Document title	**CLINICAL STUDY REPORT SYNOPSIS**
Study title	**Efficacy and safety of 3 doses of S 38093 (2, 5 and 20 mg/day) *versus* placebo in patients with mild to moderate Alzheimer's disease** A 24-week international, multi-centre, randomised, double-blind, placebo-controlled phase IIb study followed by a 24-week extension period.
Test drug code	**S 38093**
Indication	**Alzheimer's disease**
Development phase	**Phase IIb**
Protocol code	**CL2-38093-011**
Study initiation date	18 October 2011
Study completion date	21 March 2014
Main coordinator	[redacted]
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - France** **Les Laboratoires Servier** **Paveletskaya Square 2, building 3, floor 3** **Moscow 115 054 - RUSSIA**
Responsible medical officer	[redacted]
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	20 February 2015
Version of the report	**Final version**
	~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France		*(For National Authority Use only)*
Test drug **Name of Finished Product:** **NA** **Name of Active Ingredient:** **S 38093**		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**
Title of study: Efficacy and safety of 3 doses of S 38093 (2, 5 and 20 mg/day) *versus* placebo in patients with mild to moderate Alzheimer's disease. A 24-week international, multi-centre, randomised, double-blind, placebo-controlled phase IIb study followed by a 24-week extension period. Protocol No.: CL2-38093-011 EudraCT No.: 2010-024626-37 The description of the study protocol given hereafter includes the modifications of the 4 substantial amendments to the protocol.		
International coordinator: [redacted]		
Study centres: 98 centres located in 13 countries were opened, and selected and included at least one patient: Australia (9 centres - 43 patients included), Brazil (9 centres - 53 patients included), Bulgaria (6 centres – 70 patients included), Chile (4 centres - 65 patients included), Czech Republic (7 centres - 57 patients included), France (8 centres - 40 patients included), Germany (10 centres - 75 patients included), Hungary (9 centres - 48 patients included), Mexico (5 centres - 51 patients included), Portugal (2 centres - 5 patients included), Romania (6 centres - 36 patients included), Russian Federation (14 centres - 115 patients included), South Africa (9 centres - 53 patients included).		
Publication (reference): Not Applicable.		
Studied period: **ASSE-W24/WEND period** Initiation date: 18 October 2011 (date of first visit first patient) Completion date: 17 September 2013 (date of last visit last patient [ASSE-W24] period**)** **ASSE-W48/WEND (and W24-W48/WEND) period** Completion date: 21 March 2014 (date of last visit last patient [ASSE-W48] period**)**		**Phase of development of the study:** phase IIb
Objectives: The purpose of this trial was to assess the efficacy and safety of S 38093 *versus* placebo in patients with mild to moderate Alzheimer's disease (AD). **Primary objective***:* to assess the efficacy of 3 fixed doses of S 38093 (2, 5 and 20 mg/ day) *versus* placebo after 24 weeks of treatment, on cognitive performance measured with the ADAS-Cog 11-item in patients with mild to moderate AD. **Key secondary objective:** to assess the efficacy of the 3 fixed doses of S 38093 *versus* placebo after 24 weeks of treatment, on activities of daily living considering the Disability Assessment for Dementia (DAD) in patients with mild to moderate AD.		

Objectives (Cont'd)

Secondary objectives:

- *Efficacy*: To assess cognitive performance (using MMSE), clinical global impression of change, neuropsychiatric symptoms and informant burden between the 3 fixed doses of S 38093 and placebo, after 24 weeks of treatment in patients with mild to moderate AD.
  To provide S 38093 efficacy data after 48 weeks of treatment.
- *Safety:* To assess the safety of the 3 fixed doses of S 38093 *versus* placebo after 24 weeks of treatment.
  To provide S 38093 safety data after 48 weeks of treatment.
- To assess the *pharmacokinetics* of S 38093.

Exploratory objectives: to assess other cognitive domains than those covered by the ADAS-Cog 11-item (*i.e.* psychomotor speed, attention/concentration, executive functions, working memory and recognition) using brief and well-known validated tests: WAIS IV Coding, Category Fluency Test (CFT), Benton Visual Retention Test (BVRT) (*i.e.* Benton learning test multiple choice) and WAIS IV Digit Span.

This report concerns all criteria analysed over both periods (*i.e.* results over the ASSE-W24, ASSE-W48 including W24-W48 period).

Methodology:
This study was a phase IIb, international, multi-centre, randomised, double-blind, placebo-controlled, 4 parallel-group study. Six hundred (600) patients suffering from mild to moderate AD were to be included and randomly assigned to receive either S 38093 2 mg/day or S 38093 5 mg/day or S 38093 20 mg/day or placebo during a 24-week treatment period; followed by an optional 24-week treatment period during which patients continued on the same treatment, except those initially on placebo who were re-randomly assigned at W24 to receive S38093 2 or 5 or 20 mg. The study treatments were allocated at W0 and W24 by a balanced randomisation with stratification on country and on disease severity based on the MMSE total score at ASSE.

Genotyping of CYP 2C19 and ApoE was mandatory (CYP 2C19: inclusion of extensive and poor metabolisers.

The first statistical analysis had been performed as soon as all efficacy and safety data of the ASSE-W24 period were available and the second statistical analysis 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.

Number of patients:
Planned: 600 (150 in each treatment group; 300 mild AD, 300 moderate AD).
Included: 711 patients. The number of included patients was higher than planned, due to an unexpected increase in recruitment pace during the week prior to the end of selection and to the pre-specified balance between the samples size of mild and moderate AD patients.

Diagnosis and main criteria for inclusion:
Male or female out-patients, age 55-85 years, school education ≥ 4 years, with memory impairment (DSM-IV-TR criteria for dementia of AD type and NINCDS/ADRDA criteria for probable AD), Mini Mental State Examination (MMSE) at ASSE visit = 15-24 inclusive, brain Magnetic Resonance Imaging (MRI) at selection, identified informant to accompany the patient to all study visits. Patients should not have taken cholinesterase inhibitors (ChEI) or memantine (NMDA-receptor antagonist) within 8 weeks before inclusion (W0).

Study drug:
S 38093: 2 mg, 5 mg, and 20 mg tablets, 1 tablet, orally, with a glass of water, once a day, upon waking in the morning.
Batchs No. L0039271; L0042471; L0039278; L0042483; L0039285; L0042485.

Reference product:
Placebo: one tablet, orally, with a glass of water, once a day, upon waking in the morning.

Duration of treatment:

- A 2-6-week selection period without study treatment.
- A 24-week double-blind treatment period followed by a 24-week optional treatment extension period.
- A 2-week follow-up period without study treatment.

Criteria for evaluation:
Efficacy measurements:

- *Primary criterion:* Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) 11-item administered at inclusion, W12, W24, W36 and W48 or in case of premature withdrawal. The main analytical approach was the change from baseline to W24.
- *Key secondary criterion:* Disability Assessment for Dementia (DAD) administered at inclusion, W24 and W48 or in case of premature withdrawal. The main analytical approach was the change from baseline to W24.
- *Secondary criteria:* Mini Mental State Examination (MMSE) at selection, inclusion, W12, W24 and W48 or in case of premature withdrawal; Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) and Neuropsychiatric Inventory (NPI) at inclusion, W24 and W48 or in case of premature withdrawal; Zarit Burden Inventory (ZBI) at inclusion, W12, W24 and W48 or in case of premature withdrawal.
- *Exploratory criteria*: WAIS IV Coding, Category Fluency Test (CFT), Benton Visual Retention Test (BVRT) and WAIS IV Digit Span, administered at inclusion, W12, W24, W36 and W48 or in case of premature withdrawal.

Safety measurements:

- *Adverse events:* At each visit from ASSE.
- *Vital signs (blood pressure and body temperature), height and body weight:* At each visit or in case of premature withdrawal except height at selection only and weight not measured at W4.
- *12 lead-ECG (centralised):* At ASSE, W0, W4, W24, W48 and WEND or in case of premature withdrawal.
- *Biological laboratory examinations:* At each visit from selection or in case of premature withdrawal for all parameters except for thyroid hormones at selection only.

Pharmacokinetic measurements:
A total of 6 blood microsamples (2 at W4 and 4 at W12) were to be collected in all patients to determine S38093 blood concentrations. Analyses and results will be provided in a separate report.

Metabolism profiling:
Measurement of plasma endogenous biomarker metabolites at inclusion, W12 and W24 (before study treatment) to assess potential circulating biomarkers associated to the treatment with S 38093 of Alzheimer's patients. Analyses and results will be provided in a separate report.

Statistical methods:
Efficacy analyses

- **Primary and key secondary criteria**
  - *Main analysis (primary criterion)*: The superiority of at least one dose of S 38093 as compared to placebo on the cognitive performance after 24 weeks of treatment was assessed from the 11-item ADAS-Cog total score expressed in terms of change from baseline to W24, in patients of the Full Analysis Set (FAS). A mixed-effects repeated measures (MMRM) analysis using all the longitudinal observations at each post-baseline visit was used.
  - *Secondary analysis (key secondary criterion)*: The superiority of at least one dose of S 38093 as compared to placebo on activities of daily living after 24 weeks of treatment were assessed from the DAD total score expressed in terms of change from baseline at W24, in patients of the FAS. Due to only one post-baseline assessment of the key secondary criterion on the W0-W24 period, an analysis of covariance (ANCOVA) model with the Last Observation Carried Forward (LOCF) method for handling missing data was used.
  - *Sensitivity analyses:* To assess the robustness of the main and key secondary analyses results, sensitivity analyses to the method of handling missing data were performed in patients of the FAS considering a multiple imputation (MI) approach, the LOCF method and an Observed Cases (OC) analyses and using two single three-way ANCOVA models (one for each of the studied criteria) on the factors treatment, country and severity of the disease with baseline as covariate and no interaction. Main and secondary analyses were also performed in the Per Protocol Set (PPS).

Statistical methods (Cont'd):
Efficacy analyses (Cont'd)

- **Secondary criteria**
  - ADCS-CGIC score: the difference between the three S 38093 doses and placebo in the clinical global impression of change after 24 weeks of treatment was studied from the value at W24 of the ADCS-CGIC score, considering the LOCF method for handling missing data, and using a stratified Wilcoxon rank sum test using modified ridit scores with severity of the disease and country as stratification factors, in patients of the FAS.
  - Descriptive statistics of most efficacy criteria were provided in patients of the FAS, PPS, Observed Cases W48 Set (OCW48S), Re-Randomised Full Analysis Set (RFAS) and Re-Randomised Observed Cases W48 Set (ROCW48S). In addition to description by treatment group, descriptive statistics were also provided by level of severity and ApoE Ɛ4 genotype status.

Safety analysis
Descriptive statistics for serious and emergent adverse events, laboratory parameters, vital signs, ECG parameters and abnormalities were provided:

- In the Safety Set by treatment group over the ASSE-W24/WEND period.
- In SS patients on S 38093 at W0 dose by treatment group over the ASSE-W48/WEND period.
- In the RSS (*i.e.* included patients on placebo over the W0-W24 period, entering the extension period, and having taken at least one dose of S 38093 after W24) by treatment group over the W24-W48/WEND period.

SUMMARY – CONCLUSIONS
STUDY POPULATION AND OUTCOME

Overall, 1079 patients were selected and 711 patients were included and randomised: 176 patients in the S 38093 2 mg group, 175 patients in the S 38093 5 mg group, 181 patients in the S 38093 20 mg group and 179 patients in the placebo group.
During the W0-W24 period, 78 patients (11.0%) were withdrawn. The rate of withdrawals was higher in the S 38093 2 mg group (14.2%) than in the S 38093 5 mg, 20 mg and placebo groups (9.7%, 10.5% and 9.5% respectively), mainly due to non-medical reason (8.0% *versus* 5.1%, 4.4% and 3.9% respectively). The other most frequent reason for withdrawal was adverse event, with no relevant between-group differences (3.4% in the S 38093 2 mg and 5 mg, and placebo groups, and 3.9% in the S38093 20 mg group). Overall, 633 patients (89.0%) completed the W0-W24 period. Among them 619 entered the W24-W48 period: 148 patients in the S 38093 2 mg group, 155 in the S 38093 5 mg group, 158 in the S 38093 20 mg group; and 158 patients initially on placebo were re-randomised at W24 with a well-balanced distribution (53 patients in the placebo / S 38093 2 mg group, 50 patients in the placebo / S 38093 5 mg group and 55 patients in the placebo / S 38093 20 mg group).
During the W0-W48 period in patients on S 38093 at W0, 94 patients (17.7%) were withdrawn, mainly for non-medical reason (8.5%) and adverse event (7.0%). Of the 532 patients randomised on S 38093 at W0, 428 (80.5%) completed the W0-W48 period. No patient was lost to follow up during the study.

At baseline in the RS, patients were on average (± SD) 72.1 ± 7.2 years old. A majority of patients were female (62.2%). No clinically relevant differences were observed in the gender distribution. Most patients were of Caucasian origin (88.1%). No relevant difference between treatment groups were observed for clinical examination and ECG parameters, except for orthostatic hypotension, observed with a slightly higher frequency in the S 38093 2 mg group (10.8%) than in the other groups (5.7%, 7.2% and 7.8% in the S 38093 5 mg, 20 mg and placebo groups, respectively). Almost all patients were extensive metabolisers (92.8%) for CYP 2C19 and 50.6% were ApoE Ɛ4 carrier.

At selection, mean MMSE was 20.0 ± 3.3, indicating that patients had mild or moderate Alzheimer's disease on average, as required in the protocol. Mean modified Hachinski ischaemic score was 1.0 ± 0.9, indicating on average the absence of dementia related to cerebral ischaemia. Mean GDS was 2.4 ± 1.4, indicating that patients were globally not depressed. Mean duration of Alzheimer's disease before entering into the study was 3.5 ± 2.5 years. Overall 215 patients (30.2%) previously received treatment for Alzheimer, mainly donepezil (hydrochloride, 11.0% and donepezil, 5.6%). Regarding above characteristics of Alzheimer's disease, no relevant differences between groups were detected.

SUMMARY – CONCLUSIONS (Cont'd)
STUDY POPULATION AND OUTCOME (Cont'd)

As regards to ADAS-Cog and DAD total scores, mean scores at baseline were respectively 23.6 ± 10.1 and 72.6 ± 20.1%, with no relevant between-group differences. NPI-10 item mean total score was 8.7 ± 11.2 and NPI-12 item mean total score was 10.3 ± 13.2 with no relevant differences between treatment groups for total, frequency, severity and distress scores. ZBI mean total score was 22.6 ± 15.5, without relevant difference between groups.

Demographic data and other baseline characteristics in the FAS (690 patients, 97.0% of the RS) and in the PPS (569 patients, 80.0% of the RS) were similar to those described in the RS.

In the RS, mean treatment duration was 159.5 ± 34.8 days (median = 168.0 days) and mean overall compliance was 96.6 ± 11.3%. The compliance was good: 97.0% of the patients had an overall compliance between 70% and 130%. No overdose was reported. There were no relevant between-group differences.

RS patients on S 38093 at W0 (532 patients) and FAS patients on S 38093 at W0 (517 patients, 97.2% of RS patients on S 38093 at W0) consisted of patients randomised in the S 38093 2 mg, S 38093 5 mg, and S 38093 20 mg groups at W0, whether they entered the extension period or not. Their baseline characteristics were therefore those already described above.
In RS patients on S 38093 at W0, mean treatment duration was 300.8 ± 86.8 days (median = 336.0 days). Similarly to the 24-week double-blind treatment period in the RS, the compliance was good as 97.6% of patients had an overall compliance between 70% and 130% (no overdose was reported), with a mean overall compliance of 96.5 ± 11.1%. There was no relevant between-group difference.

EFFICACY RESULTS
Primary criterion

ADAS-Cog total score - Change from baseline to W24
Comparison between groups in the FAS

		S 38093 2 mg (N = 168)	S 38093 5 mg (N = 172)	S 38093 20 mg (N = 177)	Placebo (N = 173)
Baseline (W0)	n	168	172	177	173
	Mean ± SD	24.38 ± 10.11	23.27 ± 10.41	22.55 ± 9.87	23.58 ± 9.56
Change from baseline to W24	n	153	161	166	161
	Mean ± SD	-0.45 ± 5.32	0.10 ± 5.53	-0.12 ± 5.22	0.34 ± 5.55
Statistical analysis[(1)]	E (SE) [(2)]	-0.84 (0.59)	-0.27 (0.59)	-0.63 (0.58)	
	95% CI [(3)]	[-2.00 ; 0.32]	[-1.42 ; 0.88]	[-1.78 ; 0.51]	
	p-value [(4)]	0.470	1.000	0.835	

*(1) Mixed-effects Model for Repeated Measures including terms for fixed categorical effects of treatment, pooled country, severity of the disease, visit and an interaction term treatment*visit, as well as the continuous, fixed covariate of baseline ADAS-Cog total score*
(2) Estimate (Standard Error) of the difference between adjusted treatment group means: S 38093 dose minus placebo
(3) Two-sided 95% Confidence Interval of the estimate (without Bonferroni-based adjustment)
(4) Two-sided adjusted p-value, taking into account a Bonferroni-based sequentially rejective multiple test procedure for multiplicity adjustment

In the FAS, mean changes from baseline to W24 in ADAS-Cog total score did not show statistically significant difference between any S 38093 dose group and the placebo group. Results were confirmed by the sensitivity analyses.
Similar results were observed in the PPS.

Analysis by level of severity showed neither relevant change between baseline and W24, nor relevant differences between S 38093 and placebo groups.

SUMMARY - CONCLUSIONS (Cont'd)
EFFICACY RESULTS (Cont'd)

As regards to the mean ADAS-Cog total score by ApoE genotype status in the FAS, neither relevant change between baseline and W24 nor differences between S 38093 and placebo groups were observed in both ApoƐ4 carriers (50.6% of FAS patients) and ApoƐ4 non-carriers (45.7% of FAS patients). Mean changes from baseline to W24 period were as follows:

- ApoE Ɛ4 carriers: -0.2 ± 5.4 in the S 38093 2 mg group, 1.0 ± 5.8 in the S 38093 5 mg group, -0.2 ± 5.0 in the S 38093 20 mg group and 1.0 ± 5.5 in the placebo group.
- ApoE Ɛ4 non-carriers: -0.9 ± 5.2, -0.7 ± 5.3, -0.1 ± 5.3 and -0.3 ± 5.6, respectively.

Key secondary criterion

DAD total score (%) - Change from baseline to W24
Comparison between groups in the FAS

		S 38093 2 mg (N = 168)	S 38093 5 mg (N = 172)	S 38093 20 mg (N = 177)	Placebo (N = 173)
Baseline (W0)	n	161	166	170	168
	Mean ± SD	72.4 ± 20.7	73.2 ± 19.4	73.9 ± 19.2	73.3 ± 19.8
Change from baseline to W24	n	161	166	170	168
	Mean ± SD	-2.1 ± 11.2	-2.7 ± 12.3	-2.9 ± 13.5	-3.4 ± 10.9
Statistical analysis[(1)]	E (SE) [(2)]	1.3 (1.3)	0.6 (1.3)	0.5 (1.3)	
	95% CI [(3)]	[-1.3 ; 3.9]	[-2.0 ; 3.1]	[-2.01 ; 3.07]	
	p-value [(4)]	0.936	1.000	1.000	

(1) Analysis of covariance model on factors treatment, pooled country and severity of the disease with baseline as covariate and no interaction, considering the LOCF method for handling missing data at W24 and for patients with baseline and at least one post-baseline values(2) Estimate (Standard Error) of the difference between adjusted treatment group means: S 38093 dose minus placebo (3)Two-sided 95% Confidence Interval of the estimate (without Bonferroni-based adjustment)
(4) Two-sided adjusted p-value, taking into account a Bonferroni-based sequentially rejective multiple test procedure for multiplicity adjustment

In the FAS, mean changes from baseline to W24 in DAD total score did not show statistically significant difference between any S 38093 dose groups and the placebo group. Results were confirmed by the sensitivity analyses.

During the 48-week treatment period in FAS patients initially on S 38093, no relevant mean changes from baseline to W48 nor differences between the 3 dose groups were observed for:

- ADAS-Cog total score: 0.21 ± 6.03 (median 0.30) in the S 38093 2 mg group, 0.90 ± 6.99 (median -0.10) in the S 38093 5 mg group, and 1.65 ± 6.89 (median 1.70) in the S 38093 20 mg group.
- DAD total score: -5.4 ± 14.0% (median -4.4%), -8.5 ± 16.2% (median -5.0%) and -6.1 ± 17.0% (median -2.5%), respectively.

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS

Adverse events

Summary of safety results over the 24-week double-blind treatment period – Safety Set

		S 38093 2 mg (N = 176)	S 38093 5 mg (N = 175)	S 38093 20 mg (N = 180)	Placebo (N = 178)
Patients having reported					
at least one emergent adverse event	n (%)	85 (48.3)	93 (53.1)	108 (60.0)	90 (50.6)
at least one treatment-related emergent adverse event	n (%)	19 (10.8)	18 (10.3)	25 (13.9)	17 (9.6)
Patients having experienced					
at least one serious adverse event	n (%)	18 (10.2)	20 (11.4)	23 (12.8)	19 (10.7)
at least one serious emergent event (including death)	n (%)	16 (9.1)	17 (9.7)	22 (12.2)	12 (6.7)
at least one treatment-related serious adverse event	n (%)	1 (0.6)	2 (1.1)	-	-
Patients withdrawn					
due to emergent adverse event	n (%)	7 (4.0)	6 (3.4)	6 (3.3)	7 (3.9)
due to serious emergent adverse event	n (%)	3 (1.7)	4 (2.3)	3 (1.7)	4 (2.2)
due to treatment-related EAE	n (%)	4 (2.3)	3 (1.7)	3 (1.7)	1 (0.6)
due to a treatment-related serious EAE	n (%)	1 (0.6)	1 (0.6)	-	-
Patients who died	n (%)	3 (1.7)	2 (1.1)	1 (0.6)	-

In the Safety Set ***during the 24-week double-blind treatment period*****,** the percentage of patients with at least one emergent adverse event was higher in the S 38093 20 mg group than in the placebo group and similar to placebo in the S 38093 2 mg group. To a lesser extent, the percentage of patients with at least one EAE as well as the total number of EAEs tended to be slightly higher in the S 38093 5 mg group than in the placebo group (233 EAEs *versus* 198 EAEs).

Among the most frequent system organ classes affected (> 10% of patients), higher frequencies on S 38093 than on placebo were observed for infections and infestations, more frequently reported in the S 38093 5 mg and 20 mg groups than in the placebo group (18.9% and 16.7% respectively *versus* 14.0%); gastrointestinal disorders, more frequently reported in the S 38093 20 mg than in the placebo group (16.1% *versus* 7.3%); and psychiatric disorders more frequently reported in the S 38093 5 mg and 20 mg groups than in the placebo group (10.9% and 12.2% respectively *versus* 6.7%).

Among EAEs reported by at least 3% of the patients in any of the S 38093 groups, the following were more frequently reported in at least one of the S 38093 groups than in the placebo group: fall (4.5%, 4.6% and 4.4% respectively in the S 38093 2 mg, 5 mg and 20 mg groups, *versus* 2.2% in the placebo group), diarrhoea (5.0% in the S 38093 20 mg group *versus* 2.2% in the placebo group), nausea (3.9% in the S 38093 20 mg group *versus* 1.7% in the placebo group), depression (3.9% in the S 38093 20 mg group *versus* 1.1% in the placebo group), bacteriuria (4.6% in the S 38093 5 mg group *versus* 2.8% in the placebo group), hypercholesterolaemia (4.5% in the S 38093 2 mg group *versus* 1.7% in the placebo group), leukocyturia (4.0% in the S 38093 5 mg group *versus* 1.7% in the placebo group), and blood creatine phosphokinase increased (3.4% in the S 38093 2 mg group *versus* 1.7% in the placebo group).

The incidence of patients with at least one emergent orthostatic hypotension was low in all groups (3 patients [1.7%] in each of the S 38093 2 mg, 5 mg and placebo groups and 6 patients [3.3%] in the S 38093 20 mg group). When calculated based on SBP and DBP measures, emergent orthostatic hypotensions were more frequent in the S 38093 2 mg, 5 mg and 20 mg groups (17.0%, 14.2% and 17.1%, respectively) than in the placebo group (12.0%).

Severe EAEs were reported with a slightly higher incidence in the S 38093 groups than in the placebo group (4.0%, 4.0%, and 3.9% respectively in the S 38093 2 mg, 5 mg and 20 mg groups, *versus* 2.8% in the placebo group), with no particular preferred term affected, whatever the treatment-group.

Treatment-related EAEs were more frequently reported in the S 38093 20 mg group (13.9%) than in the placebo group (9.6%), and similar to placebo in the S 38093 2 mg and S 38093 5 mg groups (10.8% and 10.3%, respectively). The most frequent treatment-related EAEs in the S 38093 groups were somnolence (1.7% in the S 38093 5 mg group), dizziness (2.2% in the S 38093 20 mg group), headache (2.3% in the S 38093 5 mg group) and nausea (2.3% in the S 38093 5 mg group and 2.8% in the S 38093 20 mg group).

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Six patients died during the 24-week double-blind treatment period: from intestinal perforation, sudden death and colon cancer in the S 38093 2 mg group, pancreatitis acute and haemorrhagic stroke in the S 38093 5 mg group, and following a cardiorespiratory arrest in the S 38093 20 mg group. None of these deaths were considered as treatment-related.

During the 24-week double-blind treatment period, patients having reported serious EAEs (including deaths) were more frequent in the S 38093 groups than in the placebo group (9.1% in the S 38093 2 mg group, 9.7% in the S 38093 5 mg group, 12.2% in the S 38093 20 mg *versus* 6.7% in the placebo group). The most frequent SEAEs were fall in 11 patients overall (1.6%) with no relevant between-group differences, and depression in 7 patients overall (1.0%) with a higher incidence in the S 38093 20 mg group (5 patients, 2.8%) than in the others groups (none in the S 38093 5 mg group and 1 patient, 0.6% in both the S 38093 2 mg and placebo groups). Five SEAEs were considered as treatment-related (insomnia and somnolence, and dementia Alzheimer's type in 2 patients in the S 38093 5 mg group and thrombocytopenia and petechiae in one patient in the S 38093 2 mg group).

EAEs (including serious events) leading to study treatment withdrawal occurred in 4.0% of patient in the S 38093 2 mg group, 3.4% in the S 38093 5 mg group, 3.3% in the S 38093 20 mg group and 3.9% in the placebo group, with no specific preferred term involved.

Summary of safety results over the 48-week treatment period in SS patients on S 38093 at W0

		S 38093 2 mg (N = 176)	S 38093 5 mg (N = 175)	S 38093 20 mg (N = 180)
Patients having reported				
at least one emergent adverse event	n (%)	102 (58.0)	115 (65.7)	126 (70.0)
at least one treatment-related emergent adverse event	n (%)	22 (12.5)	24 (13.7)	31 (17.2)
Patients having experienced				
at least one serious adverse event	n (%)	29 (16.5)	30 (17.1)	36 (20.0)
at least one serious emergent event (including death)	n (%)	26 (14.8)	26 (14.9)	34 (18.9)
at least one treatment-related serious adverse event	n (%)	1 (0.6)	2 (1.1)	3 (1.7)
Patients withdrawn				
due to emergent adverse event	n (%)	12 (6.8)	10 (5.7)	10 (5.6)
due to serious emergent adverse event	n (%)	7 (4.0)	7 (4.0)	6 (3.3)
due to treatment-related EAE	n (%)	4 (2.3)	4 (2.3)	6 (3.3)
due to a treatment-related serious EAE	n (%)	1 (0.6)	1 (0.6)	2 (1.1)
Patients who died	n (%)	5 (2.8)	2 (1.1)	3 (1.7)

During the 48-week treatment period in SS patients on S 38093 at W0, the safety profile was similar to the one described during the 24-week double-blind treatment period with higher frequencies consistently with the longer exposure to treatment.

Regarding deaths, in addition to those already reported during the 24-week double-blind treatment period in SS patients on S 38093 at W0, four deaths were reported after W24 in SS patients on S 38093 at W0 (from unknown cause and lobar pneumonia in the S 38093 2 mg group, and pulmonary embolism and rectal adenocarcinoma in the S 38093 20 mg group). None of these deaths were considered as treatment-related.

In addition, during the W24-W48 extension period, in the placebo-treated patients up to W24 and re-randomised on S38093 (N = 158), one patient in the placebo / S 38093 20 mg group, died from cardiac failure acute. This event was not considered as related to the study treatment.

SUMMARY - CONCLUSIONS (Cont'd)
SAFETY RESULTS (Cont'd)

During the 48-week treatment period in SS patients on S 38093 at W0, consistently with the longer exposure to study treatment, the percentage of patients with at least one SEAE was higher than the one during the 24-week double-blind treatment period (14.8%, 14.9% and 18.9%, respectively in the S 38093 2 mg, S 38093 5 mg and S 38093 20 mg groups). Fall and depression were the most frequently reported events (2.8% and 1.5% of patients overall). In addition to those already described over the 24-week double-blind treatment period in SS patients on S 38093 at W0, 7 SEAEs in 3 patients, all reported in the S 38093 20 mg group, were considered as treatment-related: cardiac failure congestive, sinus arrhythmia, atrioventricular block first degree, supraventricular extrasystoles and cognitive disorder, grand mal convulsion and electrocardiogram QT prolonged.

In addition, during the W24-W48 extension period, in the placebo-treated patients up to W24 and re-randomised on S38093 (N = 158), 25 SEAEs were reported by 12 patients (7.6%) (7 patients, 13.2%, in the placebo / S 38093 2 mg group, 1 patient, 2.0%, in the placebo / S 38093 5 mg group and 4 patients, 7.3%, in the placebo / S 38093 20 mg group). None was reported in more than 2 patients in any group and none was considered as treatment-related.

Laboratory parameters
Neither clinically relevant changes from baseline to last post-baseline value on treatment nor differences between groups were detected for biochemical and haematological parameters over the 24-week double-blind period in the Safety Set, and the 48-week treatment period in SS patients on S 38093 at W0.
During the ASSE-W24/WEND period in the Safety Set, emergent potentially clinically significant abnormal (PCSA) values for high cholesterol were more frequently observed in the S 38093 groups than in the placebo group, especially in the 20 mg group (2.9%, 2.9% and 5.1% of patients respectively in the S 38093 2 mg, 5 mg and 20 mg groups *versus* 1.2% in the placebo group). As regards to haematological parameters, emergent PCSA values for low haematocrit were more frequently observed in the S 38093 20 mg group (2.8%) than in the placebo group (1.2%), and emergent PCSA values for low WBC more frequently observed in the S 38093 2 mg and S 38093 20 mg groups than in the placebo group (1.7% and 2.3%, respectively *versus* none).

During the ASSE-W48/WEND period in SS patients on S 38093 at W0, emergent PCSA values were detected with similar frequency in all treatment groups, except for low haematocrit in SS patients on S 38093 at W0 that was higher in the S 38093 20 mg group than in other groups (3.4% *versus* 1.7% in both S 38093 2 mg and 5 mg groups) and low WBC that was higher in the S 38093 2 mg and 20 mg groups (2.3% in both groups) than in the S 38093 5 mg group (0.6%).
Regarding endocrinology results, an increase in prolactin level over the 24-week double-blind treatment period was observed in all S 38093 groups, especially with the 20 mg dose (mean increases: 1.1 ± 6.4 µg/L, 1.3 ± 9.4 µg/L, and 3.4 ± 26.2 µg/L in the S 38093 2 mg, 5 mg and 20 mg groups *versus* -0.4 ± 11.3 µg/L in the placebo group). Similar results were observed during the 48-week treatment period in SS patients on S 38093 at W0.

Clinical examination
Neither clinically relevant changes nor differences between treatment groups were detected in vital signs or clinical examination over the 24-week double-blind period in the Safety Set, and the 48-week treatment period in SS patients on S 38093 at W0.
During the 24-week double-blind treatment period, the percentage of patients with at least one emergent ECG abnormality under treatment showed no relevant between-group differences (8.5%, 7.4%, 10.0%, and 9.0% in the S 38093 2 mg, 5 mg, 20 mg and placebo groups, respectively). Neither clinically relevant changes nor differences between treatment groups were detected over time regarding ECG parameters.
Similar results were observed during the 48-week treatment period in SS patients on S 38093 at W0.

CONCLUSION

This international, multi-centre, randomised, double-blind, placebo-controlled phase IIb study conducted in patients suffering from mild to moderate Alzheimer's Disease did not show any statistically or clinically significant effect of S 38093 on cognitive functions, functional ability, clinical global impression of change, or behavioral symptoms at the 2 mg, 5 mg or 20 mg doses *versus* placebo after 24 weeks of treatment.
In addition, no relevant changes were showed after 48 weeks of treatment in patients on S 38093 at W0.

Emergent adverse events were more frequent with S 38093 20 mg than with placebo. Emergent fall was the most common adverse event on S 38093 with a higher incidence with the 3 doses than with placebo. Regarding biological safety, S 38093 was well tolerated. A slight expected dose-dependent prolactinaemia increase was observed. No concerns were observed regarding other safety assessments, especially orthostatic hypotension and ECG abnormalities.

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