



## **A 24-week, multicentre, open evaluation of the clinical effectiveness of the rivastigmine patch in patients with probable Alzheimer's disease**

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**A 24-week, multicentre, open evaluation of the clinical effectiveness of the rivastigmine patch in patients with probable Alzheimer's disease**

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**Disclosures**

Konstantin Articus, Monika Baier and Ferenc Tracik are full-time employees of Novartis Pharma GmbH, the sponsor of this study. Novartis Pharma GmbH developed and manufactures the rivastigmine patch. Ulrich W. Preuß has financial interests/arrangements or affiliations with one or more organisations that could be perceived as a conflict of interest in the context of the subject of this manuscript. He has received research support, consultancy, or lecture fees from Pfizer, Astra-Zeneca, Eli-Lilly, Janssen-Cilag, and Novartis in the past three years. Frank Kühn and Alexander Kurz have no conflicts of interest to declare.

## Abstract

**Background:** Cholinesterase inhibitors form the mainstay of treatment for persons with mild-to-moderate Alzheimer's disease (AD). The rivastigmine patch may increase compliance and the proportion of patients maintaining an efficacious dose compared with oral cholinesterase inhibitors.

**Objective:** To investigate the proportion of patients who reached and maintained the target rivastigmine patch dose compared with the target rivastigmine capsule dose reported in clinical trials.

**Methods:** This was a multicenter, 24-week, open-label study in persons with probable AD and a Mini-Mental State Examination (MMSE) score of  $\geq 10$  and  $\leq 26$ . The primary outcome was the proportion of patients (ITT population) treated with 9.5 mg/24 h rivastigmine patch for at least 8 weeks at Week 24. Secondary outcomes included Week 24 MMSE, Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change (ADCS-CGIC), Trail Making Test Part A (TMT-A), and Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) scores.

**Results:** Overall, 208 participants received treatment and 155 (74.5%) completed the study. Within the ITT population, 147/182 patients (80.8%; 95%CI 75.0–86.5%) were treated for at least 8 weeks with the 9.5 mg/24 h rivastigmine patch; 135/182 patients (74.2%; 95%CI 67.8–80.5%) were treated for at least 8 weeks and completed the study. The most common adverse events were nausea (10.1% of patients), erythema (8.7%), pruritus (8.2%) and vomiting (7.2%). At Week 24, patients treated with the rivastigmine patch showed improvements on MMSE, ADCS-ADL, ADCS-CGIC and TMT-A scores. Caregivers reported acceptance, preference, and satisfaction with the patch.

**Conclusion:** Transdermal delivery may allow more patients to reach and maintain therapeutic doses of rivastigmine compared with oral rivastigmine.

**ClinicalTrials.gov Identifier:** NCT00561392

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**What’s known? (70 words)**

Rivastigmine is approved for the symptomatic treatment of persons with mild-to-moderate AD and PDD and has recently been approved in patch formulation for treatment of the same groups in the USA. Rivastigmine patch provides similar efficacy to the highest dose of rivastigmine capsule (12 mg/day) but with a superior tolerability profile. A sub-study of the IDEAL trial showed that the majority of caregivers preferred patches to capsules for drug delivery.

**What’s new? (70 words)**

This study investigated the safety and tolerability of the rivastigmine patch in persons with AD in an open-label setting. To complement findings from controlled clinical trials, this study was designed to mimic as closely as possible under the conditions of a clinical trial the situation in real life. The proportion of patients able to reach and maintain the maximum dose with patch exceeded previous demonstrations with an equivalent oral dose.

## Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most frequent form of senile dementia (1). The classic clinical features of AD include impairment of cognition and memory, language deterioration, decreased ability to perform activities of daily living, motor and sensory abnormalities and gait disturbances (2).

The cholinesterase inhibitors galantamine, donepezil and rivastigmine form the mainstay of treatment for persons with mild-to-moderate AD (3, 4). Rivastigmine is approved for the symptomatic treatment of persons with mild-to-moderate AD and Parkinson's disease dementia (PDD) and has recently been approved in patch formulation for treatment of the same groups in the USA. In 2007, a six-month, double-blind, randomized, placebo-controlled study (IDEAL; ENA713D2320) demonstrated the 9.5 mg/24 h rivastigmine patch to provide similar efficacy to the highest dose of rivastigmine capsule (12 mg/day) but with a superior tolerability profile (5). In addition, the caregiver preference sub-study of the IDEAL trial showed that 72% of caregivers preferred patches to capsules for drug delivery (6).

There is an increasing awareness of the importance of reaching and maintaining an optimal therapeutic dose of cholinesterase inhibitor (7). However, non-compliance with AD therapies is a wide-spread problem and is often a barrier to effective therapy (8). It is hoped that the favourable tolerability profile and convenience of use of the rivastigmine patch could translate not only to increased compliance with AD therapies, but also to a greater proportion of patients reaching and maintaining an efficacious dose. The objective of this study was to investigate the safety and tolerability of the 9.5 mg/24 h rivastigmine patch in patients with probable AD in an open-label setting. We aimed to establish the proportion of patients who reached and maintained the target rivastigmine patch dose of 9.5 mg/24 h for at least 8 weeks compared with the proportion observed to reach the target 12 mg/day capsule dose in previous trials of rivastigmine oral applications (5, 9, 10). Patient compliance and caregiver preference and satisfaction with the patch in this open-label setting were also evaluated.

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## Methods

### Participants

Patients meeting the inclusion criteria for this study were men and women not of child-bearing potential of at least 50 years of age with probable AD (according to criteria of the National Institute of Neurological and Communicative Disorders and Stroke [NINCDS] and Diagnostic and Statistical Manual of Mental Disorders, 4th Edition [DSM-IV]) and a Mini-Mental State Examination (MMSE) score of  $\geq 10$  and  $\leq 26$ . Patients were initiating therapy for the first time with a cholinesterase inhibitor (patients prescribed both rivastigmine and memantine were permitted) or had failed to benefit from previous cholinesterase inhibitor treatment. These included patients that had experienced a tolerability issue with other cholinesterase inhibitors or were at high risk of drug-drug interactions, patients treated with other cholinesterase inhibitors or memantine that had cognitive, behavioural or functional worsening, or patients that did not reach the 12 mg/day rivastigmine capsule dose due to tolerability issues. All patients were cooperative, willing to complete all aspects of the study, and capable of doing so, either alone or with the aid of a responsible caregiver. In instances where patients were living in the community alone, they were required to have contact with a responsible caregiver on a daily basis to oversee treatment.

Exclusion criteria included the patient not being treated according to the product monograph for rivastigmine capsules, being involved in a clinical trial, or having a current diagnosis of an active skin lesion or disorder that would prevent accurate assessment of adhesion and potential skin irritation of the rivastigmine patch. Other exclusion criteria included a history or presence of any contraindication for the application of the study drug, use of other investigational drugs at the time of enrolment or within 30 days (or 5 half-lives) of enrolment, history of malignancy within the past 5 years, or history of hypersensitivity to any of the study drugs or to drugs with similar chemical structures.

Patients were recruited from 32 centres in Germany. The study was designed to mimic as closely as possible under the conditions of a clinical trial the situation in real life. Thus no placebo or other control group was selected and physicians were not blinded to the medication of the patient. In addition physicians were able to adjust the dosage as needed within the study. The clinical study was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations

(including European Directive 2001/83/EC and US code of Federal Regulations Part 21), and with the ethical principles laid down in the Declaration of Helsinki.

## Interventions

This was a multicentre, 24-week, open-label study. After assessments for eligibility during a 1 to 14 day screening period, patients underwent baseline assessments and entered a 24-week open-label treatment phase. For the first four weeks, patients were treated with 4.6 mg/24 h (5 cm<sup>2</sup>) rivastigmine patch. After the Week 4 assessment, dosage was increased to 9.5 mg/24 h (10 cm<sup>2</sup>) with adjustments as necessary for safety and tolerability. Patients were then maintained at their highest well-tolerated patch-dose (according to physicians' judgment of tolerability) at or below the target dose of 9.5 mg/24 h for an additional 20 weeks.

Study drug dose adjustments and interruptions were permitted. If tolerability problems arose, the patch was removed, the dose was skipped and tolerability was reassessed following the skipped dose. If tolerability problems improved ( $\leq 3$  days missed dose) treatment could be re-started at the same dose level. If tolerability was still an issue, and the patient had been treated with the 4.6 mg/24 h patch, the patient was considered for withdrawal from the study. If the patient had been treated with 9.5 mg/24 h patch, treatment could be re-started at the lower dose level. If tolerability was still an issue, further attempts to increase the dose upward were at the investigator's discretion. If a patient had not reached his/her target dose level during the titration period, but later had resolution of tolerability problems, the investigator could perform the dose increase during the maintenance period. Dose level decreases required for tolerability problems were allowed at any time during the maintenance period.

## Outcomes

The primary outcome of this study was the proportion of patients treated with 9.5 mg/24 h rivastigmine patch for at least 8 weeks at Week 24. Evaluation of the secondary outcome measures were performed at screening (MMSE only), baseline and at Weeks 4, 8 and 24. The secondary outcomes were scores on the MMSE, Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change (ADCS-CGIC), Trail Making Test Part A (TMT-A), and Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL). Other secondary outcomes were the Alzheimer's Disease Caregiver Preference Questionnaire (ADCPQ) and Zarit Burden Interview Score (mini-Zarit score).

Safety was monitored at all visits and assessments were based mainly on the frequency of adverse events (AEs). AEs were coded by primary system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). An AE related to study drug was defined as one considered to have a suspected relationship with the study drug.

**Sample size and statistics**

Based on the results of earlier clinical trials,(5) it was estimated that at least 65% of patients would reach and maintain the target 9.5 mg/24 h transdermal patch dose. To reach 90% power with a two-sided, one group chi-squared test with a 0.050 two-sided significance level to detect the difference between the null hypothesis proportion of 0.530 and the alternative proportion of 0.650, 176 patients were required. To account for some drop-out and protocol violations, a population of 200 patients was targeted. The study was not powered for secondary efficacy variables.

For the primary endpoint, the intent-to-treat (ITT) and per-protocol (PP) populations were analyzed. The PP population consists of all patients from the ITT population for whom no major protocol violations were reported. Results are reported for the ITT population. The complementary null hypothesis was tested by the asymptomatic z-test for a binomial proportion as implemented in the BINOMIAL option in SAS (PROC FREQ). The observed proportion was reported, together with a 95% confidence interval and a p-value from the z-test. Patients who permanently discontinued the trial were counted as not having reached the target patch size.

The efficacy variables for the secondary objectives were descriptively analyzed using summary statistics. Summary statistics included, number of observations (n), mean, standard deviation, median, minimum and maximum values for continuous variables, as well as frequencies and percentages for categorical variables. For the secondary endpoints, missing values were not replaced.

The safety variables were presented using summary statistics. All safety analyses were performed on the safety population, defined as all patients that received at least one dose of study drug and had at least one post-baseline safety assessment. AEs were summarized by the number and percentage of patients in each primary system organ class and preferred term. For summaries by severity of event, the most severe occurrence for a particular preferred term was used for a given patient. Multiple occurrences of the same AE or serious AE (SAE) in the same patient were counted only once, using the worst severity and drug relationship.

## Results

### Participants

The first patient was enrolled in August 2007 and the last patient completed the study in October 2008. A total of 208 participants received the intended treatment. Of these, 155 (74.5%) completed the study as per protocol (Figure 1). In all, 67 patients had at least one major protocol violation. The most frequent protocol violation was premature discontinuation of the study (53 in total). Other frequent violations were poor compliance. The safety population comprised 208 patients (100.0%), the ITT population comprised 182 patients (87.5%) and the PP population comprised 140 patients (67.3%). No grouping was done, and analyses were performed on the ITT population. Baseline demographic data of the safety population are summarized in Table 1.

### Primary objective

#### *Compliance*

Within the ITT population, 135/182 patients (adherence rate 74.2%; 95% CI 67.8–80.5%) were treated for at least 8 weeks with the 9.5 mg/24 h rivastigmine patch and completed the study ( $p < 0.0001$ ). There were 147/182 patients (adherence rate 80.8%; 95% CI 75.0–86.5%) treated for at least 8 weeks with the 9.5 mg/24 h rivastigmine patch regardless of whether they completed the study ( $p < 0.0001$ ).

### Secondary objectives

#### *Safety and tolerability*

The number and percentage of patients experiencing AEs by system organ class (safety population) are summarized in Table 2. Only gastrointestinal disorders, psychiatric disorders and skin and subcutaneous tissue disorders were seen in more than 10% of patients. The most common AEs were nausea (10.1% of patients), erythema (8.7% of patients), pruritus (8.2% of patients), vomiting (7.2% of patients), diarrhoea and agitation (both 4.3% of patients). Similarly, the most common AEs with a suspected relation to the study drug were erythema (8.2% of patients), nausea (7.7% of patients), pruritus (7.2% of patients) and vomiting (4.8% of patients). Within the psychiatric disorders, agitation occurred in 4.3%, anxiety in 1%, depression in 1.4% and hallucination in 0.5% of patients.

There were 39 patients (18.8%) with AEs that led to permanent discontinuation of the study (serious in 6 patients). Consistent with the known safety profile of the rivastigmine patch, the most common AEs leading to discontinuation were skin and subcutaneous tissue disorders (7.2% of patients), psychiatric disorders (4.8% of patients), nervous system disorders (4.3% of patients), and gastrointestinal disorders (4.3% of patients). Three SAEs were associated with the study drug. There was one death during the study period, but the participant died of natural causes and a relationship with the study drug was not suspected.

***Cognitive and global outcomes***

The change from baseline at Week 24 on cognitive and global outcomes outcome scores (ITT population) are summarized in Table 3. Mean MMSE scores improved from screening (19.6 points) through to Week 8 (21.4 points) and remained improved compared with baseline at Week 24 (20.9 points). Mean ADCS-ADL scores improved from baseline (50.3 points) through to Week 8 (51.5 points) and remained improved compared with baseline at Week 24 (51.4 points). The TMT-A scores improved from baseline at each visit through to Week 24. Improvements on the ADCS-CGIC (minimal, moderate or marked) at Week 24 were seen in 34.6% of patients when assessed by the patient, and 29.7% of patients when assessed by the caregiver. There were a total of With respect to tolerability, mean ADCPQ scores improved from baseline (12.2 points) at Week 4 (30.5 points) and showed further improvements at Week 24 (30.7 points). The Zarit Burden Interview Score improved slightly at each visit from baseline to Week 24 (Table 3).

## Discussion

The results of this multicentre, open-label study in patients with probable AD show that the patch formulation enables an increased proportion of patients to reach and maintain the highest available dose of rivastigmine. We found that 74.2% of patients treated with the 9.5 mg/24 h rivastigmine patch were able to reach and maintain the maximum dose for 8 weeks, which exceeds previous demonstrations with an equivalent oral dose obtained with 12 mg/day rivastigmine capsules (e.g. 55–65% of participants on target dose at Week 24/26 study endpoint) (5, 9, 10). In particular, our results are consistent with the pivotal IDEAL trial, which demonstrated that 95.9% of patients in the 9.5 mg/24 h patch group and only 64.4% of patients in the 12 mg/day capsule group achieved their target therapeutic dose at the end of the maintenance period at Week 24 (5, 11). In the IDEAL study, 83.8% of participants receiving the 9.5 mg/24 h rivastigmine patch stayed in their target dose for at least 8 weeks, compared with only 53.1% of those receiving 12 mg/day rivastigmine capsules (Novartis data on file) (5). Our findings, therefore, support the clinical effectiveness of the rivastigmine patch for the treatment of patients with mild-to-moderately severe AD because it may allow patients easier access to higher doses, thereby enabling patients to stay on and benefit from effective treatment for longer (11).

With respect to secondary outcomes, at Week 24, patients treated with the rivastigmine patch showed improvements in MMSE, ADCS-ADL, ADCS-CGIC and TMT-A scores, indicating improvements in cognition, activities of daily living and general brain function. These data are similar to those in the IDEAL study, which demonstrated statistically significant differences *versus* placebo for both rivastigmine patch and rivastigmine capsule on the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog), ADCS-CGIC, ADCS-ADL, MMSE and TMT-A (5). In support of the caregiver preference sub-study of the IDEAL trial, which demonstrated 72% of caregivers to prefer patches to capsules for drug delivery (6), we found that the ADCPQ improved at Week 4 and then remained stable over the course of the study, also indicating caregiver acceptance, preference, and satisfaction with the patch. The Zarit Burden Interview Score showed minimal, but consistent improvement during the course of the study indicating a decrease in caregiver burden associated with use of the rivastigmine patch.

The most frequent AEs were diarrhoea, nausea, vomiting, erythema and pruritus. Psychiatric disorders, gastrointestinal disorders, and skin and subcutaneous tissue disorders were the most common AEs by system organ class while receiving treatment, each occurring in more than

10% of patients. However, AEs such as nausea and vomiting are common with cholinesterase inhibitors in clinical studies and can usually be managed by dose alteration. The observed SAEs were rare and correlated with the known safety profile of rivastigmine patch (5).

Adverse events associated with cholinesterase inhibitors, particularly nausea and vomiting may be dependent on the magnitude of peak plasma concentrations ( $C_{max}$ ) or the rapid rate of rise of the plasma concentration after oral administration. These effects should be lessened with the patch formulation, as  $C_{max}$  and rate of rise of plasma concentrations are lower than with oral dosing with rivastigmine capsule (12, 13). Recent studies have demonstrated that the rivastigmine patch allows steady and continuous drug delivery through the skin into the bloodstream, avoiding first-pass effects in the gut and the liver (14). Pharmacokinetic studies in AD patients have reported that the 9.5 mg/24 h rivastigmine patch delivers comparable drug exposure to the highest dose of capsules (12 mg/day), with a lower  $C_{max}$  and slower times to  $C_{max}$  ( $t_{max}$ ) (12). In the 2007, six-month, double-blind, randomized, placebo-controlled study of rivastigmine patch *versus* capsule (IDEAL; ENA713D2320) the 9.5 mg/24 h rivastigmine patch demonstrated similar effectiveness to the highest dose of rivastigmine capsule (12 mg/day) but with a superior tolerability profile (5). Further investigations of the efficacy and safety of higher doses of rivastigmine (e.g. 13.3 mg/24 h patch) are ongoing (11).

In this study we have demonstrated the 9.5 mg/24 h rivastigmine patch to have similar efficacy and safety profile as demonstrated in the IDEAL study (5). The application of rivastigmine in a patch formulation therefore significantly reduces the rate of gastrointestinal side effects compared with oral cholinesterase inhibitors while considerably increasing the adherence to higher dose therapy. Reaching a target dose of cholinesterase inhibitor and staying on it long-term may be pivotal in delaying the symptoms of AD. Higher doses of oral rivastigmine have been associated with better scores on the ADAS-cog, Clinician Interview-Based Impression of Change—plus carer interview and MMSE (15). Patients should be encouraged to reach what is considered to be an optimal therapeutic dose and to stay on treatment long-term (7).

The favourable tolerability, safety and efficacy profile of the rivastigmine patch may not only allow access to therapeutic doses of cholinesterase inhibitor, but may also increase treatment compliance among persons with AD and their caregivers. Non-compliance with AD therapies is a wide-spread problem and is often a barrier to effective therapy (8, 16, 17). However, patients who continue on rivastigmine treatment for up to 5 years have shown sustained and significant benefits over model-based untreated patients (18). A recent database analysis of a large US

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3 health plan determined that only 58% of AD patients stayed on oral treatment for at least a year  
4 and concluded that educating caregivers and physicians on the importance of medication  
5 compliance is an important intervention to potentially improve patient outcomes (19). The  
6 favourable risk–benefit profile of rivastigmine patch may provide a realistic way to increase  
7 treatment compliance with AD therapy. Approaches that improve treatment compliance may  
8 provide better long-term outcomes for patients with AD, and also offer a better quality of life to  
9 caregivers.  
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16 The strengths of our study being open-label and a real-life observational study also provide  
17 some limitations; the information it offers in terms of efficacy and tolerability of rivastigmine  
18 patch is minimal in comparison to the data from the pivotal study (5). There was no placebo or  
19 parallel control group meaning that Week 24 changes in effectiveness in the absence of  
20 rivastigmine are unknown. In addition, physicians were not blinded to study treatment and  
21 physicians were able to adjust the dosage freely as needed within the study. The 74.5%  
22 completion rate may also limit interpretation of the results, but while this discontinuation rate is  
23 slightly higher than that reported in the IDEAL study with rivastigmine patch and capsules,(5) it  
24 is consistent with or lower than those reported in other clinical trials with cholinesterase  
25 inhibitors (9, 10, 20). It is also appreciated that the proportion of patients able to reach and  
26 maintain the highest available dose of rivastigmine in this open-label setting may be due to  
27 factors additional to the mode of delivery, such as the presence of comorbidities, the level of  
28 care of therapeutic teams and the degree of engagement of relatives or caregivers. Longer-term  
29 follow-up is required to elucidate the full impact of the rivastigmine patch on treatment  
30 adherence, compliance and ability to permit access to optimal therapeutic doses of rivastigmine.  
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41 Our study demonstrates that transdermal delivery may allow a greater proportion of patients to  
42 reach and maintain therapeutic target doses of rivastigmine compared with oral rivastigmine.  
43 With increasing recognition of treatment compliance and the benefits of reaching a therapeutic  
44 dose and staying on treatment long term, the rivastigmine patch should be considered a viable  
45 option for the first-line treatment of patients with mild-to-moderately severe AD.  
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**Author contributions**

All authors contributed to the content, drafting, critical revision and approval of this manuscript. Monika Baier performed the statistical analyses on which the article is based.

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## Figure Legends

Figure 1. Flow of participants through the study.

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Table 1. Baseline demographics of the safety population.

Variable	Statistic (N = 208) <sup>†</sup>
Mean age in years (SD)	74 (7.7)
Sex, n (%)	
Male	98 (47.1)
Female	110 (52.9)
Race, n (%)	
Caucasian	208 (100.0)
Mean weight in kg (SD)	72.0 (13.2)

<sup>†</sup>N = 205 for mean weight

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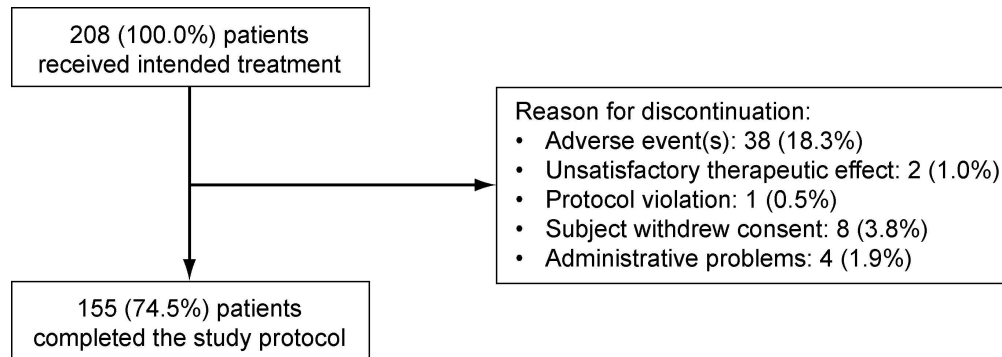
Table 2. Number and percentage of patients experiencing adverse events (AEs) by system organ class (safety population).

System organ class	n (% of patients)
Total number of patients with an AE	123 (59.1)
Cardiac disorders	3 (1.4)
Ear and labyrinth disorders	9 (4.3)
Endocrine disorders	1 (0.5)
Eye disorders	5 (2.4)
Gastrointestinal disorders	33 (15.9)
General disorders and administration site conditions	10 (4.8)
Infections and infestations	16 (7.7)
Injury, poisoning and procedural complications	4 (1.9)
Investigations	8 (3.8)
Metabolism and nutrition disorders	6 (2.9)
Musculoskeletal and connective tissue disorders	9 (4.3)
Neoplasms	3 (1.4)
Nervous system disorders	20 (9.6)
Psychiatric disorders	34 (16.3)
Renal and urinary disorders	4 (1.9)
Respiratory, thoracic and mediastinal disorders	1 (0.5)
Skin and subcutaneous tissue disorders	46 (22.1)
Surgical and medical procedures	1 (0.5)
Vascular disorders	12 (5.8)

Table 3. Change from baseline at Week 24 on secondary outcome scores (ITT population).

Outcome measure	Mean (SD) baseline score	Mean (SD) change from baseline at Week 24
MMSE*, mean (SD)	19.6 (4.3)	1.3 (3.8)
ADCS-CGIC <sup>†</sup> , n (%)		
Missing	-	2 (1.1)
No change	-	47 (25.8)
Minimal improvement	-	25 (13.7)
Moderate improvement	-	23 (12.6)
Marked improvement	-	15 (8.2)
Minimal decline	-	37 (20.3)
Moderate decline	-	12 (6.6)
Marked decline	-	5 (2.7)
ADCS-CGIC <sup>‡</sup> , n (%)		
Missing	-	1 (0.5)
No change	-	21 (11.5)
Minimal improvement	-	23 (12.6)
Moderate improvement	-	16 (8.8)
Marked improvement	-	15 (8.2)
Minimal decline	-	56 (30.8)
Moderate decline	-	20 (11.0)
Marked decline	-	14 (7.7)
TMT-A	149.2 (131.3)	-8.9 (109.5)
ADCS-ADL	50.3 (20.1)	1.3 (12.0)
ADCPQ	12.2 (2.1)	18.5 (7.0)
Zarit Burden Interview	2.6 (1.6)	-0.4 (1.6)

\*Score at Visit 1(screening); <sup>†</sup>Assessed by patient; <sup>‡</sup>Assessed by caregiver; MMSE: Mini-Mental State Examination; ADCS-CGIC: Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; TMT-A: Trail Making Test Part A; ADCS-ADL: Alzheimer's Disease Cooperative Study-Activities of Daily Living; ADCPQ: Alzheimer's Disease Caregiver Preference Questionnaire. Increased MMSE, ADCS-ADL and ADCPQ scores indicate improvement. Decreased TMT-A and Zarit Burden Interview scores indicate improvement.



Flow of participants through the study.  
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