Document title	**Clinical Study Report Synopsis**
Study title	**Safety and efficacy of S 38093 and donepezil, during 4 weeks, in patients with mild to moderate Alzheimer's Disease.** **An international, multi-centre, randomised, double-blind, placebo controlled, phase II add-on study**
Study drug	**S 38093**
Studied indication	**Alzheimer's Disease**
Development phase	**Phase IIa**
Protocol code	**CL2-38093-009**
Study initiation date	**5 November 2009**
Study completion date	**8 July 2010**
Main coordinator	[redacted] **Portugal**
Company / Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50, rue Carnot** **92284 Suresnes Cedex - France** **Laboratorios Servier** **33 Avda. de los Madronos** **28043 Madrid - Spain**
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	**Final version of 9 March 2012**

~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
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Title of study:
Safety and efficacy of S 38093 and donepezil, during 4 weeks, in patients with mild to moderate Alzheimer's Disease.
An international, multi-centre, randomised, double-blind, placebo controlled, phase II add-on study.
Protocol No.: CL2-38093-009.

Coordinators: [redacted] Italy), [redacted], Portugal), [redacted] Spain).

Study centres:
25 centres located in 3 countries were opened, and included at least one patient: Italy: (11 centres – 53 included patients), Portugal (4 centres - 18 included patients), and Spain (10 centres - 35 included patients).

Publication (reference): Not applicable

Studied period: Initiation date: 5 November 2009 Completion date: 8 July 2010	**Phase of development of the study:** IIa

Objectives:
The primary objective of this study was to assess the safety of S 38093 (5, 10 , 20 or 50 mg/day) in combination with donepezil (10 mg/day) after 4 weeks of co-administration, in patients with mild to moderate Alzheimer's disease (AD) and treated with donepezil for at least 6 months.
The secondary objectives were to assess the efficacy after 4 weeks of the co-administration of S 38093 and donepezil in patients with mild to moderate AD and treated with donepezil for at least 6 months, and to evaluate in patients the pharmacokinetic characteristics of S 38093 added to donepezil.

Methodology:
This study was a phase II, international, multi-centre, randomised, double-blind, 5 parallel-group, placebo-controlled add-on study. One hundred patients with mild to moderate AD and treated with donepezil for at least 6 months (with a stable dosage of 10 mg/day for at least four months), were to be included and randomly assigned to receive, in addition to donepezil, either S 38093 5 mg /day or S 38093 10 mg /day or S 38093 20 mg/day or S 38093 50 mg/day or placebo. The study treatments were allocated at W0 by balanced randomisation with stratification on centre.
This study was performed in strict accordance with Good Clinical Practice.

Number of patients:
Planned: 100 patients, 20 patients by group.
Included: 106 patients: 24 patients in the S 38093 5 mg group, 20 patients in the S 38093 10 mg group, 22 patients in the S 38093 20 mg group, 17 patients in the S 38093 50 mg group, and 23 patients in the placebo group.

Diagnosis and main criteria for inclusion:

Male or female out-patients, aged 55-85 years (inclusive), fulfilling DSM-IV-TR criteria for Dementia of Alzheimer's Type, and NINCDS/ ADRDA criteria for probable AD, with a Mini Mental State Examination (MMSE) between 15 and 26, inclusive, a modified Hachinski Ischemic Score ≤ 4, and a Geriatric Depression Rating Scale-15 (GDS) < 6, being treated with donepezil for at least 6 months, at the dose of 10 mg/day for at least 4 months, being an extensive metaboliser (homozygous or heterozygous) for cytochrome 2C19, and having a responsible caregiver.

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Study drug:
S 38093: 5 mg, 10 mg, and 25 mg tablets, 2 tablets, orally, once a day, in the morning before breakfast. Patients received 5 mg /day or 10 mg /day or 20 mg/day or 50 mg/day for 4 weeks. A titration was performed in the S 38093 50 mg group (20 mg of S 38093 for one week, and 50 mg of S 38093 the three remaining weeks).
Batch No. L0027934, L0027961, L0027963.

Reference product:
Placebo: 2 tablets, orally, once a day, in the morning before breakfast.

Duration of treatment:

- 2- to 6-week selection period with donepezil 10 mg/day.
- 4-week double-blind add-on treatment period.
- 2-week follow-up period with donepezil 10 mg/day.

Criteria for evaluation:

Efficacy measurements:

- CogState computerised test battery: administered at selection, W0, W1, W2, W4 and Wend or in case of premature withdrawal.
- Alzheimer's Disease Cooperative Study Unit Clinician's Global Impression of Change (ADCS-CGIC): administered at W0 and W4, or in case of premature withdrawal.
- Neuropsychiatric inventory (NPI): administered at W0 and W4, or in case of premature withdrawal.
- Epworth Sleepiness Scale (ESS): administered at W0 and W4, or in case of premature withdrawal.

Safety measurements:

- Adverse events: assessed at each visit from selection or in case of premature withdrawal.
- Laboratory tests: blood samplings were collected at each visit or in case of premature withdrawal for all parameters (biochemistry, haematology, and endocrinology) except for thyroid hormones not measured at W2 and Wend.
- Vital signs: all parameters (supine and standing SBP, DBP, and HR, respiratory rate, body weight, and body temperature) were measured at each visit or in case of premature withdrawal except height at selection visit only.
- ECG: 12-lead ECGs performed at each visit or in case of premature withdrawal.
- Physical examination, including neurological and mental status examination at each visit or in case of premature withdrawal.

Pharmacokinetic measurements:

[redacted]

Statistical methods:
Only descriptive analyses were performed for study outcome, efficacy, and safety.
Pharmacokinetic analysis: Descriptive statistics were performed on S 38093 plasma concentrations and described in the analytical report. Descriptive statistics were performed on PK parameters.

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SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

Disposition of patients

Status		**S 38093 5 mg**	**S 38093 10 mg**	**S 38093 20 mg**	**S 38093 50 mg**	**Placebo**	**All**
Included and randomised	**n**	**24**	**20**	**22**	**17**	**23**	**106**
Withdrawn due to	**n (%)**	**-**	**2 (10.0)**	**1 (4.5)**	**-**	**3 (13.0)**	**6 (5.7)**
Adverse event	n (%)	-	1 (5.0)	-	-	1 (4.3)	2 (1.9)
Protocol deviation	n (%)	-	1 (5.0)	-	-	1 (4.3)	2 (1.9)
Non-medical reason	n (%)	-	-	1 (4.5)	-	1 (4.3)	2 (1.9)
Completed the W0-W4 period	**n (%)**	**24 (100.0)**	**18 (90.0)**	**21 (95.5)**	**17 (100.0)**	**20 (87.0)**	**100 (94.3)**
Performed the follow-up visit	n (%)	*24 (100.0)*	*18 (90.0)*	*21 (95.5)*	*17 (100.0)*	*21 (91.3)*	*101 (95.3)*
Analysis sets							
Randomised Set	n	24	20	22	17	23	106
Safety set	n (%)	24 (100.0)	19 (95.0)	21 (95.5)	17 (100.0)	23 (100.0)	104 (98.1)
Full Analysis Set (FAS)	n (%)	24 (100.0)	19 (95.0)	21 (95.5)	17 (100.0)	22 (95.7)	103 (97.2)

Overall, 152 patients were selected and 106 patients were randomised: 24 patients in the S 38093 5 mg group, 20 patients in the S 38093 10 mg group, 22 patients in the S 38093 20 mg group, 17 patients in the S 38093 50 mg group and 23 patients in the placebo group.

During the W0-W4 period, 6 patients were prematurely withdrawn from the study: 2 patients in the S 38093 10 mg group, 1 patient in the S 38093 20 mg group and 3 patients in the placebo group. The reasons for withdrawals were adverse events, protocol deviation and non-medical reason (2 patients each). Finally, 100 patients (94.3%) completed the study.

At selection, in the Randomised Set, patients were 73.4 ± 7.5 years old on average (± SD). Most patients were female (54.7%). All patients were of caucasian origin. Overall, the patients had an educational level of 7.6 ± 4.0 years on average. No relevant difference between treatment groups were observed for demographic characteristic except for the percentage of female patients which ranged from 41.2% in the S 38093 50 mg group to 63.6% in the S 38093 20 mg group.

At selection, the mean MMSE was 20.1 ± 2.9, indicating that patients mild or moderate Alzheimer's disease on average. The percentage of patients with mild dementia (MMSE > 20) was lower than those with moderate (20≥MMSE≥10) dementia (42.9% *versus* 57.1%). The mild patients were more frequent in the S 38093 10 mg and placebo groups (50.0% and 52.2%, respectively) than in the other groups (39.1%, 36.4% and 35.3% in the S 38093 5 mg, 20 mg and 50 mg groups, respectively). The mean modified Hachinski ischaemic score was 0.8 ± 0.8, indicating the absence of dementia related to ischaemia on average. The mean GDS was 2.3 ± 1.8, indicating that patients had no major depression on average. All patients performed a brain imaging. All patients previously received donepezil. Concerning the characteristics of Alzheimer's disease, no relevant difference between groups were detected.

At baseline, no relevant difference between treatment groups were detected for all scores of the Cogstate computerised test battery. At baseline, the mean speeds of performance were 2.705 ± 0.169 Log10 ms for detection task, 2.713 ± 0.141 Log10 ms for re-detection task and 2.870 ± 0.115 Log10 ms for identification task. The mean change in speed of performance was -0.013 ± 0.103 Log10 ms for sustained attention. For one-back memory task, the mean accuracy of performance was 0.793 ± 0.220.

For all NPI scores at inclusion, some differences between groups were observed with the lowest median reported in the S 38093 10 mg group, and the highest median reported in the S 38093 20 mg group (median NPI 10-item total score of 3.0 and 9.0, respectively, and median NPI 12-item total score of 3.5 and 13.5, respectively).

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SUMMARY - CONCLUSIONS (cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

At inclusion, the mean ESS total score was 5.5 ± 3.9. There were no relevant differences between the treatment groups.

Baseline characteristics in the FAS were similar to those described in the RS.

In the Randomised Set, the mean treatment duration was of 27.3 ± 5.0 days (median of 28.0 days). During the W0-W4 period, the compliance was 96.3 ± 16.5% in the Randomised Set and was satisfactory (within the [70-130%] range) for 96.2% of the patients. No relevant differences between treatment groups were observed.

EFFICACY RESULTS

- Cogstate computerised test battery

  In the FAS, the mean change from baseline to the last post-baseline assessment over the W0-W4 period showed no relevant difference between each S 38093 dose group and the placebo group for all measurements (see Table below).

Cogstate computerised test battery: mean change from baseline at the last post-baseline assessment over the W0-W4 period in the FAS

		S 38093 5 mg (N = 24)	**S 38093 10 mg (N = 19)**	**S 38093 20 mg (N = 21)**	**S 38093 50 mg (N = 17)***	**Placebo (N = 22)**
Speed of performance (detection task) (Log 10 ms)	Mean ± SD	-0.013 ± 0 113	-0.044 ± 0.130	-0.011 ± 0.095	0.008 ± 0.123	-0.025 ± 0.101
Speed of performance (re-detection task) (Log 10 ms)	Mean ± SD	-0.015 ± 0.096	0.014 ± 0.126	0.041 ± 0 159	0.027 ± 0.076	0.015 ± 0.141
Speed of performance (identification task) (Log 10 ms)	Mean ± SD	-0.007 ± 0.076	-0.013 ± 0.094	-0.016 ± 0.100	-0.028 ± 0.082	-0.013 ± 0.119
Accuracy of performance (one–back memory task)	Mean ± SD	0.100 ± 0.145	0.065 ± 0.166	-0.039 ± 0.143	0.008 ± 0.204	0.053 ± 0.195
Change in speed of performance (sustained attention) (Log 10 ms)	Mean ± SD	0.005 ± 0.115	-0.054 ± 0.102	-0.035 ± 0.085	-0.016 ± 0.150	-0.041 ± 0.137

** n = 16 for re-detection task and sustained attention*

- ADCS-CGIC

  At the last assessment over the W0-W4 period, there were no relevant difference in the mean ADCS-CGIC score between each S 38093 dose group and the placebo group in the FAS:
  - S 38093 5 mg group: 3.5 ± 0.9.
  - S 38093 10 mg group: 3.7 ± 0.5.
  - S 38093 20 mg group: 4.0 ± 0.6.
  - S 38093 50 mg group: 3.9 ± 0.9.
  - Placebo group: 4.0 ± 0.6.

- NPI

  Over the W0-W4 period, in the FAS, the majority of patients in the S 38093 5 mg group had a decrease in 10-item total score at the last post-baseline assessment compared to baseline (median change of -2.0) whereas no noticeable change was observed in the other S 38093 dose groups as well as in the placebo group (median change of 0.0 in all groups). Similar results were observed for the frequency, severity and caregiver's distress total scores.

  However, as baseline scores were not similar, groups' size was low and inter patients variability was large, no conclusion can be drawn.

  As regards the 12-item total score, baseline differences do not allow any comparison of last post-baseline values.

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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

- ESS

  At the last post-baseline assessment over the W0-W4 period, the mean change from baseline in ESS total score showed no relevant difference between each S 38093 dose group and the placebo group in the FAS:
  - S 38093 5 mg group: 0.0 ± 2.6.
  - S 38093 10 mg group: 0.7 ± 3.8.
  - S 38093 20 mg group: -0.5 ± 2.4.
  - S 38093 50 mg group: 1.2 ± 4.4.
  - Placebo group: -0.8 ± 3.3.

SAFETY RESULTS

Adverse events

Overall summary of safety results

		S 38093 5 mg (N = 24)	**S 38093 10 mg (N = 19)**	**S 38093 20 mg (N = 21)**	**S 38093 50 mg (N = 17)**	**Placebo (N = 23)**
Patients having reported						
at least one emergent adverse event	n (%)	8 (33.3)	5 (26.3)	4 (19.0)	7 (41.2)	8 (34.8)
at least one treatment-related emergent adverse event	n (%)	-	2 (10.5)	-	2 (11.8)	-
Patients having experienced						
at least one serious adverse event*	n (%)	-	-	-	1 (5.9)	1 (4.3)
at least one treatment-related serious adverse event	n (%)	-	-	-	-	-
Patients withdrawn						
due to an adverse event	n (%)	-	1 (5.3)	-	-	1 (4.3)
due to a serious adverse event	n (%)	-	-	-	-	1 (4.3)
due a treatment-related adverse event	n (%)	-	1 (5.3)	-	-	-
Patients who died	n (%)	-	-	-	-	-

** None was emergent on treatment*

The percentage of patients with at least one emergent adverse event was lower in the S 38093 10 mg and 20 mg groups than in the placebo group (26.3% and 19.0% *versus* 34.8%), similar to placebo in the S 38093 5 mg group (33.3%), and higher in the S 38093 50 mg group than in the placebo group (41.2% *versus* 34.8%).

As regards S 38093 dose groups, the frequency of emergent adverse events did not increase with the dose.

Nervous system disorders was the most often affected system organ class and was the only one affected in all treatment groups. The percentage of patients concerned was lower in the S 38093 10 mg and 20 mg groups than in the placebo group (5.3% and 4.8% *versus* 8.7%), similar to placebo in the S 38093 5 mg group (8.3%), and slightly higher in the S 38093 50 mg group than in the placebo group (11.8% *versus* 8.7%).
Emergent adverse events in active treatment groups reported in 2 patients were fall and diarrhoea in the S 38093 5 mg group (8.3%) with a higher frequency than in the placebo group (none). All the other emergent adverse events were reported in one patient in at more 2 S 38093 dose groups.

No severe emergent adverse event was reported.

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SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Two patients (10.5%) in the S 38093 10 mg group, and 2 patients (11.8%) in the S 38093 50 mg group had experienced 6 emergent adverse event considered to be related to the study product.

Most emergent adverse events recovered or were recovering at the end of the study in the S 38093 5 mg (10/11), 10 mg (3/5) and 50 mg groups (9/11) as in the placebo group (8/10), and all in the S 38093 20 mg group (5/5).

No death was reported during the study. Two serious adverse events were reported during the study. None of them was emergent on treatment. One in the group 50 mg (atrial fibrillation) occurred 14 days after the last treatment intake, and one in the placebo group (thrombocytopenia) occurred one day before the first intake.
Adverse events led to treatment stop in 2 patients (1.9%). It was serious in 1 patient in the placebo group (thrombocytopenia), and non-serious and considered treatment-related in 1 patient in the S 38093 10 mg group (headache).

Laboratory tests, other safety evaluation

Neither clinically relevant changes nor differences between groups over time were detected between the baseline and the last post-baseline assessment on treatment over the selection – W4/Wend period for biochemical and haematological parameters, and thyroid hormones. For prolactin, there was a slight increase between the baseline and the last post-baseline assessment on treatment in the S 38093 10 mg and 50 mg groups (2.88 ± 4.80 mUI/L, and 2.02 ± 4.26 mUI/L, respectively) which was slightly higher than in the placebo group (1.48 ± 3.47 mUI/L), but not dose dependant.
Emergent PCSA biochemical values were sparse in all groups. Four PCSA values were reported in the S 38093 5 mg group, 3 in the S 38093 10 mg group, 1 in the S 38093 50 mg group, and 3 in the placebo group. In the active treatment groups, they concerned glucose, sodium, triglycerides and urea. No haematological or endocrinological PCSA value was reported during the study.

Vital signs

There were no relevant mean changes from baseline to last post-baseline assessment on treatment, nor relevant difference between the S 38093 4 dose groups and the placebo group for supine and standing blood pressures, respiratory rate, body temperature, weight and BMI.

ECG

It should be noticed that the ECG reading and interpretation was performed on-site by a local cardiologist or trained physician and not centralised.
There were no relevant mean changes from baseline to last post-baseline assessment on treatment in ECG parameters, nor relevant difference between the S 38093 4 dose groups and the placebo group.
As regards individual QTcF value, 4 patients on S 38093 (2 in the 10 mg group, 1 in the 20 mg and 1 in the 50 mg group) with a QTcF ≤ 450 ms from baseline to W2, had a QTcF > 450 ms at W4 (last post-baseline assessment on treatment), one of them in the S 38093 10 mg group having a QTcF > 500 ms. QTcF prolongations were less than 30 ms for 3 of them, and more than 60 ms for the last one. For all patients, the QTcF was ≤ 450 ms at Wend.

In addition, 4 patients on S 38093 (2 in the 5 mg group, 1 in the 10 mg group, and 1 in the 50 mg group) with a QTcF ≤ 450 ms at baseline, had a QTcF > 450 ms at W1 or W2 which was again ≤ 450 ms at the following visit on treatment.
In the placebo group, no patient with a QTcF ≤ 450 ms at baseline had a QTcF > 450 ms at any visit on treatment.
QTcF increase between the baseline and the last post-baseline assessment on treatment over the selection-W4/Wend period was within]30 ms ; 60 ms] in one patient in each S 38093 dose group. QTcF increase more than 60 ms was reported in one patient each in the S 38093 10 mg group (see patient above), and placebo group.

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SUMMARY - CONCLUSIONS (Cont'd)

PHARMACOKINETIC RESULTS

[redacted]

CONCLUSION

This international, multi-centre, randomised, double-blind, 5 parallel-group, placebo-controlled add-on study in patients with mild to moderate AD, treated with donepezil for at least 6 months with safety as primary objective showed that S 38093 was well tolerated at all doses tested (5 mg, 10 mg, 20 mg, and 50 mg) in combination with donepezil 10 mg regarding clinical and biological safety, vital signs and ECG. No dose dependency of emergent adverse events was observed. The 50 mg dose was the only dose with which emergent adverse events were slightly more frequent than with the placebo.

The study was designed to evaluate safety, no effect on cognitive function, patients' clinical condition, and daytime sleepiness was observed after 4 weeks of treatment with S 38093 at the 5 mg, 10 mg, 20 mg and 50 mg doses.

Date of the report: 9 March 2012