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Randomized, Double-Blind, Parallel-Group, 48-Week Study for Efficacy and Safety of a Higher-Dose Rivastigmine Patch (15 vs. 10 cm²) in Alzheimer's Disease

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Key Words

Alzheimer's disease · Functional and cognitive decline · Rivastigmine · Transdermal patch

Abstract

Aim: Determine whether patients with Alzheimer's disease demonstrating functional and cognitive decline, following 24–48 weeks of open-label treatment with 9.5 mg/24 h (10 cm²) rivastigmine patch, benefit from a dose increase in a double-blind (DB) comparative trial of two patch doses.

Methods: Patients meeting prespecified decline criteria were randomized to receive 9.5 or 13.3 mg/24 h (15 cm²) patch during a 48-week, DB phase. Coprimary outcomes were change from baseline to week 48 on the Instrumental

Activities of Daily Living domain of the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-IADL) scale and the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog). Safety and tolerability were assessed. **Results:** Of 1,584 patients enrolled, 567 met decline criteria and were randomized. At all timepoints, ADCS-IADL and ADAS-cog scores favoured the 13.3 mg/24 h patch. The 13.3 mg/24 h patch was statistically superior to the 9.5 mg/24 h patch on the ADCS-IADL scale from week 16 ($p = 0.025$) onwards including week 48 ($p = 0.002$), and ADAS-cog at week 24 ($p = 0.027$), but not at week 48 ($p = 0.227$). No unexpected safety concerns were observed. **Conclusions:** The 13.3 mg/24 h rivastigmine patch significantly reduced deterioration in IADL, compared with the 9.5 mg/24 h patch, and was well tolerated.

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Introduction

Alzheimer's disease (AD) is the most common cause of dementia, and there is an urgent need to manage affected patients optimally. The pathophysiology of AD is complex and includes degeneration of the cortically projecting cholinergic system, contributing to cognitive impairment and functional decline [1]. Functional decline is an important predictor of caregiver burden [2] and is also a strong risk factor for nursing home placement or the institutionalization of patients with AD [3–5]. Cholinesterase inhibitors are the first-line treatment for AD and provide symptomatic relief by increasing cholinergic function in the brain [6].

Rivastigmine is the only cholinesterase inhibitor available in a transdermal patch formulation, in addition to oral capsules, that is approved for the symptomatic treatment of mild-to-moderate AD in the USA and many other countries worldwide [7–11]. Both rivastigmine formulations are also widely approved for the treatment of Parkinson's disease dementia [12, 13]. Previous pharmacokinetic studies have demonstrated that once daily transdermal administration of rivastigmine provides continuous drug delivery, reducing fluctuations in drug plasma concentration, with improved tolerability compared with twice daily rivastigmine capsules [14–16]. A large, 24-week, randomized, multicentre, placebo-controlled, double-blind (DB) clinical study (IDEAL; Investigation of transDermal Exelon in Alzheimer's disease) established the 9.5 mg/24 h (10 cm²) rivastigmine patch as the currently recommended target maintenance dose in the treatment of patients with mild-to-moderate AD [8]. In the IDEAL study, the 9.5 mg/24 h patch was shown to have comparable efficacy to 12 mg/day capsules, but with improved tolerability, fewer withdrawals due to gastrointestinal (GI) adverse events (AEs) and threefold lower incidences of nausea and vomiting [8], allowing most patients on the 9.5 mg/24 h patch to achieve their target dose (95.9 vs. 64.4%, respectively) [17]. As the efficacy of rivastigmine has been shown to be dose dependent [18, 19], higher doses may provide additional benefits compared with currently approved doses [3]. The 13.3 mg/24 h (15 cm²) patch has the potential to provide access to greater efficacy, while ensuring a lower incidence of GI AEs than may be expected with a comparable oral dose.

The objective of this study was to compare the efficacy, safety and tolerability of a higher dose of the rivastigmine patch with that of the current maintenance dose (13.3 vs. 9.5 mg/24 h) in patients with mild-to-moderate

AD, who had shown functional and cognitive decline on the 9.5 mg/24 h patch during an initial open-label (IOL) phase.

Methods

Patients

Patients meeting the inclusion criteria for this study were women (not of child-bearing potential) or men aged 50–85 years with a diagnosis of dementia of the Alzheimer's type according to the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* [20], and probable AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [21]. The patients included in the study had Mini-Mental State Examination (MMSE) scores of ≥ 10 and ≤ 24 [22]. They were required to be living with someone in the community or be in daily contact with a responsible caregiver, if living alone.

Exclusion criteria consisted of: dementia or medical or neurological conditions other than AD that could interfere with the evaluation of patient response to the study medication; current diagnosis of uncontrolled seizure disorder; severe/unstable cardiovascular disease; bradycardia (≤ 50 bpm), sick-sinus syndrome or conduction defects; acute, severe or unstable asthmatic conditions; uncontrolled peptic ulceration/GI bleeding within the previous 3 months; clinically significant urinary obstruction; allergy to vitamin E-containing products; sensitivity to cholinergic compounds or a skin lesion/disorder that would prevent transdermal patch use; a history (past 5 years) of malignancy of any organ system, unless stable, and a history or current diagnosis of cerebrovascular disease. Also prohibited was the use of cholinesterase inhibitors or other approved AD treatments for 2 weeks prior to study enrolment, with the exception of stable memantine treatment (if taken for ≥ 3 months prior to study entry), and the use of investigational drugs, new psychotropic medications or dopaminergic agents, and anticholinergics if not taken at a stable dose, within the 4 weeks prior to receiving study treatment.

Patients were enrolled from 147 research centres in 7 countries: the USA (64 centres), Canada (11), Italy (34), Germany (24), France (8), Switzerland (3) and Spain (3). The study protocol was reviewed by the representative ethics committee for each centre. The study was designed and implemented in accordance with Good Clinical Practice and the local regulations and ethical principles laid down in the Declaration of Helsinki. All patients, or a legally acceptable representative, and caregivers provided written informed consent prior to participating in the study.

Study Design and Interventions

The OPTIMA (OPTimizing Transdermal Exelon In Mild-to-moderate Alzheimer's disease) study was a 72- to 96-week multicentre trial, composed of a 24- to 48-week IOL phase followed by a 48-week randomized, DB, parallel-group phase (Clinicaltrials.gov identifier NCT00506415).

Patients meeting the eligibility criteria were enrolled into a 24- to 48-week IOL phase; treatment was initiated with the 4.6 mg/24 h (5 cm²) rivastigmine patch. Patients were titrated to the once daily 9.5 mg/24 h patch after 4 weeks and were maintained on this dose for the remainder of the IOL phase. IOL baseline efficacy and safety assessments were performed on day 1, prior to administration of the first dose of study drug. The inclusion criteria for entering the DB phase were functional and cognitive decline during the IOL phase. Patients were evaluated at weeks 24, 36 and 48 of the IOL phase for functional decline (by investigator judgement) and cognitive decline (≥ 2 -point decline in MMSE score from the previous visit, or ≥ 3 -point decline in MMSE score from baseline). Patients meeting the decline criteria at week 24, 36 or 48 then entered the DB phase and were randomized 1:1 to receive 9.5 mg/24 h or 13.3 mg/24 h rivastigmine patch, and were maintained at their target dose for an additional 48 weeks. Dose adjustments and interruptions were permitted for patients unable to tolerate the specified dose, until tolerability improved. Only patients tolerating the 9.5 mg/24 h patch were eligible to enter the DB phase. Patients who did not meet the decline criteria were given the option to enter an extended open-label (EOL) treatment phase with the 9.5 mg/24 h rivastigmine patch.

Primary Outcomes

Primary outcomes were the change from baseline of the DB phase to week 48 of the DB phase on the Instrumental Activities of Daily Living domain (items 7–23) of the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-IADL) scale [23] and the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog) [24].

Secondary Outcomes

Secondary outcomes were the time to functional decline on the ADCS-IADL scale during the 48-week DB phase, and the change from DB baseline to week 48 of the DB phase in the Trail Making Test parts A and B (TMT-A and TMT-B) [25, 26], the 10-item Neuropsychiatric Inventory (NPI-10) [27], and the NPI-caregiver distress scale (NPI-D) [28].

Time to functional decline was the interval between the DB baseline to first decline on the ADCS-IADL scale. Decline was defined by either a ≥ 1 -point decrease at a visit and confirmed by the following visit, or a ≥ 2 -point decrease in total ADCS-IADL score from DB baseline.

Safety evaluations included the frequency of AEs and serious AEs (SAEs), the discontinuation rate due to AEs, monitoring of vital signs and 12-lead electrocardiogram.

Concomitant Medications

Medications and/or therapies that were started prior to the first dose of study drug, and concomitant medications/therapies that were administered on or after the first dose of study drug were coded using the World Health Organization Drug Reference List that employs the Anatomical Therapeutic Chemical classification system.

Sample Size, Randomization and Blinding

It was estimated that a sample size of 410 patients in each group at the end of the DB phase was required to have 85% power to detect a treatment difference of 1.9 points on the coprimary efficacy variables, the ADCS-IADL and the ADAS-cog, in the intent-to-treat (ITT) population. This was assuming a common standard deviation of 8 for both the coprimary efficacy variables, using a two-group t test with a 0.05 two-sided significance level. A correlation of 0.35 between the coprimary efficacy variables was assumed. To adjust for 5% of patients who may not be included in the ITT population, a total of 864 patients (432 per group) was estimated to be needed at the time of DB randomization (the end of the IOL phase). Based on the long-term study of rivastigmine capsules [29], it was assumed that the percentage of patients who would show cognitive decline in the IOL phase would be 55%. Thus, it was estimated that 1,571 patients would be needed to be enrolled in the IOL phase to ensure that at least 864 declining patients would be available for randomization.

Randomization of patients in the DB phase was performed using an interactive voice response system, which uses a validated system to automate the assignment of patients to randomization numbers.

Treatment was not blinded during the IOL phase; however, from the time of randomization in the DB phase, patients, investigator staff, individuals performing the assessments and data analysts all remained blind to the identity of the treatment. A DB, double-dummy design was used whereby all patients received an identical-looking patch of each size: patients randomized to receive the 9.5 mg/24 h patch dose were supplied with 9.5 mg/24 h (10 cm²) rivastigmine patches and 15 cm² placebo patches. Patients randomized to receive the 13.3 mg/24 h patch dose were supplied with 13.3 mg/24 h (15 cm²) rivastigmine patches and 10 cm² placebo patches. Unblinding occurred only in the case of patient emergencies and at the end of the study.

Statistical Analysis

In all efficacy analyses of the DB phase, patient data were analysed according to the treatment randomized. The primary analysis was based on the ITT population in the DB phase (ITT-DB) using a last-observation carried forward (LOCF) imputation [ITT(DB)-LOCF]. The ITT-DB population consisted of all patients who received at least 1 dose of study drug and had at least 1 postrandomization assessment for both coprimary efficacy variables (ADCS-IADL and ADAS-cog) during the DB phase. The primary analysis was also conducted using observed cases (OC) based on the ITT-DB population [ITT(DB)-OC], as well as based on the per-protocol (PP) population using both LOCF and OC approaches [PP(DB)-LOCF and -OC]. The PP-DB population was defined as all ITT-DB patients without any major protocol deviations and who had at least 1 postrandomization assessment for both coprimary efficacy variables (ADCS-IADL and ADAS-cog) on or after DB week 24 on target dose, during the DB phase. The safety population during the DB phase consisted of all patients who were randomized, who received at least 1 dose of study drug and who had at least 1 postrandomization safety assessment during the DB phase. Safety data were analysed descriptively according to the treatment received and the study period.

Changes from baseline on scores of the ADCS-IADL and ADAS-cog were compared between treatment groups using least-squares (LS) means derived by analysis of covariance using the following explanatory variables: treatment, country and corresponding baseline score. To assess the robustness of both coprimary efficacy variable analyses, comparison of the treatments was also performed with LOCF via the non-parametric van Elteren test, stratified by country as a supportive analysis [ITT(DB)-LOCF]. Sensitivity analyses were performed for both coprimary efficacy variables based on a mixed-effects repeated measures model examining the treatment group differences as a function of time [ITT(DB)-OC]. Additional sensitivity analyses were performed to evaluate the possibility that missing primary efficacy measure data may not be missing at random utilizing multiple imputations under missing at random (MAR) and different missing not at random (MNAR) scenarios using penalty scores.

The time to functional decline as assessed by the ADCS-IADL over the 48-week DB phase was analysed using the log-rank test for interval censored data, based on the ITT population without imputation [ITT(DB)-OC]. A Cochran-Mantel-Haenszel test, with country as a stratification variable, was used for comparison of the percentage of patients showing decline in the ADCS-IADL in the two treatment groups. Additional supportive analyses were performed for time to functional decline and percentage of subjects with functional decline during the DB phase on the PP-DB population. Change from DB baseline in total time to perform the TMT-A and TMT-B, and in the NPI-10 and NPI-D total scores were compared between treatment groups using LS means derived by analysis of covariance [ITT(DB)-LOCF and -OC populations] with similar explanatory variables to those used for the analyses on coprimary efficacy variables.

Results

Participants

The first patient was screened in June 2007, and the last patient completed the study in May 2011. Of the 1,979 patients screened, 1,584 were enrolled in the IOL phase (USA, 589 patients; Canada, 164; Italy, 356; Germany, 268; France, 129; Switzerland, 40; Spain, 38), and 1,582 were exposed to study drug. In total, 567 patients (35.8%) were classified as decliners and were randomized into the DB phase: 280 to the 13.3 mg/24 h rivastigmine patch and 287 to the 9.5 mg/24 h rivastigmine patch (fig. 1). One patient in the 9.5 mg/24 h rivastigmine patch group did not receive the randomized study drug and discontinued before the start of the DB phase. The reason for discontinuation of this patient was documented as part of the IOL phase. In the 13.3 mg/24 h patch group, 207 participants (73.9%) completed the DB phase, compared with 203 participants (70.7%) in the 9.5 mg/24 h patch group. The most common reasons for discontinuation

during the DB phase were similar in both the 13.3 and the 9.5 mg/24 h patch groups (fig. 1).

The ITT-DB population comprised 265 and 271 patients in the 13.3 and 9.5 mg/24 h patch groups, respectively. The safety population during the DB phase comprised 280 and 283 patients in the 13.3 and 9.5 mg/24 h patch groups, respectively. Baseline demographics and background characteristics were comparable between the two treatment groups (table 1). At DB baseline, the mean and median durations of time since the first AD symptom had been noticed by the patient/caregiver or was diagnosed by a physician were slightly longer in the 9.5 mg/24 h group than in the 13.3 mg/24 h group (table 1). At IOL baseline, the mean MMSE score tended to be lower in decliners (i.e. those randomized in the DB phase) compared with non-decliners (i.e. those who entered the extended open-label phase).

Dosing

During the DB phase, the mean exposure to study drug was similar in both the 13.3 mg/24 h (41.4 ± 14.3 weeks) and 9.5 mg/24 h (41.3 ± 13.6 weeks) treatment groups (safety population during the DB phase).

Primary Efficacy Assessments

ADCS-IADL Scores

Both treatment groups showed decline on the ADCS-IADL total score from baseline during the 48-week DB phase. This decline was less at all time points in patients randomized to receive the 13.3 mg/24 h rivastigmine patch. Significantly less decline was observed on ADCS-IADL total scores at weeks 16, 24, 32 and 48 (primary end point; $p = 0.025, 0.005, <0.001$ and 0.002 , respectively) in patients receiving the 13.3 mg/24 h patch compared with the 9.5 mg/24 h patch (fig. 2a; table 2).

ADAS-cog Scores

Both treatment groups demonstrated cognitive decline from baseline at weeks 24–48 in the ITT(DB)-LOCF population. At all time points, cognitive decline was less in the 13.3 mg/24 h rivastigmine patch group compared with the 9.5 mg/24 h patch group (fig. 2b; table 2). Between-group differences did not reach significance at week 48 ($p = 0.227$); significant treatment differences in favour of the 13.3 mg/24 h patch were observed at week 24 ($p = 0.027$).

Results consistent with those from the primary analyses were documented on the ADCS-IADL and ADAS-cog in the OC analysis (table 2), and several sensitivity analyses (mixed-effects repeated measures model, van Elteren

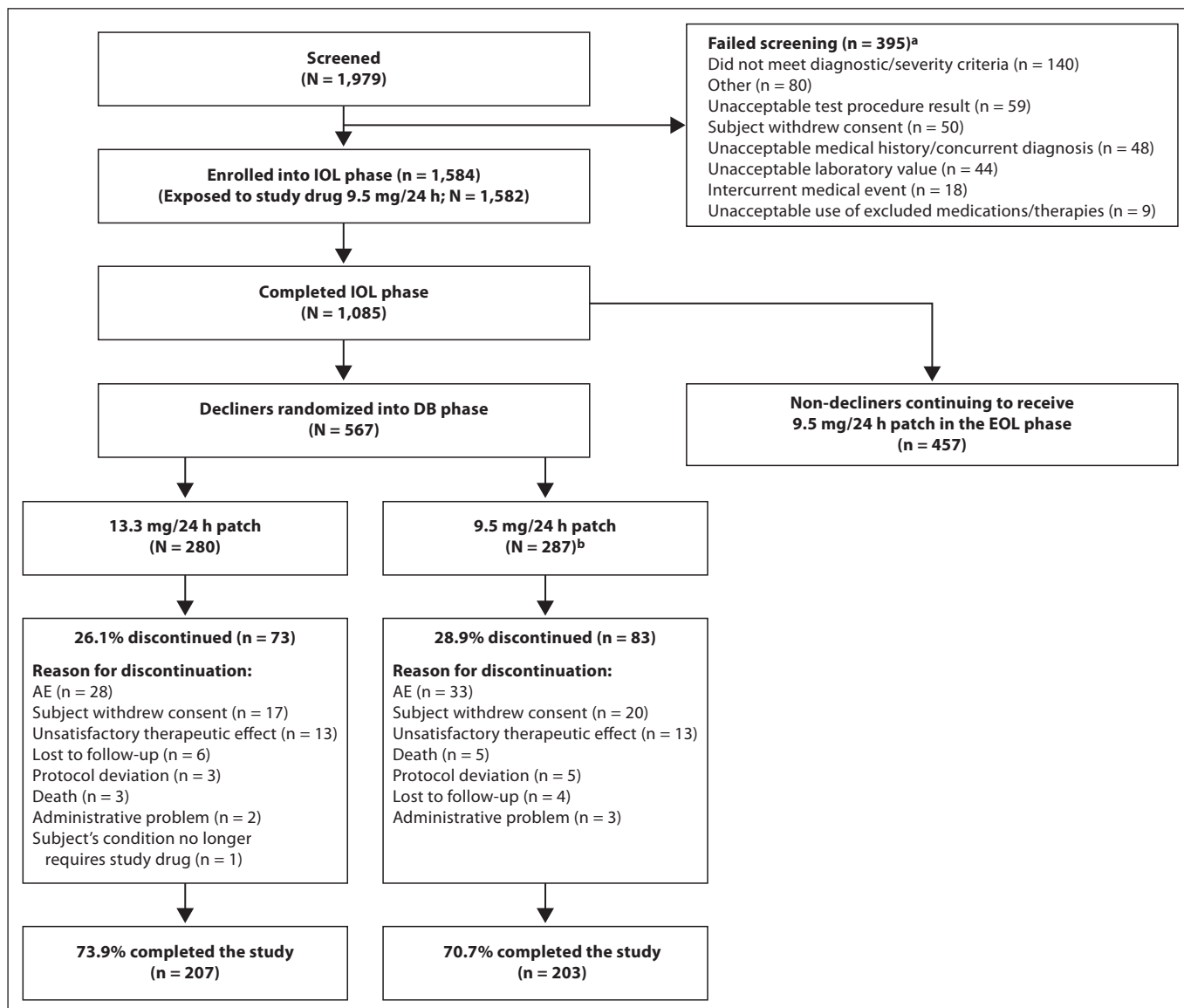


Fig. 1. Study design and patient flow through the study. N = Number of patients in the population; n = number of patients with an assessment. ^a A patient with multiple reasons for screening failure is counted in each category. ^b One patient (decliner) was randomized to receive the 9.5 mg/24 h rivastigmine patch but was not treated with the randomized study drug in the DB phase. The patient discontinued before the start of the DB phase, and the reason for discontinuation was documented in the IOL phase. Data relating to patients entering the EOL phase will be described separately in further publications.

test, and multiple imputations under MAR and various MNAR scenarios). In the PP-DB population (LOCF and OC analyses), significantly less decline was observed at all time points on the ADCS-IADL (weeks 8–48), and less cognitive decline was observed at all time points on the ADAS-cog, although between-group differences did not reach significance.

Secondary Efficacy Assessments

Time to Functional Decline

Functional decline on the ADCS-IADL [ITT(DB)-OC] tended to occur later in the 13.3 mg/24 h patch group than in the 9.5 mg/24 h patch group, although the observed difference did not reach significance. Over the 48-week DB phase, the proportion of patients with func-

Table 1. Patient demographics and background characteristics (IOL baseline and DB baseline)

	IOL phase			DB phase		
	non-decliners (n = 459)	decliners (n = 567)	discontinued (n = 558)	13.3 mg/24 h rivastigmine patch (n = 280)	9.5 mg/24 h rivastigmine patch (n = 287)	total (n = 567)
Mean age, years	74.6±7.0	74.5±7.1	75.6±7.3	75.6±7.4	75.9±6.8	75.7±7.1
Range	52.0–85.0	51.0–85.0	50.0–85.0	54.0–87.0	53.0–87.0	53.0–87.0
Female patients, n (%)	265 (57.7)	367 (64.7)	360 (64.5)	185 (66.1)	182 (63.4)	367 (64.7)
Race, %						
Caucasian	96.3	96.6	93.5	95.0	98.3	96.6
Black	2.0	1.8	4.1	2.9	0.7	1.8
Other	1.7	1.6	2.3	2.1	1.0	1.6
Mean weight, kg	70.3±14.6 ^a	68.7±14.6 ^b	68.8±13.6	69.5±15.5	67.9±13.9	68.7±14.7
Range	40.5–119.0	39.0–121.0	41.0–124.3	38.0–118.4	40.0–110.6	38.0–118.4
Mean number of years of formal education	10.2±4.0	10.6±4.0 ^b	10.8±4.2	10.5±4.0 ^c	10.6±4.0	10.6±4.0 ^b
Range	0.0–23.0	2.0–22.0	2.0–25.0	2.0–20.0	3.0–22.0	2.0–22.0
Mean time since first AD symptom was noticed by patient/caregiver, years	3.4±2.6	4.1±2.8	3.9±2.9	3.9±2.8	4.3±2.8	4.1±2.8
Median	2.7	3.4	3.1	3.2	3.6	3.4
Range	0.1–19.2	0.2–17.7	0.4–19.4	0.2–17.7	0.3–15.6	0.2–17.7
Mean time since first symptom of AD was diagnosed by physician, years	1.4±1.7	1.9±2.0	1.7±2.0	1.8±1.8	2.0±2.1	1.9±2.0
Median	0.7	1.3	1.0	1.25	1.4	1.3
Range	0.0–10.3	0.0–12.6	0.0–11.9	0.0–10.9	0.0–12.6	0.0–12.6
Mean baseline MMSE score	18.8±3.3	16.9±3.6	17.8±3.4	14.1±4.8	14.2±4.6	14.2±4.7
Range	10.0–24.0	10.0–25.0	10.0–24.0	0.0–24.0	2.0–26.0	0.0–26.0
Concomitant memantine, n (%)	94 (20.5)	183 (32.3)	141 (25.4)	92 (32.9)	90 (31.8)	182 (32.3)

Results are expressed as means ± SD unless otherwise stated. Decliners = patients meeting the decline criteria during the IOL phase who were randomized in the DB phase; non-decliners = patients not meeting the decline criteria during the IOL phase who then entered the EOL phase. Demographic information was collected at screening (IOL baseline) for the non-decliners vs. the decliners. For the decliners randomized into the DB phase, demographic information was collected at DB baseline, the last assessment in the IOL phase.

^a n = 458.

^b n = 566.

^c n = 279.

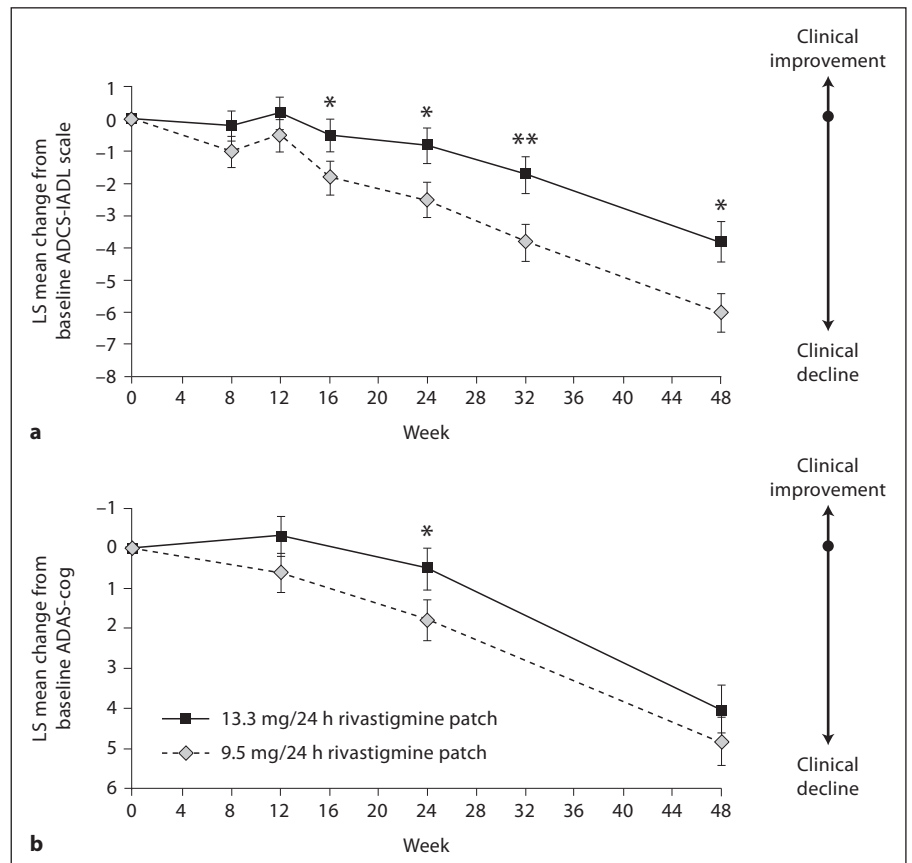
tional decline was also lower in the 13.3 mg/24 h patch group (77.0%) compared with the 9.5 mg/24 h patch group (81.2%), but the difference was not statistically significant.

Other Secondary Efficacy Assessments

There were no significant between-group differences on the other secondary efficacy outcomes. The mean time to complete the TMT-A and TMT-B was slightly longer in the 9.5 mg/24 h patch group compared with the 13.3

mg/24 h patch group at DB baseline. Patients in the 13.3 mg/24 h patch group had numerically smaller increases in time to complete the TMT-A at DB weeks 24 and 48 compared with those in the 9.5 mg/24 h patch group. The greatest differences between groups were observed at week 24; differences in LS means (DLSM) were not significant for the ITT(DB)-LOCF (table 3) or -OC populations (data not shown). The 13.3 mg/24 h patch group had numerically larger increases in time to complete the TMT-B at weeks 24 and 48 compared with the 9.5 mg/

Fig. 2. LS mean change from baseline during the 48-week DB phase on the ADCS-IADL (a) and ADAS-cog (b) in the ITT(DB)-LOCF population. Error bars represent the standard error of the mean; * $p < 0.05$, ** $p < 0.001$ for 13.3 mg/24 h vs. 9.5 mg/24 h rivastigmine patch. The differences in LS means, 95% confidence intervals and p values are based on an analysis of covariance model adjusted for country and baseline score (ADCS-IADL or ADAS-cog).



24 h patch group. The greatest DLSSM was observed at week 24; however, there were no significant differences between groups at any time point in the ITT(DB)-LOCF (table 3) or -OC populations (data not shown).

Both treatment groups showed slight deterioration or no change from baseline at the study end point for both the NPI-10 and NPI-D scales. Between-dose treatment differences were not significantly different (table 3).

Safety Assessments

Deaths, SAEs and Discontinuations

There were no unexpected safety effects of treatment with either rivastigmine patch dose. The incidences of SAEs and deaths were similar between treatment groups in the DB phase (SAEs: 15.7 and 15.5%, 13.3 and 9.5 mg/24 h patch, respectively; deaths: 1.1 and 1.8%, 13.3 and 9.5 mg/24 h patch, respectively). No deaths were considered to be related to the study medication. The most frequently reported SAEs in the DB phase, by primary system organ class, were infections and infestations (4.6 vs. 4.2%, 13.3 and 9.5 mg/24 h patch, respectively)

and nervous system disorders (5.0 vs. 3.9%, respectively). The incidence of AEs and SAEs leading to discontinuation in the DB phase was lower with the 13.3 mg/24 h patch than with the 9.5 mg/24 h patch (AEs leading to discontinuation: 9.6 vs. 12.7%, 13.3 and 9.5 mg/24 h patch, respectively; SAEs leading to discontinuation: 4.3 vs. 6.4%, respectively). The most common AEs leading to discontinuation were GI disorders, general disorders and administration site conditions, and psychiatric disorders.

Incidence of AEs

Overall, in the DB phase AEs were reported in a greater proportion of patients in the 13.3 mg/24 h patch group than the 9.5 mg/24 h patch group (table 4). The most frequently reported AEs in the DB phase, by primary system organ class, were GI disorders (29.3 vs. 19.1%, 13.3 and 9.5 mg/24 h patch, respectively), psychiatric disorders (25.4 vs. 21.6%, respectively) and nervous system disorders (21.4 vs. 18.4%, respectively). Skin and subcutaneous tissue disorders were less frequently observed with the 13.3 mg/24 h than the 9.5 mg/24 h patch (2.1 vs.

Table 2. Mean ADCS-IADL and ADAS-cog scores and change from baseline at weeks 24 and 48 in the ITT(DB)-LOCF and ITT(DB)-OC populations

		13.3 mg/24 h rivastigmine patch		9.5 mg/24 h rivastigmine patch		DLSM	p value
		n	score	n	score		
ADCS-IADL	ITT(DB)-LOCF						
	Baseline	265	27.5	271	25.8	–	–
	Change at week 24	265	–1.5	271	–2.8	1.7 (0.5, 2.9)	0.005
	Change at week 48	265	–4.4	271	–6.2	2.2 (0.8, 3.6)	0.002
	ITT(DB)-OC						
	Baseline for week 24	232	27.8	243	26.3	–	–
	Change at week 24	232	–1.0	243	–3.0	2.3 (1.0, 3.6)	<0.001
	Change at week 48	209	–4.6	198	–6.9	2.5 (0.8, 4.1)	0.004
ADAS-cog	ITT(DB)-LOCF						
	Baseline	264	34.4	268	34.9	–	–
	Change at week 24	264	1.0	268	2.2	–1.3 (–2.5, –0.2)	0.027
	Change at week 48	264	4.1	268	4.9	–0.8 (–2.1, 0.5)	0.227
	ITT(DB)-OC						
	Baseline for week 24	238	34.2	238	34.5	–	–
	Change at week 24	238	0.9	238	2.1	–1.3 (–2.5, 0.1)	0.035
	Change at week 48	211	4.3	193	5.3	–1.2 (–2.7, 0.4)	0.141

Figures in parentheses indicate 95% confidence limits. DLSM = difference of LS means; n = number of patients with an assessment at baseline (last assessment in the IOL phase) and either the corresponding visit (for the OC) or with at least 1 postbaseline assessment (for the LOCF). 95% confidence limits and p values are based on an analysis of covariance model adjusted for country and baseline score (ADCS-IADL or ADAS-cog).

6.0%, respectively). Cholinergic GI AEs were more frequently reported with the 13.3 mg/24 h patch than with the 9.5 mg/24 h patch and were most commonly: nausea, vomiting, weight decreased, appetite decreased and upper abdominal pain (table 4). When AEs were summarized according to time during the DB phase, i.e. those with onset during weeks 1–24 and those with onset during weeks 25–48 (>24 weeks), the percentages of patients with these events decreased over time in both treatment groups, with the exception of ‘weight decreased’. The percentage of patients treated for >24 weeks who reported an AE of vomiting was comparable in the 13.3 and 9.5 mg/24 h patch groups (table 4). Application site erythema and application site pruritus were reported in comparable proportions of patients in the two treatment groups (table 4), and the percentage of patients with these events decreased over time in both treatment groups. The percentage of patients treated for >24 weeks who reported an AE of application site erythema or pruritus was lower

with the 13.3 mg/24 h patch than with the 9.5 mg/24 h patch (table 4).

The incidence of AEs leading to a dose adjustment or study medication interruption in the DB phase was 13.9% in the 13.3 mg/24 h patch group and 5.3% in the 9.5 mg/24 h patch group.

There were no clinically relevant changes from baseline to the end of the DB phase for any vital sign parameter in either treatment group. During the DB phase, the incidence of patients experiencing newly occurring electrocardiogram abnormalities was low and was similar in the two patch groups (17.5 vs. 15.2%, 13.3 mg/24 h patch vs. 9.5 mg/24 h patch).

Concomitant Medications

During the DB phase, a similar percentage of patients in both the 13.3 and 9.5 mg/24 h patch groups were receiving at least 1 drug from 3 prespecified classes of CNS medications (antipsychotics, antidepressants or hypnotic/

Table 3. Secondary efficacy outcomes [ITT(DB)-LOCF population]

	13.3 mg/24 h rivastigmine patch	9.5 mg/24 h rivastigmine patch	DLSM	p value
TMT-A				
N	254	258		
Baseline	191.3	199.4	–	–
Change from baseline at week 24	4.2	10.2	–7.8 (–17.3, 1.7)	0.105
Change from baseline at week 48	16.3	18.2	–3.8 (–14.3, 6.6)	0.473
TMT-B				
N	235	236		
Baseline	372.2	380.8	–	–
Change from baseline at week 24	5.5	0.9	1.6 (–9.9, 13.1)	0.784
Change from baseline at week 48	9.3	5.8	0.8 (–10.1, 11.8)	0.881
NPI-10				
n	265	271		
Baseline	12.4	14.4	–	–
Change from baseline at week 48	1.4	0.9	–0.1 (–1.9, 1.7)	0.927
NPI-D				
n	265	271		
Baseline	6.5	8.1	–	–
Change from baseline at week 48	0.6	0.0	0.2 (–0.7, 1.2)	0.647

Figures in parentheses indicate 95% confidence limits. DLSM = difference of LS means; N = number of patients with an assessment at baseline and at least 1 postbaseline assessment; n = number of patients with an assessment at baseline and at the DB end point (week 48). For patients who were unable to complete the TMT-B, a maximum time of 420 s was recorded.

anxiolytics; 30.0 and 31.1%, 13.3 and 9.5 mg/24 h patch groups, respectively). Approximately 20% of patients in both treatment groups initiated treatment with at least one of these medications during the DB phase. Similar percentages of patients in both groups initiated treatment with antidepressants (10.0 and 8.5%, 13.3 and 9.5 mg/24 h patch groups, respectively), antipsychotics (8.9 and 9.9%, respectively) and hypnotics/anxiolytics (6.1 and 6.4%, respectively). During the DB phase, the overall mean duration of treatment with these medications in the 13.3 and 9.5 mg/24 h patch groups was: 37.0 and 39.8 weeks for antidepressants; 26.7 and 29.5 weeks for antipsychotics; 33.0 and 33.2 weeks for hypnotics/anxiolytics.

Discussion

In this study, patients with AD demonstrating functional and cognitive decline while receiving the currently approved maintenance dose of 9.5 mg/24 h rivastigmine as a patch showed additional benefit with titration to the higher-dose 13.3 mg/24 h patch.

The 13.3 mg/24 h rivastigmine patch demonstrated statistically superior efficacy on functional outcomes over the 9.5 mg/24 h patch from week 16 onwards. Patients receiving the 13.3 mg/24 h patch also showed less decline at all time points on the ADAS-cog and demonstrated statistically superior efficacy over the 9.5 mg/24 h patch at week 24 of the DB phase ($p = 0.027$), but failed to show a significant difference at week 48 (coprimary end point). Other supportive and sensitivity analyses confirmed the results obtained in the ITT-LOCF population. The rivastigmine patch has previously been associated with reduced caregiver burden [30]. Since functional decline is an important predictor of caregiver burden [2], the superior efficacy of the 13.3 mg/24 h patch, particularly on IADLs, may translate into clinically important benefits for patients and their caregivers.

There were no between-dose statistically significant differences in the time to functional decline, and performance on the TMT-A and TMT-B tests for executive function. Likewise, no significant effect of the higher-dose patch was observed on the behavioural scales, the NPI-10 and NPI-D. However, numerical trends towards greater efficacy of the 13.3 mg/24 h patch were observed

Table 4. Most frequent ($\geq 3\%$ in any treatment group) AEs in the 48-week DB phase by time period (weeks 0–48, 0–24 and >24), treatment and preferred term (Safety population in the DB phase)

Preferred term	Week 0–48		Week 0–24		Week >24	
	13.3 mg/24 h rivastigmine patch (n = 280)	9.5 mg/24 h rivastigmine patch (n = 283)	13.3 mg/24 h rivastigmine patch (n = 280)	9.5 mg/24 h rivastigmine patch (n = 283)	13.3 mg/24 h rivastigmine patch (n = 241)	9.5 mg/24 h rivastigmine patch (n = 246)
Total	210 (75.0)	193 (68.2)	181 (64.6)	155 (54.8)	102 (42.3)	99 (40.2)
Nausea	34 (12.1)	14 (4.9)	27 (9.6)	10 (3.5)	10 (4.1)	4 (1.6)
Vomiting	29 (10.4)	13 (4.6)	25 (8.9)	8 (2.8)	6 (2.5)	6 (2.4)
Fall	21 (7.5)	17 (6.0)	12 (4.3)	10 (3.5)	9 (3.7)	7 (2.8)
Weight decreased	19 (6.8)	8 (2.8)	7 (2.5)	4 (1.4)	13 (5.4)	5 (2.0)
Application site erythema	18 (6.4)	16 (5.7)	16 (5.7)	13 (4.6)	2 (0.8)	4 (1.6)
Decreased appetite	18 (6.4)	7 (2.5)	15 (5.4)	6 (2.1)	4 (1.7)	1 (0.4)
Diarrhoea	18 (6.4)	13 (4.6)	14 (5.0)	12 (4.2)	4 (1.7)	1 (0.4)
Urinary tract infection	15 (5.4)	12 (4.2)	8 (2.9)	7 (2.5)	8 (3.3)	6 (2.4)
Agitation	14 (5.0)	15 (5.3)	11 (3.9)	9 (3.2)	3 (1.2)	6 (2.4)
Depression	14 (5.0)	13 (4.6)	8 (2.9)	8 (2.8)	6 (2.5)	5 (2.0)
Dizziness	12 (4.3)	2 (0.7)	8 (2.9)	1 (0.4)	4 (1.7)	1 (0.4)
Application site pruritus	11 (3.9)	11 (3.9)	10 (3.6)	8 (2.8)	1 (0.4)	3 (1.2)
Headache	11 (3.9)	11 (3.9)	10 (3.6)	10 (3.5)	1 (0.4)	1 (0.4)
Insomnia	11 (3.9)	7 (2.5)	5 (1.8)	3 (1.1)	6 (2.5)	4 (1.6)
Upper abdominal pain	10 (3.6)	3 (1.1)	8 (2.9)	2 (0.7)	2 (0.8)	1 (0.4)
Anxiety	10 (3.6)	7 (2.5)	6 (2.1)	5 (1.8)	4 (1.7)	2 (0.8)
Confusional state	9 (3.2)	7 (2.5)	5 (1.8)	6 (2.1)	4 (1.7)	1 (0.4)
Hypertension	9 (3.2)	8 (2.8)	7 (2.5)	5 (1.8)	2 (0.8)	3 (1.2)
Urinary incontinence	9 (3.2)	5 (1.8)	6 (2.1)	4 (1.4)	3 (1.2)	1 (0.4)
Psychomotor hyperactivity	7 (2.5)	9 (3.2)	5 (1.8)	7 (2.5)	4 (1.7)	2 (0.8)
Aggression	6 (2.1)	9 (3.2)	3 (1.1)	7 (2.5)	3 (1.2)	2 (0.8)

Results are expressed as numbers of patients reporting an AE during the DB phase, with percentages in parentheses. n = number of patients in the safety DB population at the beginning of the treatment period. AEs are sorted by descending frequency in the 13.3 mg/24 h rivastigmine patch group. A patient with multiple occurrences of the same AE within a treatment group was counted only once in each period.

in all but one (TMT-B) of these secondary outcomes. Interpretation of the TMT-B test results was limited due to the fact that the majority of patients were not able to perform the test within the given time period at DB baseline and later assessments. This may contribute to the observed lack of treatment effect on the TMT-B since a maximum time of 420 s was recorded for these patients. The NPI-D provides a reliable measure of caregiver distress related to neuropsychiatric symptoms and behavioural disturbances [28]; global measures of caregiver burden and quality of life were not assessed. However, these measures may show treatment-related benefits as a result of the reduced decline in the patients' ability to perform IADLs seen in this study.

The selection of a population demonstrating functional and cognitive decline was a novel aspect of this trial design,

and while it more closely represents a 'real-life' clinical scenario, the resultant clinical profile of the patients should be noted. At the beginning of the DB phase, the mean MMSE score for all patients randomized was 14.2 (range 0.0–26.0) indicating that a large proportion of the patients had reached moderate-to-severe stages of AD. The ADAS-cog is best suited for assessing mild-to-moderate stages of dementia [31, 32] due to floor effects in patients with more severe AD [31]. The ADAS-cog may not have been sensitive enough to detect dose-related differences reliably as patients progressed to the later time points of the study. Decline on the 9.5 mg/24 h patch in the IOL phase was less than the original assumption for the sample size calculation, which was based on a long-term study with rivastigmine capsules [29]. Although this resulted in a smaller sample size in the DB population than anticipated (567 vs. 864 predict-

ed), one of the coprimary end points reached significance (ADCS-IADL) and the second showed consistent numerical superiority (ADAS-cog). Specifically, the 13.3 mg/24 h patch was statistically superior to the 9.5 mg/24 h patch at week 24 on the ADAS-cog, a time point which has typically been used as the primary end point in pivotal studies of dementia medications [8, 33–35]. In addition, numerical improvements in DLSSM of 1.3 and 0.8 points in ADAS-cog at weeks 24 and 48, respectively with the 13.3 mg/24 h patch compared with the active comparator (9.5 mg/24 h patch) can be considered clinically meaningful, based on published data indicating that a decline of approximately 1–2 points may be expected in patients with mild-to-moderate AD receiving placebo over a 6-month trial period [8, 35].

The efficacy of cholinesterase inhibitors has previously been shown to be dose dependent [18, 19], and there is increasing awareness surrounding the importance of reaching and maintaining optimal therapeutic doses [36]. To our knowledge, this study is unique in providing DB, randomized data on cholinesterase inhibitor efficacy and tolerability extending beyond 24 weeks, in addition to providing comparative data on two active doses of the same drug, for which there are very few published data [37]. Current findings from the OPTIMA trial (up to 48 weeks of DB treatment) support high-dose efficacy. The administration of the higher-dose (13.3 mg/24 h) rivastigmine patch had no new or unexpected concerns relating to safety and tolerability. The 13.3 mg/24 h patch was not associated with an increase in the incidence of SAEs, and despite a modest increase in reported AEs, fewer patients discontinued treatment as a result of AEs compared with those in the lower-dose (9.5 mg/24 h) patch group. An increased incidence of AEs is often associated with a dose titration step [37]. AEs in the OPTIMA study decreased over time, with a similar incidence of most AEs reported in both treatment groups in the second half of the DB phase (weeks 25–48). Throughout the course of the study, slightly more patients in the higher-dose group experienced an AE of ‘weight decreased’. The potential weight loss in patients receiving the 13.3 mg/24 h patch may require clinical attention and consideration of possible counteracting interventions such as protein-enriched nutritional supplements. The overall decrease in the incidence of AEs observed over time may have contributed to the high degree of persistence and low rate of discontinuations observed with both patch doses. Overall, safety data confirm the good tolerability of the rivastigmine patch. The most common AEs were cholinergic in nature and were as expected when compared

with previous studies of rivastigmine treatment, including IDEAL [8].

The high-dose rivastigmine patch would enable physicians to optimize efficacy, while maintaining good tolerability, for appropriate patients. Such patients could include those who show signs of functional decline on current stable therapy, or those whom the physician perceives would gain additional benefit from up-titration, in order to achieve optimal efficacy. In all cases, the decision to up-titrate from the maintenance dose of 9.5 to the 13.3 mg/24 h patch should be based on good tolerability of the current dose and be considered after a minimum of 4 weeks of treatment at previous dose levels.

In summary, the OPTIMA study has demonstrated higher-dose efficacy of the 13.3 mg/24 h rivastigmine patch on functional outcomes, without compromising safety and tolerability. These findings are clinically relevant as the higher-dose 13.3 mg/24 h patch demonstrated long-term efficacy over the 48-week DB study period and an additional benefit over the currently approved maintenance patch dose of 9.5 mg/24 h. The potential to enhance functional integrity of the patient could offer important benefits, including less dependence on family and/or caregivers and the possibility of delayed institutionalization [3]. The higher-dose rivastigmine patch would provide physicians with an additional therapeutic option for the treatment of patients with mild-to-moderate AD.

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J.L.C. has provided consultation to Abbott, Acadia, Adamas, Anavex, Astellas, Avanir, Baxter, Bristol-Myers Squibb, Eisai, Elan, EnVivo, Forest, Genentech, GlaxoSmithKline, Janssen, Ely Lilly, Lundbeck, Medtronic, Merck, Neurokos, Neuronix, Novartis, Otsuka, Pain Therapeutics, Pfizer, Plexxicon, Prana, QR, Sanofi, Sonexa, Takeda and Toyama pharmaceutical companies. J.L.C. has also provided consultation to Bayer, Avid, GE Healthcare, MedAvante, Neurotrax and UBC. J.L.C. owns stock in Adamas, Prana, Sonexa, MedAvante, Neurotrax, Neurokos and QR Pharma. He has participated as a speaker/lecturer for Eisai,

Forest, Janssen, Novartis, Pfizer and Lundbeck. J.L.C. owns the copyright of the Neuropsychiatric Inventory. J.L.C. has provided expert witness consultation regarding olanzapine and ropinerol.

L.F. has received fees for board membership from Eisai, Elan/Wyeth, Eli Lilly, GE Healthcare, Janssen-Cilag, Lundbeck, Merz Pharma, Novartis, Pfizer and Schering-Plough. L.F. has provided consultation to AstraZeneca, Merz Pharma, Myriad, Neurochem, Novartis, Pfizer and Schering-Plough. He has provided an expert testimony to Apotex Inc. L.F. has also received grants or has grants pending from Novartis and Pfizer. He has received honoraria from Allergan, Eisai, Elan/Wyeth, Janssen-Cilag, Lundbeck, Merz Pharma, Neurochem Inc., Novartis and Pfizer. L.F. has received payment for the development of educational presentations including service on speakers' bureau from Novartis. He has also received travel/accommodation expenses from Merz Pharma.

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S.B. acted as the main investigator for France. He has no current commercial interests; however, in the past 4 years he has received honoraria for consulting or paid conferences from Eisai, Janssen-Cilag, Lundbeck, Novartis, Roche and Sanofi-Aventis.

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