

# Efficacy of 13.3 mg/24 h versus 4.6 mg/24 h rivastigmine patch on activities of daily living in severe Alzheimer's disease

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Joseph L Micca<sup>1</sup>, James E Galvin<sup>2</sup>, Drew M Velting<sup>3</sup> and Xiangyi Meng<sup>3</sup>

## Abstract

**Objective:** Investigate efficacy of 13.3 mg/24 h rivastigmine patch in patients with severe Alzheimer's disease on Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale–Severe Impairment Version items and domains.

**Methods:** Retrospective analysis of the 24-week, randomized, double-blind ACTivities of daily living and cognitIOn (ACTION) study, using factor analysis to establish “best fit” for Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale–Severe Impairment Version items into domains. Treatment differences (13.3 vs 4.6 mg/24 h patch) on items and domains were assessed.

**Results:** Overall, 632 patients provided Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale–Severe Impairment Version data. Factor analysis yielded four domains. The 13.3 versus 4.6 mg/24 h patch demonstrated significantly greater efficacy on “Daily function” ( $p=0.038$ ), supported by greatest effect sizes on items within this domain, and trend toward greater efficacy on “Communication” ( $p=0.052$ ). No significant between-group differences were observed on “Independence” ( $p=0.600$ ) or “Environment” ( $p=0.261$ ).

**Conclusion:** The 13.3 mg/24 h patch was superior to 4.6 mg/24 h patch on “Daily function” in severe Alzheimer's disease.

## Keywords

Activities of Daily Living, Alzheimer's disease, factor analysis, patch, rivastigmine, severe

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## Introduction

Progressive impairment in the ability to perform activities of daily living (ADL) is a clinical characteristic of Alzheimer's disease (AD).<sup>1</sup> ADL deficiency initially manifests as difficulties in performing instrumental ADL (IADL), that is, planning meals, handling finances, driving, shopping and other everyday activities.<sup>2</sup> For patients with severe AD, performing more basic ADL can become a challenge, for example, operating a faucet or light switch or carrying out fundamental aspects of personal care, such as grooming, bathing, toileting and dressing.<sup>2,3</sup>

The majority of patients with AD are cared for in the community, until functional, behavioral and cognitive impairments progress to a point where family caregivers are no longer able to manage the patient and transition to higher levels of care is required.<sup>4</sup> Loss of independence can be deeply distressing to both the patient and family caregivers,

with a reduced capacity to perform ADL cited as the main factor affecting quality of life in patients with dementia.<sup>5</sup>

Stabilization or reduction in ADL deterioration are clearly important aspects of AD management.<sup>6</sup> Cholinesterase inhibitors (ChEIs) are the current mainstay of AD treatment. For patients with mild-to-moderate AD, there are three ChEI treatments available: rivastigmine,<sup>7,8</sup> donepezil<sup>9</sup> and galantamine.<sup>10</sup>

<sup>1</sup>Private Practice, Marietta, GA, USA

<sup>2</sup>Alzheimer Disease Center, Departments of Neurology and Psychiatry, New York University Langone Medical Center, New York, NY, USA

<sup>3</sup>Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

## Corresponding author:

Joseph L Micca, Private Practice, 1938 Rand Ridge Ct, Marietta, GA 30062, USA.

Email: JLMicca@aol.com



For patients with moderate-to-severe AD, there are three approved treatments: two ChEIs—rivastigmine patch (Exelon® Patch; Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA)<sup>7</sup> and donepezil<sup>9</sup>—and memantine, an *N*-methyl-D-aspartate receptor antagonist.<sup>11</sup> Rivastigmine is the only ChEI available in both oral and transdermal patch formulations.<sup>7,8</sup> Transdermal delivery of rivastigmine provides a favorable pharmacokinetic profile, which is associated with a reduced incidence of gastrointestinal adverse events (AEs) compared with the capsule formulation.<sup>12</sup>

The efficacy of rivastigmine patch to reduce decline in the ability to perform ADL in severe AD was demonstrated in the ACTivities of daily living and cognitIOn (ACTION; ClinicalTrials.gov NCT00948766) study.<sup>13</sup> In this study, the high-dose 13.3 mg/24 h rivastigmine patch was significantly superior to the 4.6 mg/24 h patch on the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale–Severe Impairment Version (ADCS-ADL-SIV) at Week 24 ( $p=0.025$ ), with no marked dose-related increase in AEs (74.6% with 13.3 mg/24 h patch vs 73.3% with 4.6 mg/24 h patch).<sup>13</sup> Understanding whether efficacy of rivastigmine patch on ADL is cumulative (i.e. changes on multiple items) or driven by strong effects on particular tasks may inform physicians managing patients with severe AD with regard to treatment response. Here, we report the findings of a retrospective analysis of the ACTION study that analyzed the efficacy of high-dose 13.3 mg/24 h versus the low- (initiation) dose 4.6 mg/24 h patch on new domains of the ADCS-ADL-SIV derived using factor analysis and each of the individual ADCS-ADL-SIV items.

## Material and methods

### Study design

ACTION was a 24-week, prospective, randomized, parallel-group, double-blind, double-dummy, multicenter trial conducted at 82 centers in the United States; full details of the design and conduct have been published previously.<sup>13,14</sup> Briefly, patients enrolled in the ACTION study were male or female, aged  $\geq 50$  years, with probable AD (original 1984 National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association criteria)<sup>15</sup> and a Mini-Mental State Examination (MMSE)<sup>16</sup> score of  $\geq 3$  to  $\leq 12$ .<sup>13,14</sup>

Inclusion criteria of particular pertinence to the ADL assessment in this study were the inclusion of ambulatory patients (or those ambulatory with aid) and the requirement that patients be cooperative, willing to complete all aspects of the study, and capable of doing so with the aid of a responsible caregiver.<sup>14</sup> In addition, it was required that a responsible caregiver be present and able to provide input into efficacy and safety assessments in accordance with all protocol requirements.<sup>14</sup> Patients were required to be residing with someone in the community, or be in regular contact

with the primary caregiver.<sup>14</sup> Patients likely to be placed in a nursing home within 7 months of study initiation were excluded,<sup>14</sup> as were those with a disability, for example, deafness or blindness, which would have prevented the patient from completing all aspects of the study. Patients were excluded if they had received ChEIs or other approved treatments for AD during the 2 weeks prior, with the exception of stable memantine if taken for  $\geq 3$  months.<sup>13,14</sup> The percentages of patients receiving concomitant memantine were 61.0% and 60.6% for 13.3 mg/24 h and 4.6 mg/24 h treatment groups, respectively. Patients were excluded from the study if they had a Diagnosis and Statistical Manual of Mental Disorders IV diagnosis of major depression, unless it was successfully treated with a stable dose of an antidepressant without anticholinergic properties for  $\geq 4$  weeks prior.<sup>13,14</sup>

Eligible patients were randomly assigned (1:1) to 13.3 mg/24 h or 4.6 mg/24 h rivastigmine patch.<sup>13,14</sup> Primary outcome measures were the change from baseline at Week 24 on the Severe Impairment Battery<sup>17</sup> and ADCS-ADL-SIV.<sup>3</sup>

The study was conducted in accordance with Good Clinical Practice and the ethical principles of the Declaration of Helsinki. The study protocol, and all amendments, was reviewed by the Independent Ethics Committee or Institutional Review Board for each center. Prior to participation, all patients (or their legally authorized representative) provided written informed consent.<sup>13</sup>

### Factor analysis

Baseline ADCS-ADL-SIV data from the ACTION study population were used to establish a “best fit” for the 19 ADCS-ADL-SIV items<sup>3</sup> into new domains, determined by factor analysis. This was performed using the PROC FACTOR factor analysis procedure in Statistical Analysis Software (SAS Institute Inc., Cary, NC, USA). Initial common factor extraction was conducted using the principal component method; four domains with eigenvalues of at least 0.5 were retained. Loading estimates were obtained using varimax rotation. Domains took the sum of each item with a loading score of at least 0.3; items loaded to multiple factors were assigned to domains with the highest loadings. Based on item loadings, labels for each domain were generated and agreed upon by author consensus.

### Outcome measures

The change from baseline at Week 24 was calculated for each newly defined domain and individual ADCS-ADL-SIV item and compared between the two treatment groups (13.3 mg/24 h and 4.6 mg/24 h rivastigmine patch).

### Statistical analyses

Analyses were based on the modified full analysis set (MFAS), which included all randomized patients who had

**Table 1.** Calculated effect sizes (Cohen's *d*) based on the mean change from baseline at Week 24 on the newly defined ADCS-ADL-SIV domains and their comprising ADCS-ADL-SIV items (MFAS-LOCF).

Newly defined ADCS-ADL-SIV domain	Cohen's <i>d</i> effect size
ADCS-ADL-SIV items	
<i>Daily function</i>	0.135
1 Eating	−0.001
2 Walking	0.109
3 Toileting	0.024
4 Bathing	0.238
5 Grooming	0.135
6 Dressing	0.170
7 Telephone	0.003
10 Clear dishes	0.175
11 Find personal belongings	−0.019
12 Beverage	0.063
13 Dispose of garbage	−0.074
14 Travel	0.004
<i>Communication</i>	0.092
8.1 Watch television—Select program	0.096
8.2 Watch television—Talk about program while watching it	−0.018
8.3 Watch television—Talk about program 24 h after watching it	0.066
9 Conversation	0.062
<i>Independence</i>	0.060
15.1 Left alone—Away from home, for ≥15 min	−0.007
15.2 Left alone—At home, for ≥1 h	0.050
15.3 Left alone—At home, for <1 h	0.089
<i>Environment</i>	0.026
16 Run a faucet	0.047
17 Turn off faucet	−0.035
18 Turn on lights	0.007
19 Turn off lights	0.046

ADCS-ADL-SIV: Alzheimer's Disease Cooperative Study—Activities of Daily Living Scale—Severe Impairment Version; MFAS-LOCF: modified full analysis set with a last-observation-carried-forward imputation. Number of patients with an assessment: 13.3 mg/24 h = 310–315; 4.6 mg/24 h = 307–316.

received at least one dose of study medication and had at least one post-baseline assessment on the ADCS-ADL-SIV. Missing data were imputed using the last-observation-carried-forward (LOCF) method.

Between-group differences in newly defined ADCS-ADL-SIV domain scores were estimated using an analysis of covariance model, with treatment and center as factors, and corresponding baseline as a covariate.

Effect sizes (Cohen's *d*) were calculated, based on mean and standard deviation (SD) values, to compare the change from baseline at Week 24 on each of the newly defined domains and individual items of the ADCS-ADL-SIV in

patients randomized to receive 13.3 mg/24 h or 4.6 mg/24 h rivastigmine patch.

## Results

### Participants

Week 24 ADCS-ADL-SIV data were available for 631 patients randomized to 13.3 mg/24 h patch (*N*=315) or 4.6 mg/24 h patch (*N*=316). Baseline demographics and characteristics for each treatment group were comparable.<sup>13</sup> In the MFAS, mean (SD) ADCS-ADL-SIV scores at baseline were 29.7 (11.3) in patients receiving 13.3 mg/24 h patch and 29.1 (11.9) in patients receiving 4.6 mg/24 h patch.<sup>13</sup>

### ADCS-ADL-SIV domain analysis

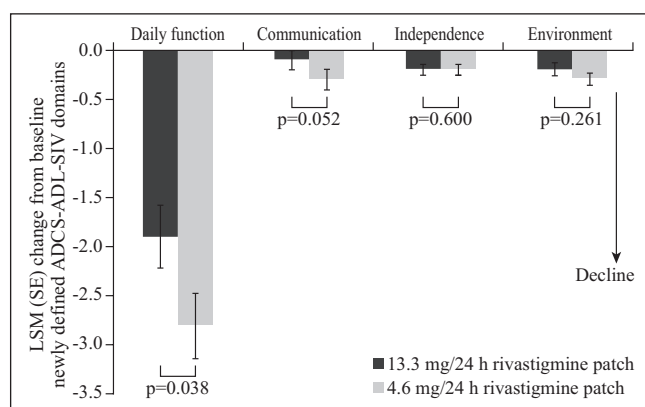
Table 1 shows the four newly defined domains derived from the factor analysis. The domains were named by author consensus after review of the individual ADCS-ADL-SIV items assigned to each domain: “Daily function,” “Communication,” “Independence” and “Environment.”

Mean scores on all four newly defined ADCS-ADL-SIV domains had decreased from baseline at Week 24 in both treatment groups, indicating functional decline (Figure 1). Positive treatment effect sizes, indicating less decline with 13.3 mg/24 h versus 4.6 mg/24 h rivastigmine patch, were observed on all four domains (Figure 2; Table 1). The observed greater efficacy (i.e. less functional deterioration) of 13.3 mg/24 h versus 4.6 mg/24 h rivastigmine patch reached significance on the newly defined ADCS-ADL-SIV domain of “Daily function” (*p*=0.038), and there was a trend toward greater efficacy on “Communication” (*p*=0.052) (Figure 1). No significant between-group differences were observed on “Independence” (*p*=0.600) or “Environment” (*p*=0.261) (Figure 1).

### ADCS-ADL-SIV item analysis

Treatment effect sizes for the majority of ADCS-ADL-SIV items were positive (>0, range 0.003–0.238), demonstrating numerically less functional decline with the 13.3 mg/24 h versus 4.6 mg/24 h rivastigmine patch at Week 24 (Figure 3; Table 1). The greatest treatment effect sizes (>0.1, range 0.109–0.238) were observed on items contained within the newly defined “Daily function” domain: “Bathing” (0.238), “Clear dishes” (0.175), “Dressing” (0.170), “Grooming” (0.135) and “Walking” (0.109) (Figure 3; Table 1).

Effect sizes ≥0.05 and <0.1 were seen for three items in the “Communication” domain: “Watch television—Select program” (0.096), “Watch television—Talk about program 24 h after watching it” (0.066) and “Conversation” (0.062), and two of three items associated with independence: “Left alone—At home, for <1 h” (0.089) and “Left alone—At home, ≥1 h” (0.050) (Figure 3; Table 1).



**Figure 1.** LSM change from baseline at Week 24 on the newly defined ADCS-ADL-SIV domains (MFAS-LOCF).

ADCS-ADL-SIV: Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale–Severe Impairment Version; LSM: least squares mean; MFAS-LOCF: modified full analysis set with a last-observation-carried-forward imputation; SE: standard error.

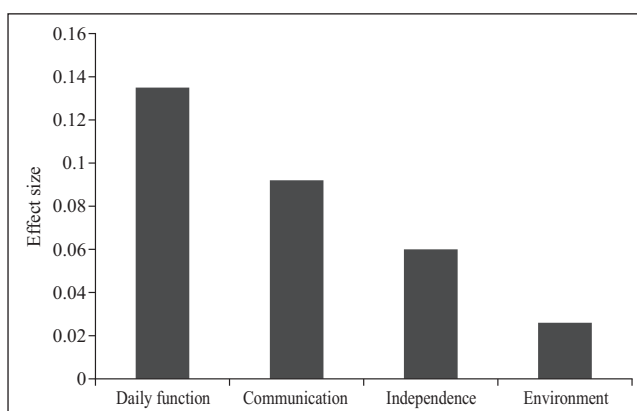
Error bars represent the SE of the LSM. Number of patients with an assessment: 13.3 mg/24h = 310–315; 4.6 mg/24h = 307–316.

## Discussion

The ACTION study demonstrated superior efficacy of 13.3 mg/24h versus 4.6 mg/24h rivastigmine patch on the ADCS-ADL-SIV at Week 24 in patients with severe AD.<sup>13</sup> Supporting this primary outcome, in this post hoc analysis of ADCS-ADL-SIV data from the ACTION study,<sup>13</sup> the high-dose 13.3 mg/24h rivastigmine patch demonstrated significantly superior efficacy to 4.6 mg/24h patch on the newly defined “Daily function” domain and numerically less functional decline on all other domains and most of the individual ADCS-ADL-SIV items.

The ACTION study was not powered to assess treatment outcomes for specific ADCS-ADL-SIV items—indeed, it would not be feasible to enroll the required numbers of study participants to determine efficacy for individual items.<sup>13</sup> However, by grouping specific items in this factor analysis, based on baseline ACTION study data, it was possible to investigate the efficacy of rivastigmine patch therapy on specific ADL domains. Of note, the lack of power to detect significant between-group differences on the ADCS-ADL-SIV items and subscales was considered a limitation of this analysis, along with its post hoc nature. As such, these analyses were considered hypothesis forming and should be interpreted as such. Although identification of potentially responsive ADL items or item clusters in this way may be useful to predict a treatment response in patients, further ADL-focused studies in patients with severe AD would be required to confirm these findings.

Based on treatment effect sizes, numerically less decline was observed with 13.3 mg/24h versus 4.6 mg/24h rivastigmine patch on all four newly defined domains (“Daily function,” “Communication,” “Independence” and “Environment”), indicating a broad benefit of rivastigmine patch therapy on



**Figure 2.** Calculated effect sizes (Cohen's *d*) based on the mean change from baseline at Week 24 on the newly defined ADCS-ADL-SIV domains (MFAS-LOCF).

ADCS-ADL-SIV: Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale–Severe Impairment Version; MFAS-LOCF: modified full analysis set with a last-observation-carried-forward imputation.

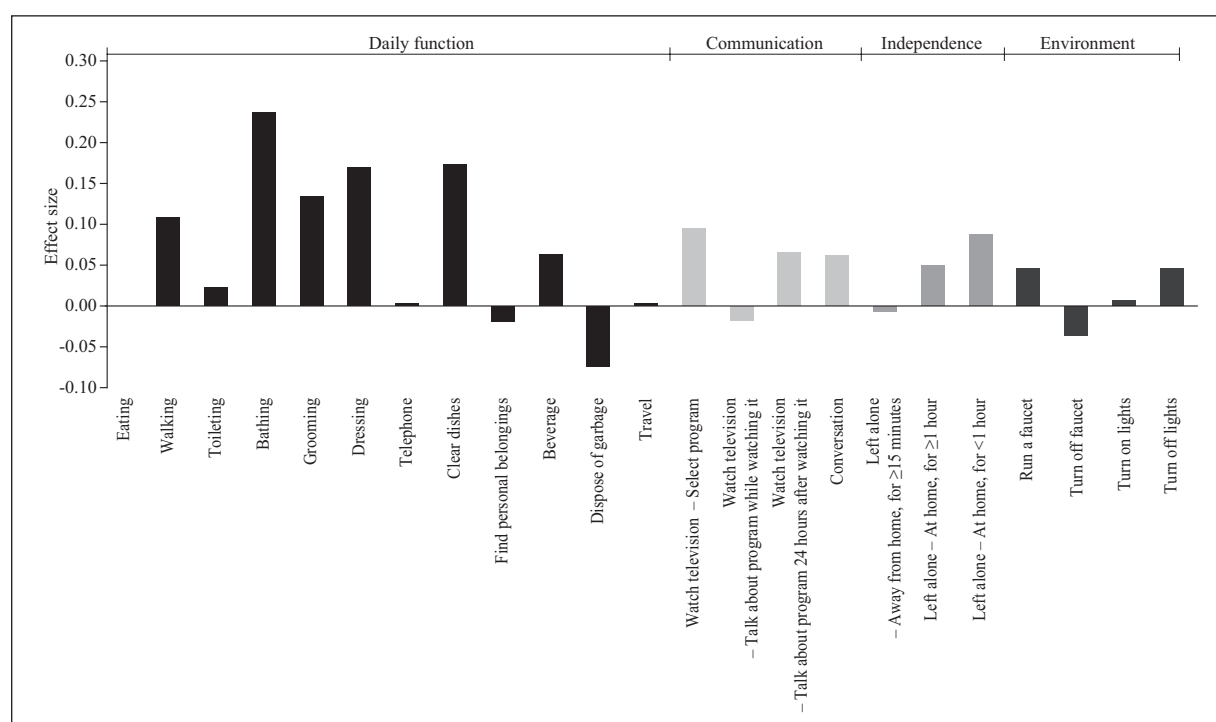
Number of patients with an assessment: 13.3 mg/24h = 310–315; 4.6 mg/24h = 307–316. Positive treatment effect sizes indicate numerically less functional decline with 13.3 mg/24h versus 4.6 mg/24h patch.

performance of ADL in patients with severe AD. The observed greater efficacy of 13.3 mg/24h versus 4.6 mg/24h rivastigmine patch reached significance on the newly defined domain of “Daily function” (with a trend toward greater efficacy on “Communication”), suggesting the benefits of high-dose patch on ADL performance may be particularly apparent on activities associated with daily function. The reason for a lack of significant treatment effects on “Environment,” “Communication” and “Independence,” despite efficacy on the total ADCS-ADL-SIV is unclear, but could be due in part to the retrospective nature of these analyses and relatively small sample sizes.

At Week 24, numerically less, or no reduction in, functional decline, as demonstrated by positive or neutral treatment effect sizes, respectively, with 13.3 mg/24h versus 4.6 mg/24h rivastigmine patch was observed for the majority of individual items of the ADCS-ADL-SIV. Supporting the domain level findings, the highest individual treatment effect sizes were observed for items allocated to the “Daily function” domain, specifically “Bathing,” “Dressing,” “Grooming,” “Clear dishes” and “Walking.” These observations have implications when managing patients with severe AD with 13.3 mg/24h rivastigmine patch, as they suggest potential benefits of high-dose rivastigmine patch treatment on aspects of daily function, alongside stabilization of the majority of items assessing communication, independence and environment.

Items with an effect size close to zero were generally those activities that required a slightly higher level of functioning than tasks that assess more basic ADL. Only a small number of patients with severe AD would have been expected to be able to perform relatively more complex tasks such as “Dispose of garbage” or “Find personal belongings” before treatment initiation, and the small mean change from baseline on these items indicates that performance of these





**Figure 3.** Calculated effect sizes (Cohen's *d*) based on the mean change from baseline at Week 24 on ADAS-ADL-SIV items (MFAS-LOCF).

ADAS-ADL-SIV: Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale–Severe Impairment Version; MFAS-LOCF: modified full analysis set with a last-observation-carried-forward imputation.

Number of patients with an assessment: 13.3 mg/24 h = 311–315; 4.6 mg/24 h = 312–316. Positive treatment effect sizes indicate numerically less functional decline with 13.3 mg/24 h versus 4.6 mg/24 h patch. Negative treatment effect sizes indicate numerically less functional decline with 4.6 mg/24 h versus 13.3 mg/24 h patch.

activities does not drive decline in the severe AD population. For this reason, it is important to convey realistic expectations of treatment to the family or caregivers of a patient with severe AD.

Previously, patients with severe AD (defined as a MMSE score  $\geq 7$  to  $\leq 12$ ) have shown greater worsening in ADAS-ADL scores over time than those at less advanced disease stages.<sup>18</sup> More specifically, the current analysis in patients with severe AD (MMSE score  $\geq 3$  to  $\leq 12$ ) demonstrates that decline predominantly occurs in the newly defined “Daily function” domain of the ADAS-ADL-SIV. These findings suggest that loss of the ability to perform ADL in patients with severe AD, resulting in increased caregiver burden and institutionalization,<sup>19–22</sup> is driven by decline in “Daily function.”

“Daily function” ADL, referring largely to basic ADL, have previously been identified as markers of progression from moderate AD to more severe stages of the disease.<sup>2,3</sup> Consequently, therapeutic benefits of treatment on basic ADL are an important treatment goal for this population. The observation that 13.3 mg/24 h versus 4.6 mg/24 h rivastigmine patch demonstrates significant efficacy on the “Daily function” domain reflects the importance of this domain in disease progression and reinforces the potential benefits of

high-dose rivastigmine patch on key aspects of function in patients with severe AD.

ACTION is the first study to investigate rivastigmine patch in severe AD; however, previous factor analyses of data from clinical studies in patients with mild-to-moderate AD have identified specific ADL domains where rivastigmine patch demonstrates therapeutic effects. In a post hoc analysis of the Investigation of transDermal Exelon in Alzheimer's disease (IDEAL; ClinicalTrials.gov NCT00099242) study, 9.5 mg/24 h rivastigmine patch showed numerically less deterioration at Week 24 on two of three factor analysis-derived ADAS-ADL subscales, “Basic ADL” and “High-level function ADL,” and significantly superior efficacy on the third subscale, “Autonomy ADL,” compared with placebo.<sup>23</sup> Furthermore, post hoc analyses of the 48-week OPTimizing Transdermal Exelon In Mild-to-moderate Alzheimer's disease (OPTIMA; ClinicalTrials.gov NCT00506415) study data confirmed significantly less decline with 13.3 mg/24 h compared with 9.5 mg/24 h rivastigmine patch at Week 48 on both the “Higher level functioning” and “Autonomy” subscales of the Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living Scale (ADAS-IADL).<sup>6</sup> The therapeutic benefit seen in mild-to-moderate AD on “Autonomy” ADL compared with effects on more basic ADL

observed in the current analysis reflects the natural course of disease progression.<sup>2</sup> With the ability to perform IADL likely to be diminished in patients with severe AD,<sup>2</sup> clinically meaningful treatment effects may be more apparent on relatively more preserved “Basic ADL” compared with the more complex “Higher level functioning” or “Autonomy.” In a factor analysis of the Tariot et al. study, memantine 20 mg/day provided statistically significant benefits in the domains of “Higher level functions” and “Connectedness/autonomy” rather than “Simple motor skills/praxis” or “Basic ADL” (comprising basic ADL items such as “Grooming,” “Walking” and “Bathing”) domains,<sup>24,25</sup> perhaps reflecting the milder disease exhibited by a proportion of the moderate-to-severe AD population included in this study compared with the ACTION study.

Previous clinical studies with the other pharmacological agents approved for use in the severe AD patient population have shown varied efficacy in reducing decline in ADL. Reported benefits of donepezil in stabilizing ADL function in patients with severe AD, assessed using the ADCS-ADL-SIV, have been inconsistent; Black et al.<sup>26</sup> reported no statistically significant benefit with donepezil treatment compared with placebo, while a significant treatment effect of donepezil versus placebo ( $p=0.03$ ) was observed in a Swedish study.<sup>27</sup> Two placebo-controlled studies assessing memantine efficacy (including significant effects on the ability to perform ADL in patients with moderate-to-severe AD using the ADCS-ADL-SIV) supported the approval of memantine for the treatment of moderate-to-severe AD.<sup>11,24,28</sup> Yet in the more recent Donepezil and Memantine in Moderate-to-Severe Alzheimer’s Disease (DOMINO; ClinicalTrials.gov NCT00866060) study, there were no significant benefits of the combination of donepezil and memantine over donepezil alone.<sup>29</sup> It is of note that these studies compare the study drug against placebo. The inclusion of an active comparator in the ACTION study design, rather than a placebo control arm, is likely to have masked the absolute benefit of 13.3 mg/24 h rivastigmine patch treatment on performance of ADL in this study.

In the ACTION study, patients living in a nursing home, permanently placed in a nursing home during the study or likely (physicians’ opinion) to be placed in a nursing home within 7 months of enrollment were excluded from study entry.<sup>13,14</sup> As such, these data provide evidence for the efficacy, safety and tolerability of 13.3 mg/24 h patch in community-living patients with severe AD and may be less representative of severe AD patients in long-term care settings. The performance scales used in the ACTION study depend on patient interview with caregiver input. If the patient became institutionalized during the trial, the caregiver’s role in directly observing the patient and providing care would change dramatically since this would be replaced, in part, by the staff and clinical milieu of the institutionalized environment. This change would impact on study findings, leading to potentially misleading and invalidated results.

Also, comparing outcomes of chronically institutionalized patients and community-living patients in the same trial would be difficult since the institutional milieu itself is geared toward ADL assistance in a way very different than the outpatient setting. Loss of function is a strong predictor of transition into nursing home care; delaying or reducing deterioration in the ability to perform ADL is likely to extend the time patients with AD can remain in their own homes.<sup>19,21</sup> Since nursing home fees are the main drivers of dementia care costs, prolonging community residence for patients with AD also has potential to reduce the economic burden of AD.<sup>30</sup> Benefits on ADL have important implications for the burden on patients and caregivers, as patients with severe ADL deficiencies are more dependent, need more care and have a lower quality of life than those in milder stages of the disease.<sup>5,13,20–22</sup>

## Conclusion

In this post hoc analysis of ADCS-ADL-SIV data from the ACTION study,<sup>13</sup> the high-dose 13.3 mg/24 h rivastigmine patch demonstrated significantly superior efficacy to 4.6 mg/24 h patch on the newly defined “Daily function” domain and numerically less functional decline on all other domains and most of the individual ADCS-ADL-SIV items, in a severe AD population. Consequently, high-dose 13.3 mg/24 h rivastigmine patch may help to stabilize or reduce deterioration in the ability to perform ADL in patients with severe AD and may be particularly effective in slowing symptomatic decline in more basic ADL, specifically those associated with daily function.

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Data were previously presented as a poster at the US Psychiatric and Mental Health Congress, Las Vegas, NV, USA, 30 September–3 October 2013; the 66th American Academy of Neurology (AAN) Annual Meeting, Philadelphia, PA, USA, 26 April–3 May 2014 and the Joint Congress of European Neurology (JCEN), Istanbul, Turkey, 31 May–3 June 2014.

Trial registration: ACTION ClinicalTrials.gov NCT00948766

## Declaration of conflicting interests

Joseph Micca has served on advisory boards and speaker bureaus for both Novartis Pharmaceuticals Corporation and Eli Lilly. James Galvin has received honoraria for acting as scientific advisor, investigator or consultant for Pfizer, Eisai, Merck, Novartis, Forest, Baxter, Bayer, Bristol-Myers Squibb, Takeda, Accera, Medavante, AstraZeneca and Eli Lilly. Drew Velting and Xiangyi Meng are full-time employees and stock holders of Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA.

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