Effect of rivastigmine on delay to diagnosis of Alzheimer's disease from mild cognitive impairment: the InDDEx study

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Summary

Objective **To assess the effect of rivastigmine in patients with mild cognitive impairment (MCI) on the time to clinical diagnosis of Alzheimer's disease (AD) and the rate of cognitive decline.**

Methods **The study was a double-blind, randomised, placebo-controlled trial of up to 48 months. All patients had MCI operationally defined by having cognitive symptoms, a global clinical dementia rating stage of 0·5, a score of less than 9 on the New York University delayed paragraph recall test, and by not meeting the diagnostic criteria for AD. Primary efficacy variables were time to clinical diagnosis of AD, and change in performance on a cognitive test battery. This study is registered with the US National Institutes of Health clinical trials database (ClinicalTrials.gov), number NCT00000174.**

Findings **Of 1018 study patients enrolled, 508 were randomly assigned to rivastigmine and 510 to placebo; 17·3% of patients on rivastigmine and 21·4% on placebo progressed to AD (hazard ratio 0·85 [95% CI 0·64–1·12]; p=0·225). There was no significant difference between the rivastigmine and placebo groups on the standardised Z score for the cognitive test battery measured as mean change from baseline to endpoint (–0·10 [95% CI –0·63 to 0·44], p=0·726). Serious adverse events were reported by 141 (27·9%) rivastigmine-treated patients and 155 (30·5%) patients on placebo; adverse events of all types were reported by 483 (95·6%) rivastigmine-treated patients and 472 (92·7%) placebo-treated patients. The predominant adverse events were cholinergic: the frequencies of nausea, vomiting, diarrhoea, and dizziness were two to four times higher in the rivastigmine group than in the placebo group.**

Interpretation **There was no significant benefit of rivastigmine on the progression rate to AD or on cognitive function over 4 years. The overall rate of progression from MCI to AD in this randomised clinical trial was much lower than predicted. Rivastigmine treatment was not associated with any significant safety concerns.**

Introduction

The term mild cognitive impairment (MCI) has emerged as a nosological construct that describes a cognitive state associated with ageing that is abnormal yet not diagnosable as dementia.[1] Although proposed criteria and definitions of MCI are still evolving, the most commonly used definition of MCI specifies the following criteria: both subjective and objective impairments in memory, preserved overall cognitive function outside memory, and normal basic activities of daily living.[2] This MCI phenotype has been consistently reported to carry an increased risk of progression or conversion to Alzheimer's disease (AD) or dementia.[3,4] The annual rates of progression from MCI to AD or dementia of this clinical phenotype have generally been reported to be 10–15% per year.[4–6] This identification of MCI as a risk state for progression to AD or dementia holds the potential to allow testing of early treatment interventions that might improve cognitive symptoms, slow the rate of symptom progression towards dementia, and even delay the time to diagnosis or prevent AD or dementia.

Pharmacological treatment of the cholinergic dysfunction of AD with cholinesterase inhibitors has been the most widely used for mild and moderate stages of AD, with symptomatic efficacy shown for up to 1 year in placebo-controlled randomised clinical trials.[7] Cholinergic abnormalities have been detected in early AD stages,[8–11] including abnormalities in other markers of the cholinergic system, such as signal transduction,[12] p75 neurotrophin receptor concentrations,[13] and beta-amyloid peptides.[14] These abnormalities have triggered interest in investigating the effect of cholinesterase inhibitors on progression to AD and cognitive function in patients with MCI.[15–18]

Our aims were to investigate whether rivastigmine delays the time to progression to AD in patients with MCI, and whether rivastigmine benefits cognitive function in patients with MCI.

Methods

Patients

A total of 1526 patients were screened for the study. All patients were identified at entry to have MCI operationally defined by having cognitive symptoms, a global clinical dementia rating (CDR) stage of 0·5,[19] and a score of less than 9 on the New York University delayed paragraph recall test.[20] There was no specification

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of the onset or course of the presenting cognitive symptoms of MCI. Patients were excluded if they met either the AD diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (fourth edition text revision; DSM-IV-TR),[21] or the AD criteria of the National Institute of Neurological and Communicative Disorders and Stroke-AD and Related Disorders Association (NINCDS-ADRDA).[22] To exclude depression as a potential confounder of MCI, all patients were required to have an entry score of less than 13 on the 17-item Hamilton rating scale for depression (HAM-D),[23] with a HAM-D item 1 (depressed mood) of 1 or lower. Other exclusion criteria were as follows: any known primary neurodegenerative disease; any advanced, severe unstable medical condition that could interfere with primary and secondary variable assessment; an uncontrolled seizure disorder; a score of more than 4 on the modified Hachinski ischaemic scale; a documented history of transient ischaemic attack; any severe or unstable cardiovascular disease or asthmatic conditions; or a known hypersensitivity to cholinesterase inhibitors. Patients who had received any cholinergic drugs during the 2 weeks before the beginning of the trial, or had received rivastigmine during the previous 4 weeks, or who had taken part in a previous clinical study of rivastigmine, were also excluded. Of the 1526 patients screened, 1018 aged 55–85 years were enrolled at 65 research centres in 14 countries between May, 1999, and April, 2000. The last patient completed the study on April 27, 2004.

Recruitment was done through referral to the research centres, through advertising, or from patients known to the investigators at the participating research centres. The study protocol, informed consent procedure, and other information given to patients were approved by the institutional review boards at each participating centre. The intended duration of the study was 3 years, but because progression to AD was slower than expected in the first 2 years of the trial, the protocol was amended so that patients who were still in the study were asked to consent to a 1-year extension of the study. All procedures were in accordance with the ethical standards of each centre's committee on human experimentation and with the Declaration of Helsinki (revised 1996).[24]

Procedures

The study was a double-blind, parallel-group, placebo-controlled, randomised clinical trial with three phases. The initial phase was a double-blind period with randomisation to either rivastigmine (3–12 mg/day) or placebo on a one-to-one basis. Within this phase there was an initial 18-week dose titration period. Rivastigmine was started at 0·5 mg twice daily. After 2 weeks, doses were increased to 1·5 mg twice daily, and then by a further 1·5 mg twice daily at a minimum of 4-week intervals. If patients were unable to tolerate the protocol increments they were allowed to stay at their highest tolerated dose through the dose-titration phase; however, to remain in the study they had to tolerate a minimum of at least 3 mg daily by the end of the dose-titration phase. Beyond the titration phase, the investigators could attempt to increase the dose during the study to a maximum of 12 mg daily. Dummy dose titration was also performed for the placebo treated group with doses received as 1 capsule twice daily, whether rivastigmine or placebo. The double-blind phase continued until either progression to AD had occurred or the study had ended.

Patients could move to the second, open-label phase of the trial after progression to AD as clinically determined by the investigator. In this phase, patients received open-label rivastigmine. Those patients who chose to enter the open-label phase with rivastigmine after progression to AD received dose titration from a starting dose of 1·5 mg twice daily, irrespective of their treatment assignment during the double-blind phase. Allocation concealment with respect to the treatment received during the double-blind phase was maintained to the end of the study. Patients who discontinued treatment during the double-blind or open-label phase of the study were encouraged to enter the retrieved-dropout phase and return for regular scheduled visits for the remainder of the trial. During the retrieved-dropout phase subjects could be treated with any of the acetylcholinesterase inhibitors.

The randomisation procedure used a validated interactive voice-response system with an automated assignment of treatment groups. To preserve the blinding, the rivastigmine and placebo capsules were identical in shape, size, and colour. Study drugs were dispensed in bottles labelled with unique numbers. All personnel directly involved in the study were blind to the treatment group allocation until all patients had completed the trial and all data had been finalised for analysis.

The time to the clinical diagnosis of AD was determined through investigator assessments that were done at each of the scheduled 3-monthly visits. Additional assessments could be made by the investigators if there was clinical concern that progression to AD might have occurred between visits. For progression to AD to be diagnosed at a follow-up visit, patients had to meet both the DSM-IV-TR and NINCDS-ADRDA criteria for AD. This determination was made in reference to the previous visits and by examination, and all previous assessments apart from the neuropsychological test battery for secondary outcome measures. If progression to AD was suspected, the investigator also provided a summary narrative with the evidence of progression to the diagnosis monitoring committee. The diagnosis monitoring committee (HHF, PS, ES, NH) reviewed all proposed materials, and for study analytic purposes either accepted the

progression or requested additional evidence before acceptance in a further submission. A majority opinion in favour of conversion was needed to confirm the event for study purposes. If this did not occur, the investigator was asked to resubmit with additional evidence to support conversion. The date of progression to AD used in the analysis was the date when the investigator made the diagnosis of dementia.

The co-primary outcome measure was the difference between rivastigmine and placebo in cumulative *Z* scores between baseline and endpoint visits (last timepoint at which outcome assessments were made) on a 10-test neuropsychological test battery that was determined through investigator assessments done every 6 months. This battery included the New York University paragraph recall (immediate and delayed),[20] delayed word list recall,[25] letter number sequencing,[26] Buschke free and cued selective reminding test,[27–29] symbol-digit modalities task,[30] digit cancellation task,[25] maze,[25] verbal fluency categories subtest,[31] and clock drawing.[32,33] The investigators and the diagnosis monitoring committee were blinded to the cognitive test battery results throughout the study.

Secondary study outcome measures included performance on the AD assessment scale cognitive subscale (ADAS-cog; 11 items, 70 points)[34] and the mini-mental state examination (MMSE; 11 items, 30 points),[35] as well as ratings on the AD study cooperative activities of daily living scale (ADCS-ADL; 24 items, 54 points),[36] the global deterioration scale (GDS; 7 points),[37] the CDR scale (5 points),[38] the Beck depression inventory (21 items, 63 points),[39] the neuropsychiatric inventory (NPI; 12 items, 144 points),[40] and quality of life (13 items, 52 points) as rated by patients and caregivers (see supplementary online text for visit schedule).[41]

Other secondary outcome measures included the rate of volumetric changes in whole brain, ventricles, and hippocampi assessed from serial MRI (see supplementary online text for methods).[42]

Safety assessments included the recording of all adverse events, laboratory tests (at screening and at months 12, 24, 36, and 48), electrocardiogram results (at screening, and at months 12, 24, 36, and 48), and vital signs (at all visits). Adverse events were coded by use of a standard glossary, and a central laboratory did all clinical laboratory examinations, including DNA extraction.

Optional pharmacogenetic substudies were developed as per protocol to assess whether differences in apolipoprotein E (APOE) genotype and retrospective analyses of butyrylcholinesterase (BCHE) genotype,[43] or sex, affected time to progression to AD or deterioration on the neuropsychological test battery, or both. In addition, the influence of these factors on the secondary outcome measures was assessed. These genomic studies were selected because the APOE genotype has been shown to be a strong predictor of progression to AD from MCI in ε4 carriers,[15,44] whereas the BCHE-K variant has been associated with a slower average rate of decline in AD, and has been associated with treatment response to rivastigmine.[45,46] Genomic DNA was extracted from blood samples at a central laboratory using the Puregene DNA Isolation kit (D-50K; Gentra, Minneapolis, MN, USA). Genotyping for APOE ε4 and BCHE-K was done as described previously.[47] For individuals who agreed to participate in the pharmacogenetic analysis after the initial genotyping tests had been done, TaqMan technology was used to genotype APOE ε4 and BCHE-K alleles according to the manufacturer's instructions (Applied Biosystems, Foster City, CA, USA). Genotyping was done at a separate laboratory, and was independent of randomisation.

In addition to the prospective hypotheses and pre-planned analyses, several post-hoc analyses were done to identify demographic and baseline characteristics that predicted progression to AD and response to treatment.

Statistical analyses

The sample size was calculated on the basis of the difference in projected rates of progression to AD between rivastigmine and placebo groups. For the initally planned 3-year duration of the study, there was an estimated 30% event rate in placebo recipients, a 20% event rate in rivastigmine recipients, and a dropout of 10% per year, for which a sample of 830 patients was calculated as providing sufficient power to achieve statistical significance at $p<0\cdot05$ for a two-sided test. To allow for a higher than expected dropout rate, a sample of approximately 1000 patients needed to be enrolled.

Study participants who had at least one dose of study drug and at least one safety assessment were included in safety analyses. The main efficacy population for all primary and secondary outcomes (except MRI variables) was predefined as a modified intention-to-treat (MITT) population (n=1018), which aimed to create a score for every randomised patient, irrespective of whether study drug was received or post-baseline assessments were done. The endpoint score was determined in the following manner: if a confirmed clinical diagnosis of AD was reached, the last assessment at which AD was diagnosed was used (for efficacy variables other than progression to AD, if no data were available for the visit at which AD was diagnosed, the last visit before this was used). For patients who did not progress to AD, the study endpoint assessment was used (month 36 or 48). If the endpoint assessment was missing, the retrieved-dropout assessment was used. If this assessment was unavailable, then the last observation available on the patient was used. A classic intention-to-treat (ITT) analysis was also done, which differed from the MITT analysis in that assessments that took place after AD diagnosis (but before entry into the open-label phase)

were also included in the analysis. The classic ITT analysis was used for the MRI variables, because MRI assessments were often done after the scheduled visits for the other outcome measures, and the MITT analysis would have excluded this valuable data.

Further efficacy analyses included the following: an observed-case analysis (n=431), with data from all patients who did not discontinue prematurely and who were available for assessment at the designated times (patients from double-blind and open-label phases); a retrieved-dropout analysis (n=168) of patients who entered the retrieved-dropout phase; and a combined observed-case and retrieved-dropout analysis (n=599). A traditional US Food and Drug Administration Division of Neuropharmacological Drug Products analysis (n=995), which creates a score for every patient who received at least one dose of designated treatment, and had at least one post-treatment outcome assessment while receiving treatment, was also used. If the endpoint assessment was unavailable, the last non-missing observation while on treatment was used. The main efficacy population for analyses of MRI variables was the classic ITT population.

Differences in baseline characteristics between treatment groups were assessed by use of chi-squared tests. Comparisons of patients who progressed to AD versus those who did not progress to AD were done using chi-squared tests (for categorical variables) or *t* tests (Satterthwaite's approximation, for continuous variables).

The analysis of time to diagnosis of AD was done using Cox's proportional hazards regression model, with treatment, sex, age group (<75 years, ≥75 years), and education level at baseline as explanatory variables, without modelling for interval censorship. Country was used as a stratification variable. Significance values were calculated using the Wald test. Kaplan-Meier estimates were calculated as supporting non-parametric analyses, with significance tested using the log-rank test.

For each of the 10 cognitive tests comprising the composite score, the mean ($\bar{X}_b$) and standard deviation (S_b) of the raw scores were calculated using data from all patients at baseline. The *Z* score for a test for each patient at each visit (including baseline visit) was calculated from the raw score (X):

$$Z=(X-\bar{X}_b)/S_b$$

The composite *Z* score for each patient at each visit was calculated by summing the *Z* scores of the 10 tests in the cognitive battery. The main analysis of cognitive function was based on the change in composite *Z* score after applying the prespecified imputation scheme for the efficacy population (MITT analysis). The treatment groups were compared using an analysis of covariance (ANCOVA) model with the following explanatory variables: treatment, country, sex, age, education level, and composite *Z* score at baseline. A supplementary analysis of the composite *Z* score was done using a mixed model for repeated measures. Tests of significance on the variables were done using Wald's chi-squared test. A Bonferroni correction for multiple comparisons was done for the individual tests of the cognitive battery.

For continuous secondary efficacy variables, an ANCOVA model was used for the change from baseline to endpoint with the corresponding baseline score as covariate, and treatment, country, age group, sex, and years of education at baseline as main effects. For categorical variables, a Cochran-Mantel-Haenszel test was used. Robustness of results was tested with Wilcoxon and Van Elteren tests. For rate of change from baseline in MRI variables, an ANCOVA model was used with the corresponding baseline score as a covariate and treatment as the main effect. A Bonferroni correction was applied to the secondary outcome measures. The alpha level at which tests should be done was 0·00217.

The effects of the genotypes APOE ε4 and BCHE-K variant at baseline on time to progression to AD were explored by adding the respective variables into the Cox's proportional hazards model as explanatory variables. Comparisons of time to progression to AD, and changes from baseline to endpoint in composite *Z* score and ADAS-cog in APOE ε4 carriers versus non-carriers were done.

The following post-hoc analyses were done. Cox's proportional hazards regression model was used to retrospectively identify baseline variables that had a significant influence on progression to dementia. A stepwise selection process was used with p=0·25 or p=0·15 for explanatory variables entering or remaining in the model, respectively. The results of the primary and secondary outcomes in all subgroups with relevant treatment differences in time to diagnosis to AD were characterised. The results of the sex and BCHE genotype subgroups are described. The correlation of the change rate at endpoint of MRI variables by treatment group with progression to AD was explored using a biserial correlation to assess the relation between the continuous MRI variable and the dichotomous variable of progression to AD.

This trial has been registered with the US National Institutes of Health clinical trials database (ClinicalTrials.gov), number NCT00000174.

Role of the funding source

Study design and planning were done in conjunction with the study sponsor (Novartis Pharma AG). The study drugs and the funding for the study were provided by the sponsor. The corresponding author had full access to the study data and had final responsibility for the decision to submit the study for publication.

	All randomised patients (MITT)		Patients with DMC-confirmed progression to AD		Patients who did not progress to AD	
	Rivastigmine (n=508)	Placebo (n=510)	Rivastigmine (n=88)	Placebo (n=109)	Rivastigmine (n=420)	Placebo (n=401)
Demographics						
Age (years)	70·3 (7·4)	70·6 (7·6)	74·1 (6·5)	73·6 (6·6)	69·5 (7·3)	69·8 (7·7)
Sex						
Men	238 (46·9%)	248 (48·6%)	41 (46·6%)	44 (40·4%)	197 (46·9%)	204 (50·9%)
Women	270 (53·1%)	262 (51·4%)	47 (53·4%)	65 (59·6%)	223 (53·1%)	197 (49·1%)
Education (years)	11·0 (4·0)	11·1 (4·1)	10·5 (4·1)	10·6 (4·1)	11·1 (4·0)	11·2 (4·2)
Psychological assessment						
CDR	1·5 (0·8)	1·4 (0·8)	1·9 (0·8)	1·9 (0·9)	1·4 (0·7)	1·3 (0·7)
HAM-D total	2·8 (2·6)	2·7 (2·6)	2·6 (2·6)	2·8 (2·9)	2·8 (2·6)	2·7 (2·5)
MHIS	0·7 (0·9)	0·6 (0·9)	0·9 (1·0)	0·6 (0·8)	0·7 (0·8)	0·6 (0·9)
ADAS-cog	10·5 (5·0)*	10·2 (4·9)*	14·1 (5·4)	14·6 (4·7)*	9·7 (4·5)*	9·0 (4·2)
MMSE	27·0 (2·6)†	26·9 (2·8)*	25·1 (3·3)	24·7 (3·7)	27·4 (2·3)†	27·5 (2·1)*
GDS	2·4 (0·5)†	2·4 (0·5)*	2·7 (0·5)	2·7 (0·5)	2·4 (0·5)†	2·3 (0·5)*
NPI	3·2 (5·3)‡	2·9 (5·0)†	4·3 (5·1)	3·7 (4·6)	3·0 (5·3)‡	2·7 (5·1)†
ADCS-ADL	57·7 (8·5)§	58·4 (7·8)†	53·8 (8·2)	53·2 (8·5)	58·5 (8·3)§	59·8 (7·0)†
MRI assessment¶	(n=220)	(n=221)	(n=52)	(n=54)	(n=168)	(n=167)
Baseline total hippocampal volume	3·6 (0·8)	3·6 (0·7)	3·1 (0·7)	3·1 (0·6)	3·8 (0·7)	3·7 (0·6)
Pharmacogenetics‖						
APOE ε4 genotype	(n=252)	(n=248)	(n=36)	(n=49)	(n=216)	(n=199)
Carriers	92 (36·5%)	115 (46·4%)	20 (55·6%)	29 (59·2%)	72 (33·3%)	86 (43·2%)
Non-carriers	160 (63·5%)	133 (53·6%)	16 (44·4%)	20 (40·8%)	144 (66·7%)	113 (56·8%)
BCHE genotype	(n=242)	(n=248)	(n=35)	(n=55)	(n=207)	(n=193)
Wild-type/wild-type	175 (72·3%)	159 (64·1%)	23 (65·7%)	35 (63·6%)	152 (73·4%)	124 (64·2%)
K variant**	67 (27·7%)	89 (35·9%)	12 (34·3%)	20 (36·4%)	55 (26·6%)	69 (35·8%)

Data are mean (SD) or numbers (%), unless otherwise indicated. DMC=Diagnosis Monitoring Committee; MMSE=mini-mental state examination; ADAS-cog=AD assessment scale, cognitive subscale; ADCS-ADL=AD Co-operative Study activities of daily living; CDR=clinical dementia rating; GDS=global deterioration scale; HAM-D=Hamilton rating scale for depression; MHIS=modified Hachinski ischaemic scale. *Data missing for 1 patient. †Data missing for 2 patients. ‡Data missing for 4 patients. §Data missing for 5 patients. ¶Based on a subpopulation of patients who agreed to MRI testing (n=550). Hippocampal volumes were adjusted for whole brain volume and are expressed as (total hippocampal volume x 1000)/whole brain volume. Although 513 patients received hippocampal volume scans, only 441 received whole brain volume scans, therefore only 441 are included. ‖Based on a subpopulation of patients who agreed to pharmacogenetic testing at baseline (APOE=500; BCHE=490). **Homozygous or heterozygous. Patients who developed other types of dementia are included in the group who did not progress to Alzheimer's disease (AD).

***Table 1*: Baseline characteristics of study participants (modified intention-to-treat population)**

Results

The baseline characteristics of the InDDEx study population are summarised in table 1. Figure 1 shows the flow of patients through the study. Of the 1526 patients screened for this study, 374 (24%) were screening failures, and 134 (9%) were still in active screening when the study was closed to further randomisation. The randomised groups did not differ in demographic characteristics or in their mean baseline scores. Of the full study sample, 500 patients (49·1%) participated in the APOE genotyping substudy. Within this sample there were more APOE ε4 carriers in the placebo group than in the rivastigmine group (46·4% *vs* 36·5%; p=0·025; table 1). 490 (48·1%) patients were included in the BCHE genotyping substudy, with a larger proportion of K-variant patients in the placebo group (35·9% *vs* 27·7%; p=0·051; table 1). MRI scans were available for 513 patients (50·4%) at their baseline visit, of whom 259 (50·5%) were in the rivastigmine group and 254 (49·5%) were in the placebo group. At least one post-baseline assessment for hippocampal volume was available for all 513 patients, and at least one post-baseline assessment for whole brain volume was available for 441 patients.

Almost all patients (n=992, 97·4%) had a history of a continuing medical condition at baseline without any significant differences between the two treatment groups. The most common medical disorders at baseline were hypertension (n=332, 32·6%), hypercholesterolaemia (n=214, 21·0%), and insomnia (n=138, 13·6%). 457 (90·0%) patients randomised to rivastigmine and 466 (91·4%) patients randomised to placebo were receiving one or more concomitant drugs at baseline.

Placebo-treated patients who progressed to AD were older (p<0·0001) and were more likely to be women (p=0·052) than were placebo-treated patients who did not progress to AD. At baseline, they had smaller adjusted hippocampal volumes (p<0·0001), higher dementia stage scores on GDS and CDR (p≤0·0001), and had higher levels of impairment on MMSE (p<0·0001), ADAS-cog (p<0·0001), and NPI (p=0·048; online supplementary data).

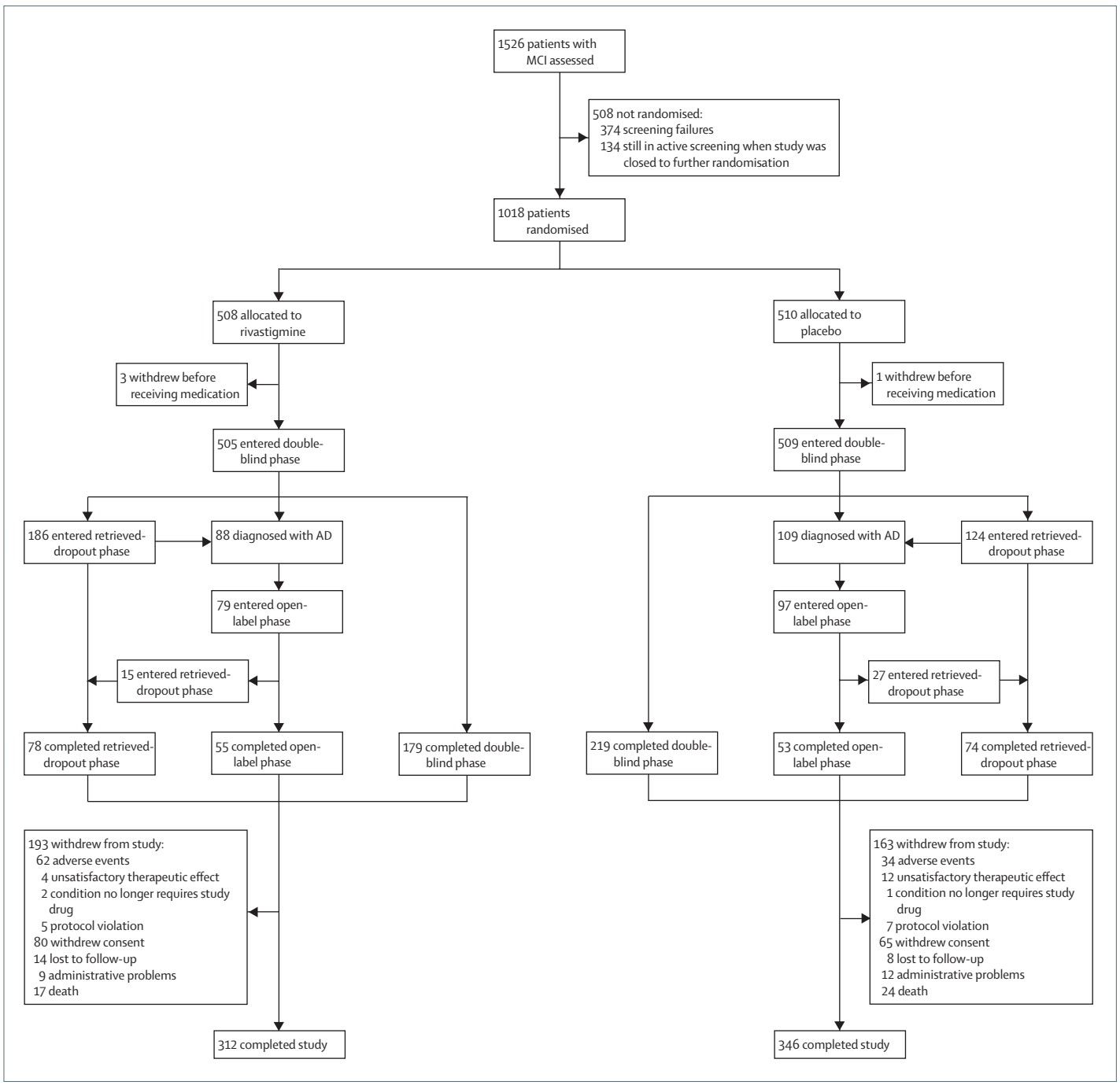

Figure 1: **Trial profile**

MCI=mild cognitive impairment. Withdrawals are presented for the overall study rather than for each separate stage. Patients in the retrieved-dropout phase were allowed to enter open-label treatment if diagnosed with AD. If those who had been diagnosed with AD discontinued open-label treatment, they could subsequently re-enter and then later withdraw from the retrieved-dropout phase. Allocation of withdrawal to a particular study phase is not possible as some patients would then be counted more than once.

During the double-blind phase, the mean daily dose of rivastigmine was 5·67 mg (SD 3·20). 325 patients (64·0%) received an average daily dose of less than 6 mg, and 183 patients (36·0%) received a mean daily dose of at least 6 mg. The median daily dose of rivastigmine during the maintenance phase (excluding the 18-week titration phase) was 6 mg.

The mean time to AD progression in all phases of the trial was 1318 days (SE 15·08) in the rivastigmine group (n=508) and 1289 days (SE 16·28) in the placebo group

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(n=510). Over the 3–4-year study duration, 17·3% (n=88) of patients on rivastigmine and 21·4% (n=109) of patients on placebo progressed to AD (hazard ratio 0·85 [95% CI 0·64–1·12; p=0·225; figure 2). Of the patients who progressed to dementia 197 (97·5%) were diagnosed with AD and only 5 (2·5%) with other dementias.

Performance on the neuropsychological test battery was similar at baseline between rivastigmine and placebo groups. There was no significant difference between the rivastigmine and placebo groups on the standardised *Z* score for the cognitive test battery measured as change from baseline to endpoint (–0·10 [95% CI –0·63 to 0·44], p=0·726). No significant treatment differences were seen on the individual cognitive tests after Bonferroni correction for multiple comparisons (online supplementary data). For the secondary outcome measures, after the application of Bonferroni corrections, there were no significant differences between treatment groups in either the MITT or observed-case analyses (online supplementary data).

There were no significant differences between treatment groups with regard to change from baseline to endpoint on any of the outcome measures derived by MRI assessment in the classic ITT population. The increase in ventricular volume was greater in the placebo group at 12 months (p=0·009) and 24 months (p=0·019) but not at the end of the study (p=0·371; figure 3). Although these differences in ventricular volume favoured rivastigmine at 12 and 24 months, these results were not significant after Bonferroni correction for multiple comparisons.

Of the 500 patients who consented to pharmacogenetic testing, 207 (41·4%) had at least one APOE ε4 allele. During the study period, 20 rivastigmine-treated APOE ε4 carriers progressed to AD (21·7%), compared with 29 (25·2%) in the placebo group (p=0·623). In APOE ε4 non-carriers, 16 (10·0%) rivastigmine-treated and 21 (15·0%) placebo-treated patients progressed to AD (p=0·214). Between-treatment differences did not reach significance in APOE ε4 carriers on the Kaplan-Meier analysis of the time to a clinical diagnosis of AD, standardised *Z* score, or ADAS-cog. No interaction was seen between APOE ε4 status and change from baseline in composite *Z* score or ADAS-cog score. However, when the Cox proportional hazards multivariate regression analyses were re-run to include APOE ε4 as an additional independent variable, APOE ε4 did predict progression to AD (p=0·024).

In a post-hoc analysis of patients within the placebo group who progressed to dementia (n=109) there were 65 women (24·8%) and 44 men (17·7%), p=0·053. Post-hoc Cox proportional hazards multivariate regression analyses showed significant associations between progression to dementia and patient's age (hazard ratio 1·051 per year [95% CI 1·021–1·082]; p<0·0007),

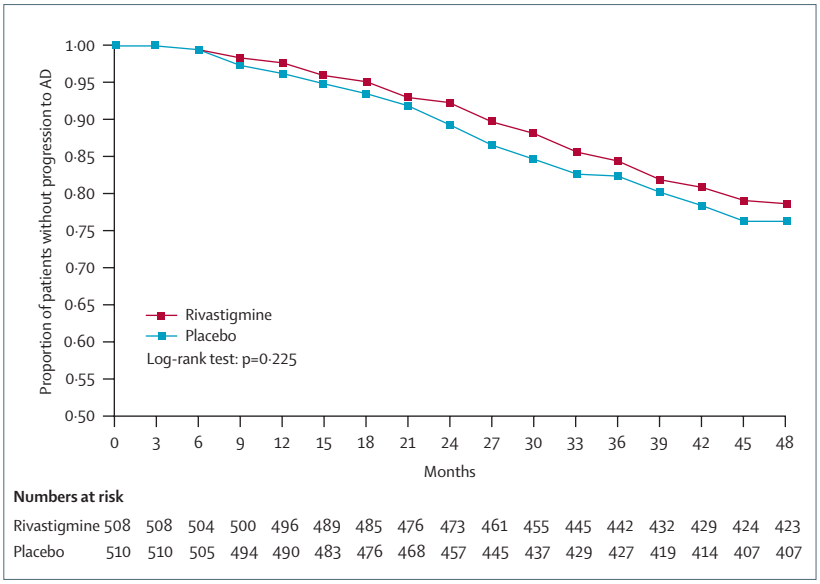

Figure 2: **Kaplan-Meier estimates for time to progression to AD in MCI patients receiving rivastigmine or placebo for up to 4 years (modified intention-to-treat analysis)**
Note truncation of y-axis.

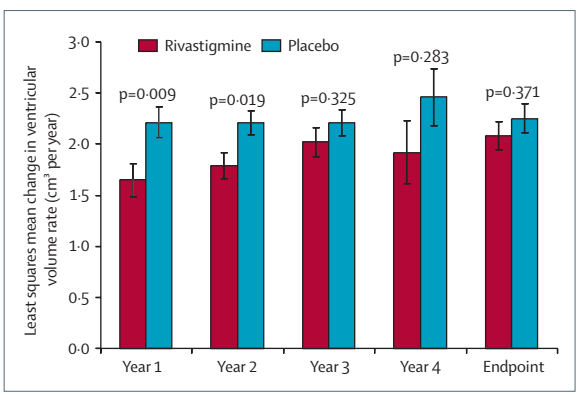

Figure 3: **Absolute change from baseline per year in ventricular volume by treatment group (intention-to-treat analysis)**
Calculated using least squares means from ANCOVA, with adjustment for treatment and baseline values. p values all not significant after Bonferroni correction for multiple comparisons.

behaviour at baseline (NPI>0 *vs* NPI=0, hazard ratio 1·955 [95% CI 1·168–3·271], p=0·011; NPI apathy item >0 *vs* NPI apathy item=0, hazard ratio 1·665 [95% CI 1·062–2·615], p=0·027), and low scores (worst 50% *vs* best 50%) on executive function and attention tests (digit span, hazard ratio 1·867 [95% CI 1·127–3·096]; p=0·015; verbal fluency (worst 50% *vs* best 50%), hazard ratio 2·087 [95% CI 1·289–3·380]; p=0·003).

Pharmacogenetic analyses showed fewer progressions to AD in rivastigmine-treated women who were homozygous for the wild-type BCHE genotype (wt/wt), compared with those receiving placebo (12·9% *vs* 30·0%; hazard ratio 0·46 [95% CI 0·233–0·911], p=0·026). This was confirmed by the Kaplan-Meier log-

	Rivastigmine (n=505)	Placebo (n=509)
Any adverse event	483 (95·6%)	472 (92·7%)
Nausea	249 (49·3%)	73 (14·3%)
Vomiting	164 (32·5%)	37 (7·3%)
Dizziness	125 (24·8%)	78 (15·3%)
Diarrhoea	117 (23·2%)	47 (9·2%)
Headache	108 (21·4%)	77 (15·1%)
Depression	62 (12·3%)	63 (12·4%)
Insomnia	62 (12·3%)	43 (8·4%)
Fatigue	59 (11·7%)	31 (6·1%)
Upper abdominal pain	56 (11·1%)	36 (7·1%)
Asthenia	52 (10·3%)	15 (2·9%)
Arthralgia	47 (9·3%)	54 (10·6%)
Hypertension	47 (9·3%)	62 (12·2%)

*Reported by at least 10% of patients in either group.

Table 2: **Most frequently reported* adverse events during double-blind phase (safety population)**

rank test (–0·182; [95% CI 0·338–0·025], p=0·014). Ventricular volume expansion was significantly reduced in rivastigmine-treated women in this group (p=0·012). This effect was apparent in BCHE wt/wt women (p=0·035) but not in women carrying the BCHE K-variant allele (p=0·284; see baseline demographics by sex and BCHE genotype in online supplementary data).

Post-hoc correlational analyses showed that changes in ventricular volume were related to the likelihood of progression to AD (rivastigmine, r=0·461, p<0·0001; placebo, r=0·427, p<0·0001), baseline-to-endpoint changes in the composite Z score of the neurocognitive test battery (rivastigmine, r=-0·559, p<0·0001; placebo, r=-0·465, p<0·0001), and baseline-to-endpoint changes in ADAS-cog scores (rivastigmine, r=-0·517, p<0·0001; placebo, r=-0·506, p<0·0001). Whole brain atrophy was also related to the likelihood of progression to AD (rivastigmine, r=-0·477, p<0·0001; placebo, r=-0·263, p<0·0013), baseline-to-endpoint changes in the composite Z score of the neurocognitive test battery (rivastigmine, r=0·582, p<0·0001; placebo, r=0·403, p<0·0001), and baseline-to-endpoint changes in ADAS-cog scores (rivastigmine, r=0·634, p<0·0001; placebo, r=0·412, p<0·0001). The rate of change in hippocampal volume at endpoint was not related to changes on any outcome measure. Post-hoc analyses showed that whole-brain volume decline was reduced in rivastigmine-treated women compared with those receiving placebo (p=0·05). Ventricular volume expansion was also significantly reduced in rivastigmine-treated women compared with those receiving placebo (p=0·009). These post-hoc analyses are only for generating hypotheses and will require confirmation in future prospective studies.

During the 4 years of the double-blind treatment phase, similar numbers of patients on rivastigmine (n=483, 95·6%) and placebo (n=472, 92·7%) reported adverse events. The predominant adverse events were cholinergic in nature; the frequencies of nausea, vomiting, diarrhoea, and dizziness were two to four times higher in the rivastigmine group than in the placebo group. Fatigue, abdominal pain and headache were 1·9, 1·6, and 1·4 times higher in rivastigmine-treated patients than in the placebo group, respectively (table 2). Most adverse events were mild or moderate in both groups. 141 (27·9%) patients on rivastigmine and 155 (30·5%) patients on placebo had serious adverse events during the double-blind phase. Approximately twice as many patients in the double-blind placebo group had serious cardiac disorders compared with the rivastigmine group (8·3% *vs* 4·4%; p=0·014).

Total discontinuation rates (including all study phases) due to adverse events were 12·2% in the rivastigmine group and 6·7% in the placebo group. Overall (including all study phases), 17 (3·3%) rivastigmine-treated patients and 24 (4·7%) placebo-treated patients died (p=0·345).

Discussion

MCI has been recognised as an at-risk state for progression to dementia, particularly AD. Rates of progression are 10–15% per year in studies of up to 5 years or longer.[2,5,6] As a result, MCI is a potentially compelling target for therapeutic intervention. To delay the time to develop AD could have significant clinical, economic, and social consequences.

The InDDEx study investigated the effect of rivastigmine over 3–4 years on the rate of progression from MCI to AD, in addition to the effects on the patients' results on a cognitive test battery. Neither of the primary outcome measures indicated a benefit for rivastigmine treatment. Although there was a small numerical advantage in favour of rivastigmine on delaying the time to a clinical diagnosis of AD, this did not reach significance. There were no benefits of rivastigmine on global, functional, or neuropsychiatric outcomes. The safety profile of rivastigmine included high rates of gastrointestinal cholinergic side-effects, particularly nausea and vomiting. Although these rates were higher than those reported in AD trials with rivastigmine, the discontinuation rates related to these side-effects were much lower. No other significant or unexpected safety concerns arose with treatment of MCI patients. Mortality and occurrence of cardiac serious adverse events had a favourable profile with rivastigmine, supporting its safety in MCI.

The overall rate of progression to AD was much lower than predicted. Whereas the study design was based on a progression rate of 10% per year, the study achieved only a 5% rate per year over 4 years. Indeed, the study needed to be extended from 3 years to 4 years to achieve the necessary numbers of patients progressing to AD to meet the minimum sample size required. We suspect

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that the inclusion criteria of MCI had a major influence on the study outcomes. Our MCI inclusion criteria were based on a CDR stage of 0·5 with a screening test of episodic memory (NYU delayed paragraph recall) that had a cut-off point that was corrected for neither age nor education. Published age and education cut-offs for this test were not available at the time of study design. The importance of these test-score adjustments in defining the study population is better recognised now than when this study was designed.[48] Moreover, patients with symptoms of depression at baseline were specifically excluded, whereas these symptoms are now recognised as common in patients with MCI and have predictive use in identifying individuals who are more likely to progress to AD.[49–51] These study design factors may have led to the enrolment of a more heterogeneous study population than that intended, which subsequently had a lower proportion of individuals destined to progress to AD. This study indicates that this proportion critically depends on the inclusion criteria.

This study also identifies several important clinical and neuroimaging markers that are associated with the risk of progression to AD. The increasing severity of MCI, as measured by global staging (CDR and GDS), global cognitive performance (ADAS-cog and MMSE total scores), and overall functional disability (ADCS-ADL total score), was associated with an increased rate of progression to AD. In post-hoc analyses of clinical factors that predicted progression to AD, there were significant associations with increasing age, the presence of neuropsychiatric symptoms at entry (particularly apathy), and performance on tests of executive function and attention. From the neuroimaging perspective, baseline total hippocampal volume was associated with progression to AD, whereas the rate of change of hippocampal volume did not correlate with changes on any clinical outcome measure. There was a strong correlation between changes in ventricular volume and whole brain atrophy and the likelihood of progression to AD. These findings indicate that the severity of MCI is associated with progression to AD, as are some of the important MRI measures of hippocampal, whole brain, and ventricular volumetric measures. Future MCI trials may benefit from the use of these clinical and neuroimaging variables to enrich study samples with subjects having higher likelihoods of progressing to AD.

These results join those of the other cholinesterase inhibitors, donepezil and galantamine, that have failed to achieve a significant longer term (>2 year) treatment benefit, either on time to progression to AD or on cognitive test batteries.[15–18] Overall, the limited longer-term efficacy of cholinesterase inhibitor therapy in these studies may arise from the relatively modest cholinergic deficits at the MCI stage.[52,53] Within the InDDEx study, there was also a dose-tolerability issue, because the mean tolerated dose of rivastigmine was below 6 mg daily, with more than 59% of patients receiving less than 6 mg daily at their last double-blind phase assessment. Therefore a significant proportion of the study population received less than the usual therapeutically effective dose for AD. Although it is possible that patients with MCI could obtain therapeutic effects from lower doses of drug, given the more modest cholinergic deficits, a definitive conclusion as to the long-term efficacy of rivastigmine in MCI at the higher doses typically achieved in AD cannot be reached in this study.

Among the biological risk factors, the APOE genotype has been well recognised as an important predictor of progression of MCI to AD.[15,48] The prevalence of APOE ε4 carriers recruited into this study was lower than some of the other MCI randomised controlled trials.[54,55] In the InDDEx study, 41·4% of patients were APOE ε4 carriers (36% in the rivastigmine group), whereas in the ADCS donepezil-vitamin E study, 55% of patients were APOE ε4 carriers (58% in the donepezil group).[15] In turn, the donepezil-vitamin E study cohort was more impaired at entry and had greater rates of decline across the cognitive and functional outcome measures used in both studies. The donepezil-vitamin E study also reported a significantly higher rate of progression to AD (16% *vs* 5% per year). Donepezil delayed the progression to AD in the subpopulation of patients with an APOE ε4 allele over 3 years, whereas no similar effect in the InDDEx study was noted. The explanation for this difference in treatment interaction between cholinesterase inhibitors and APOE ε4 is not currently understood. In the InDDEx study, only 50% of patients consented to APOE testing, which may have limited the comparison. Although post-hoc analyses did not identify any obvious differences between patients who were tested versus those who were not tested, the possibility of some bias cannot be excluded.

We also did several exploratory analyses to investigate the role of BCHE genotyping, a genetic risk factor with potential pharmacogenomic use. Fewer rivastigmine-treated women who were homozygous for wild-type BCHE genotype progressed to AD compared with those receiving placebo. These patients also showed reduced ventricular expansion compared with those on placebo. During 2 years, AD patients with this wild-type genotype have shown a greater response to rivastigmine compared with those with the BCHE-K variant polymorphism.[56,57] These exploratory findings need confirmation in further prospective studies.

There are other limitations within this study. In its design, the sample size was calculated on the basis of the time to diagnosis of AD only. No separate calculation was done for the co-primary variable, the composite *Z* score neuropsychological battery. Therefore the sample size may not have been sufficient to achieve significance on this outcome measure. Furthermore, the overall trend in the study population was for deterioration in

neuropsychological and neuroimaging assessments over time. Thus, when patients progressed to AD or withdrew from the study, their assessment at progression or withdrawal was carried forward in subsequent analyses, and any further progression of these patients was not assessed. The loss of this valuable information may have resulted in an underestimation of the overall effect of rivastigmine over time, particularly as there were more progressions to AD in the placebo group.

In the absence of biomarkers that predict which patients have MCI of the AD type and are likely to progress over a few years of follow up, future MCI treatment trials might be well advised to seek patients with more advanced MCI, and who are phenotypically and genotypically closer to AD. This could allow a clearer view of the therapeutic potential of the drug being investigated in those patients clinically diagnosed with MCI but who were in the preclinical stage of AD.

In summary, this study did not show a delay in progression to AD with rivastigmine treatment. No significant treatment differences were seen on the cognitive battery or on measures of cognition, behaviour, or activities of daily living. Rivastigmine was not associated with any significant unexpected serious safety concerns in patients with MCI.

Contributors

HHF contributed to the study design, data analysis, and was chiefly responsible for the writing of the manuscript. SF assisted in the design and implementation of the study, and contributed to the data analysis and manuscript editing. BW, AB, TdS, JC, DI, J-MO, and HS helped design and implement the trial, and contributed to the manuscript writing. PS, ES, and NH contributed to the study design and data analysis, as well as to the manuscript writing. MF and SP participated in the study design, interpretation of data, and writing of the manuscript. ST, LM, and RL contributed to the implementation and conduct of the study, data analysis, and the writing of the manuscript. NS did the statistical analyses and contributed to the writing of the manuscript. YH did the genotyping and related data analysis as well as the writing of the manuscript. NF did the analysis of total brain and ventricular volume, with measurements provided by the Dementia Research Centre, Institute of Neurology, University College London, UK, and contributed to the writing of the manuscript. HCC did total brain and hippocampal analysis, with measurements provided by the Duke Image Analysis Laboratory, Duke University, Durham, NC, USA, and contributed to the writing of the manuscript.

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Conflicts of interest

HHF has been a consultant and speaker for Novartis, and has received either grant support or served as consultant or speaker on behalf of Pfizer, Eisai, Janssen, Lilly, AstaZeneca, Sanofi Synthelabo, GlaxoSmithKline, Servier, Myriad, Targacept, Lundbeck, Forest, and Axonyx. SF, JC, TdS, and PS have served as consultants for Novartis. BW and J-MO have received honoraria from Novartis for their participation

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on the advisory board of the InDDEx study. HS has received honoraria from Novartis as a member of the study steering committee of the InDDEx study. SP has received honoraria as a consultant and speaker, and obtained grant support from Novartis. NF received honoraria from Novartis for participation in the InDDEx study and as an invited speaker. NH has received research support and speaker's honoraria from Novartis, Pfizer, Janssen, and Lundbeck. MF is a consultant for Novartis and serves on spearker's bureaus for Novartis, Forest, Pfizer, and Eisai. RL, NS, LM, and ST are employees of Novartis with stock ownership.

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