Featured Article

A 24-week double-blind placebo-controlled study of the efficacy and safety of the AMPA modulator S47445 in patients with mild to moderate Alzheimer’s disease and depressive symptoms

Katy Bernarda,*, Sylvie Gouttefangeasa, Sylvie Bretina, Stéphanie Galtiera, Philippe Robertb, Vjera Holthoff-Dettoc, Jeffrey Cummingsd, Maria Pueyoa

aInstitut de Recherches Internationales Servier (IRIS), Suresnes Cedex, France
bCoBTeK IA lab, Memory Center, Université Côte d’azur, Nice, France
cAlexianer Krankenhaus Hedwigshöhe, Berlin, Germany
dDepartment of Brain Sciences, Cleveland Clinic Lou Ruvo Center for Brain Health and University of Nevada Las Vegas, Las Vegas, NV, USA

Abstract

Introduction: S47445 is a novel positive allosteric modulator of alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors that may emerge as a favorable candidate for the symptomatic treatment of cognitive and depressive disorders in patients suffering from Alzheimer’s disease (AD) of mild to moderate severity and with depressive symptoms.

Methods: For this double-blind, placebo-controlled 24-week phase II trial, 520 outpatients aged between 55 and 85 years, with probable AD at mild to moderate stages (a Mini-Mental State Examination score of 24-15 inclusive) and exhibiting depressive symptoms (Cornell Scale for Depression in Dementia [CSDD]) were recruited in twelve countries and randomized to 3 doses of S47445 (5-15-50 mg) or placebo. The primary end point was the change from baseline in the 11-item Alzheimer’s Disease Assessment Scale-Cognitive subscale (ADAS-Cog) total score at week 24. Secondary measures included the Disability Assessment for Dementia, Mini-Mental State Examination, ADAS-Cog 13-item, CSDD, Clinical Global Impression of Change (Alzheimer’s Disease Cooperative Study-CGIC), Neuropsychiatric Inventory (NPI), and safety criteria.

Results: Baseline characteristics were comparable between the 4 groups. After 24 weeks, no statistically significant treatment difference was demonstrated between S47445 (5, 15 or 50 mg/d) and placebo on cognition (ADAS-Cog), function (Disability Assessment for Dementia), or depressive symptoms (CSDD). An improvement on neuropsychiatric symptoms assessed by NPI was evidenced at the lower dose 5 mg/d (\( \Delta = -2.55, P = .023 \), post hoc analysis) compared to placebo. CSDD and total NPI scores improved in all groups including placebo. There were no specific and/or unexpected safety signals observed with any of the S47445 doses.

Discussion: S47445 administered for 24 weeks was safe and well tolerated by patients with mild to moderate AD; the compound did not show significant benefits over placebo on cognition, function, or depressive symptoms.

© 2019 The Authors. Published by Elsevier Inc. on behalf of the Alzheimer’s Association. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
1. Introduction

Patients with Alzheimer’s disease (AD) present with a progressive cognitive decline leading to functional impact. Besides cognitive deficits, neuropsychiatric symptoms (NPS) are highly prevalent in patients with AD as up to 90% of patients will experience significant NPS in the course of their disease [1]. Among them, depressive symptoms are present in approximately 50% of patients [2]. They are common in mild to moderate dementia and seem less prevalent in severe dementia, possibly reflecting the difficulty in assessing depressive symptoms at a later stage [3].

Depression in dementia has been associated with a greater decline in cognition, quality of life and disability in daily life activities, earlier institutionalization, and increased risk of mortality [2,4,5].

Diagnosis of depression in AD (dAD) is complex due to not only deficits in verbal expression and other cognitive alterations but also other common symptoms such as sleep disturbances and apathy. dAD may differ from other depressive disorders [6] and is diagnosed in the presence of three or more symptoms of major depression, including additional nonsomatic symptoms (irritability, social withdrawal) but without including the difficulty to concentrate [7]. The National Institute of Mental Health dAD criteria identify a greater proportion of patients with AD as depressed than several other established tools [8,9].

There is an urgent need for treatments for AD patients with NPS, in particular depressive symptoms. Patients are often treated with antidepressants, despite scarce evidence of their efficacy [3,10-13]. Antidepressants and/or antipsychotics are often prescribed off label for the management of these symptoms [14,15].

Most clinical trials evaluating treatments for cognition in AD often excluded patients with depression, limiting data on these patients. Progress in diagnostic criteria allowing inclusion in a clinical trial of the appropriate population is an essential step for testing drugs that may improve such symptoms and consequently quality of life of patients and caregivers [16].

S47445 is a selective positive allosteric modulator of alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors (AMPA-PAM) that emerged as a favorable candidate for the treatment of memory deficits, depressive symptoms, and synaptic dysfunction associated with AD. S47445 demonstrated both procognitive and antidepressant-like properties in animal models [17,18]. Furthermore, S47445 modulates synaptic plasticity by enhancing long-term potentiation, preserving age-dependent loss of synaptic markers, and increasing neurotranspheric factor expression in aged rodents [19,20]. In healthy elderly volunteers, S47445 was safe and well tolerated, enhanced functional connectivity between brain networks involved in cognition (working memory, attention and Default Mode Networks), and increased glutamate concentration in posterior cingulate cortex [21]. Collectively, functional magnetic resonance imaging results and cerebrospinal fluid levels of S47445 showed that the drug crossed the blood–brain barrier.

The objectives of this phase 2 study were (1) to describe baseline characteristics of an AD population at mild to moderate stage with depressive symptoms and (2) to evaluate the safety and efficacy on cognition and activities of daily living (primary and key secondary objectives, respectively), and depression, global impression of change, and neuropsychiatric symptoms of three doses of S47445 administered for 6 months (secondary objectives) vs. placebo.

2. Methods

2.1. Study design

This was a 6-month, double-blind, randomized, fixed dose, placebo-controlled study, conducted in AD patients enrolled from 75 sites in twelve countries. The study was conducted in compliance with the protocol, good clinical practice, and the applicable regulatory requirements. Eligible patients, their legal representative if applicable, and the informant provided written informed consent before participating in the study.

The study comprised a 3- to 6-week selection period without study treatment followed by a 24-week double-blind treatment period with 4-parallel groups. Eligible patients were randomized to receive S47445 5 mg, 15 mg, 50 mg, or placebo. Treatment with cholinesterase inhibitors or memantine was not allowed. Stratification on severity of the disease (mild/moderate) according to the Mini-Mental Status Examination (MMSE) total score at inclusion visit was performed. After 24 weeks of treatment, patients had the possibility to participate in an optional extension period of 28 weeks. During this period, patients continued to take their study treatment in coadministration with donepezil. The objective was to evaluate the safety of the combination of both drugs during the second period.

2.2. Patients

Patients were male or female, 55–85 years old, with probable AD according to the Diagnostic and Statistical Manual for Mental Disorders, text revision criteria for Dementia of Alzheimer’s Type and depressive symptoms according to National Institute of Mental Health provisional criteria for dAD. Patients were required to have a MMSE score of...
In order to meet the primary and key secondary objectives, at least one dose of S45447 was assessed in the FAS on the cognitive performance from the 11-item ADAS-Cog total score and on daily living from the DAD total score expressed in terms of change from baseline to week 24 compared to placebo (primary analysis and key secondary analysis, respectively).

In order to take into account the multiplicity of comparisons, a Holm-based gatekeeping procedure with two families of null hypotheses was used [22]. A fixed sequence test procedure per dose was used, meaning that the key secondary null hypothesis for one dose is tested only if the primary null hypothesis associated to the same dose is rejected before.

A mixed-effect model repeated measures analysis using all the postbaseline visits’ observations was used for the primary and key secondary analyses, including the fixed effects of treatment, severity of the disease (mild/moderate), visit and treatment-by-visit and severity-by-visit interactions, as well as covariates of baseline and visit-by-baseline interaction. The analyses fitted an unstructured covariance matrix.

For other secondary end points, the difference between the three S45447 doses and placebo was analyzed through inferential statistics using the same model as the primary analysis (without adjustment to control the type I error) or descriptive statistics, on all secondary efficacy endpoints.

For every safety measurement, descriptive statistics were provided by the treatment group in the safety set (all included patients having taken at least one dose of medication).

The sample size was determined considering the primary end point for a difference between at least one S45447 dose and placebo in the FAS, based on a two-sided Student’s t-test for independent samples and using the Bonferroni correction in order to maintain the familywise type I error at 5% (bilateral situation). Per treatment group, 125 patients would allow demonstration that at least one S45447 dose is superior to placebo with a power of around 90% if the true difference is 2.8 points with a standard deviation of 6 points.

### 3. Results

We screened 717 patients, of whom 520 were included and randomized: 129 in the placebo group and 391 in the S47445 groups. 53% were mild (MMSE score ≥ 20) and 47% at a moderate (MMSE score ≤ 19) stage of the disease (Fig. 1). During the 24-week period, 9.4% of the randomized patients were withdrawn from the study (7.75% in placebo, 6.97% in 5 mg, 10.7% in 15 mg, and 12.1% in 50 mg); the main reasons were nonmedical (4.2%) and adverse events (3.8%) without a significant difference between groups.

Baseline characteristics between the four groups were comparable for age, ratio of male/female, education level, AD duration, duration of the current depressive symptoms, and score on scales (Table 1). Patients presented depression with a mean CSDD total score of 11.9 corresponding to a probable major depression and neuropsychiatric symptoms with a mean NPI 12-item total score of 22.4. Most patients had the following NPI items: depression, anxiety, apathy, irritability, sleep, and appetite disorders.

### 2.4. Outcomes

The primary end point was the Alzheimer’s Disease Assessment Scale-Cognitive subscale (ADAS-Cog) 11-item total score at week 24, expressed as change from baseline. A key secondary end point was the Disability Assessment for Dementia (DAD) total score, expressed as change from baseline. Secondary efficacy end points at week 24 assessed cognition using MMSE and ADAS-Cog 13-item, depressive symptoms using CSDD, neuropsychiatric symptoms using Neuropsychiatric Inventory (NPI), and global effects using the Alzheimer’s Disease Cooperative Study-Clinical Global Impression of Change. The raters who assessed patients using the Alzheimer’s Disease Cooperative Study-Clinical Global Impression of Change were blinded for any other patient safety and cognitive assessments.

Safety was evaluated by recording of adverse events, vital signs, laboratory tests, ECGs, physical examination findings, and suicide risk (CSDD, item 16).

All safety measures were performed at each visit and the end of the study or end of treatment in cases of premature withdrawal.

### 2.5. Statistical analysis

The efficacy analyses were performed in the full analysis set (FAS) (intention-to-treat principle).

In order to meet the primary and key secondary objectives of the study, the superiority of at least one dose of S45447 was assessed in the FAS on the cognitive performance from the 11-item ADAS-Cog total score and on daily living from the DAD total score expressed in terms of change from baseline to week 24 compared to placebo (primary analysis and key secondary analysis, respectively).

In order to take into account the multiplicity of comparisons, a Holm-based gatekeeping procedure with two families of null hypotheses was used [22]. A fixed sequence test procedure per dose was used, meaning that the key secondary null hypothesis for one dose is tested only if the primary null hypothesis associated to the same dose is rejected before.

A mixed-effect model repeated measures analysis using all the postbaseline visits’ observations was used for the primary and key secondary analyses, including the fixed effects of treatment, severity of the disease (mild/moderate), visit and treatment-by-visit and severity-by-visit interactions, as well as covariates of baseline and visit-by-baseline interaction. The analyses fitted an unstructured covariance matrix.

For other secondary end points, the difference between the three S45447 doses and placebo was analyzed through inferential statistics using the same model as the primary analysis (without adjustment to control the type I error) or descriptive statistics, on all secondary efficacy endpoints.

For every safety measurement, descriptive statistics were provided by the treatment group in the safety set (all included patients having taken at least one dose of medication).

The sample size was determined considering the primary end point for a difference between at least one S45447 dose and placebo in the FAS, based on a two-sided Student’s t-test for independent samples and using the Bonferroni correction in order to maintain the familywise type I error at 5% (bilateral situation). Per treatment group, 125 patients would allow demonstration that at least one S45447 dose is superior to placebo with a power of around 90% if the true difference is 2.8 points with a standard deviation of 6 points.

### 2.3. Training

All raters received training and/or qualification for all scales, and a clinical training focused on the study population.

### 2.4. Outcomes

The primary end point was the Alzheimer’s Disease Assessment Scale-Cognitive subscale (ADAS-Cog) 11-item total score at week 24, expressed as change from baseline. A key secondary end point was the Disability Assessment for Dementia (DAD) total score, expressed as change from baseline. Secondary efficacy end points at week 24 assessed cognition using MMSE and ADAS-Cog 13-item, depressive symptoms using CSDD, neuropsychiatric symptoms using Neuropsychiatric Inventory (NPI), and global effects using the Alzheimer’s Disease Cooperative Study-Clinical Global Impression of Change. The raters who assessed patients using the Alzheimer’s Disease Cooperative Study-Clinical Global Impression of Change were blinded for any other patient safety and cognitive assessments.

Safety was evaluated by recording of adverse events, vital signs, laboratory tests, ECGs, physical examination findings, and suicide risk (CSDD, item 16).

All safety measures were performed at each visit and the end of the study or end of treatment in cases of premature withdrawal.
About 20% of patients had previously been treated with AChEI or memantine, and 18% of patients had previously received antidepressant treatment.

### 3.1. Primary outcome

After 24 weeks, there were no significant differences between S47445 groups and placebo on cognition (ADAS-Cog 11-item) (Fig. 2). The highest difference compared to placebo on ADAS-Cog 11-item total scores was observed with the S47445 15 mg group (−0.90 point; P value = .290). The adjusted mean changes from baseline to week 24 in ADAS-Cog total score were 0.35 (standard deviation 5.53) with placebo and −0.20 (4.91), −0.74 (5.43), and −0.05 (5.82) with S47445 5, 15, and 50 mg, respectively. Similar results were observed for the sensitivity analyses.

### 3.2. Secondary outcomes

None of the effects of S47445 on key (DAD) and secondary efficacy end points was statistically significantly different from placebo, except on neuropsychiatric symptoms. The difference between S47445 5 mg

---

**Table 1**

| Baseline demographic characteristics (FAS) | All | S47445 5 mg | 15 mg | 50 mg | Placebo |
|------------------------------------------|-----|-------------|------|------|---------|
| No. of patients (FAS)                    | 518 | 129         | 130  | 130  | 129     |
| Age (years)                              | 71.7 (7.3) | 72.2 (7.3) | 71.7 (7.7) | 71.7 (6.5) | 71.4 (7.7) |
| Male/female (%)                          | 30.3/69.7 | 36.4/63.6 | 26.2/73.9 | 28.5/71.5 | 30.2/69.8 |
| ApoE4 carriers (%)                       | 47.2 | 56.6       | 38.2  | 47.2  | 46.9    |
| School education (years)                 | 11.1 (3.3) | 11.2 (3.4) | 10.9 (3.3) | 11.2 (3.4) | 11.0 (3.3) |
| Disease duration of AD (years)           | 3.6 (2.2) | 3.4 (1.7)  | 3.8 (2.3) | 3.7 (2.4) | 3.6 (2.2) |
| Duration of the current depressive symptoms (years) | 1.3 (2.0) | 1.1 (1.0)  | 1.3 (1.7) | 1.6 (2.8) | 1.3 (2.1) |
| MMSE                                    | 19.7 ± 2.8 | 19.7 ± 2.9 | 19.7 ± 2.7 | 19.6 ± 2.8 | 19.7 ± 2.8 |
| ADAS-Cog 11-item                         | 23.56 ± 8.98 | 23.76 ± 9.50 | 23.00 ± 8.72 | 24.22 ± 8.88 | 23.26 ± 8.84 |
| ADAS-Cog 13-item                         | 34.86 ± 10.68 | 35.21 ± 11.09 | 34.25 ± 10.54 | 35.41 ± 10.61 | 34.54 ± 10.57 |
| DAD                                     | 68.04 ± 18.61 | 67.87 ± 18.74 | 68.13 ± 19.19 | 68.11 ± 18.09 | 68.04 ± 18.62 |
| CSDD                                    | 11.98 ± 3.52 | 11.68 ± 3.31 | 11.92 ± 3.55 | 12.36 ± 3.55 | 11.94 ± 3.66 |
| NPI 12-item                              | 22.4 ± 13.4 | 23.0 ± 12.7 | 20.8 ± 12.5 | 24.5 ± 15.8 | 21.1 ± 12.0 |

**NOTE.** Data are presented as mean (standard deviation) or n (%).

Abbreviations: AD, Alzheimer’s disease; ADAS-Cog, Alzheimer’s Disease Assessment Scale-Cognitive subscale; CSDD, Cornell Scale for Depression in Dementia; DAD, Disability Assessment for Dementia; FAS, full analysis set; MMSE, Mini-Mental Status Examination; NPI, Neuropsychiatric Inventory.
and placebo on NPI 12-item total score was meaningful \((-2.55\) points [standard deviation \(= 1.27\); 95% confidence interval \(-5.06\) to \(-0.05\); \(P = .023\); post hoc analysis), consistent with an improvement of neuropsychiatric symptoms in this group, compared to placebo. Domains which improved were agitation, depression, anxiety, apathy, irritability, and sleep disorders.

Over the 24-week period, CSDD and NPI 12-item total scores were decreased in all treatment groups over time including the placebo group (Fig. 3).

In the placebo group, patients (46%) exhibiting a higher score in depression at baseline (CSDD \(\geq 12\)) showed a greater improvement on depressive symptoms (CSDD total score) and no worsening on cognition (ADAS-Cog 11-item score) over time compared to patients with fewer depressive symptoms (Fig. 4).

### 3.3. Safety

The number of patients who had at least one emergent adverse event (EAE) at week 26 was higher in the placebo group (50.4%; 65/129 patients) than in the total S47445 group (45.3%; 177/391 patients; 46.5% in the S47445 5-mg group, 37.7% in the 15-mg group, and 51.5% in the 50-mg group). Most EAEs in the S47445 groups were of mild (64.2%) or moderate (30.4%) intensity, resolved spontaneously or with an appropriate treatment (79.9%), and did not lead to treatment discontinuation (4.6% EAE that led to treatment withdrawal vs. 3.9% in placebo group).

Across all doses of S47445, the AE profiles were close to placebo. Treatment-emergent AEs occurring in at least 3% of the patients in either group are summarized in Table 2.

Serious EAEs were reported by 22 patients in the S47445 groups (5.6%) versus 7 patients in the placebo group (5.4%). Serious events reported by more than 1 patient in either group were fall, aggression, delirium, and chronic cardiac failure. No seizure was reported in any of the groups.

Two patients died during the first period of the study: one in the S47445 50-mg group and the other one in the placebo group.

There were no significant differences between groups in clinical laboratory values, blood pressure, weight, temperature, or ECG, including QT interval.

During the 28-week extension period with concomitant treatment of donepezil, there was no relevant difference between S47445 groups and placebo regarding the frequency of EAEs. Four patients died: 2 patients in the S47445 15- and 50-mg groups and 2 patients in the placebo group.

In summary, this study showed a good safety profile of S47445 alone and in association with donepezil.

### 4. Discussion

AMPA-PAMs have been studied as potential therapeutics for the cognitive component of neurological disorders [23] and have been studied more intensively in the last decade.

---

**Fig. 2.** Adjusted mean of the change from Baseline in ADAS-Cog 11-item total score (FAS) during the 24-week follow-up. Abbreviations: ADAS-Cog, Alzheimer’s Disease Assessment Scale-Cognitive subscale; FAS, full analysis set.
Among drugs developed for AD [27], S47445 is the only agent to target the AMPA receptor through its allosteric modulation. Based on preclinical findings and human phase I studies [17,18], we conducted a 24-week, phase II randomized controlled trial of S47445, a positive AMPA modulator. The trial outcomes demonstrate that a six-month course of three daily doses of the compound has no significant efficacy over placebo on the primary outcome,

Fig. 3. Adjusted mean of the change from Baseline in CSDD total score and in NPI 12-item total score (FAS) during the 24-week follow-up. *P < .05. Abbreviations: CSDD, Cornell Scale for Depression in Dementia; FAS, full analysis set; NPI, Neuropsychiatric Inventory.

Fig. 4. Adjusted mean for the change from Baseline in ADAS-Cog 11-item and CSDD total score (FAS) during the 24-week follow-up for subjects with CSDD < 12 and with CSDD ≥ 12. Abbreviations: ADAS-Cog, Alzheimer’s Disease Assessment Scale-Cognitive subscale; CSDD, Cornell Scale for Depression in Dementia; FAS, full analysis set.
Apathy and depression relate to the patients’ performance loss of interest, cognitive worsening, and irritability. Both due to the overlap of signs such as fatigue, withdrawal, prevalence of the association of both syndromes could be symptomatology, irritability, sleep, and appetite disorders. Depression neurosyndromes (NPI total score at baseline). These symptoms included apathy, anxiety, irritability, sleep, and appetite disorders. Depression and apathy are often present concomitantly [32]. The high prevalence of the association of both syndromes could be due to the overlap of signs such as fatigue, withdrawal, loss of interest, cognitive worsening, and irritability. Both apathy and depression relate to the patients’ performance.

In the present study, a placebo effect on cognition was observed, especially on the first 3 months and to a greater extent on depression and neuropsychiatric symptoms throughout the study [10,11]. On the subset of subjects with “probable major depression” (baseline CSDD score ≥ 12), these patients may be more sensitive to the placebo effect of the study. Finally, the lack of accurate reporting by the patient/informant, overlap of symptoms of depression and dementia, inadequate sensitization of clinicians to data collection, and limitations of tools may have led to difficulties in diagnosis and assessment of treatment.

There was a mild cognitive decline of the placebo group which was particularly evident during the last 3 months of the study. These observations raise questions on the duration of the clinical trial for a symptomatic treatment, the care given to patient and informant, and the standard assessment tools used on this population. Recent studies show that up to 30% of patients with the clinical phenotype of AD do not have brain amyloidosis when studied with amyloid positron emission tomography or cerebrospinal fluid amyloid studies and do not have the clinico-biological syndrome of AD [33]. The modest rate of apolipoprotein e4 carriers (47% compared to 65% of biologically confirmed AD) suggests that some non-AD patients were included in this trial. The trajectory and treatment response profile of the non-AD patients included in trials is unknown. In addition, the exclusion of patients on cholinesterase inhibitors and memantine may have resulted in recruiting a somewhat atypical AD population into the trial. These factors may have contributed to the negative outcome of this trial and represent issues to be considered in other trials of symptomatic agents.

Our findings are similar to those obtained in AD patients with another AMPA-PAM (LY451395, mibampator) which

### Table 2

Summary of emergent adverse events (safety data set) for main period*  

| Event                      | Placebo, N = 129 | S47445 5 mg, N = 130 | S47445 15 mg, N = 130 | S47445 50 mg, N = 132 | Overall, N = 391 |
|----------------------------|------------------|----------------------|----------------------|----------------------|------------------|
| Nasopharyngitis            | 6 (4.7%)         | 4 (3.1%)             | 3 (2.3%)             | 7 (5.3%)             | 14 (3.6)         |
| Blood creatine phosphokinase increased | 2 (1.6%)         | 1 (0.8%)             | 1 (0.8%)             | 2 (1.5%)             | 5 (1.3)          |
| Diarrhea                   | 4 (3.1%)         | 2 (1.6%)             | 1 (0.8%)             | 1 (0.8%)             | 4 (1.0)          |
| Fall                       | 2 (1.6%)         | 4 (3.1%)             | 3 (2.3%)             | 4 (3.1%)             | 7 (1.8)          |
| Headache                   | 5 (3.9%)         | 3 (2.3%)             | 4 (3.1%)             | 4 (3.1%)             | 11 (2.8)         |
| Type 2 diabetes mellitus   | 1 (0.8%)         | 4 (3.1%)             | 1 (0.8%)             | 1 (0.8%)             | 6 (1.5)          |
| Abdominal pain upper       | 0                | 2 (1.6%)             | 1 (0.8%)             | 4 (3.0%)             | 7 (1.8)          |

NOTE. N is the number of patients per group and n is the number of patients with at least one EAE; %: (n/N)*100.

Abbreviation: EAE, emergent adverse event.

*Adverse events are listed according to the preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA), version 19.1.

†Treatment-emergent adverse events occurring in at least 3% of patients in either group.
Acknowledgments

The authors would like to acknowledge Vanessa Mourlon for her helpful assistance during all the study and thank all patients, informants, sites and their staff, principal investigators, and national coordinators.

List of principal investigators on each country:

**BRG**: Pr Latchezar Traykov, Pr Ivan Milanov, Dr Penka Atanassova, Pr Ara Kaprelyan, Pr Lyubomir Haralanov.

**BRA**: Pr Paulo Henrique Ferreira Bertolucci, Dr Paulo Brito, Dr Marcia Lorenia Fagundes Chaves, Dr Hamilton Grabowski, Pr Acioyi LT Lacerda, Dr José Ibiapina Siqueira Neto, Dr Viviane Zetola, Dr Antonio Carlos da Silva.

**CHL**: Dr Manuel Lavados, Dr Sergio Gloger, Dr Luis Bara Ahumada, Dr Jaime Solis, Dr Alberto Mario Vargas Cañas.

**CZE**: Dr Michal Bajacek, Dr Ilona Divacka, Dr Jiri Pisvječ, Dr Petra Votypkova, Dr Klaudia Vodickova-Borzova, Dr Michaela Klubasayová.

**DEU**: Pr Matthias Riemenschneider, Dr Heike Benes, Pr Joerg Berrouschat, Dr Ralf Bodenschutz, Dr Joerg Peltz, Dr Joachim Springub, Pr Georg Adler.

**HUN**: Pr Janos Kalman, Dr Attila Valikovics, Dr Tibor Kovacs, Dr Maria Satori, Pr Sandor Fekete, Dr Gabor Feller, Dr Robert Karpati, Dr Alexander Kancsev, Dr Eva Mathe.

**JPN**: Dr Tomofumi Shinozaki, Dr Satoshi Nakamura, Dr Shuta Toru, Dr Takashi Asada.

**MEX**: Pr Santiago Ramirez Diaz, Dr Ricardo Salinas Martinez, Dr Abraham Vazquez Garcia, Mario Valdés Dávila.

**POL**: Dr Maciej Czarniecki, Dr Andrzej Fidor, Pr Andrzej Szcudluk, Dr Dorota Ussorowska, Dr Izbela Halina Winkel, Pr Catalina Tudoze, Dr Rita Ioana Platana.

**RUS**: Pr Svetlana Gavrilova, Dr Yaroslav Kalyn, Dr Tatiana Safarova, Pr Nadezhda Korobeynikova, Pr Miroslav Odinak, Pr Vladimir Parfenov, Pr Sofia Sluchevskaya, Dr Inna Kiseleva, Pr Dina Khasanova, Pr Oleg Shiryaev.

**SVK**: Dr Livia Vavrusova, Dr Jana Greskova, Dr Ivan Doci.

**ZAF**: Dr Felix Potocnik, Dr Gert Bosch, Dr Jaco Cilliers, Dr Christo Coetzee, Dr Jannie van der Westhuizen, Dr Chris Verster.

Funding for this study was provided by Institut de Recherches Internationales Servier (Suresnes, France).
References

[1] Robert PH, Verhey FR, Byrne EJ, Hurt C, De Deyn PP, Nobili F, et al. Grouping for behavioral and psychological symptoms in dementia: clinical and biological aspects. Consensus paper of the European Alzheimer disease consortium. Eur Psychiatry 2005;20:490–6.

[2] Lyketsos CG, Olin J. Depression in Alzheimer’s disease: overview and treatment. Biol Psychiatry 2002;52:243–52.

[3] Lyketsos CG, Steinberg M, Tschanz JT, Norton MC, Steffens DC, Breiter JC. Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging. Am J Psychiatry 2000;157:708–14.

[4] Fernandez-Martinez M, Castro J, Molano A, Zarranz JJ, Rodrigo RM, Ortega R. Prevalence of neuropsychiatric symptoms in Alzheimer’s disease and vascular dementia. Curr Alzheimer Res 2008;5:61–9.

[5] Barca ML, Persson K, Eldholm R, Benth JS, Kersten H, Knapskog AB, et al. Trajectories of depressive symptoms and their relationship to the progression of dementia. J Affect Disord 2017;222:146–52.

[6] Lee HB, Lyketsos CG. Depression in Alzheimer’s disease: heterogeneity and related issues. Biol Psychiatry 2003;54:353–62.

[7] Olin JT, Schneider LS, Katz IR, Meyers BS, Alexopoulos GS, Breiter JC, et al. Provisional diagnostic criteria for depression of Alzheimer’s disease. Am J Geriatr Psychiatry 2002:10:125–8.

[8] Teng E, Ringman JM, Ross LK, Mulnard RA, Dick MB, Bartekis G, et al. Diagnosing depression in Alzheimer disease with the national institute of mental health provisional criteria. Am J Geriatr Psychiatry 2008;16:167–74.

[9] Sephry AA, Lee PE, Hsiung GR, Beattie BL, Feldman HH, Jacova C. The 2002 NIMH Provisional Diagnostic Criteria for Depression of Alzheimer’s Disease (PDC-dAD): Gauging their Validity over a Decade Later. J Alzheimers Dis 2017;58:449–62.

[10] An H, Choi B, Park KW, Kim DH, Hong CH, et al. The Effect of Escitalopram on Mood and Cognition in Depressive Alzheimer’s Disease Subjects. J Alzheimers Dis 2017;55:727–35.

[11] Banerjee S, Haller J, Dewey M, Romeo R, Ballard C, Baldwin R, et al. Sertraline or mirtazapine for depression in dementia (HTA-SADD): a randomised, multicentre, double-blind, placebo-controlled trial. Lancet 2011;378:403–11.

[12] Munro CA, Longmire CF, Drye LT, Martin BK, Frangakis CE, Meinert CL, et al. Cognitive outcomes after sertraline treatment in patients with depression of Alzheimer disease. Am J Geriatr Psychiatry 2012;20:1036–44.

[13] Rao V, Sprio JR, Rosenberg PB, Lee HB, Rosenblatt A, Lyketsos CG. An open-label study of escitalopram (Lexapro) for the treatment of ‘Depression of Alzheimer’s disease’ (dAD). Int J Geriatr Psychiatry 2006;21:273–4.

[14] Sephry AA, Lee PE, Hsiung GY, Jacova C. Stay the course—is it justified? Lancet 2012;379:220.

[15] Harding R, Peel E. ‘He was like a zombie’: off-label prescription of antipsychotic drugs in dementia. Med L. Rev Mar 2013;21:243–77.

[16] Cummings J, Zhong K. Trial design innovations: Clinical trials for treatment of neuropsychiatric symptoms in Alzheimer’s Disease. Clin Pharmacol Ther 2015;98:483–5.

[17] Bretin S, Louis C, Seguin L, Wagner S, Thomas JY, Challal S, et al. Pharmacological characterisation of S47445, a novel positive allosteric modulator of AMPA receptors. PLoS One 2012;7:e0184429.

[18] Mendez-David I, Guilloux JP, Papp M, Tischler L, Mocaer E, Gardier AM, et al. S47445 Produces Antidepressant- and anti-dementia drugs in home care and residential care and associations with neuropsychiatric symptoms: a cross-sectional study. BMC Geriatr 2015;15:100.

[19] Kuronen M, Koponen H, Nykanen I, Karppi P, Hartikainen S. Use of anti-dementia drugs in home care and residential care and associations with neuropsychiatric symptoms: a cross-sectional study. J Alzheimers Dis 2016;31:389–408.

[20] Johnson SA, Simmon VF. Randomized, double-blind, placebo-controlled international clinical trial of the AMPA receptor CX5316 in elderly participants with mild cognitive impairment: a progress report. J Mol Neurosci 2012;49:197–200.

[21] Ciuciu P, Bougacha S, Boumezbeur F, Desmidt S, Ginisty C, Laurier L, et al. Effect of S47445 on functional connectivity at rest and during a task, and on glutamate concentrations in elderly subjects. J Prev Alzheimers Dis 2016;3:S274–5. 9th Clinical Trials on Alzheimer’s Disease (CTAD), San Diego, CA (08/12/2016 - 10/12/2016).

[22] Dmitrienko A, Tamhane AC. Mixtures of multiple testing procedures for gatekeeping applications in clinical trials. Stat Med 2011;30:1473–88.

[23] Lee K, Goodman L, Fournier C, Schenk S, Leitch B, Montgomery JM. AMPA Receptors as Therapeutic Targets for Neurological Disorders. Adv Protein Chem Struct Biol 2016;103:203–61.

[24] Morrow JA, Maclean JK, Jamieson C. Recent advances in positive allosteric modulators of the AMPA receptor. Curr Opin Drug Discov Devel 2006;9:571–9.

[25] Pirotte B, Francotte P, Goffin E, de TP. AMPA receptor positive allosteric modulators: a patent review. Expert Opin Ther Pat 2013; 23:615–28.

[26] Ward SE, Bax BD, Harries M. Challenges for and current status of research into positive modulators of AMPA receptors. Br J Pharmacol 2010;160:181–90.

[27] Cummins JL, Morstorf T, Lee G. Alzheimer’s drug-development pipeline: 2016. Alzheimer Dement 2016;2:222–32.

[28] Szczysny JS, Beiser A, Seshadi S, Auerbach S, Wolf PA, Au R. Depressive symptoms and risk of dementia. Neurology 2010; 75:35–41.

[29] Steinberg M, Shao H, Zandi P, Lyketsos CG, Welsh-Bohmer KA, Norton MC, et al. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. Int J Geriatr Psychiatry 2008;23:170–7.

[30] Craig D, Mirakhur A, Hart DJ, McIlroy SP, Passmore AP. A cross-sectional study of neuropsychiatric symptoms in 435 patients with Alzheimer’s disease. Am J Geriatr Psychiatry 2005;13:460–8.

[31] Benoit M, Staccini P, Brocker P, Benhamat T, Bertogliati C, Lechowski L, et al. [Behavioral and psychologic symptoms in Alzheimer’s disease: results of the REAL.FR study]. Rev Med Interne 2003;24(Suppl 3):319–324a.

[32] Benoit M, Berrut G, Doussant J, Bakchine S, Bonin-Guillaume S, Frémont P, et al. Apathy and depression in mild Alzheimer’s disease: a cross-sectional study using diagnostic criteria. J Alzheimers Dis 2012;31:325–34.

[33] Sevigny J, Suhy J, Chiao P, Chen T, Klein G, Purcell D, et al. Amyloid PET screening for enrichment of early-stage Alzheimer disease clinical trials: experience in a Phase 1b clinical trial. Alzheimer Dis Assoc Disord 2016;30:1–7.

[34] Chappell AS, Gonzales C, Williams J, Witte MM, Mohs RC, Sperling R. AMPA potentiator treatment of cognitive deficits in Alzheimer disease. Neurology 2007;68:1008–12.

[35] Borsook D, Becerra L, Fava M. Use of functional imaging across clinical phases in CNS drug development. Transl Psychiatry 2013;3:e282.

[36] Trzepacz PT, Cummings J, Konechnik T, Forrester TD, Chang C, Denney EB, et al. Mibampator (LY451395) randomized clinical trial for agitation/aggression in Alzheimer’s disease. Int Psychogeriatr 2013;25:707–19.

[37] Kuronen M, Koponen H, Nykanen I, Karppi P, Hartikainen S. Use of anti-dementia drugs in home care and residential care and associations with neuropsychiatric symptoms: a cross-sectional study. BMC Geriatr 2015;15:100.

[38] Mullane K, Williams M. Preclinical Models of Alzheimer’s Disease: Relevance and Translational Validity. Curr Protoc Pharmacol 2016;84:e37.

[39] Johnson SA, Simmon VF. Randomized, double-blind, placebo-controlled international clinical trial of the AMPA receptor CX5316 in elderly participants with mild cognitive impairment: a progress report. J Mol Neurosci 2002;19:197–200.
[40] Lynch G, Granger R, Ambros-Ingerson J, Davis CM, Kessler M, Schehr R. Evidence that a positive modulator of AMPA-type glutamate receptors improves delayed recall in aged humans. Exp Neurol 1997;145:89–92.

[41] Wezenberg E, Verkes RJ, Ruigt GS, Hulstijn W, Sabbe BG. Acute effects of the ampakine faramipator on memory and information processing in healthy elderly volunteers. Neuropsychopharmacology 2007;32:1272–83.