RESEARCH

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Efficacy of Rivastigmine on Executive Function in Patients with Parkinson's Disease Dementia

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SUMMARY

Background and objective: Rivastigmine is approved in the USA for the treatment of mild to moderate Alzheimer's disease and Parkinson's disease dementia (PDD). Executive function (EF) deficits are a core symptom of PDD. The current objective was to investigate the effects of rivastigmine capsules versus placebo on EF in PDD, focusing on secondary outcome measures from a large, international, randomized, double-blind, placebo-controlled, 24-week trial (EXPRESS, CENA713B2311). **Methods:** Secondary outcomes included Delis–Kaplan Executive Function System (D-KEFS) measures of EF. Data from three D-KEFS subtests (Card Sorting, Letter Fluency, Color–Word Interference), plus the Symbol Digit Modalities Test were analyzed in the observed case (OC) population. Changes from baseline in the rivastigmine versus placebo groups were evaluated using the van Elteren test blocking for country. **Results:** Of 541 patients in the EXPRESS study, 402, 71, 97, and 65 patients provided data for Letter Fluency, Card Sorting and Color-Word Interference subtests, and the Symbol Digit Modalities Test, respectively. On Letter Fluency, rivastigmine was associated with improvements in correct responses, set loss errors, and responses made (all $P < 0.05$), but not repetition errors. Higher Card Sorting recognition description score ($P = 0.03$), and more correct substitutions on the Symbol Digit Modalities Test ($P = 0.02$) were also recorded. **Conclusion:** Rivastigmine was associated with significant improvements over placebo on EF tests evaluating flexibility of thinking, problem solving and planning in patients with PDD. These findings support the hypothesis that rivastigmine may affect frontal subcortical circuits, which potentially contributes to observed clinical improvement associated with EF.

Introduction

Executive function (EF) is defined as the ability to dynamically plan, organize, and adapt current and past knowledge to future behaviors [1]. EFs regulate other higher cognitive functions and control the execution of complex activities [1]. Therefore, deficits in EF are strongly associated with difficulties with attention, concentration, and the ability to perform activities of daily living (ADLs). Their impairment may underlie other symptoms associated with dementia. Conversely, an improvement in EF may impact positively on other symptoms, including ADLs and behavior.

EFs are primarily mediated by the prefrontal cortex, and EF deficits are associated with damage to the cortico-subcortical circuits and subcortical lesions [2]. More specifically, dysexecutive function has been linked with disruptions in three frontal–subcortical circuits: the dorsolateral (reasoning, organization, set-shifting, and goal setting), orbitofrontal (empathy, tact, and mood stability), and anterior cingulate (motivation, interest, and creativity) circuits [3]. This may explain why deficits in

EF have been recognized as being particularly impaired in conditions such as Parkinson's disease dementia (PDD) [4], in which the frontal lobe is often markedly affected [3].

While the depletion of dopamine and deficits in cholinergic transmission are both features of PDD, cholinergic deficits are consistently associated with cognitive and neuropsychiatric symptoms and are included in the diagnostic criteria of PDD [5,6]. Among commonly used dementia therapies, the cholinesterase inhibitor rivastigmine (Exelon®, Novartis) is approved for the treatment of mild to moderate PDD in the USA. Moreover, data from metabolic imaging studies suggest that rivastigmine exhibits some selectivity for frontal cholinergic circuits [7], which might be involved in EF [8]. Rivastigmine demonstrated significant treatment effects versus placebo on the symptoms of dementia, including one measure of EF, in a large PDD study [9]. *Post hoc* analyses of this PDD study assessed patients' attention on the Cognitive Drug Research (CDR) computerized cognitive assessment system. Significant benefits of rivastigmine versus placebo were seen on all aspects of attention assessed: sustained attention, focused attention, consistency of responding, and central processing speed [10]. The current objective was to further examine the impact of rivastigmine on deficits in EF in PDD. Although the primary findings of the PDD trial are published (EXPRESS [9]), this is the first analysis of all detailed EF data from this clinical trial.

Methods

Study Design

The development program for rivastigmine capsules included a 24-week, double-blind study (the EXPRESS study) in patients with a diagnosis of mild to moderate PDD. The full methodology has been published previously [9]. In summary, this was a multicenter, double-blind, placebo-controlled, parallel-group study. Patients were recruited from centers in Austria, Belgium, Canada, France, Germany, Italy, the Netherlands, Norway, Portugal, Spain, Turkey, and the United Kingdom. Patients were randomized to rivastigmine or placebo in a 2:1 ratio. Patients in the rivastigmine group were started at 3 mg/day and titrated up every 4 weeks to maximum-tolerated doses of rivastigmine of up to 12 mg/day. Primary efficacy parameters were the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) [11] and the Alzheimer's Disease Cooperative Study–Clinician's Global Impression of Change (ADCS-CGIC) [12]. In addition to cognition, attention, ADLs and behavior, secondary outcome assessments included the Delis–Kaplan Executive Function System (D-KEFS) subtests and the Symbol Digit Modalities Test [13], the subject of this report, which assess key components of EF [14].

Current Analysis of Executive Function

The current analysis investigated findings from the D-KEFS subtests of Letter Fluency, Card Sorting, Color–Word Interference, and Symbol Digit Modalities Test [13,14]. D-KEFS assessments were evaluated from baseline to Week 24. The D-KEFS tests were performed at 68 centers (French- and English-speaking only). Because this was a selection of the number of centers included in the EXPRESS study, analyses were based on the observed case (OC) population and included only patients who performed the tests [9].

Letter Fluency

On D-KEFS Letter Fluency, patients are asked to generate as many words as possible beginning with a specified letter within a set time (e.g., words beginning with the letter 'F' in 1 min). This test evaluates language and executive retrieval functions. The D-KEFS version provides four separate subscores that can be used to determine changes from baseline and intergroup differences: the total number of correct responses; the total number of incorrect responses; the number of repetition errors (i.e., forgetting which words have already been said); and the total number of responses, irrespective of whether they are correct or incorrect.

Card Sorting

On D-KEFS Card Sorting, patients are asked to sort cards into two groups according to set rules, or to identify the rules used by an examiner sorting the cards. This test evaluates the patient's ability to display flexibility in the face of changing schedules of reinforcement ('set shifting'). As such, it assesses strategic planning, organized searching, use of environmental feedback to shift cognitive sets, and goal-directing behavior. It provides five subscores: the number of errors in reading instructions; the number of errors in understanding instructions; the number of correctly identified rules for examiner-sorted cards; the number of incorrectly identified rules for examiner-sorted cards; and the number of correctly repeated rules for examiner-sorted cards.

Symbol Digit Modalities Test

On the Symbol Digit Modalities Test, patients substitute numbers for randomized presentations of geometric figures using a reference key. The patient has 90 seconds to

pair specific numbers with given geometric figures. Responses can be written or oral. This substitution task is believed to assess sorting abilities and speed of cognitive processing dependent on EF. It provides three subscores: the total number of correct responses; the total number of responses, irrespective of whether they are correct or incorrect; and the total number of self-corrected errors.

Color–Word Interference

On D-KEFS Color–Word Interference, patients read words denoting colors that are printed another color (e.g., to read the word 'red' even though it is printed in green ink), or *vice versa*, and they are asked to alternate between naming the dissonant ink color and reading the conflicting word. The main score is the number of correct words named in the given time for each of the subtasks. This test measures concentration effectiveness and processing speed.

Statistical Method

Background and demographic characteristics, and efficacy variables at baseline were compared between rivastigmine and placebo groups using the ANOVA model with treatment and country as factors for continuous variables and the Cochran Mantel-Haenszel test controlled by country for categorical variables. Comparisons were made for patients with D-KEFS, for patients with Card Sorting data, for patients with Color-Word Interference data, and for patients with Symbol Digit Modalities Test data at both baseline and Week 24. Changes from baseline to Week 24 in each EF were compared between rivastigmine and placebo groups by employing the van Elteren test blocking for country. Effect sizes were also calculated. No adjustments were made for multiple comparisons.

Results

Of 541 patients participating in the PDD study [9], 402 provided data for the D-KEFS test of Letter Fluency at both baseline and Week 24, 71 provided Card Sorting data, 97 provided Color–Word Interference data, and 65 provided data for the Symbol Digit Modalities Test. Demographic data for the overall study population have been published (mean age 72.7 years, 35% women); there were no significant differences in these characteristics between the rivastigmine and placebo groups [9]. In addition, no differences were observed between the rivastigmine and placebo groups for patients with EF test data.

Week 24 changes from baseline were significantly different in the rivastigmine group versus placebo on several measures of EF (Fig. 1). On Letter Fluency, rivastigmine was associated with significantly more correct responses, fewer set loss errors, and more total responses made (within the time available), compared with placebo (all $P < 0.05$ vs. placebo; respective effect sizes of 0.42, 0.14, and 0.34). There was no significant difference in total repetition errors ($P = 0.57$).

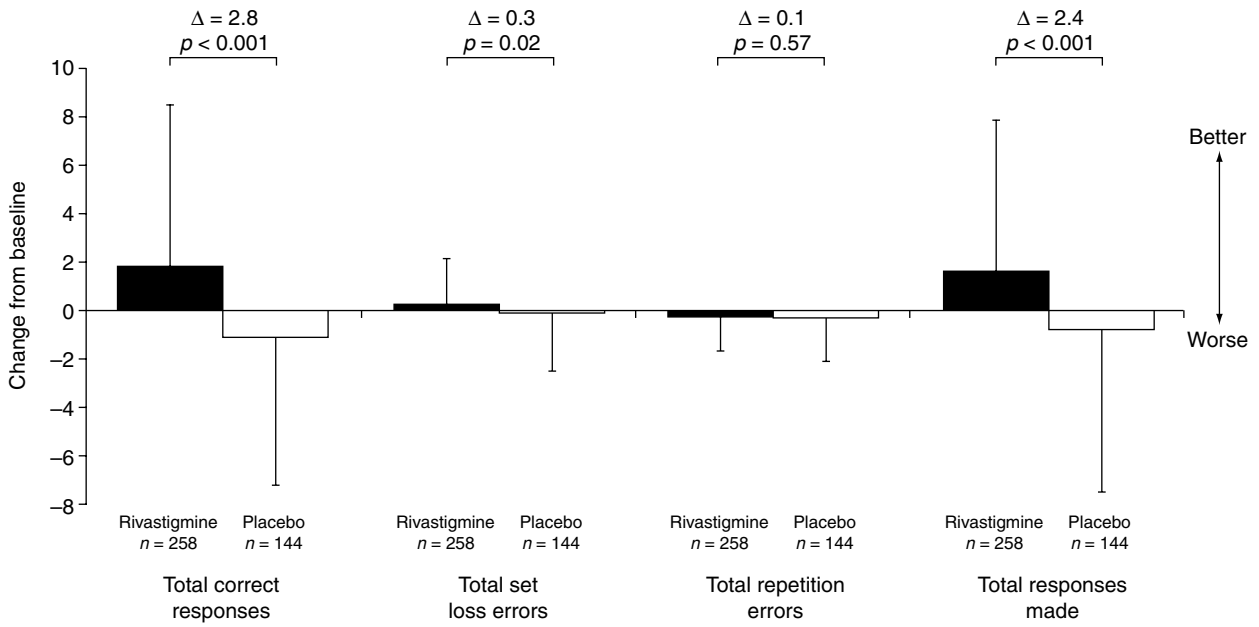
Rivastigmine was also associated with a significantly higher Card Sorting recognition description score ($P = 0.03$ vs. placebo; effect size 0.56). Differences in word reading errors, word comprehension and sort recognition errors (incorrect and repeated descriptions) were not significant (Fig. 2). There were significantly more correct substitutions on the Symbol Digit Modalities Test ($P = 0.02$ vs. placebo; effect size 0.50) (Fig. 3). While there was no statistically significant difference in the number of self-corrected errors, the difference between numbers of stimuli completed on the Symbol Digit Modalities Test in the rivastigmine versus placebo groups was close to being statistically significant ($P = 0.050$; effect size 0.45). Treatment differences that were not statistically significant were generally those with large standard deviations (SD) around the Mean (Figs. 1–3).

Rivastigmine treatment was associated with significantly fewer self-corrected errors on the Color–Word Interference inhibition/switching subtest, compared with placebo ($P = 0.049$; effect size 0.62). Treatment differences in numbers of correct responses on this subtest were also verging on statistical significance ($P = 0.050$). Other treatment differences in this battery of EF tests were not statistically significant.

Discussion

Impaired EF is part of the constellation of cognitive changes associated with PD and PDD [15], and some studies have suggested that EF impairment in PD can predict the evolution to PDD and are likely to be even more involved in PDD cases [16]. Frontostriatal components of PD are well recognized [17], and functional imaging studies of EF in PD have implicated both nigrostriatal and mesocortical dopamine as underlying EF changes in PD [18], while cognitive tasks linked to dorsolateral prefrontal cortex appear to be impacted by PD [19].

Although this study was not powered to detect significant treatment differences on individual tests of EF, the current analyses suggested significant effects of rivastigmine versus placebo on tests of Letter Fluency, Card Sorting and Symbol Digit Modalities. The tendency for consistent superiority of rivastigmine over placebo on



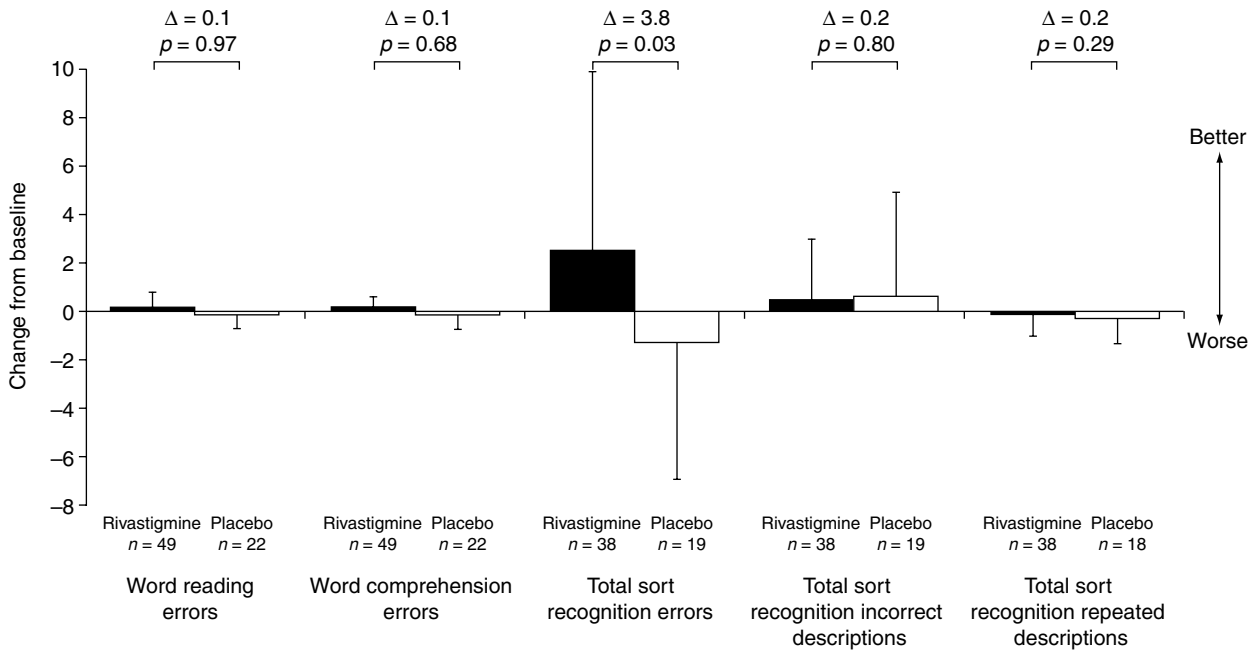
Total correct responses: number of correct responses provided by patients asked to generate lists of words beginning with a certain letter (baseline scores 13.9 and 14.5 in the rivastigmine and placebo groups, respectively)
Total set loss errors: number of incorrect responses provided by patients asked to generate lists of words (error scale inversed so negative changes indicate deterioration; baseline scores 1.6 and 1.4, respectively)
Total repetition errors: for example, forgetting which words have already been said (error scale inversed; baseline scores 0.5 and 0.7, respectively)
Total responses made: number of responses (correct or incorrect) provided by patients asked to generate lists of words (baseline scores 16.0 and 16.4, respectively)

Figure 1. Mean (SD) Week 24 changes from baseline in D-KEFS scores of Letter Fluency. Observed case analysis.

these tests supports the robustness of the findings, although care should always be taken in interpreting retrospective analyses such as this. EFs regulate other higher cognitive functions and their deficit is strongly associated with difficulties with attention, concentration, and the ability to perform ADLs. Their impairment may underlie other symptoms associated with dementia and improvements may impact positively on other symptoms, including ADLs and behavior [1].

It is interesting to consider how a cholinesterase inhibitor may exert its effects on these symptom domains. Reflecting an affinity for the G1 form of acetylcholinesterase [20,21], it has been demonstrated previously that rivastigmine may show brain region-selectivity for areas such as the hippocampus and cortex [7]. In addition, rivastigmine appears to improve blood flow in the frontal, parietal and temporal cortices of patients with AD, particularly in the medial frontal and anterior cingulate cortical areas [22]. As noted previously, executive dysfunction appears to be associated with damage to these brain regions [2,3]. Therefore, the current findings are consistent with the hypothesis that rivastigmine impacts on cholinergic neurons and neurotransmission in these specific regions of the human brain.

The three EF tests for which rivastigmine provided significantly different effects versus placebo evaluated aspects of cognition that could be broadly classified as flexibility of thinking, problem solving and planning skills. Rivastigmine did not separate significantly from placebo on a fourth test, Color–Word Interference. While this test may be considered a measure of concentration and processing speed, it is much more complex and may also require a number of other functions, including inhibition of overlearned impulses and attention shift. The results of the Color–Word Interference test were unexpected since in the original PDD study rivastigmine showed significant effects versus placebo on the CDR computerized attention battery, which assesses similar domains [9]. As well as providing significant treatment effects on the total CDR battery score, an additional analysis also suggested significant effects of rivastigmine on four measures derived from this battery of tasks: Power of Attention, Continuity of Attention, Cognitive Reaction Time, and Reaction



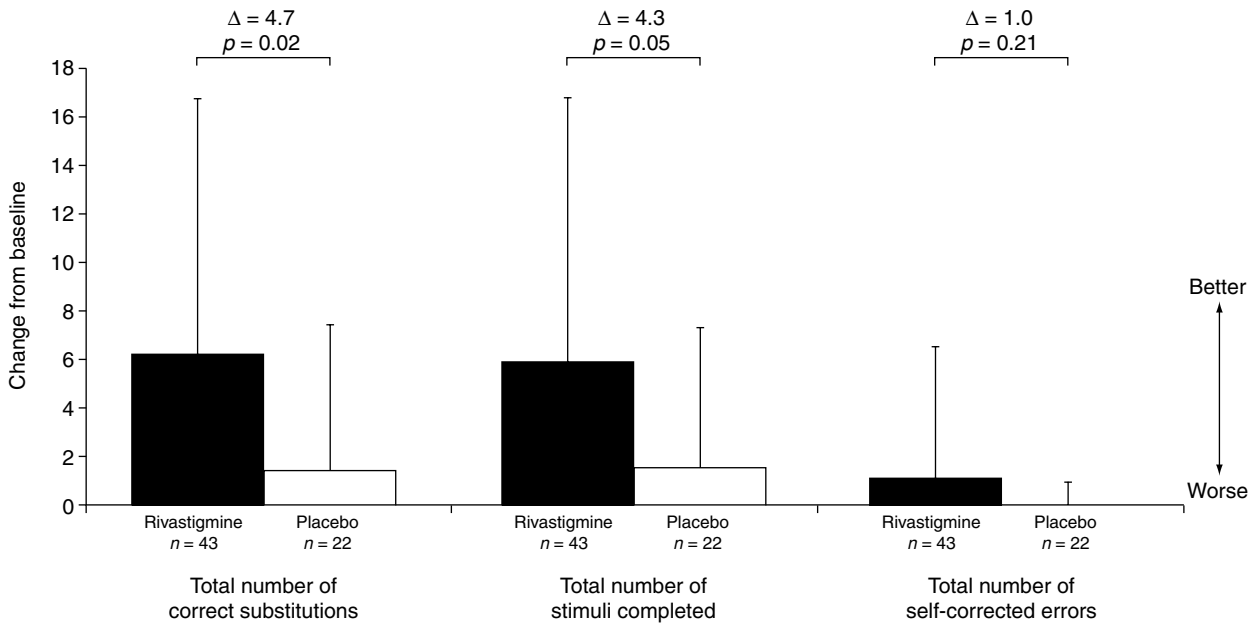
Word reading errors: number of errors in reading instructions (error scale inversed so negative changes indicate deterioration; baseline scores 0.5 and 0.3 in the rivastigmine and placebo groups, respectively)
Word comprehension errors: number of errors in understanding instructions (error scale inversed; baseline scores 0.3 and 0.4, respectively)
Total sort recognition descriptions: number of correctly-identified rules for examiner-sorted cards (baseline scores 7.8 and 6.3, respectively)
Total sort recognition incorrect descriptions: number of incorrectly-identified rules for examiner-sorted cards (error scale inversed; baseline scores 1.7 and 1.4, respectively)
Total sort recognition repeated descriptions: number of correctly repeated rules for examiner-sorted cards (baseline scores 0.5 and 0.3, respectively)

Figure 2. Mean (SD) Week 24 changes from baseline in D-KEFS Card Sorting scores. Observed case analysis.

Time Variability [10]. Since Power of Attention is supposed to reflect concentration and Cognitive Reaction is supposed to reflect processing speed [10], similar positive effects might have been expected with the D-KEFS Color–Word Interference task, which also assesses these aspects of attention. The fact that this was the only D-KEFS task that failed to demonstrate a significant treatment effect emphasizes the importance of identifying appropriate outcome measures for any test population, and of caution when considering retrospective analyses such as these.

This analysis is limited by its retrospective nature. Not all study centers performed the EF tests, therefore relatively small numbers of patients provided data for individual tests (e.g., 65 patients provided data for the Symbol Digit Modalities Test, representing less than 15% of the total study population). As well as affecting the power of the statistical analyses, the smaller sample sizes make the results potentially less generalizable to the real world. Furthermore, to fulfill the primary inclusion criteria for the EXPRESS study, patients were required to have an MMSE score of 10–24, indicative of mild to moderately severe dementia [9]. The MMSE is based almost entirely on verbal assessment of memory and attention and it is insensitive to frontal-executive dysfunction. The efficacy of rivastigmine on EF in this study may therefore be underestimated as severity of disease assessed by MMSE may not directly reflect the severity of frontal dysexecutive symptoms at baseline. Due to the fact that this was an exploratory analysis, the results were not corrected for multiplicity, and this may also impact on the robustness of the data. Although these results are statistically significant, further research is required to determine the clinical relevance of the treatment differences observed. Nevertheless, the data have credence for hypothesis-formation, which was the original objective.

We would conclude that rivastigmine appears to have significant effects on Letter Fluency, Card Sorting and Symbol Digit Modalities Tests of EF, potentially reflecting an impact on flexibility of thinking, problem solving



Total number of correct substitutions: number of correct responses provided by patients asked to substitute numbers for randomized presentations of geometric figures, using a reference key (baseline scores 12.7 and 9.6 in the rivastigmine and placebo groups, respectively)
Total number of stimuli completed: number of numbers substituted for geometric figures (baseline scores 14.6 and 11.0, respectively)
Total number of self-corrected errors: number of errors that the patient corrects his or herself (baseline scores 0.2 in both groups)

Figure 3. Mean (SD) Week 24 changes from baseline in D-KEFS scores of Symbol Digit Modalities. Observed case analysis.

and planning. These treatment effects may underlie or positively influence other symptoms in this population, including ADLs and behavior [9]. However, the current results pertaining to concentration and attention were not consistent with previous findings [10], and further research may be required to determine the reasons for this – those findings may in turn inform future trial designs.

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Author Contributions

The analyses were conceptualized by Drs Schmitt and Olin, with contributions from Drs Farlow and Tekin. Dr Tekin led and participated in the protocol design, trial execution, data collection and analyses of the EXPRESS study, from which current analyses were derived. The current statistical analyses were designed and executed by Dr Meng. All authors had full access to the data on which this manuscript was based, they all contributed to the review and critique of the manuscript, and they all provided guidance for the writing assistance provided by Alpha-Plus Medical Communications Ltd (UK).

Conflict of interest

The PDD study for which the current data were collected, and the current data analyses, were sponsored by Novartis. Dr Farlow receives research grant support from Bristol Myers Squibb, Elan, Eli Lilly and Co, Forest, Janssen, Medivation, Novartis, OctaPharma, Pfizer, and Sonexa. Dr. Farlow receives consulting fees from Accera, Adamas, Adlyfe, Astra Zeneca, Astellas, Bayer,

Bristol Myers Squibb, CoMentis, Eisai, Eli Lilly and Co, GlaxoSmithKline, Medivation, Merck, Novartis, Noven, OctaPharma, Prana, QR Pharm, the sanofi-aventis Group, Schering-Plough, Sonexa, and Toyama Pharm, and he is a speaker for Eisai, Forest, Janssen, Pfizer, and Novartis. Drs Olin, Meng and Tekin are full-time employees of Novartis Pharmaceuticals Inc, New Jersey, USA. Drs Olin, Meng and Tekin own stock of Novartis AG. Dr Schmitt has no potential conflict of interest to declare.

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