2. SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France</td><td rowspan="2">(For National Authority Use only)</td></tr>
<tr><td colspan="2">Test drug
Name of Finished Product:
Not applicable
Name of Active Ingredient:
S 47445</td></tr>
<tr><td>Individual Study Table Referring to Part of the Dossier</td><td>Volume:</td><td>Page:</td></tr>
<tr><td colspan="3">Title of study: Efficacy and safety of 3 doses of S 47445 versus placebo in patients with Alzheimer’s disease at mild to moderate stages with depressive symptoms.
A 24-week international, multi-centre, randomized, double-blind, placebo-controlled phase II study in monotherapy followed by an optional 28-week extension period in co-administration with donepezil.
Protocol No.: CL2-47445-011
EudraCT No.: 2014-001519-38
The description of the study protocol given hereafter includes the modifications of the 7 substantial amendments to the protocol.</td></tr>
<tr><td colspan="3">National coordinators:
[redacted]</td></tr>
<tr><td colspan="3">Study centres:
520 patients were included in 70 centres located in 12 countries: Brazil (8 centres, 48 patients), Bulgaria (5 centres, 56 patients), Chile (5 centres, 83 patients), Czech Republic (6 centres, 66 patients), Germany (7 centres, 32 patients), Hungary (9 centres, 63 patients), Japan (4 centres, 4 patients), Mexico (4 centres, 28 patients), Poland (5 centres, 37 patients), Russia (8 centres, 73 patients), Slovakia (3 centres, 11 patients), South Africa (6 centres, 19 patients).</td></tr>
<tr><td colspan="3">Publication (reference):
Not applicable</td></tr>
<tr><td colspan="2">Studied period:
Initiation date: 13 February 2015 (date of first visit first patient)
Completion date: 20 September 2017 (date of last visit last patient including extension period)</td><td>Phase of development of the study:
Phase II</td></tr>
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Objectives:
The purpose of this trial was to assess the efficacy and safety of S 47445 *versus* placebo in patients with Alzheimer's disease (AD) at mild to moderate stages with depressive symptoms. An optional 28-week extension period was performed to evaluate safety/tolerance and efficacy of S 47445 in co-administration with donepezil.
The primary objective of the study was to assess efficacy of three doses of S 47445 *versus* placebo, after 24 weeks of treatment, on cognitive performance measured with the 11-item AD Assessment Scale-Cognitive (ADAS-Cog).
The key secondary objective of the study was to assess efficacy of three doses of S 47445 *versus* placebo, after 24 weeks of treatment, on activities of daily living considering the Disability Assessment for Dementia (DAD).
The secondary objectives were:

- To assess the efficacy of three doses of S 47445 *versus* placebo, after 24 weeks of treatment on other criteria assessing cognitive performance (ADAS-Cog 13-item, Mini-Mental State Examination - MMSE), depressive symptoms (Cornell Scale for Depression in Dementia - CSDD), neuropsychiatric symptoms (Neuropsychiatric Inventory - NPI), clinical global impression of change (AD Cooperative Study-Clinical Global Impression of Change - ADCS-CGIC) and functionality (gait task).
- To assess the safety and the tolerance of three doses of S 47445 after 24 and 52 weeks of treatment.
- To provide S 47445 safety/tolerance and efficacy data in co-administration with donepezil after 28 weeks of treatment.
- To assess the pharmacokinetics (PK) of S 47445 and/or its metabolites.

Methodology:
This was a phase II dose ranging international, multi-regional, multi-centre, randomised, double-blind, placebo-controlled study. A 3-6-week selection period without study treatment was followed by a 24-week double-blind treatment period with 4-parallel groups (doses: 5, 15 and 50 mg/day of S 47445 and placebo) and an optional 28-week treatment extension period in co-administration with donepezil (patients were assigned at W24 to receive donepezil in co-administration of their previous treatment at the same dose: 5 or 15 or 50 mg/day of S 47445 or placebo) and a 2-week follow-up period.
Stratification: on region (Japan and other) and severity of the disease mild/moderate (MMSE total score).
The first statistical analysis was done as soon as all efficacy and safety data of the ASSE-W24 period were available and the second statistical analysis was done once all data of the entire study were available.

This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.
The main analysis was done in June 2017 with full efficacy and safety data of the ASSE-W24 period. Based on these results, the Sponsor decided to discontinue the study and the development of S 47445 in AD. In this context, an abbreviated study report was written.

Number of patients:
Planned: 500 patients (at least 40% mild AD, at least 40% moderate AD), 125 patients in each group.
Included: a total of 520 patients were included (129 in the S 47445 5 mg group, 130 in the S 47445 15 mg group, 132 in the S 47445 50 mg group and 129 in the placebo group), among these patients 468 entered in the 28-week extension period.

Diagnosis and main criteria for inclusion:

Target population was patients suffering from mild to moderate AD with depressive symptoms.

Main inclusion criteria

Out-patients, age 55-85 years, school education ≥ 4 years, with memory impairment [Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV-TR) criteria for dementia of AD type)], with depressive symptoms [National Institute of Mental Health provisional criteria for depression in AD (NIMH-dAD)] criteria for depressive symptoms of AD, CSDD total score ≥ 8, MMSE = 15-24 both inclusive, brain Magnetic Resonance Imaging (MRI) at selection, identified informant to accompany the patient to all study visits. Patients who have never been treated with AD treatment (cholinesterase inhibitors or memantine (NMDA-receptor antagonist)) or patients who have stopped AD treatment for whatever reason (wash-out period: 8 weeks before inclusion W0). Patients either not currently treated with an antidepressant or patients being treated with an antidepressant at the recommended dose for at least 8 weeks without clinical efficacy, who could stop this treatment according to the investigator's opinion. If a tapering of the antidepressant was needed according to the approved Summary of Product Characteristics (SmPC), this could be initiated at the selection visit. In any case, the antidepressant treatment should have been completely stopped at least 3 weeks before the inclusion visit.

Investigational Medicinal Products (IMPs):

Test drug: tablets of 5 mg, 15 mg and 50 mg of S 47445
Two tablets, one tablet corresponding to 5 or 15 or 50 mg of S 47445 and one tablet of placebo, taken orally, with a glass of water, once a day, during breakfast, starting the day after the inclusion visit and ending the day of the W24 visit (main period) or starting the day after the inclusion visit and ending the day of the W 52 visit (period including main period and optional extension period).

Comparator: placebo tablets (matching the test drug for double-blind masking)
Two tablets of placebo, taken orally, with a glass of water, once a day, during breakfast, starting the day after the inclusion visit and ending the day of the W24 visit or starting the day after the inclusion visit and ending the day of the W52 visit.

Non IMP (NIMP): donepezil as tablet of 3 mg (for Japan only), 5 mg and 10 mg.
One tablet of donepezil, taken orally, with a glass of water, once a day either in the morning or in the evening according to the prescription of the treating physician, either on the day of the W24 visit (evening administration) or on the day after the W24 visit (morning administration) and ending either the day prior to the W52 visit (evening administration) or the day of the W52 visit (morning administration).

Duration of treatment:
Run-in period: no treatment during the 3-6 weeks of selection period.
Treatment period: 24 or 52-weeks treatment period.
Follow-up period: no study treatment during the 2-week follow up period.

Criteria for evaluation:

Efficacy measurements:

Primary endpoint: ADAS-Cog 11-items total score.

Key secondary endpoint*:* DAD total score.

Secondary endpoints: ADAS-Cog 13-items (the same as ADAS-Cog 11-items), MMSE, CSDD, NPI, ADCS-CGIC, Gait Task (GT).

Safety measurements: adverse events (AEs), vital signs, 12-lead ECG, CSDD suicide item, biological laboratory examinations.

Pharmacokinetic measurements: S 47445 and/or its metabolites blood concentrations and donepezil plasma concentrations.

Genomic biomarkers (optional, in patients having given a specific consent): blood sample at W0.

Statistical methods:
Analysis Set:
Period W0-W24

- Randomised Set (RS): all included and randomised (according to IRS procedure) patients.
- Full Analysis Set (FAS): all patients of the RS having taken at least one dose of IMP and having a value at baseline and at least one post-baseline value for the primary endpoint.
- Safety Set (SS): all included patients having taken at least one dose of IMP.

Period W0-W52

- Extension Period Set (EPS): all patients entering the extension period.
- Full Analysis EPS (FAEPS): all patients of the EPS, having taken at least one dose of IMP after W24 and having a value at W24 and at least one post-W24 value for primary endpoint.
- Safety Extension Period Set (SEPS): all patients of EPS, having taken at least one dose of IMP after W24.
- Safety Set (SS): all included patients having taken at least one dose of IMP during the W0-W52 period.

Efficacy analysis:
Primary endpoint
The primary efficacy endpoint was the 11-item ADAS-Cog total score, expressed mainly in term of change from baseline to W24.

Primary analysis
The superiority of at least one dose of S 47445 as compared to placebo on cognitive performance after a 24-week treatment period was assessed from the 11-item ADAS-Cog total score expressed in terms of change from baseline to W24, in patients of the FAS. A restricted maximum likelihood (REML)-based, mixed-effects repeated measures approach (so called Mixed-effects Model for Repeated Measures – MMRM) using all the longitudinal observations at each post-baseline visit (W4, W12 and W24) was used.

Study outcome and safety analysis: Descriptive statistics were provided.

Pharmacokinetic analysis: no PK analysis was performed (only individual data provided).

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

Disposition of patients over W0-W24 in the Randomised Set (N = 520)

Status		**S 47445 5 mg**	**S 47445 15 mg**	**S 47445 50 mg**	**Placebo**	**ALL**
Included and Randomised	**N**	**129**	**130**	**132**	**129**	**520**
Withdrawn on W0-W24 due to	**n (%)**	**9 (7.0)**	**14 (10.8)**	**16 (12.1)**	**10 (7.8)**	**49 (9.4)**
Withdrawal non-medical reason	n (%)	6 (4.7)	7 (5.4)	5 (3.8)	4 (3.1)	22 (4.2)
Adverse event	n (%)	1 (0.8)	6 (4.6)	7 (5.3)	6 (4.7)	20 (3.8)
Lack of efficacy	n (%)	1 (0.8)	1 (0.8)	3 (2.3)	-	5 (1.0)
Lost to follow-up	n (%)	1 (0.8)	-	-	-	1 (0.2)
Protocol violation	n (%)	-	-	1 (0.8)	-	1 (0.2)
Completed the W0-W24 period	**n (%)**	**120 (93.0)**	**116 (89.2)**	**116 (87.9)**	**119 (92.2)**	**471 (90.6)**
Entering the extension period	**n (%)**	**119 (92.2)**	**115 (88.5)**	**115 (87.1)**	**119 (92.2)**	**468 (90.0)**

*N number of patients by group; n number of patients related to the status; % = (n/N)*100*

Disposition of randomised patients over W0-W52 in the Extension Period Set (N = 468)

Status		**S 47445 5 mg**	**S 47445 15 mg**	**S 47445 50 mg**	**Placebo**	**ALL**
Included and Randomised	**N**	**119**	**115**	**115**	**119**	**468**
Withdrawn on W0-W52 period due to	**n (%)**	**32 (26.9)**	**32 (27.8)**	**38 (33.0)**	**33 (27.7)**	**135 (28.8)**
Withdrawal non-medical reason	n (%)	26 (21.8)	26 (22.6)	34 (29.6)	27 (22.7)	113 (24.1)
Adverse event	n (%)	6 (5.0)	4 (3.5)	4 (3.5)	5 (4.2)	19 (4.1)
Lack of efficacy	n (%)	-	1 (0.9)	-	-	1 (0.2)
Lost to follow-up	n (%)	-	-	-	1 (0.8)	1 (0.2)
Protocol violation	n (%)	-	1 (0.9)	-	-	1 (0.2)
Completed the W0-W52 period	**n (%)**	**87 (73.1)**	**83 (72.2)**	**77 (67.0)**	**86 (72.3)**	**333 (71.2)**

*N number of patients by group; n number of patients related to the status; % = (n/N)*100*

BASELINE CHARACTERISTICS

At baseline in the RS, the mean (± SD) age was 71.8 ± 7.3 years, a majority of patients were female (69.8%) and the mean educational level was 11.1 ± 3.4 years without relevant differences between the groups.

AD lasted on average for 3.6 ± 2.2 years. The frequency of patients with previous treatment for AD (mainly donepezil 6.7%, memantine 6.5% and donepezil hydrochloride 4.2%) was higher in the S 47445 groups (20.9%, 22.3% and 22.7% in the S 47445 5 mg, 15 mg and 50 mg group, respectively) than in the placebo group (15.5%). The frequency of patients with previous treatment for current depressive symptoms (mainly selective serotonin reuptake inhibitors, 14.4%) was lower in the S 47445 5 mg group (12.4%) than in the S 47445 15 mg, S 47445 50 mg and the placebo groups (22.3%, 22.0% and 18.6%, respectively).

Almost all patients (99.2%) had AD at either mild (15 ≤ MMSE ≤ 19 for 46.5% of patients) or moderate stage (20 ≤ MMSE ≤ 24 for 52.7% of patients). The mean MMSE total score was 19.7 ± 2.8. Regarding these AD characteristics, no relevant difference between groups was observed. The mean duration of the current depressive symptoms was 1.3 ± 2.0 years.

No relevant difference between groups was also observed for alcohol consumption and smoking, weight, blood pressures. Regarding ECG parameters, a total of 21 patients (4.0%) had a QTcF value within]450 ; 480] ms with a higher frequency in the S 47445 50 mg group (8.3%) than in the S 47445 5 mg (2.3%), S 47445 15 mg (1.5%) and placebo (3.9%) groups. Significant ECG abnormality was reported for a total of 33 patients (6.3%) with a higher frequency in the S 47445 5 mg (9.3%) and S 47445 50 mg (8.3%) groups than in the S 47445 15 mg and placebo groups (3.9% in each latter group). No relevant difference between groups was observed for other baseline characteristics (medical history, concomitant treatments, vitamin B12, HbA1c, free thyroxine and thyrotropin).

Overall, 47.2% of patients were ApoE ε4 carriers with higher frequency in the S 47445 5 mg group (56.6%) than in the S 47445 15 mg, S 47445 50 mg and placebo groups (38.3%, 47.3% and 46.9%, respectively).

Regarding the 11-Item ADAS-Cog (primary efficacy endpoint) and DAD total scores (key secondary efficacy endpoint), mean scores were 23.5 ± 9.0 and 68.1 ± 18.6, respectively, with no relevant difference between groups.

BASELINE CHARACTERISTICS (Cont'd)

CSDD mean total score was 12.0 ± 3.6 with a score equal to 12 or higher for 46.2% of patients with no relevant difference between groups. The mean 12-Item NPI total score and 10-Item NPI total score were 22.4 ± 13.3 and 17.4 ± 10.8, respectively, with no relevant difference between groups. No relevant difference between groups was also observed for walking velocities from gait task.

Informants were mainly the daughter/son (45.0%) and the spouse of the patient (43.9%). The time of personal contact with the patient was on average 81.2 ± 53.2 hours per week without relevant difference between groups. At least 99.0% of patient informants were present at each visit during W0-W24.

Baseline characteristics in the FAS (N = 518, 99.6% of the RS) and in the PPS (N = 421, 81.0% of the RS) were similar to those observed in the RS.

During W0-W52 period in the EPS, baseline characteristics of patients were similar to those observed in RS.

Considering the W24-W52 period in the EPS, at the W24 baseline, no relevant difference between groups was observed for vital signs and ECG parameters with quite unchanged values between W0 and W24. At W24, there was no relevant difference between groups in 11-Item ADAS-Cog and DAD total scores and these were quite unchanged between W0 and W24.

EXTENT OF EXPOSURE

The mean treatment duration was 162.4 ± 29.5 days during W0-W24, 176.9 ± 40.4 days during W24-W52 and 346.4 ± 40.8 days during W0-W52. The overall compliance was good with a mean of 97.3 ± 8.6%, 96.5 ± 11.0% and 98.0 ± 5.1%, respectively. There was no relevant difference between groups.

EFFICACY RESULTS

Primary efficacy endpoint

In the FAS, main analysis failed to demonstrate a statistically significant superiority to placebo of any S 47445 doses for the change from baseline to W24 in the 11-item ADAS-Cog total score (primary efficacy endpoint, see below) as well as for the change in DAD total score (key secondary efficacy endpoint). These results were confirmed with sensitivity analyses to the method of handling missing value.

11-item ADAS-Cog - Change from baseline to W24
Difference between S 47445 doses and placebo in the FAS (N = 518) - Primary analysis

		S 47445 5 mg (N = 129)	S 47445 15 mg (N = 130)	S 47445 50 mg (N = 130)	Placebo (N = 129)
Baseline (W0)	n	129	130	130	129
	Mean ± SD	23.76 ± 9.50	23.00 ± 8.72	24.22 ± 8.88	23.26 ± 8.84
	Median	22.00	23.30	23.70	21.30
	Min ; Max	9.3 ; 51.7	4.0 ; 46.3	8.7 ; 47.3	5.3 ; 48.3
Change W24-W0	n	120	118	121	121
	Mean ± SD	-0.20 ± 4.91	-0.74 ± 5.43	-0.05 ± 5.82	0.35 ± 5.53
	Median	-0.50	-0.85	0.30	0.00
	Min ; Max	-12.3 ; 14.7	-18.0 ; 14.7	-25.7 ; 19.0	-12.0 ; 17.7
Statistical analysis					
Change W24-W0 (1)	E (SE) (2)	-0.47 (0.69)	-0.90 (0.69)	-0.34 (0.69)	
	95% CI (3)	[-1.83 ; 0.89]	[-2.26 ; 0.46]	[-1.70 ; 1.01]	
	p-value (to be compared to 0.025) (4)	0.534	0.290	0.534	

*(1) Mixed-effects Model for Repeated Measures including terms for fixed categorical effects of treatment, severity of the disease (Mild/Moderate), visit (W4, W12 and W24) and interaction terms of treatment*visit and severity*visit, as well as the continuous fixed covariate of baseline 11-item ADAS-Cog total score and an interaction term baseline*visit*

(2) Estimate (Standard Error) of the difference between adjusted treatment group means S 47445 dose minus Placebo

(3) Two-sided 95% Confidence Interval of the estimate (without Holm-based adjustment)

(4) One-sided adjusted p-value (to be compared to 0.025), taking into account Holm-based procedure for multiplicity adjustment

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS

Adverse events

Summary for adverse events over the 24-week treatment period in the SS

		S 47445 5 mg (N = 129)	S 47445 15 mg (N = 130)	S 47445 50 mg (N = 132)	Placebo (N = 129)
Patients having reported at least one:					
EAE	n (%)	60 (46.5)	49 (37.7)	68 (51.5)	65 (50.4)
Treatment-related EAE	n (%)	9 (7.0)	12 (9.2)	12 (9.1)	9 (7.0)
Serious AE	n (%)	4 (3.1)	12 (9.2)	6 (4.5)	7 (5.4)
Serious EAE	n (%)	4 (3.1)	11 (8.5)	5 (3.8)	6 (4.7)
Treatment-related serious EAE	n (%)	-	-	-	1 (0.8)
EAE leading to treatment withdrawal	n (%)	2 (1.6)	7 (5.4)	9 (6.8)	5 (3.9)
Serious EAE leading to treatment withdrawal	n (%)	-	4 (3.1)	2 (1.5)	1 (0.8)
Treatment-related EAE leading to treatment withdrawal	n (%)	1 (0.8)	3 (2.3)	1 (0.8)	1 (0.8)
Treatment-related serious EAE leading to treatment withdrawal	n (%)	-	-	-	-
Patients who died	n (%)	-	-	1 (0.8)	1 (0.8)*

*N Number of patients by group n Number of patients ; % n/N*100*

**serious EAE occurred the day after the last IMP intake and led to death*

In the SS during the 24-week treatment period (N = 520), the frequency of patients with at least one EAE was similar among S 47445 5 mg, S 47445 50 mg and placebo groups. This frequency was lower in the S 47445 15 mg group than in the placebo group.

The most frequent affected SOC (> 10% of patients in any S 47445 groups) was Infections and infestations with lower or similar frequency in all S 47445 groups (from 9.2% in the S 47445 15 mg group to 15.9% in the S 47445 50 mg group) than in the placebo group (14.0%).

The most frequent (at least 4 patients) EAE reported in any of the S 47445 groups was nasopharyngitis (5.3% in S 47445 50 mg group) and blood creatine phosphokinase increased (4.5% in S 47445 50 mg group) without relevant difference with the placebo group (4.7% and 3.1%, respectively). Among less frequently reported EAEs, the following ones were more common in at least one S 47445 group than in the placebo group: type 2 diabetes mellitus (3.1% in S 47445 50 mg *versus* 0.8% in the placebo group), abdominal pain upper (3.0% in S 47445 50 mg *versus* none), both hyperglycaemia and orthostatic hypotension (2.3% in S 47445 15 mg *versus* none) and leukopenia (2.3% in S 47445 50 mg group *versus* none). No increase of PT frequency was observed with dose increase.

The frequency of severe EAEs was lower in the S 47445 5 mg group (3.1%) than in the S 47445 15 mg (8.4%), S 47445 50 mg (6.0%) and placebo (6.9%) groups.

The frequency of treatment-related EAEs was similar in each group. Most of PTs affected a single patient, without relevant difference between groups. Overall, 2 severe treatment-related EAEs were reported (headache, both in S 47445 5 mg and 15 mg groups).

The frequency of patients with at least one EAE leading to treatment withdrawal was higher in the S 47445 50 mg group than in the placebo group. EAEs were sparsely distributed with, for most of them, a single patient affected by each PT, without relevant difference between groups regarding PTs in more than 1 patient.

The frequency of serious EAEs (SEAEs) was similar in the S 47445 5 mg, S 47445 50 mg and placebo groups while it was higher in the S 47445 15 mg group than in the other groups. SEAEs were sparsely distributed with a single patient affected by PT in all treatment groups for most of them except fall more frequently reported in S 47445 5 mg group (2.3%) than in placebo group (none).

One patient died on-treatment in the S 47445 50 mg group from multiple organ dysfunction syndrome (not treatment-related) in a context of sepsis. Another patient in the placebo group died from a fatal subarachnoid haemorrhage and coma (both treatment-related) which occurred the day after the last IMP intake over the 24-week treatment period.

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Among patients not entering in the extension period in SS during the 24-week treatment period (N = 52), the percentage of patients with at least one EAE in all S 47445 groups was lower than in the placebo group: 4 patients (40%) had at least one EAE in S 47445 5 mg, 11 patients (73.3%) in S 47445 15 mg, 12 patients (70.6%) in S 47445 50 mg and 9 patients (90.0%) in the placebo group. Most of PTs affected a single patient in the S 47445 groups, without relevant difference between groups regarding PTs in more than 1 patient.

Treatment-related EAEs were reported in 1 patient in the S 47445 5 mg group, 3 patients each in S 47445 15 mg and 50 mg groups, and 2 patients in the placebo group. All PTs concerning treatment-related EAEs affected a single patient.

The frequency of patients with at least one SEAE was similar or lower in the S 47445 groups than in the placebo group: none in S 47445 5 mg, 40.0% (6 patients) in S 47445 15 mg, 29.4% (5 patients) in S 47445 50 mg, and 40.0% (4 patients) in the placebo group. SEAEs were sparsely distributed without relevant difference between groups. Among patients not entering in the extension period, 2 patients died (see above).

Summary for adverse events over the 28-week treatment extension period in the SEPS

		S 47445 5 mg (N = 119)	S 47445 15 mg (N = 115)	S 47445 50 mg (N = 115)	Placebo (N = 119)
Patients having reported at least one:					
EAE	n (%)	54 (45.4)	49 (42.6)	46 (40.0)	46 (38.7)
Treatment-related EAE	n (%)	2 (1.7)	2 (1.7)	2 (1.7)	4 (3.4)
Serious AE	n (%)	12 (10.1)	22 (19.1)	11 (9.6)	13 (10.9)
Serious EAE	n (%)	8 (6.7)	16 (13.9)	10 (8.7)	10 (8.4)
Treatment-related serious EAE	n (%)	-	-	-	2 (0.4)
EAE leading to treatment withdrawal	n (%)	6 (5.0)	1 (0.9)	4 (3.5)	3 (2.5)
Serious EAE leading to treatment withdrawal	n (%)	-	1 (0.9)	3 (2.6)	2 (1.7)
Treatment-related EAE leading to treatment withdrawal	n (%)	-	-	-	-
Patients who died	n (%)	-	1 (0.9)	1 (0.9)	2 (1.7)

*N Number of patients by group n Number of patients ; % n/N*100*

In the SEPS during the 28-week extension period (N = 468), the percentage of patients with at least one EAE was slightly higher in the S 47445 5 mg group than in the placebo group.

The most frequently affected SOCs (> 10% of patients in any S 47445 groups) were Gastrointestinal disorders (13.4% in S 47445 5 mg, 11.3% in S 47445 15 mg, 10.4% in S 47445 50 mg), Infections and infestations (13.4%, 7.8%, 7.0%, respectively), Nervous system disorders (10.9%, 6.1%, 5.2%, respectively) and Metabolism and nutrition disorders (5.9%, 13.0%, 8.7%, respectively). Frequencies of affected SOC were lower or similar in any of the S 47445 groups than in the placebo group, except for Metabolism and nutrition disorders with higher frequency in the S 47445 groups (5.9%, 13.0%, 8.7% in S 47445 5 mg, 15 mg and 50 mg groups) *versus* placebo group (5.0%) and Nervous system disorders (10.9% in S 47445 5 mg group *versus* 6.7%).

Among EAEs reported in at least 3% of patients in one of the S 47445 groups, the following were more frequent in at least one of the S 47445 groups than in the placebo group: viral upper respiratory tract infection (6.2% in S 47445 5 mg group *versus* none in placebo group), diarrhoea (4.2% in S 47445 5 mg and 5.2% in S 47445 5 mg *versus* 1.7%), blood creatine phosphokinase increased (4.2% in S 47445 5 mg *versus* 1.7%), dizziness postural (3.4% in S 47445 5 mg *versus* 0.8%), fall (6.1% in S 47445 15 mg *versus* 3.4%) and both decreased appetite and arthralgia (for each of the two, 3.5% in S 47445 15 mg *versus* 0.8%). Among the less frequently reported PTs, the two following were more common in at least one of the S 47445 group than in the placebo group: asthenia (2.5% in S 47445 5 mg *versus* none), hypercholesterolaemia (2.6% in S 47445 15 mg *versus* none) and dizziness (2.6% in S 47445 50 mg *versus* none). No increase of PT frequency was observed with dose increase.

All PTs concerning treatment-related EAEs affected a single patient in all groups. The frequency of patients with at least one EAE leading to treatment withdrawal was higher in S 47445 5 mg (5.0%) than in other groups (0.9% in S 47445 15 mg, 3.5% in S 47445 50 mg and 2.5% in placebo).

The frequency of SEAEs was similar in the S 47445 5 mg, S 47445 50 mg and placebo groups while it was higher in the S 47445 15 mg group. SEAEs were sparsely distributed except fall which was more frequently reported in S 47445 15 mg than in placebo (5.2% *versus* 1.7%).

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

During the 28-week extension period, 4 patients died: 1 patient in S 47445 15 mg group (ischaemic stroke), 1 patient in S 47445 50 mg group (general physical health deterioration in a context of metastatic cancer) and 2 patients in placebo group (ischaemic stroke and loss of consciousness in one patient and cardiac failure in the other patient).

Summary for adverse events over the 52-week treatment period (W0-W52) in the SS

		S 47445 5 mg (N = 129)	S 47445 15 mg (N = 130)	S 47445 50 mg (N = 132)	Placebo (N = 129)
Patients having reported at least one:					
EAE	n (%)	81 (62.8)	75 (57.7)	82 (62.1)	81 (62.8)
Treatment-related EAE	n (%)	10 (7.8)	14 (10.8)	13 (9.8)	13 (10.1)
Serious AE	n (%)	12 (9.3)	28 (21.5)	16 (12.1)	18 (14.0)
Serious EAE	n (%)	11 (8.5)	27 (20.8)	16 (12.1)	17 (13.2)
Treatment-related serious EAE	n (%)	-	-	-	4 (3.1)
EAE leading to treatment withdrawal	n (%)	8 (6.2)	9 (6.9)	13 (9.8)	9 (7.0)
Serious EAE leading to treatment withdrawal	n (%)	-	5 (3.8)	5 (3.8)	4 (3.1)
Treatment-related EAE leading to treatment withdrawal	n (%)	1 (0.8)	4 (3.1)	1 (0.8)	3 (2.3)
Treatment-related serious EAE leading to treatment withdrawal	n (%)	-	-	-	2 (1.6)
Patients who died	n (%)	-	1 (0.8)	2 (1.5)	3 (2.3)

*N Number of patients by group n Number of patients ; % n/N*100*

In the SS during the 52-week treatment period (N = 520), the percentage of patients with at least one EAE was similar between any of S 47445 groups and the placebo. As expected, this percentage during W0-W52 was higher than during W0-W24 in all groups.

The most frequent SOCs affected (> 15% of patients in any S 47445 groups) were Infections and infestations, Gastrointestinal disorders, Nervous system disorders, Metabolism and nutrition disorders. For these most frequent SOCs, incidence in the S 47445 groups was lower or similar to the placebo group, except for Metabolism and nutrition disorders more frequent in S 47445 15 mg than in placebo group (18.5% *versus* 9.3%) and Nervous system disorders more frequent in S 47445 5 mg than in placebo group (17.8% *versus* 14.7%).

Among EAEs reported in at least 3% of patients in one of the S 47445 groups, the following were more frequent in at least one of the S 47445 groups than in the placebo group: nausea (6.2% in the S47445 5 mg *versus* 4.7% in the placebo), viral upper respiratory tract infection (6.2% in S47445 5 mg and 6.8% in S47445 50 mg *versus* 4.7%), diarrhoea (6.2% in S47445 15 mg *versus* 4.7%), hypertriglyceridaemia (4.7% in S47445 5 mg *versus* 2.3%), fall (7.7% in S47445 15 mg *versus* 4.7%), hypercholesterolaemia (3.1% each in S47445 5 mg and S47445 15 mg groups *versus* 0.8%), GGT increased (3.1% in S47445 5 mg *versus* 0.8%), decreased appetite (4.6% in S47445 15 mg *versus* 0.8%), hyperglycaemia and orthostatic hypotension (3.1% each in S 47445 15 mg *versus* none), arthralgia (3.1% in S47445 15 mg *versus* 0.8%). Among the other less frequently reported EAEs, the following ones were more common in at least one of the S 47445 group than in the placebo group: syncope (2.3% in S 47445 5 mg *versus* none in the placebo), dizziness exertional and contusion (both 2.3% in S 47445 15 mg *versus* none), abdominal pain upper and leukopenia (both 2.3% in the S 47445 50 mg *versus* none in the placebo) and dizziness (2.3% in both S 47445 15 mg and 50 mg *versus* none). No increase of PT frequency was observed with the dose increase.

Frequency of severe EAEs was lower in all S47445 groups (from 4.7 to 8.4%) than in the placebo group (9.8%).

During W0-W52, the percentage of patients with at least one EAE treatment-related was similar as during W0-W24 in all groups. All PTs concerning treatment-related EAEs mostly affected a single patient. Treatment-related EAEs reported in more than 1 patient during W0-W52 in the S 47445 groups were those reported during W0-W24 with the addition, of accidental overdose (2 patients in S 47445 50 mg group).

The frequency of patients with at least one EAE leading to treatment withdrawal was higher in the S 47445 50 mg group than in the placebo group. These EAEs were sparsely distributed without relevant difference between groups.

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Similarly as during W0-W24, the frequency of SEAEs was similar in the S 47445 5 mg, S 47445 50 mg and placebo groups while it was higher in the S 47445 15 mg group than in the other groups. SEAEs were sparsely distributed with a single patient affected in most PTs. Among those reported in at least 2 patients in one of the S 47445 groups, fall was more frequent in S 47445 15 mg than in placebo group (5.4% *versus* 1.6%).

During W0-W52, 6 patients died: 2 during W0-W24 and 4 during W24-W52 (see above).

In the SEPS during the 52-week treatment period (N = 468*, i.e.* 90% of the SS), results were roughly similar to those in the SS. In SEPS, the frequency of SEAE was slightly lower in all groups than those observed in the SS (9.2%, 18.3% and 9.6% in S 47445 5 mg, 15 mg and 50 mg groups and 10.9% in placebo).

Patients who withdrew for AE during W0-W24 (n = 24) were excluded from the SEPS. Consequently, the frequency of patients with EAE leading to treatment withdrawal during W0-W52 was lower in the SEPS than in the SS.

Laboratory parameters

Changes in mean value over time

Neither clinically relevant changes from baseline nor differences between groups were detected except increase in creatine phosphokinase (mean change: 13.1 ± 82.6 IU/L in S 47445 15 mg group during W0-W24, 19.6 ± 102.0 IU/L and 18.6 ± 99.5 IU/L in the S 47445 5 mg group during W24-W52 and W0-W52, respectively).

Emergent potentially clinically significant abnormal (PCSA) values

In SS during W0-W24, emergent PCSA biochemical values were higher in at least one S 47445 group than in placebo for low glucose (2.4% in S 47445 5 mg *versus* none in placebo), high chlolesterol (5.6% in S 47445 5 mg *versus* 2.3%), high creatine phosphokinase (3.1% in S 47445 15 mg *versus* none) and low bicarbonate (16.2% and 12.4% in S 47445 15 mg and 50 mg *versus* 10.2%). Emergent PCSA haematological values were sparse in all groups.

Among patients not entering in the extension period in SS, emergent PCSA biochemical values were sparse except low bicarbonate (3 patients in S 47445 50 mg *versus* none in placebo) and emergent haematological PCSA values did not show relevant difference between groups.

In SEPS during W24-W52, emergent PCSA biochemical values were higher in at least one S 47445 group than in placebo for low glucose (2.6% in S 47445 5 mg *versus* none), high glucose (3.8% in S 47445 50 mg *versus* none), high urea (5.2% in S 47445 5 mg *versus* 1.8%), high urate (2.7% in S 47445 15 mg *versus* none) and low bicarbonate (8.7% and 8.5% in S 47445 5 mg and 50 mg *versus* 6.3%). Emergent PCSA haematological values were sparse in all groups for most of parameters without relevant difference between groups.

In SS during W0-W52, emergent PCSA biochemical values were higher in at least one S 47445 group than in placebo for low sodium (2.3% both in S 47445 15 mg and 50 mg *versus* none), low glucose (4.7% and 2.3% in S 47445 5 mg and 50 mg *versus* none), high glucose (3.8% in S 47445 50 mg *versus* 2.3%), high urate (3.8% in S 47445 15 mg *versus* 1.6%), high GGT (3.1% in S 47445 5 mg *versus* 0.8%), high cholesterol (7.0% in S 47445 5 mg *versus* 3.1%), high creatine phosphokinase (5.4% in S 47445 15 mg *versus* 1.6%) and low bicarbonate (19.2% and 17.6% in S 47445 15 mg and 50 mg *versus* 14.0%). Emergent PCSA haematological values were sparse for most of parameters without relevant difference between groups.

In SEPS during W0-W52, results for laboratory parameters were similar to those in SS.

Other safety criteria

Neither clinically relevant changes from baseline nor differences between groups were detected in vital signs during all treatment periods.

During W0-W24 in SS, the frequency of emergent orthostatic hypotension (calculated) was higher in the S 47445 groups than in the placebo group (12.5%, 13.1% and 5.6% in the S 47445 5 mg, 15 mg and 50 mg groups, respectively, *versus* 2.5%). Orthostatic hypotension reported as EAE by the investigator was less frequent than those calculated in the S 47445 groups: 0.8%, 2.3% and none, respectively in the S 47445 5 mg, 15 mg and 50 mg groups). Similar results were observed during W24-W52 and W0-W52, including during W0-W24 for patients not entering in the extension period.

No clinically relevant difference between groups was observed regarding mean changes from baseline in quantitative ECG parameters during all treatment periods. No QTcF values greater than 480 ms nor QTcF prolongation greater than 60 ms were detected on treatment in all S 47445 groups. Frequency of emergent clinically significant ECG abnormality was lower or similar in all S 47445 groups compared to placebo group.

Most of patients had a score equal to 0 for suicide item of CSDD at each post-baseline visit during all treatment periods without relevant difference between groups. Overall, 2 patients had a score equal to 2 on treatment, each at W12: 1 patient in S 47445 50 mg and 1 in placebo, both patients reported suicidal ideation EAE (not treatment-related, non-serious, recovered).

CONCLUSION

This international, multicentre, randomised, double-blind, placebo-controlled phase II study conducted in patients suffering from mild to moderate Alzheimer's disease with depressive symptoms and treated during 24 weeks did not show superiority for any of the S 47445 doses *versus* placebo on the 11-item ADAS-Cog total score as well as on DAD total score.

After the first 24-week treatment period, patients optionally entered in a 28-week extension period with co-administration of donepezil. During these two periods as well as during the overall 52-week period, the tolerance of S 47445 was good. No relevant difference between S 47445 groups and placebo regarding the frequency of emergent adverse events. It was observed a higher frequency of emergent orthostatic (calculated) hypotension in the S 47445 groups than in the placebo group during all treatment periods. This study showed a good safety profile of S 47445 alone and in association with donepezil.

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