

## ORIGINAL ARTICLE

# Evaluating Response to High-Dose 13.3 mg/24 h Rivastigmine Patch in Patients with Severe Alzheimer's Disease

Martin R. Farlow,<sup>1</sup> Carl H. Sadowsky,<sup>2,3</sup> Drew M. Velting,<sup>4</sup> Xiangyi Meng<sup>4</sup> & M. Zahur Islam<sup>4</sup><sup>1</sup> Department of Neurology, Indiana University School of Medicine, Indianapolis, IN, USA<sup>2</sup> Division of Neurology, Nova Southeastern University, Fort Lauderdale, FL, USA<sup>3</sup> Premiere Research Institute, Palm Beach Neurology, West Palm Beach, FL, USA<sup>4</sup> Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

## Keywords

Alzheimer disease; Predictor; Rivastigmine; Receiver-operating characteristic; Transdermal patch.

## Correspondence

Martin R. Farlow, Department of Neurology, Indiana University School of Medicine, Indianapolis, IN 46202, USA.

Tel.: +1-317-963-7402;

Fax: +1-317-963-7533;

E-mail: mfarlow@iupui.edu

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## SUMMARY

**Aims:** To identify factors predicting improvement/stabilization on the Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change (ADCS-CGIC) and investigate whether early treatment responses can predict long-term outcomes, during a trial of 13.3 mg/24 h versus 4.6 mg/24 h rivastigmine patch in patients with severe Alzheimer's disease (AD). **Methods:** Logistic regression was used to relate Week 24 ADCS-CGIC score to potential baseline predictors. Additional analyses based on receiver-operating characteristic curves were performed using Week 8/16 ADCS-CGIC scores to predict response (13.3 mg/24 h patch) at Week 24. ADCS-CGIC score of (1) 1–3 = “improvement,” (2) 1–4 = “improvement or no change”. **Results:** “Treatment” (13.3 mg/24 h patch) and increased age were significant predictors of “improvement” ( $P = 0.01$  and  $P = 0.003$ , respectively), and “treatment” ( $P = 0.001$ ), increased age ( $P = 0.002$ ), and prior AD treatment ( $P = 0.03$ ) for “improvement or no change”. At Week 8 and 16, ADCS-CGIC scores of 4 and 5 were optimal thresholds in predicting “improvement,” and “improvement or no change,” respectively, at Week 24. **Conclusions:** A significant therapeutic effect of high-dose rivastigmine patch on ADCS-CGIC response was observed. The 13.3 mg/24 h patch was identified as a predictor of “improvement” or “improvement or no change”. Patients with minimal worsening/improvement/no change after treatment initiation may be more likely to respond following long-term therapy.

## Introduction

The 13.3 mg/24 h rivastigmine transdermal patch is approved in the USA for the symptomatic treatment of mild-to-moderate and severe Alzheimer's disease (AD) [1]. Approval for the severe indication was based on proven efficacy of the high-dose 13.3 mg/24 h rivastigmine patch in the ACTION (ACTivities of daily living and cognitIOn) study [1,2].

The ACTION study was a 24-week, randomized, double-blind comparative study of 13.3 mg/24 h versus 4.6 mg/24 h rivastigmine patch in patients with severe AD (ClinicalTrials.gov identifier: NCT00948766) [2,3]. In this study, significantly less decline was observed with 13.3 mg/24 h versus 4.6 mg/24 h rivastigmine patch on both co-primary endpoints, the change from baseline at Week 24 on the Severe Impairment Battery (SIB;  $P < 0.0001$ ) and the Alzheimer's Disease Cooperative Study–Activities of Daily Living scale–Severe Impairment Version (ADCS-ADL-SIV;  $P = 0.025$ ) [2]. Significant between-group differences at Week 24 were also observed on the Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change (ADCS-CGIC), a secondary measure of global function [2].

Despite the greater efficacy demonstrated with 13.3 mg/24 h versus 4.6 mg/24 h rivastigmine patch, similar proportions of patients in both treatment groups reported adverse events (AEs; 74.6% and 73.3%, respectively) [2].

Patients with severe AD are likely to experience continuous functional and cognitive decline, regardless of whether or not they are receiving treatment. Achieving short-term improvement, longer-term stabilization or a slowed decline in one or more clinically relevant symptom domains may therefore represent a therapeutic benefit [4]. If clinically relevant factors predictive of a response on the ADCS-CGIC (improvement or stabilization) can be identified, this could guide clinicians' decision-making when managing patients with severe AD and encourage an individualized approach to patient management.

In addition to identifying relevant patient characteristics associated with a response, analysis of early treatment outcomes can be used to predict whether a patient is likely to respond to treatment [5]. This investigation can be enhanced through the application of receiver-operating characteristic (ROC) curve analysis [5]. ROC analysis examines all possible outcomes for a predictive measure, with each outcome yielding an estimated sen-

sitivity and specificity, which equates to the probability of a true response or true nonresponse, respectively [5].

Here, we present additional analysis of the ADCS-CGIC data collected during the ACTION study. The objectives of the current analyses were 2-fold: first, to identify patient characteristics at baseline that may predict a response (improvement or stabilization) on the ADCS-CGIC; and second, to evaluate whether global functional status (ADCS-CGIC score) early after treatment initiation, and following a further 8 weeks of treatment, can be used to predict subsequent clinical outcomes with the 13.3 mg/24 h rivastigmine patch.

## Materials and Methods

### Study Design and Patients

Detailed methodology of the ACTION study has been published previously [2,3]. Briefly, patients were male or female, at least 50 years of age, with probable AD (original 1984 National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association criteria) [6] and a Mini-Mental State Examination (MMSE) [7] score of 3–12, inclusive. Patients were excluded if they had received cholinesterase inhibitors (ChEIs) and/or other approved treatments for AD during the previous 2 weeks, with the exception of stable memantine if taken for at least 3 months prior to screening. Eligible patients ( $N = 716$ ) were randomized in a 1:1 ratio to 13.3 mg/24 h or 4.6 mg/24 h rivastigmine patch for 24 weeks. Patients randomized to 13.3 mg/24 h patch followed an 8-week titration schedule (via 4.6 mg/24 h and 9.5 mg/24 h patch doses) before being uptitrated to the target dose. Patients randomized to 4.6 mg/24 h patch remained at that dose throughout the 8-week titration. Target doses were maintained for 16 weeks from the end of the titration period.

The ACTION study was conducted in accordance with Good Clinical Practice and the ethical principles of the Declaration of Helsinki [2]. All patients, or their legally authorized representative, provided written informed consent prior to participating [2].

### Outcome Measures

The co-primary outcome measures in the ACTION study were the change from baseline at Week 24 on the SIB [8] and the ADCS-ADL-SIV [2,3,9]. The SIB was developed to evaluate cognitive dysfunction in patients with severe AD [8]. The version of the SIB used in this study evaluated 40 items, with a possible range of scores from 0 to 100 [8,10]. The ADCS-ADL-SIV is a caregiver-based activities of daily living (ADL) scale, composed of 19 items (score range 0–54), designed to assess ability to perform basic and instrumental ADL in patients with severe AD [9].

The secondary efficacy measures included the ADCS-CGIC score at Week 24 [2,3,11]. The ADCS-CGIC is a 7-point clinical change scale [11]. Each patient is assigned a score, derived based on the clinician's perception of the patient's change in global clinical status over time, where 1 = "marked improvement," 2 = "moderate improvement," 3 = "minimal improvement," 4 = "no change," 5 = "minimal worsening," 6 = "moderate worsening," and 7 = "marked worsening" [11].

These *post hoc* analyses of response were conducted by applying definitions for "improvement" and "improvement or no change," stated in the original analysis plan, to the ADCS-CGIC scale. A score of 1–3 on the ADCS-CGIC at Week 24 was defined as "improvement," and a score of 1–4 at Week 24 was defined as "improvement or no change."

## Statistical Analyses

### Proportion of Responders

The proportion of patients showing a response ("improvement" or "improvement or no change") on the ADCS-CGIC with 13.3 mg/24 h or 4.6 mg/24 h patch was a preplanned analysis. *P*-values comparing the proportion of patients in the two treatment groups showing "improvement" and the proportion showing "improvement or no change" were calculated using Cochran–Mantel–Haenszel statistics, controlling for pooled center.

This analysis was based on the modified full analysis set (MFAS), which included all randomized patients who received at least one dose of study medication and had at least one postbaseline measurement on the ADCS-CGIC. Missing values were imputed using the last observation carried forward (LOCF) approach.

### Predictors of "Improvement" and "Improvement or No Change"

In the *post hoc* analysis, a logistic regression model was used to relate potential baseline predictors ("treatment" [13.3 mg/24 h vs. 4.6 mg/24 h rivastigmine patch], gender [male vs. female], prior AD treatment [treatment naïve vs. previously treated], time since first symptoms of AD, MMSE score, age, body mass index [BMI], and concomitant memantine use) to the response on the ADCS-CGIC scale at Week 24. *P*-values and 95% confidence intervals (CI) associated with coefficients of predictors were calculated using Wald chi-square statistics. In addition, the effect on response from interactions of treatment-by-prior AD treatment, treatment-by-time since first symptom of AD, treatment-by-MMSE score, treatment-by-age, treatment-by-BMI, and treatment-by-concomitant memantine use was assessed in separate logistic regression models in addition to their corresponding main effects. These analyses were also based on the MFAS with missing data imputed using the LOCF approach.

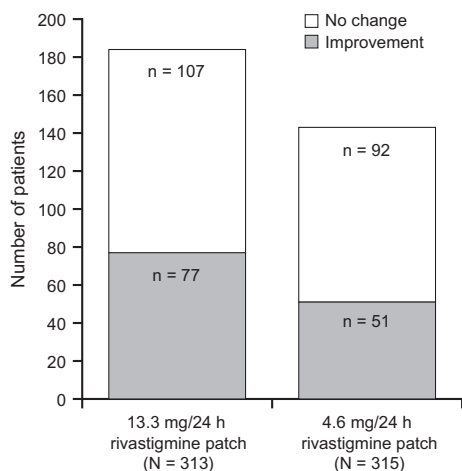
### Predictive Value of Early Treatment Response (ROC Analysis)

Prediction of response to high-dose rivastigmine patch at Week 24 was investigated through the application of ROC curve analyses based on early treatment outcomes using the MFAS. ROC curves were generated using Week 8 and Week 16 ADCS-CGIC scores to predict response ("improvement" or "improvement or no change") to 13.3 mg/24 h rivastigmine patch at Week 24. To enable the selection of an optimal threshold value for the ADCS-CGIC at Week 8 and Week 16, Youden's index [12], a function of both specificity and sensitivity, was plotted for each ROC curve. The maximum value of the Youden's index was used to pick the optimum predictor threshold.

## Results

### Study Population

Overall, 356 patients were randomized to 13.3 mg/24 h rivastigmine patch, and 360 patients were randomized to 4.6 mg/24 h rivastigmine patch [2]. ADCS-CGIC data were available for 307 patients randomized to 13.3 mg/24 h rivastigmine



**Figure 1** Proportion of patients showing “improvement,” and “improvement or no change” on the ADCS-CGIC at Week 24 (MFAS-LOCF). ADCS-CGIC, Alzheimer’s Disease Cooperative Study–Clinical Global Impression of Change, MFAS-LOCF, modified full analysis set with a last observation carried forward imputation.

patch at Week 8, 312 patients at Week 16, and 313 patients at Week 24. Of the 4.6 mg/24 h patch group, 309 patients provided ADCS-CGIC data at Week 8, 314 at Week 16, and 315 patients at Week 24. Baseline demographics and characteristics were similar between treatment groups [2].

### Proportion of Responders

At Week 24, 24.6% of patients (77/313) in the high-dose (13.3 mg/24 h rivastigmine patch) group demonstrated “improvement” on the ADCS-CGIC scale; this was significantly higher compared with the 16.2% of patients (51/315) demonstrating “improvement” in the low-dose (4.6 mg/24 h rivastigmine patch) group ( $P = 0.01$ ; Figure 1). Significantly, more patients in the high-dose group demonstrated “improvement or no change” compared with the low-dose group (58.8% [184/313] and 45.4% [143/315], respectively;  $P = 0.001$ ; Figure 1).

### Predictors of “Improvement” and “Improvement or No Change”

Treatment with high-dose 13.3 mg/24 h versus 4.6 mg/24 h rivastigmine patch and age were significant predictors of “improvement” at Week 24 (odds ratio [OR] = 1.65; 95% CI 1.10, 2.47;  $P = 0.01$ ; and 1.04; 95% CI 1.01, 1.07;  $P = 0.003$ , respectively; Table 1); these factors were also significant predictors of “improvement or no change” at Week 24 (OR = 1.69; 95% CI 1.23, 2.34;  $P = 0.001$  and 1.03 95% CI 1.01, 1.05;  $P = 0.002$ , respectively, Table 1). The observed ORs suggest a 65% greater chance of “improvement” and a 69% greater chance of

**Table 1** Predictors of “improvement” and “improvement or no change” from the logistic regression model (MFAS-LOCF)

Parameter	Maximum likelihood estimate*	Standard error	$Pr > ChiSq$	Odds ratio [95% CI]
<b>“Improvement” at Week 24</b>				
“Treatment” (13.3 mg/24 h vs. 4.6 mg/24 h patch)	0.25	0.10	0.01	1.65 [1.10, 2.47]
Gender (male vs. female)	−0.03	0.11	0.79	0.94 [0.62, 1.45]
Time since first AD symptoms	−0.03	0.04	0.42	0.97 [0.89, 1.05]
Prior AD treatment (treatment naïve vs. previously treated)	0.03	0.18	0.86	1.07 [0.53, 2.15]
MMSE score	0.07	0.04	0.09	1.07 [0.99, 1.15]
Age	0.04	0.01	0.003	1.04 [1.01, 1.07]
BMI	0.04	0.02	0.10	1.04 [0.99, 1.08]
Concomitant memantine use	0.13	0.11	0.26	1.29 [0.83, 2.02]
<b>“Improvement or no change” at Week 24</b>				
“Treatment” (13.3 mg/24 h vs. 4.6 mg/24 h patch)	0.26	0.08	0.001	1.69 [1.23, 2.34]
Gender (male vs. female)	−0.09	0.09	0.30	0.83 [0.59, 1.18]
Time since first AD symptoms	0.01	0.03	0.73	1.01 [0.95, 1.08]
Prior AD treatment (treatment naïve vs. previously treated)	0.37	0.17	0.03	2.09 [1.08, 4.03]
MMSE score	0.03	0.03	0.30	1.03 [0.97, 1.09]
Age	0.03	0.01	0.002	1.03 [1.01, 1.05]
BMI	0.02	0.02	0.21	1.02 [0.99, 1.06]
Concomitant memantine use	0.07	0.09	0.42	1.16 [0.81, 1.67]

AD, Alzheimer’s disease; ADCS-CGIC, Alzheimer’s Disease Cooperative Study–Clinical Global Impression of Change; BMI, body mass index; CI, confidence interval; MFAS-LOCF, modified full analysis set with a last observation carried forward imputation; MMSE, Mini-Mental State Examination. \*A positive maximum likelihood estimate indicates increased odds of “improvement” or “improvement or no change” when increasing the value of the covariate or when in the given category. A negative estimate indicates a reduced odds of “improvement” or “improvement or no change.” “Improvement” is defined as a Week 24 ADCS-CGIC score of 1–3, and “improvement or no change” as a Week 24 ADCS-CGIC score of 1–4.

“improvement or no change” when treated with high-dose versus low-dose rivastigmine patch.

Being treatment-naïve was a significant predictor of “improvement or no change” (OR = 2.09; 95% CI 1.08, 4.03;  $P = 0.03$ ), but not “improvement” alone at Week 24 (Table 1). Treatment naïve patients (who accounted for 9% of the patients in the analysis) demonstrated an estimated 109% greater chance of “improvement or no change” when compared with those who had received previous therapies.

No other baseline factors (gender, time since the first symptoms of AD, MMSE score, BMI, or concomitant memantine use) were shown to predict a response on the ADCS-CGIC (“improvement” or “improvement or no change”; Table 1).

Interaction effects of “treatment” (13.3 mg/24 h vs. 4.6 mg/24 h rivastigmine patch) with prior AD treatment, MMSE score, time since first symptoms of AD, age, BMI, or concomitant memantine use were not observed for either definition of response.

### Predictive Value of Early Treatment Response

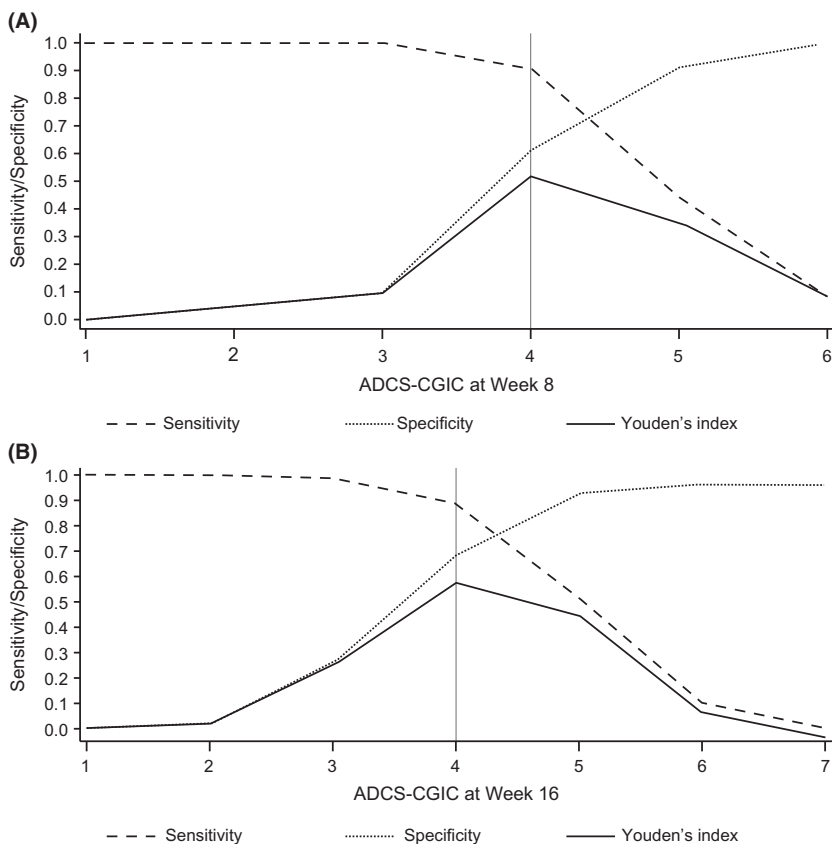
An ADCS-CGIC score of 4 at Week 8, indicating “no change,” was the optimal threshold predictor of “improvement” on the ADCS-CGIC at Week 24, with a sensitivity of 0.91 and a specificity of 0.61 (Figure 2A). A synthesis of the analysis showed that 100% of patients with an ADCS-CGIC score of 1–3 and 91% of patients with a score of 4 at Week 8 demonstrated “improvement” at Week

24. Similarly, an ADCS-CGIC score of 4 at Week 16 was the optimal threshold predictor of “improvement” at Week 24 (sensitivity, 0.89; specificity, 0.69; Figure 2B).

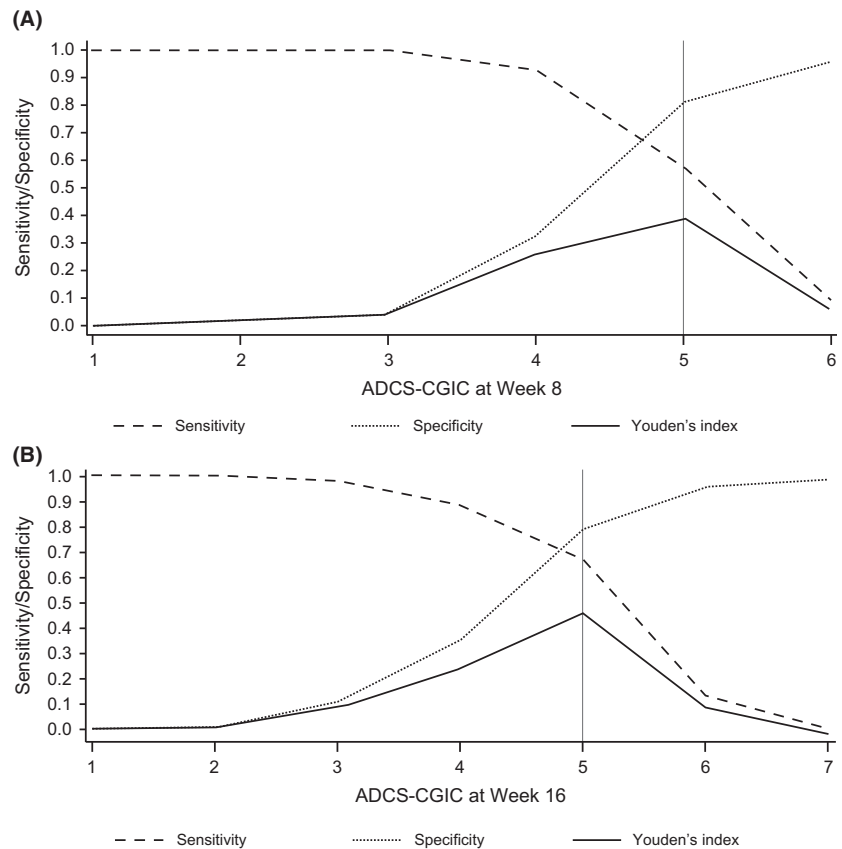
An ADCS-CGIC score of 5, indicating “minimal worsening,” at Week 8 was the optimal threshold predictor of “improvement or no change” on the ADCS-CGIC at Week 24, with a sensitivity of 0.58 and a specificity of 0.81 (Figure 3A). All (100%) patients with an ADCS-CGIC score of 1–3, 93% of patients with a score of 4, and 58% of patients with a score of 5 at Week 8 demonstrated “improvement or no change” at Week 24. When using Week 16 data for the ROC analysis, a score of 5 was also the optimal threshold predictor of “improvement or no change” at Week 24 (sensitivity, 0.67; specificity, 0.79; Figure 3B).

### Discussion

One of the key objectives of this retrospective analysis was to investigate whether certain baseline patient characteristics, specifically rivastigmine patch treatment, gender, time since manifestation of first AD symptoms, prior AD treatment, MMSE score, age, BMI, and concomitant memantine use, could be used to predict improvement or stabilization on the ADCS-CGIC in patients with severe AD. Logistic regression analyses demonstrated that treatment with 13.3 mg/24 h rivastigmine patch and increased age were significant predictors of “improvement” or “improvement or no change” in the patient’s global function, assessed using the ADCS-CGIC, at the study endpoint (Week 24).



**Figure 2** Prediction of “improvement” on the ADCS-CGIC at Week 24 based on (A) Week 8 and (B) Week 16 ADCS-CGIC scores (MFAS). ADCS-CGIC, Alzheimer’s Disease Cooperative Study–Clinical Global Impression of Change; MFAS, modified full analysis set.



**Figure 3** Prediction of “improvement or no change” on the ADCS-CGIC at Week 24 based on (A) Week 8 and (B) Week 16 ADCS-CGIC scores (MFAS). ADCS-CGIC, Alzheimer’s Disease Cooperative Study–Clinical Global Impression of Change; MFAS, modified full analysis set.

These findings extend previously published analyses from the core ACTION study, where 13.3 mg/24 h rivastigmine patch demonstrated significantly greater efficacy at Week 24 on the total SIB, ADCS-ADL-SIV, and ADCS-CGIC versus the 4.6 mg/24 h patch dose [2].

In another recent analysis of data from the ACTION study, younger age was identified as being a single factor that predisposed patients to rivastigmine patch application site skin reactions [13]. It is interesting to note that not only are older patients more likely to respond to rivastigmine patch therapy, but they are also more likely to tolerate therapy.

A previous subanalysis of the IDEAL (Investigation of transDermal Exelon in ALzheimer’s disease) study in a population with mild-to-moderate AD demonstrated that, on the ADCS-CGIC, the greatest rivastigmine–placebo differences were observed in patients with more severe AD, compared with milder disease stages [14]. This prior observation suggests that the probability of a treatment effect increases with advancing disease stage and provides a rationale for maintaining patients with severe AD on treatment [14]. In the current analysis of patients with severe AD, baseline MMSE score was not found to be a significant predictor of treatment response. The inclusion criteria for the IDEAL study were an MMSE score of 10–20 (inclusive); therefore, patients with more severe disease in this study had scores overlapping the mildest patients included in the ACTION study. Whether MMSE score is a predictor of improvement or stabilization in severe AD over the long term is unknown.

In the current analysis, patients who were treatment naïve also demonstrated a greater likelihood of “improvement or no change” compared with those who had previously received treatment for AD. The reason for this is unclear; however, it could be hypothesized that patients may have discontinued previous treatment for AD due to a perceived poor response. Although unconfirmed, deterioration following even temporary withdrawal of a ChEI may reduce the ability of the cholinergic system to benefit following reintroduction of therapy. Alternatively, due to the exclusion criterion that patients were not permitted to have received ChEI treatment during the 2 weeks prior to the baseline visit, there may have been residual unseen therapeutic effects (perhaps stabilization) in previously treated patients that reduced the overall observed magnitude of the treatment effect when reintroducing treatment. It should be noted, however, that treatment-naïve patients accounted for only 9% of the patients in the analysis, which would also have influenced findings. Perhaps more importantly, pharmacological differences are known to exist between the ChEIs [15]. Information on prior and concomitant use of AD medications was collected in the ACTION study; as such, it is, in theory, possible to investigate the individual effect of each ChEI (donepezil, galantamine, and rivastigmine) on subsequent treatment response. However, there are multiple confounding factors not limited to the number of medications received, duration of washout, and in many cases incomplete data regarding the treatment period that affect the ability to perform these analyses and draw clinically meaningful conclusions from the data

generated. Further studies would be needed to investigate whether the observed findings in treatment-naïve patients are upheld regardless of prior ChEI treatment received; such studies should include a larger pool of treatment-naïve patients, where possible.

A previous study applied multiple definitions of response to identify baseline factors that may predict response to ChEI treatment [16]. One definition incorporated a measure of global function, the Clinician's Interview-Based Impression of Change (CIBIC) [16]. In this analysis, a lower baseline MMSE score and faster pretreatment disease progression were significant predictors of response, defined as a  $\geq 2$ -point improvement on the MMSE and CIBIC score of 1–3, after 2 months of treatment [16]. Faster pretreatment disease progression remained a significant predictor after 6 months of treatment, although no differences were observed with regard to the MMSE score [16]. Supporting the current analysis, neither gender nor duration of disease was found to be a predictor of response on the CIBIC/MMSE [16].

To our knowledge, these were the first analyses to investigate predictors of clinical outcomes in patients with severe AD. *Post hoc* responder analyses have been performed on data from the OPTIMA (OPTimizing Transdermal Exelon study In Mild-to-moderate Alzheimer's disease) study, a 48-week, double-blind comparison of 13.3 mg/24 h versus 9.5 mg/24 h rivastigmine patch in patients with mild-to-moderate AD who demonstrated decline on the 9.5 mg/24 h patch dose [17,18]. In this analysis, treatment with 13.3 mg/24 h rivastigmine patch and MMSE score were significant predictors of improvement ( $\geq 4$ -point improvement on the Alzheimer's Disease Assessment Scale–cognitive subscale and no change on the Alzheimer's Disease Cooperative Study–ADL scale) or no decline at Week 24 [18]. Treatment with 13.3 mg/24 h rivastigmine patch was also a significant predictor of improvement, and MMSE score of no decline, at Week 48 [18]. The current findings suggest that as well as being a predictor of response in patients with mild-to-moderate AD, treatment with 13.3 mg/24 h rivastigmine patch may also be relevant at severe disease stages.

Gender was found to be a significant predictor of "improvement" at Week 48, but not Week 24, in the OPTIMA study [18]. As noted above, in the current analysis, neither gender, time since the first symptoms of AD, BMI, nor concomitant memantine use was shown to predict "improvement" or "improvement or no change" on the ADCS-CGIC at Week 24. The longer duration of the OPTIMA study compared with the ACTION study provides evidence that baseline characteristics could also be used to predict long-term patient outcomes; however, whether this translates to a patient population with severe disease requires further investigation.

A further objective of the current analysis was to use ROC curves to evaluate whether global functional status early after treatment initiation can predict clinical outcomes. These analyses suggest that patients with minimal worsening, no change, or improvement on the ADCS-CGIC at Week 8 may benefit from long-term treatment with 13.3 mg/24 h patch. Data from these ROC analyses can help a physician to decide after 8 weeks of treatment with 13.3 mg/24 h rivastigmine patch whether a patient should continue on the same treatment until Week 24. The findings at Week 8 were supported by those at Week 16. In

the ACTION study, at Week 8, patients were titrated from 9.5 mg/24 h to 13.3 mg/24 h patch. Therefore, as well as informing physicians on potential long-term outcomes following treatment, these findings also support a rationale for uptitrating to maximum tolerated doses, in order to achieve optimal therapeutic outcomes.

Although understanding the factors predictive of improvement or stabilization on the ADCS-CGIC and the potential for early treatment responses to predict long-term outcomes may guide physicians when managing patients with severe AD, these findings should be interpreted with caution. These *post hoc* analyses were intended to be hypothesis forming and should be interpreted as such. The ADCS-CGIC was a secondary efficacy measure in the ACTION study, and the study was not powered to identify predictors of response on this scale. In addition, analyses based on a different definition of a clinical outcome, or analyses based on other scales, may yield different findings. Additional studies designed with analyses of this kind prospectively planned would be required to confirm these potentially valuable observations.

Although a therapeutic approach that leads to improvement or stabilization of symptoms represents a clinical benefit, it is important to remember that, in severe AD, decline in global function is inevitable [19]. Whereas the ROC analyses considered patients demonstrating "improvement" or "improvement or no change" on the ADCS-CGIC, as "responders," the OPTIMA and ACTION studies have demonstrated significantly less decline on multiple symptom domains with 13.3 mg/24 h patch versus an active comparator [2,17]. This suggests that reduced deterioration may also be considered a clinical benefit of treatment with rivastigmine patch in patients with AD and again supports uptitration to the highest tolerated treatment doses. With this in mind, the potential for patient characteristics to influence treatment outcomes, the importance of conveying realistic expectations of treatment, and taking an individualized, adaptive approach to managing AD cannot be overemphasized.

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## Conflict of Interest

Martin R. Farlow has served as a paid consultant for Accera, Alltech, Astellas, Avanir, Bayer, Biogen, Bristol-Myers Squibb, Eisai Medical Research, GE Healthcare, Grifols, Helicon, INC Research, Medavante, Medivation Inc., Merck & Co. Inc., Novartis Pharma, Pfizer, Prana Biotech, QR Pharma, Sanofi Aventis Groupe, Schering-Plough, Eli Lilly, Shire Pharmaceuticals, and Toyama; is a paid speaker for Eisai, Forest, Novartis, Eli Lilly, and Pfizer; and receives research support from Accera, Biogen, Eisai, Eli Lilly and Co., Genentech, Navidea, Novartis Pharma, and

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and Mental Health Congress, Las Vegas, NV, USA, September 30–October 3, 2013, the American Academy of Neurology Annual Meeting, Philadelphia, PA, USA, April 26–May 3, 2014, and the Joint Congress of European Neurology, Istanbul, Turkey, May 31–June 2, 2014.

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