Battery (SIB), and ADCS–Clinical Global Impression of Change (ADCS-CGIC) were assessed. Overall, 197 patients continued on 13.3 mg/24 h patch; 199 up-titrated from 4.6 mg/24 h to 13.3 mg/24 h patch. The incidence of adverse events (AEs), serious AEs and discontinuations due to AEs was similar in patients who continued on, and patients who up-titrated to, 13.3 mg/24 h patch (AEs: 57.9% and 59.8%; serious AEs: 16.2% and 16.1%; discontinuations: 11.2% and 12.1%, respectively). Larger mean changes from DB baseline were observed in patients up-titrated on the ADCS-ADL-SIV (−4.6 [standard deviation 8.7]) and SIB (−7.0 [16.6]), than those who continued on 13.3 mg/24 h patch (−3.9 [8.0] and −4.7 [16.8], respectively). ADCS-CGIC scores were comparable. There were no clinically relevant between-group differences in safety and tolerability. Greater decline was observed in patients with delayed up-titration to high-dose 13.3 mg/24 h patch than patients who continued on high-dose patch.

Key words: severe Alzheimer's disease, rivastigmine, transdermal patch, open-label clinical trial

Introduction

Alzheimer's disease (AD) is a neurodegenerative illness and the most common cause of dementia.[1] As the disease progresses, patients experience degeneration of cortically projecting cholinergic neurons,[2] resulting in progressive impairments in cognition, particularly memory, behavior, and performance of activities of daily living (ADL).[1] Cholinesterase inhibitors (ChEIs) are the mainstay of treatment and provide symptomatic benefits by partially compensating for the cholinergic deficits associated with AD.[2] In the absence of disease-modifying therapies, there remains a need to optimize use of available therapies at all stages of AD.

Currently, several agents are approved in the USA to manage patients with AD. Three ChEIs are indicated for the treatment of mild-to-moderate AD: rivastigmine (Exelon®, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA), donepezil (Aricept®, Eisai Inc., Woodcliff Lakes, NJ, USA), and galantamine (Razadyne®, Janssen Pharmaceutical NV, Beerse, Belgium).[3-6] Donepezil and an N-methyl-D-aspartate receptor antagonist (memantine [Namenda XR™], Forest Pharmaceuticals Inc., St Louis, MO, USA) are indicated for the treatment of severe AD.[3, 7] Rivastigmine is currently the only approved treatment for AD available in both oral and transdermal formulations.[4, 5] The transdermal system was initially indicated for the treatment of mild-to-moderate AD at rivastigmine dosages of 4.6 mg/24 h and 9.5 mg/24 h.[5] A 13.3 mg/24 h dosage strength was later approved based on data from the OPTIMA (OPtimising Transdermal Exelon In Mild-to-moderate Alzheimer's disease) study, described elsewhere.[8]

In June 2013, the US Food and Drug Administration approved an expanded indication for the 13.3 mg/24 h rivastigmine transdermal system to include the symptomatic treatment of patients with severe AD.[5] Approval was based on the ACTION (ACTivities of Daily Living and CognitION in Patients with Severe Dementia of the Alzheimer's Type) study, a 24-week, randomized, double-blind (DB) study that compared the

efficacy, safety and tolerability of rivastigmine 13.3 mg/24 h patch with 4.6 mg/24 h patch in patients with severe AD.[9, 10] The 13.3 mg/24 h patch demonstrated statistically significantly ($P < 0.05$) less decline in overall cognition and function in patients with severe AD at Week 24, as assessed using the Severe Impairment Battery (SIB) and the Alzheimer's Disease Cooperative Study–ADL scale–Severe Impairment Version (ADCS-ADL-SIV), respectively (co-primary outcomes).[9] A similar proportion of both treatment groups (13.3 mg/24 h and 4.6 mg/24 h patch) reported adverse events (AEs; 74.6% and 73.3%, respectively) and serious AEs (SAEs; 14.9% and 13.6%, respectively).[9]

In the current manuscript, we present the main findings of an open-label extension (OLE) to the DB ACTION study. This extension study was designed to investigate the effects of 13.3 mg/24 h rivastigmine patch over a longer term with regards to safety and clinical outcomes in patients with severe AD. These data have previously been presented in poster form at the Alzheimer's Association International Conference, Boston, MA, USA, July 13–18 2013,[11] the American College of Clinical Pharmacology Annual Meeting, Bethesda, MD, USA,[12] September 22–24 2013, and the World Congress of Neurology, Vienna, Austria, September 21–26 2013.[13]

Methods

Patients and Study Design

The methodology for the ACTION study has been previously described,[9, 10] and the clinical study is registered (ClinicalTrials.gov Identifier: NCT00948766). The protocol and amendments were reviewed by Independent Ethics Committees or Institutional Review Boards and the study was conducted in accordance with Good Clinical Practice and the ethical principles of the Declaration of Helsinki. All patients, or if they lacked capacity, their legally authorized representative, provided written informed consent before participating in the DB study and OLE.

Patients enrolled in the DB study were male and female, aged ≥50 years with a clinical diagnosis of AD, according to the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association [NINCDS/ADRDA] criteria.[14] In addition, patients were required to score between 3–12 (inclusive; severe AD) on the Mini-Mental State Examination at DB baseline.[15] The brain scan (magnetic resonance imaging or computed tomography) used for establishing the NINCDS/ADRDA criteria must have been performed within 2 years prior to the baseline visit.

Patients were excluded from the DB study if they had any advanced, severe, progressive, or unstable disease that could interfere with the efficacy and safety assessments; were currently residing or likely to be placed in a nursing home within the next 7 months; or had any medical or neurological conditions other than AD that could be the primary cause of dementia. Additional exclusion criteria for the DB study have been previously described.[9, 10]

Patients who completed the 24-week, prospective, randomized, parallel-group, DB, multicenter ACTION study were eligible to continue in an open-label, forced-titration, 24-week extension. Patients continuing in the OLE were required to have met all inclusion (and no exclusion) criteria at DB baseline. There was a continued requirement for patients to be residing with someone in the community or be in regular contact with the primary caregiver; and have a primary caregiver willing to accept responsibility for supervising treatment. In addition, patients were required (investigator's opinion) to be medically stable and tolerating their current dose of rivastigmine patch.

At the end of the DB study (Week 24) patients who chose to participate in the OLE were switched from DB treatment with rivastigmine 13.3 mg/24 h or 4.6 mg/24 h patch to open-label treatment with rivastigmine 9.5 mg/24 h patch. Patients remained blind to

treatment assignment in the core study. After 4 weeks on the maintenance dose (9.5 mg/24 h patch), patients continued on open-label treatment with the higher-dose rivastigmine 13.3 mg/24 h patch for an additional 20 weeks (Weeks 28–48).

Dose adjustments and interruptions were permitted for patients who were not able to tolerate the specified dosing regimen. If a patient experienced a problem with tolerability, the patch was removed, and 1 or 2 days of no treatment were permitted. Tolerability was reassessed after the 1- or 2-day period. If tolerability had improved and there were no more than 3 consecutive days of interruption, treatment was reinstated at the same dosage. If tolerability was not improved after 3 consecutive days or if treatment was interrupted for more than 3 consecutive days, treatment was reinitiated at the 4.6 mg/24 h patch dose. After a minimum of 2 weeks, the dose could be titrated up to 9.5 mg/24 h patch and again after a minimum of 2 weeks up to 13.3 mg/24 h patch. If the intolerability persisted, the patient was discontinued from the study.

Study Objectives

The primary objective of this OLE of the 24-week DB ACTION study was to investigate the long-term safety of rivastigmine 13.3 mg/24 h patch in patients with severe AD. Secondary objectives were to investigate the long-term efficacy of rivastigmine 13.3 mg/24 h patch in this patient population.

Outcomes

Safety and tolerability was assessed throughout the study and included reporting of the incidence of AEs, SAEs, and the rate of discontinuation due to AEs and SAEs. Safety assessments included regular monitoring of vital signs, physical condition, and body weight. Laboratory tests, electrocardiogram, and physical examination were performed at Week 48 or when the patient withdrew or discontinued the study.

Efficacy was assessed by calculating the mean change from DB baseline to Week 48 on the ADCS-ADL-SIV and SIB, and the Week 48 score on the ADCS–Clinical Global Impression of Change (ADCS-CGIC).[16-18]

Statistical Analysis

Analysis of the primary outcome (long-term safety) was based on the safety set for the OLE and included all patients who received at least one dose of rivastigmine patch and had at least one safety assessment during the OLE. The incidence of AEs and SAEs and discontinuation due to AEs and SAEs was summarized by primary system organ class and preferred term. The relationship of the observed AE to study drug, action taken, duration and severity were also recorded. For laboratory evaluations and vital signs, the change from baseline and proportion of patients experiencing clinically notable laboratory evaluations were calculated.

Analyses of the secondary outcomes (long-term efficacy variables [ADCS-ADL-SIV, SIB and ADCS-CGIC]) were based on the modified full analysis set (MFAS) for the OLE. The MFAS comprised all patients who received at least one dose of rivastigmine patch and had at least one efficacy assessment during the OLE. Imputation of missing values was performed following the last-observation-carried-forward (LOCF) approach. Data from the DB study were not carried forward for the efficacy summary from the open-label study. Data were analyzed according to treatment group in the randomized, DB treatment phase (rivastigmine 13.3 mg/24 h or 4.6 mg/24 h patch). Additional supportive analyses (observed case [OC]) were performed to confirm whether imputations influenced the results.

For continuous efficacy and safety variables, number of patients with observed values (n), mean, standard deviation (SD), 95% confidence intervals, minimum and maximum values were calculated. Categorical efficacy and safety variables were summarized by frequency counts and percentages. Unless otherwise specified, all statistical tests were conducted against a 2-sided alternative hypothesis; *P*-values below 0.05 were considered significant.

Results

Participants

Of the 463 patients who completed the DB study, 396 patients entered the OLE and received rivastigmine patch: 197 continued on the rivastigmine 13.3 mg/24 h patch; 199 were switched from the rivastigmine 4.6 mg/24 h patch to the 13.3 mg/24 h patch. A similar proportion of both groups completed the OLE (76.8% [n = 152] for 13.3 mg/24 h patch and 77.4% [n = 154] for the group originally randomized to 4.6 mg/24 h patch in the DB phase; **Figure 1**).

Overall, AEs (based on DB treatment allocation, 9.6% [n = 19] for 13.3 mg/24 h patch and 12.1% [n = 24] for 4.6 mg/24 h patch) and consent withdrawal (8.1% and 8.0%, respectively [n = 16 for both groups]; **Figure 1**) were the most commonly reported reasons for discontinuation. No imbalance was observed between treatment groups. Generally, baseline demographics and characteristics were comparable between the rivastigmine 13.3 mg/24 h and 4.6 mg/24 h patch groups (**Table 1**).

Safety and Tolerability

The mean duration of exposure to rivastigmine during the OLE was comparable between patients who received 13.3 mg/24 h patch and those who received 4.6 mg/24 h patch in the DB phase; the mean duration was 21.7 weeks for patients who continued treatment with 13.3 mg/24 h patch and 21.2 weeks for those who switched to the high-

dose patch. When exposure to rivastigmine during the DB study was included, the mean duration was 46.3 weeks and 45.8 weeks, respectively.

No new safety findings from long-term treatment with the rivastigmine patch were seen based on the incidence of individual AEs or SAEs, individual AEs resulting in discontinuation, laboratory or electrocardiogram results, or vital signs.

Overall, there was a comparable incidence of AEs between patients who continued on rivastigmine 13.3 mg/24 h patch (57.9%) and those switched from 4.6 mg/24 h patch (59.8%; **Table 2**). The most commonly reported AEs (≥10% in either group) with 13.3 mg/24 h rivastigmine patch (DB 13.3 mg/24 h and 4.6 mg/24 h, respectively) defined by primary system organ class were: infections and infestations (18.8% and 18.1%); psychiatric disorders (14.2% and 19.1%); gastrointestinal (GI) disorders (13.2% and 16.6%); nervous system disorders (14.2% and 13.6%); investigations (e.g. procedures, abnormal laboratory results; 13.2% and 13.1%); general disorders and administration site conditions (10.7% and 11.6%); and injury, poisoning, and procedural complications (10.2% and 8.5%). By preferred term, patients who continued on rivastigmine 13.3 mg/24 h patch reported fewer incidences of vomiting, fall, agitation, and diarrhea compared with those randomized to receive rivastigmine 4.6 mg/24 h patch in the DB phase; the converse was observed with regard to the incidence of urinary tract infection (**Table 2**). Application site erythema and dermatitis were experienced by a similar percentage of patients in both groups (based on DB treatment allocation, 13.3 mg/24 h patch: 1.5% and 2.0%, respectively; 4.6 mg/24 h patch: 2.0% for each). The majority of reported AEs were mild or moderate in severity. AEs of mild severity were experienced by 26.4% of patients who continued on 13.3 mg/24 h patch and 27.6% of patients who switched from 4.6 mg/24 h patch (moderate: 20.8% and 23.1%, respectively; severe: 10.7% and 9.0%, respectively).

During the OLE, a comparable incidence of SAEs was observed in those patients who continued on (16.2%) and those switched to (16.1%) 13.3 mg/24 h patch (**Table 3**), with nervous system disorders the most commonly reported (6.6% and 4.5%, respectively). A numerically higher incidence of discontinuation due to SAEs was observed in those patients continued on the 13.3 mg/24 h patch (7.1% [n = 14]) compared with those switched from the 4.6 mg/24 h patch (5.0% [n = 10]) (**Table 3**). Conversely, discontinuations due to non-serious AEs were numerically higher for those patients switched from the 4.6 mg/24 h patch (7.5% [n = 15]) compared with those continued on the 13.3 mg/24 h patch (4.6% [n = 9]) (**Table 3**).

Four (2.0%) deaths were reported for patients who continued on the 13.3 mg/24 h patch (**Table 3**); none of these deaths were suspected to be related to the study drug. Two of the four deaths were related to cardiac events, one was due to dementia related to AD, and one was due to chemical poisoning. No deaths were reported for patients switched from 4.6 mg/24 h to 13.3 mg/24 h patch.

Efficacy Outcomes

SIB

During the DB study, patients treated with the rivastigmine 13.3 mg/24 h patch demonstrated significantly less decline on the SIB at Week 24, compared with those treated with the 4.6 mg/24 h patch ($P < 0.0001$).[9] During the OLE, both groups demonstrated clinical decline. A larger mean (SD) change from DB baseline at Week 48 in SIB total score was observed in those patients switched from rivastigmine 4.6 mg/24 h patch at the start of the OLE (−7.0 [16.6], $P < 0.0001$ for change from DB baseline) than for those continued on rivastigmine 13.3 mg/24 h patch throughout (−4.7 [16.8], $P = 0.0002$ for change from DB baseline; **Figure 2A**), indicating less decline among patients continued on the 13.3 mg/24 h patch relative to those switched from 4.6 mg/24 h patch. Results were similar for the MFAS-OC population.

ADCS-ADL-SIV

During the overall 48-week period, decline in functional performance (as measured by the ADCS-ADL-SIV) was observed in both rivastigmine patch groups. During the DB study, patients treated with the 13.3 mg/24 h patch had significantly less decline on the ADCS-ADL-SIV at Week 24 compared with the 4.6 mg/24 h patch ($P = 0.025$).[9] During the OLE, patients switched from rivastigmine 4.6 mg/24 h patch (−4.6 [8.7], $P < 0.0001$ for change from DB baseline) showed a larger mean (SD) change from DB baseline at Week 48 compared with those patients who continued on the 13.3 mg/24 h patch (−3.9 [8.0], $P < 0.0001$ for change from DB baseline; **Figure 2B**) indicating less decline among patients continued on the 13.3 mg/24 h patch relative to those switched from the 4.6 mg/24 h patch. Results were similar for the MFAS-OC population.

ADCS-CGIC

A similar percentage of patients in both rivastigmine patch groups improved, worsened, or showed no change in ADCS-CGIC ratings (**Figure 2C**). At Week 48, 16.5% of all patients showed improvement in mental/cognitive state, behavior, and functioning. No change in ADCS-CGIC ratings was seen in 26.2% of all patients and 57.2% showed minimal to marked worsening of their medical condition.

Discussion

Overall, no new safety or tolerability issues were reported during this 24-week OLE to the DB ACTION study, in patients with severe AD. The overall incidence of AEs was comparable between patients who continued on 13.3 mg/24 h rivastigmine patch throughout the DB study and OLE, and those who up-titrated from 4.6 mg/24 h to 13.3 mg/24 h patch at the start of the OLE (57.9% *versus* 59.8%). The core 24-week, DB ACTION study also reported a similar incidence of AEs between patients randomized to 4.6 mg/24 h or 13.3 mg/24 h patch (73.3% and 74.6%, respectively).[9]

Discontinuations due to skin irritation were few in the DB phase of the study (1.7% *versus* 2.5%, 13.3 mg/24 h and 4.6 mg/24 h rivastigmine patch, respectively; 2.1% overall) and decreased further in the OLE to less than 1% of patients. Good long-term skin tolerability means patients are unlikely to discontinue treatment with rivastigmine patch owing to skin reactions.

Previous studies have pointed to an association between GI AEs, such as nausea, vomiting, and diarrhea, and ChEI dose.[19] In a 28-week OLE to the 24-week IDEAL (Investigation of transDermal Exelon in ALzheimer's disease) trial, the incidence of GI AEs with 9.5 mg/24 h patch was greater in those patients who previously received placebo during the DB phase compared with those who had received rivastigmine (9.5 mg/24 h patch, 17.4 mg/24 h patch or 12 mg/day capsules).[20] This led to the recommendation that the rivastigmine patch dose be increased in a 4-week step-wise manner, starting on the low-dose 4.6 mg/24 h rivastigmine patch for a minimum of 4 weeks before increasing to 9.5 mg/24 h rivastigmine patch.[5, 20] In the DB OPTIMA trial, GI AEs were more frequently reported in patients up-titrated from 9.5 mg/24 h to 13.3 mg/24 h patch than for patients continuing on 9.5 mg/24 h patch.[8] Likewise, in the DB ACTION study the incidence of GI AEs was higher in patients receiving 13.3 mg/24 h compared with 4.6 mg/24 h patch (nausea: 6.2% *versus* 2.8%; vomiting 7.0% *versus* 2.5%; diarrhea: 6.5% *versus* 5.3%, respectively).[9] It is also now recommended that patients receive 9.5 mg/24 h patch for a minimum of 4 weeks before up-titrating to the 13.3 mg/24 h patch dose.[5]

In the ACTION study OLE, the frequency of GI AEs was lower in those patients who continued on 13.3 mg/24 h patch than those who switched from 4.6 mg/24 h to 13.3 mg/24 h patch (nausea: 1.5% *versus* 4.0%; vomiting 3.0% *versus* 8.0%; diarrhea: 2.5% *versus* 5.0%, respectively). These safety data support previous findings that GI AEs are associated with initial rivastigmine dose increase.[8, 20] Once patients are established on the high dose, GI AE frequency decreases, suggesting that patient tolerability of

13.3 mg/24 h rivastigmine patch improves with time. Further supporting this, the reported incidence of overall AEs was lower for patients continuing on 13.3 mg/24 h in the 24-week OLE than those randomized to 13.3 mg/24 h in the first 24 weeks of rivastigmine patch treatment (DB phase) (57.9% *versus* 74.6%, respectively).[9] The 48-week DB OPTIMA trial of patients with mild-to-moderate AD declining on 9.5 mg/24 h rivastigmine patch, who were randomized either to continue on 9.5 mg/24 h patch or up-titrate to 13.3 mg/24 h patch, reported a similar decline in AEs with time (Week 0–24, 64.6% and 54.8%; Week 24–28, 42.3% and 40.2%, 13.3 mg/24 h and 9.5 mg/24 h, respectively).[8] In light of these findings, patients with poor tolerability of 13.3 mg/24 h patch who have down-titrated to a lower maintenance dose may later show improved tolerability to the high-dose patch after a more prolonged exposure to lower-dose rivastigmine patch treatment.

The OLE collected efficacy data for long-term 13.3 mg/24 h rivastigmine patch treatment, in addition to assessing safety and tolerability. An important objective of treatment when managing a patient with severe AD is achieving stabilization of, or reducing decline in, cognitive function and the ability to perform ADL. As expected, given the advanced disease stage of the population under study,[21] at 48 weeks patients in both treatment groups showed decline in cognitive ability (SIB) and their ability to perform ADL (ADCS-ADL-SIV). However, numerically less decline was observed in those who continued on 13.3 mg/24 h patch long term compared with those patients who up-titrated from 4.6 mg/24 h to 13.3 mg/24 h patch at the start of the OLE. At the end of the DB study (Week 24), patients receiving 4.6 mg/24 h rivastigmine patch already showed significantly greater decline in cognitive and functional ability compared with patients randomized to 13.3 mg/24 h rivastigmine patch.[9] The effect of temporary down-titration to 9.5 mg/24 h patch in the 13.3 mg/24 h patch group for the first four weeks of the OLE on the study findings is unknown, but it may have increased the rate of decline in this treatment arm. However, overall, the

extension data confirm the superior symptomatic efficacy of 13.3 mg/24 h compared with 4.6 mg/24 h rivastigmine patch: patients with delayed switching to 13.3 mg/24 h patch do not ‘catch-up’ in the longer-term. These observations suggest that early and sustained intervention with 13.3 mg/24 h rivastigmine patch is needed to achieve a maximum delay in symptomatic progression in patients with severe AD.

There were no marked differences in the distribution of ADCS-CGIC ratings between treatment groups, suggesting the global function of patients was similar in those who continued on 13.3 mg/24 h patch for the duration of the study, and those who up-titrated to 13.3 mg/24 h patch. At the end of the DB phase, a significantly higher percentage of patients displayed improvement in clinical status when receiving 13.3 mg/24 h rivastigmine patch compared with 4.6 mg/24 h (P = 0.0094). However, caution should be exercised when drawing comparisons between the OLE and the initial DB study owing to differences in study design. Limitations of this extension study include its open-label nature, and that it was not powered for statistical analysis between treatment groups on this, or any other outcome measure, hence between-group comparisons are based on numerical differences. In terms of blinding, between-group measurements are unlikely to be affected by open-label status, as prior DB randomization was not revealed to OLE participants. Regarding overall efficacy, the severity of AD in the study population is likely to mitigate any patient-bias in assessments.

As this was the first trial of rivastigmine patch treatment in patients with severe AD, the 4.6 mg/24 h dose was selected as a low-dose active comparator to fully evaluate the efficacy of high-dose rivastigmine. Using 4.6 mg/24 h rivastigmine patch as a comparator in this study may mask the true treatment effect of rivastigmine patch compared with placebo. However, for patients with AD, 9.5 mg/24 h rivastigmine patch is currently the minimum effective dose. It would be interesting to compare these findings with patients who up-titrate to 13.3 mg/24 h from 9.5 mg/24 h rivastigmine

patch straight away (after a 4-week step-wise dose increase, as performed in the OLE) compared with delaying up-titration to 13.3 mg/24 h, as a more accurate reflection of the real-world clinical setting.

Previous studies report that transdermal delivery is the preferred route of administration by caregivers of patients with AD, compared with capsules, and greater satisfaction with rivastigmine patch is associated with higher rates of adherence.[22-24] In practical terms, transdermal delivery has a number of advantages over oral capsules for patients with AD and their caregivers; the patch acts as a visual reminder that medication has been taken;[25] patch administration is easier, particularly in patients who are confused or display behavioral problems;[25] patch delivery is well-suited for patients who have difficulty swallowing. Although caregiver preference for transdermal *versus* oral formulations has not been confirmed in a sub-population of patients with severe AD, it is anticipated that the simple treatment regimen offered by a transdermal patch would also appeal to caregivers of patients with more advanced disease.

Conclusion

In summary, no clinically relevant differences were observed in safety and tolerability between patients switched from the 4.6 mg/24 h to 13.3 mg/24 h rivastigmine patch and those who continued long-term treatment with the high-dose patch in the OLE study. Safety results appeared to be broadly consistent with those previously reported with the 13.3 mg/24 h patch in patients with mild-to-moderate AD,[8] with tolerability improving with time on rivastigmine treatment. Greater, but more variable, decline in cognitive function and on the ability to perform ADL was observed in patients switched from 4.6 mg/24 h to 13.3 mg/24 h patch at the start of the OLE, compared with those patients who continued on 13.3 mg/24 h patch long term. Early and sustained administration of 13.3 mg/24 h rivastigmine patch may provide clinically relevant benefits for patients with severe AD.

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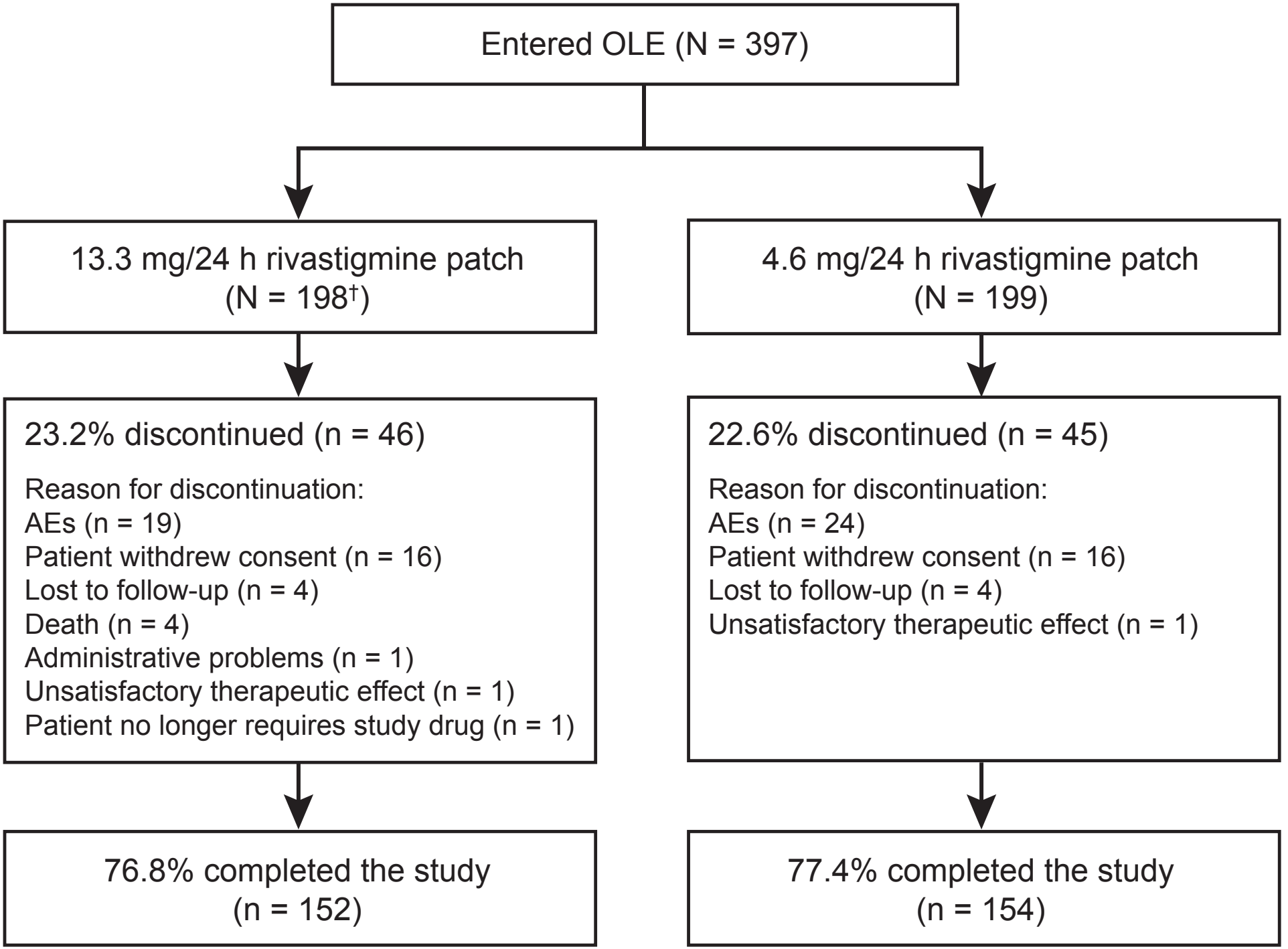
Figure legends

Figure 1: Patient disposition throughout the study by DB treatment group.

AEs, adverse events; DB, double-blind; N, number of patients in the population; n, number of patients; OLE, open-label extension. [†]One patient was randomized but was not exposed to study medication.

Figure 2: Change from baseline to Week 48 on (A) SIB score and (B) ADCS-ADL-SIV, and (C) categorical analysis of change in score at Week 48 on the ADCS-CGIC (MFAS–LOCF).

ADCS-ADL-SIV, Alzheimer's Disease Cooperative Study–Activities of Daily Living scale–Severe Impairment Version; ADCS-CGIC, Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change; LOCF, last observation carried forward; MFAS, modified full analysis set; OLE, open-label extension; SEM, standard error of the mean; SIB, Severe Impairment Battery. Error bars represent the SEM. *$P < 0.05$ 13.3 mg/24 h *versus* 4.6 mg/24 h patch; **$P < 0.0001$ 13.3 mg/24 h *versus* 4.6 mg/24 h patch. For the SIB, 13.3 mg/24 h patch, n = 183–185 and 4.6 mg/24 h patch, n = 192–194. For the ADCS-ADL-SIV, 13.3 mg/24 h patch, n = 182–183 and 4.6 mg/24 h patch, n = 187–189.


Entered OLE (N = 397)
13.3 mg/24 h rivastigmine patch (N = 198†)
4.6 mg/24 h rivastigmine patch (N = 199)
23.2% discontinued (n = 46)
Reason for discontinuation:
AEs (n = 19)
Patient withdrew consent (n = 16)
Lost to follow-up (n = 4)
Death (n = 4)
Administrative problems (n = 1)
Unsatisfactory therapeutic effect (n = 1)
Patient no longer requires study drug (n = 1)
22.6% discontinued (n = 45)
Reason for discontinuation:
AEs (n = 24)
Patient withdrew consent (n = 16)
Lost to follow-up (n = 4)
Unsatisfactory therapeutic effect (n = 1)
76.8% completed the study (n = 152)
77.4% completed the study (n = 154)

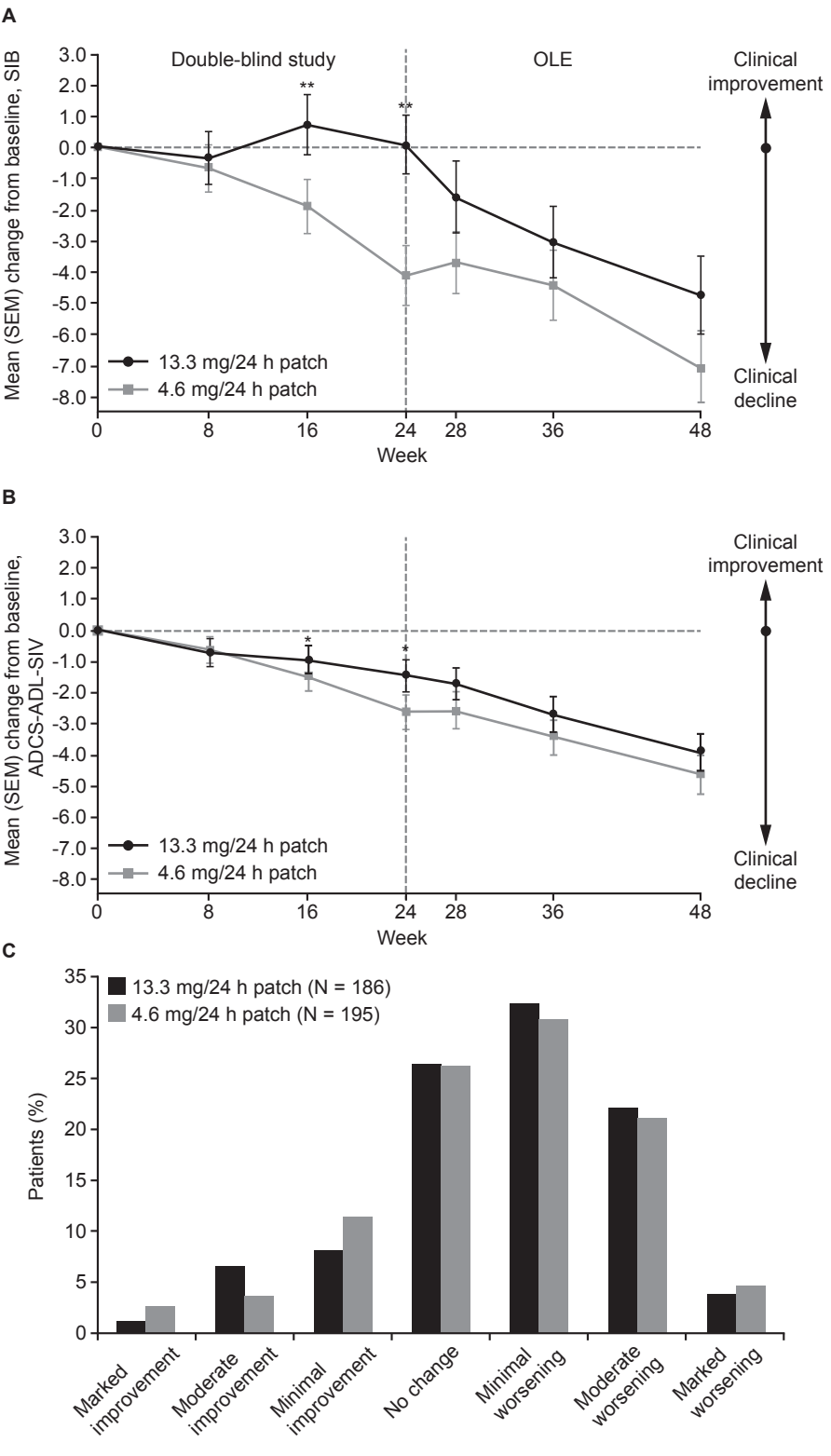

A
Double-blind study
OLE
Clinical improvement
Clinical decline
Mean (SEM) change from baseline, SIB
3.0
2.0
1.0
0.0
-1.0
-2.0
-3.0
-4.0
-5.0
-6.0
-7.0
-8.0
**
**
13.3 mg/24 h patch
4.6 mg/24 h patch
0
8
16
24
28
36
48
Week
B
Clinical improvement
Clinical decline
Mean (SEM) change from baseline, ADCS-ADL-SIV
3.0
2.0
1.0
0.0
-1.0
-2.0
-3.0
-4.0
-5.0
-6.0
-7.0
-8.0
*
*
13.3 mg/24 h patch
4.6 mg/24 h patch
0
8
16
24
28
36
48
Week
C
13.3 mg/24 h patch (N = 186)
4.6 mg/24 h patch (N = 195)
Patients (%)
35
30
25
20
15
10
5
0
Marked improvement
Moderate improvement
Minimal improvement
No change
Minimal worsening
Moderate worsening
Marked worsening

Table 1: Patient demographics and background characteristics by treatment group (safety set)

	Rivastigmine Patch		
Demographic or characteristic	**13.3 mg/24 h (N = 197)**	**4.6 mg/24 h (N = 199)**	**Overall (N = 396)**
Age, years			
Mean (SD)	78.0 (8.3)	76.1 (9.1)	77.1 (8.8)
Gender, %			
Female	63.5	68.3	65.9
Race, %			
Caucasian	83.2	85.9	84.6
Black	9.1	7.0	8.1
Other	7.6	7.0	7.3
MMSE at screening			
Mean (SD)	9.15 (2.7)	9.19 (2.9)	9.17 (2.8)
Range	3.0–13.0	3.0–19.0	3.0–19.0
Years since diagnosis of AD			
Mean (SD)	4.28 (2.7)	3.73 (2.4)	4.00 (2.6)
Years since diagnosis of severe dementia			
Mean (SD)	1.09 (1.8)	1.05 (1.5)	1.07 (1.7)
Living situation, %			
Home	90.4	89.4	89.9
Assisted-living facility	7.6	8.5	8.1
Other	2.0	2.0	2.0

AD, Alzheimer's disease; MMSE, Mini-Mental State Examination; N, number of patients in the population; SD, standard deviation.

Table 2: Most frequent adverse events[†] in the OLE study (safety set).

	Rivastigmine patch	
AEs, n (%)	**13.3 mg/24 h (N = 197)**	**4.6 mg/24 h (N = 199)**
Patients with ≥1 AE	114 (57.9)	119 (59.8)
Urinary tract infection	22 (11.2)	21 (10.6)
Weight decreased	15 (7.6)	15 (7.5)
Fall	9 (4.6)	12 (6.0)
Agitation	9 (4.6)	11 (5.5)
Vomiting	6 (3.0)	16 (8.0)
Diarrhea	5 (2.5)	10 (5.0)

AEs, adverse events; N, number of patients in the population; n, number of patients reporting AE; OLE, open-label extension. [†]AEs occurring in ≥5.0% of patients in either treatment group are shown. A patient with multiple occurrences of an AE was counted only once in the AE category. AEs are presented by descending frequency in the 13.3 mg/24 h patch group.

Table 3: Incidence of SAEs, deaths and discontinuations due to AEs and SAEs (safety set).

	Rivastigmine patch	
	13.3 mg/24 h (N = 197) n (%)	**4.6 mg/24 h (N = 199) n (%)**
SAEs	32 (16.2)	32 (16.1)
Deaths	4 (2.0)	0 (0.0)
Discontinued due to SAEs	14 (7.1)	10 (5.0)
Discontinued due to non-serious SAEs	9 (4.6)	15 (7.5)
Discontinued due to gastrointestinal AEs	2 (1.0)	6 (3.0)
Discontinued due to application site irritations	2 (1.0)	1 (0.5)

AEs, adverse events; N, number of patients in the population; n, number of patients reporting SAE, death or discontinuation; SAE, serious adverse event.