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| *Document title* | **Clinical Study Report Synopsis** |
| *Study title* | **Exploratory study of S 38093 versus placebo in patients with mild to moderate Alzheimer's Disease.**<br>**An international, multicentre, randomised, double-blind, placebo-controlled phase IIa study.** |
| *Study drug* | **S 38093** |
| *Studied indication* | **Alzheimer's Disease** |
| *Development phase* | **Phase IIa** |
| *Protocol code* | **CL2-38093-005** |
| *Study initiation date* | **13 May 2009** |
| *Study completion date* | **13 September 2010** |
| *Scientific advisors* | [redacted] **Canada**<br>[redacted] **- France** |
| *Sponsors* | **Institut de Recherches Internationales Servier (I.R.I.S.)**<br>**50 rue Carnot**<br>**92284 Suresnes Cedex - France**<br>**Servier Canada Inc - 235, Armand-Frappier Blvd.**<br>**Laval, Quebec, Canada H7V 4A7**<br>**Servier Research and Development International Centre for Therapeutic Research**<br>**Gallions Wexham Springs, Framewood Road,**<br>**Wexham Slough SL3 6RJ - United Kingdom** |
| *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 1 March 2012** |

**~~CONFIDENTIAL~~**

## 2. SYNOPSIS

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**Title of study:** Exploratory study of S 38093 *versus* placebo in patients with mild to moderate Alzheimer's Disease. An international, multi-centre, randomised, double-blind, placebo-controlled phase IIa study.
Protocol No.: CL2-38093-005.

**Coordinators:** [redacted], Australia), [redacted], Austria), [redacted] Germany), [redacted], France) [redacted] South Africa), [redacted], United Kingdom) replaced by [redacted], United Kingdom).
**Scientific advisors:** [redacted] (Canada) and [redacted] (France).

**Study centres:**
42 centres located in 7 countries were opened, and selected and included at least one patient: Australia (7 centres – 48 included patients), Austria (4 centres – 17 included patients), Canada (1 centre – 3 included patients), France (9 centres – 33 included patients), Germany (11 centres – 52 included patients), South Africa (5 centres – 39 included patients), United Kingdom (5 centres – 18 included patients).

**Publication (reference):** Not applicable

| **Studied period:** | **Phase of development of the study:** |
|---|---|
| Initiation date: 13 May 2009<br>Completion date: 13 September 2010 | IIa |

**Objective:**
The objective of this exploratory study was to evaluate, in patients with mild to moderate Alzheimer's Disease (AD), the safety of S 38093 as compared to placebo, the efficacy of S 38093 on cognitive performances, on neuropsychiatric symptoms and symptoms associated with dementia (including apathy and daytime sleepiness) and on the Clinical Global Impression of Change as compared to placebo, as well as the S 38093 plasma concentrations which were then used in a population pharmacokinetic analysis.

**Methodology:**
This study was a phase IIa, international, multi-centre, randomised, double-blind, 4 parallel-group, placebo-controlled study. Two hundred (200) patients suffering from mild to moderate AD were to be included and randomly assigned to receive either S 38093 5 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: 200 patients, 50 patients per group.
Included: 210 patients, 52 patients in the S 38093 5 mg group, 52 patients in the S 38093 20 mg group, 53 patients in the S 38093 50 mg group and 53 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 Clinical Dementia Rating (CDR) $\geq$ 0.5 with memory sub-score $\geq$ 1.0, a modified Hachinski Ischemic Score $\leq$ 4, and a Geriatric Depression Rating Scale-15 (GDS) < 6, having a predictive phenotype of rapid, extensive or intermediate metaboliser (homozygous or heterozygous) for cytochrome 2C19 (rapid and intermediate metabolisers were specified in the Amendment No. 1) and having a responsible caregiver. Patients had to have brain imaging performed within 1 year prior (or at) to the selection visit.

**Study drug:**
S 38093: 5 mg, 10 mg, and 25 mg tablets, 2 tablets, orally, with a glass of water, once a day, in the morning before breakfast. Patients received 5 mg/day or 20 mg/day or 50 mg/day for 12 weeks.
Batch No.: L0027934, L0027961, L0027963.

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**Reference product:**
Placebo: 2 tablets, orally, with a glass of water, once a day, in the morning before breakfast.

**Duration of treatment:**

- A 2-6-week selection period without treatment.
- A 12-week double-blind treatment period.
- A 2-week follow-up period without treatment.

**Criteria for evaluation:**

***Efficacy measurements:***

- CogState computerised test-battery: administered at selection, W0, W2, W4, W8 and W12 or in case of premature withdrawal.
- Alzheimer's Disease Cooperative Study Unit Clinician's Global Impression of Change (ADCS-CGIC): administered at W0, W4 and W12, or in case of premature withdrawal.
- Neuropsychiatric inventory (NPI): administered at W0, W4 and W12, or in case of premature withdrawal.
- Apathy Evaluation Scale (AES): administered at W0, W4 and W12, or in case of premature withdrawal.
- Epworth Sleepiness Scale (ESS): administered at W0, W4 and W12, 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 from selection or in case of premature withdrawal for all parameters (biochemistry, haematology, and endocrinology) except for thyroid hormones measured at selection, W4 and W12, or in case of premature withdrawal. Urinalysis was performed at each visit from selection or in case of premature withdrawal.
- Vital signs and physical examination: all parameters (supine SBP, DBP, and HR, respiratory rate, body temperature, height and body weight) were measured at each visit from selection or in case of premature withdrawal except height (at selection only).
- ECG: 12-lead ECG was performed at each visit from selection or in case of premature withdrawal.

***Pharmacokinetic measurements:***
For each patient, 6 blood samples were to be collected: 2 samples during each visit W2, W4 and W12. Pharmacokinetic results are the subject of a separate report. An additional sample was taken in case of SAE considered to be related to the study drug or of overdose.

**Statistical methods:**
***Efficacy analysis:***
Descriptive statistics of all efficacy criteria analytical approaches were provided in patients of the FAS and the OCS. In addition to description by treatment group, descriptive statistics were also provided by treatment group and ApoE genotyping result.
For the change from baseline to last post-baseline values obtained over ASSE-W12 period from the CogState computerised test battery, the estimate of the difference between adjusted treatment group means, its standard error and two-sided 95% confidence interval were provided for each dose of S 38093 and as compared to placebo, using a two-way analysis of covariance on factors treatment and centre (random effect), with baseline as covariate and without interaction:

- In patients of the FAS and the OCS.
- In patients of the FAS with on one hand mild AD (MMSE total score > 20) and on the other hand moderate AD (15 ≤ MMSE total score ≤ 20) (unplanned analysis).

***Safety analysis:*** Descriptive statistics were provided by treatment groups in the Safety Set.

***Pharmacokinetic analysis***: Descriptive statistics were performed on S 38093 plasma concentration-time data and displayed in the analytical report. Descriptive statistics were performed on PK S 38093 parameters.

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**SUMMARY - CONCLUSIONS**

STUDY POPULATION AND OUTCOME

**Disposition of patients**

| | | S 38093 5 mg | S 38093 20 mg | S 38093 50 mg | Placebo | All |
|---|---|---|---|---|---|---|
| **Included (randomised)** | **n** | **52** | **52** | **53** | **53** | **210** |
| **Withdrawn** | **n (%)** | **7 (13.5)** | **2 (3.8)** | **9 (17.0)** | **4 (7.5)** | **22 (10.5)** |
| due to adverse event | **n (%)** | 1 (1.9) | 1 (1.9) | 4 (7.5) | 1 (1.9) | 7 (3.3) |
| due to non-medical reason | **n (%)** | 4 (7.7) | - | 2 (3.8) | 2 (3.8) | 8 (3.8) |
| due to protocol deviation | **n (%)** | 2 (3.8) | 1 (1.9) | 3 (5.7) | 1 (1.9) | 7 (3.3) |
| **Completed the W0-W12 period** | **n (%)** | **45 (86.5)** | **50 (96.2)** | **44 (83.0)** | **49 (92.5)** | **188 (89.5)** |
| **Full Analysis Set (FAS)** | **n (%)** | **51 (98.1)** | **52 (100.0)** | **50 (94.3)** | **52 (98.1)** | **205 (97.6)** |
| **Observed Cases Set (OCS)** | **n (%)** | **45 (86.5)** | **50 (96.2)** | **44 (83.0)** | **50 (94.3)** | **189 (90.0)** |
| **Safety Set (SS)** | **n (%)** | **52 (100.0)** | **52 (100.0)** | **52 (98.1)** | **53 (100.0)** | **209 (99.5)** |
| **Pharmacokinetic Set** | **n (%)** | **50 (96.1)** | **49 (94.2)** | **46 (86.8)** | **NA** | **145 (69.0)** |

Overall, 262 patients were selected and 210 patients were included and randomised: 52 patients in the S 38093 5 mg group, 52 patients in the S 38093 20 mg group, 53 patients in the S 38093 50 mg group and 53 patients in the placebo group. During the W0-W12 period, 22 patients withdrew: 8 (3.8%) due to non-medical reason, 7 (3.3%) due to adverse event and 7 (3.3%) due to protocol deviations. The rate of withdrawals was higher in the S 38093 5 mg and 50 mg groups (13.5% and 17.0%, respectively) than in the S 38093 20 mg and placebo groups (3.8% and 7.5%, respectively). The highest rate of withdrawals for AE was observed in the S 38093 50 mg group (7.5%) compared to placebo and other dose groups (1.9%). No patient was lost to follow-up. Overall, 188 patients (89.5%) completed the W0-W12 period.

At selection, in the RS, patients were on average (± SD) 73.0 ± 7.5 years old. Male and female were equally distributed: 103 women (49.1%) and 107 men (51.0%): the ratio was well balanced except in the S 38093 20 mg group (61.5% of men and 38.5% of women). Most patients were of Caucasian origin (97.6%). No relevant difference between treatment groups were observed for risk factors, clinical examination and ECG means parameters. Patients with QTcF baseline value > 450 ms at baseline were more frequent in the S 38093 50 mg group (5 patients) than in other groups (1 patient in each group). All patients were extensive, intermediate or ultrarapid metabolisers for CYP 2C19 and 58.6% were ApoE e4 positive, the percentage ranging from 51.0% in the S 38093 5 mg group to 68.6% in the placebo group.

At selection, mean MMSE was 21.7 ± 3.1, indicating that patients had mild or moderate Alzheimer's disease (65.9% had mild AD and 34.1% had moderate AD).
Regarding CDR, most of the patients had global score equal to 1 (55.2%), corresponding – as the MMSE- mainly to patients with mild AD. Mean modified Hachinski ischaemic score was 0.7 ± 0.8, indicating on average the absence of dementia related to cerebral ischaemia. Mean GDS was 2.2 ± 1.5, indicating that patients were globally not depressed. All patients performed a brain imaging, mainly MRI (68.1% of the patients). Overall 60 patients (28.6%) previously received treatment for Alzheimer, mainly donepezil. Regarding above characteristics of Alzheimer's disease, no relevant difference between groups were detected.

Regarding CogState computerised test battery at baseline, speed of performance was on average 2.612 ± 0.161 Log10 ms for detection task, 2.659 ± 0.157 Log10 ms for re-detection task and 2.809 ± 0.122 Log10 ms for identification task; change in speed of performance was on average -0.048 ± 0.111 Log10 ms for sustained attention and for one-back memory task, the mean accuracy of performance was 0.925 ± 0.293. Scores were lower in the S 38093 20 mg group for detection, re-detection and identification tasks and higher for one-back memory task and sustained attention, indicating that at baseline, patients in the S 38093 20 mg group had better CogState scores than patients in the other groups.
Mean total score was 40.0 ± 10.2 for AES and 5.1 ± 3.8 for ESS without relevant difference between groups. NPI-10 item mean total score was 7.6 ± 10.3 (median 3.0) and mean NPI-12 item total score was 8.9 ± 11.3 (median 4.1) with generally higher scores in the S 38093 groups than in the placebo group, specifically in the S 38093 5 mg dose group.

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**SUMMARY – CONCLUSIONS (Cont'd)**

STUDY POPULATION AND OUTCOME (Cont'd)

Demographic data and other baseline characteristics in the FAS (205 patients, 97.6% of the RS) and in the OCS (189 patients, 90.0% of the RS) were similar to those described in the RS.

In the RS, mean treatment duration was 78.2 ± 19.3 days (median: 84.0 days) without relevant difference between groups. The mean overall compliance was 95.2 ± 17.1% without relevant difference between groups The compliance was good: 94.3% of the patients had an overall compliance between 70% and 130%.

EFFICACY RESULTS

**CogState computerised test battery**

**CogState computerised test battery - ASSE-W12 period in the FAS**
**Change from baseline to last post-baseline value– Difference between treatment groups**

| | | **S 38093 5 mg (N = 51)** | **S 38093 20 mg (N = 52)** | **S 38093 50 mg (N = 50)** | **Placebo (N = 52)** |
|---|---|---|---|---|---|
| **Detection task** (Speed of performance) (Log10 ms) | | | | | |
| Baseline** | n | 51 | 51 | 49 | 51 |
| | Mean ± SD | 2.615 ± 0.139 | 2.581 ± 0.165 | 2.632 ± 0 180 | 2.625 ± 0 164 |
| Change from baseline* | n | 51 | 51 | 49 | 51 |
| | Mean ± SD | 0.001 ± 0.182 | 0.019 ± 0.136 | 0.006 ± 0 102 | -0.013 ± 0.118 |
| *Statistical analysis* | E (SE)[1] | 0.010 (0.025) | 0.016 (0.025) | 0.021 (0.025) | |
| | 95% CI [2] | [-0.039 ; 0.059] | [-0.033 ; 0.065] | [-0.028 ; 0.070] | |
| **Re-detection task** (Speed of performance) (Log10 ms) | | | | | |
| Baseline** | n | 51 | 50 | 47 | 51 |
| | Mean ± SD | 2.659 ± 0.136 | 2.626 ± 0.158 | 2.679 ± 0 156 | 2.668 ± 0 178 |
| Change from baseline* | n | 51 | 50 | 47 | 51 |
| | Mean ± SD | 0.007 ± 0.095 | 0.012 ± 0.092 | 0.011 ± 0 107 | -0.016 ± 0.105 |
| *Statistical analysis* | E (SE)[1] | 0.023 (0.018) | 0.021 (0.018) | 0.028 (0.019) | |
| | 95% CI [2] | [-0.013 ; 0.059] | [-0.016 ; 0.057] | [-0.009 ; 0.065] | |
| **Identification task** (Speed of performance) (Log10 ms) | | | | | |
| Baseline** | n | 51 | 51 | 50 | 51 |
| | Mean ± SD | 2.815 ± 0.113 | 2.796 ± 0.130 | 2.817 ± 0.113 | 2.813 ± 0.133 |
| Change from baseline* | n | 51 | 51 | 50 | 51 |
| | Mean ± SD | -0.025 ± 0.071 | 0.000 ± 0.068 | -0.016 ± 0.070 | -0.013 ± 0.103 |
| *Statistical analysis* | E (SE)[1] | -0.012 (0.014) | 0.008 (0.014) | -0.002 (0.014) | |
| | 95% CI [2] | [-0.040 ; 0.016] | [-0.020 ; 0.037] | [-0.030 ; 0.027] | |
| **One-back memory task** (Accuracy of performance) | | | | | |
| Baseline** | n | 51 | 51 | 49 | 52 |
| | Mean ± SD | 0.912 ± 0.248 | 0.989 ± 0.266 | 0.905 ± 0 316 | 0.897 ± 0 339 |
| Change from baseline* | n | 51 | 51 | 49 | 52 |
| | Mean ± SD | 0.063 ± 0.223 | 0.069 ± 0 257 | 0.056 ± 0 228 | 0.053 ± 0 291 |
| *Statistical analysis* | E (SE)[1] | 0.010 (0.044) | 0.040 (0.044) | 0.003 (0.044) | |
| | 95% CI [2] | [-0.077 ; 0.098] | [-0.047 ; 0.128] | [-0.085 ; 0.091] | |
| **Sustained attention** (Change in speed of performance) (Log10 ms) | | | | | |
| Baseline** | n | 50 | 50 | 47 | 51 |
| | Mean ± SD | -0.036 ± 0.113 | -0.046 ± 0.107 | -0.051 ± 0.098 | -0.044 ± 0.116 |
| Change from baseline* | n | 50 | 50 | 47 | 51 |
| | Mean ± SD | -0.025 ± 0.135 | 0.008 ± 0 127 | 0.000 ± 0 111 | 0.004 ± 0 148 |
| *Statistical analysis* | E (SE)[1] | -0.021 (0.017) | 0.002 (0.017) | -0.010 (0.017) | |
| | 95% CI [2] | [-0.055 ; 0.012] | [-0.032 ; 0.036] | [-0.045 ; 0.024] | |

** To last post-baseline value ** Value at W0, or if missing, value at ASSE.*

*General linear model with centre as random effect and baseline as covariate.*

*(1) Estimate (Standard Error) of the difference between adjusted treatment group means S 38093 dose minus Placebo – Negative difference was in favour of S 38093 for detection, re-detection and identification tasks; positive difference was in favour of S 38093 for one-back memory tasks and sustained attention.*

*(2) Two-sided 95% Confidence Interval of the estimate.*

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**SUMMARY – CONCLUSIONS (Cont'd)**

EFFICACY RESULTS (Cont'd)

In the FAS, mean change from baseline to last post-baseline value in CogState computerised test battery did not show significant difference between any S 38093 dose groups and the placebo group whatever the test. Similar results were observed in the OCS.

In patients with moderate AD (15 ≤ MMSE total score ≤ 20 at baseline) in the FAS, a strong favorable trend was observed in the 20 mg dose group, on detection (psychomotor speed) and one-back memory (working memory) tasks. A favorable trend was observed on detection (psychomotor speed), identification (attention) and one-back memory (working memory) tasks in the S 38093 5 mg dose group as well as on identification task (attention) in the 20 mg dose group and on one-back memory task (working memory) in the S 38093 50 mg dose group. However, taking into account the low number of patients (13 to 21 patients per group) and the difference in scores observed at baseline, those results should be carefully interpreted.

**CogState computerised test battery - ASSE-W12 period in the FAS - Patients with moderate AD**
**Change from baseline to last post-baseline value – Difference between treatment groups**

| | | **S 38093 5 mg (N = 13)** | **S 38093 20 mg (N = 17)** | **S 38093 50 mg (N = 18)** | **Placebo (N = 21)** |
|---|---|---|---|---|---|
| **Detection task** (Speed of performance) (Log10 ms) | | | | | |
| Baseline** | n | 13 | 17 | 18 | 21 |
| | Mean ± SD | 2.665 ± 0.137 | 2.578 ± 0.196 | 2.768 ± 0 171 | 2.707 ± 0.178 |
| Change from baseline* | n | 13 | 17 | 18 | 21 |
| | Mean ± SD | -0.004 ± 0.167 | -0.019 ± 0.162 | -0.017 ± 0.126 | 0.017 ± 0.141 |
| *Statistical analysis* | E (SE)[1] | -0.041 (0.043) | -0.099 (0.042) | -0.004 (0.040) | |
| | 95% CI [2] | [-0.128 ; 0.045] | [-0.182 ; -0.015] | [-0.084 ; 0.076] | |
| **Re-detection task** (Speed of performance) (Log10 ms) | | | | | |
| Baseline** | n | 13 | 17 | 16 | 21 |
| | Mean ± SD | 2.716 ± 0.091 | 2.613 ± 0.162 | 2.809 ± 0 123 | 2.764 ± 0.178 |
| Change from baseline* | n | 13 | 17 | 16 | 21 |
| | Mean ± SD | 0.031 ± 0.128 | -0.008 ± 0.079 | 0.023 ± 0 103 | -0.019 ± 0.129 |
| *Statistical analysis* | E (SE)[1] | 0.036 (0.037) | -0.030 (0.037) | 0.053 (0.035) | |
| | 95% CI [2] | [-0.038 ; 0.111] | [-0.104 ; 0.043] | [-0.017 ; 0.123] | |
| **Identification task** (Speed of performance) (Log10 ms) | | | | | |
| Baseline** | n | 13 | 17 | 17 | 21 |
| | Mean ± SD | 2.884 ± 0.114 | 2.786 ± 0.157 | 2.894 ± 0 107 | 2.876 ± 0.135 |
| Change from baseline* | n | 13 | 17 | 18 | 21 |
| | Mean ± SD | -0.055 ± 0.095 | -0.012 ± 0.064 | -0.008 ± 0.095 | -0.012 ± 0.147 |
| *Statistical analysis* | E (SE)[1] | -0.039 (0.032) | -0.040 (0.031) | 0.011 (0.030) | |
| | 95% CI [2] | [-0.104 ; 0.026] | [-0.102 ; 0.022] | [-0.048 ; 0.071] | |
| **One-back memory task** (Accuracy of performance) | | | | | |
| Baseline** | n | 13 | 17 | 17 | 21 |
| | Mean ± SD | 0.796 ± 0.144 | 0.845 ± 0.230 | 0.699 ± 0 296 | 0.723 ± 0.223 |
| Change from baseline* | n | 13 | 17 | 18 | 21 |
| | Mean ± SD | -0.032 ± 0.202 | 0.038 ± 0.229 | 0.071 ± 0 186 | -0.046 ± 0.230 |
| *Statistical analysis* | E (SE)[1] | 0.041 (0.070) | 0.130 (0.066) | 0.110 (0.065) | |
| | 95% CI [2] | [-0.100 ; 0.183] | [-0.002 ; 0.263] | [-0.020 ; 0.240] | |
| **Sustained attention** (Change in speed of performance) (Log10 ms) | | | | | |
| Baseline** | n | 13 | 17 | 16 | 21 |
| | Mean ± SD | -0.034 ± 0.203 | -0.019 ± 0.151 | -0.028 ± 0.154 | 0.038 ± 0.180 |
| Change from baseline* | n | 13 | 17 | 16 | 21 |
| | Mean ± SD | -0.034 ± 0.203 | -0.019 ± 0.151 | -0.028 ± 0.154 | 0.038 ± 0.180 |
| *Statistical analysis* | E (SE)[1] | -0.068 ± 0.035 | -0.030 ± 0.032 | -0.043 ± 0.033 | |
| | 95% CI [2] | [-0.138 ; 0.002] | [-0.095 ; 0.035] | [-0.110 ; 0.024] | |

** To last post-baseline value ** Value at W0, or if missing, value at ASSE.*
*General linear model with centre as random effect and baseline as covariate.*
*(1) Estimate (Standard Error) of the difference between adjusted treatment group means S 38093 dose minus Placebo – Negative difference was in favour of S 38093 for detection, re-detection and identification tasks; positive difference was in favour of S 38093 for one-back memory task and sustained attention.*
*(2) Two-sided 95% Confidence Interval of the estimate.*

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**SUMMARY – CONCLUSIONS (Cont'd)**

EFFICACY RESULTS (Cont'd)

- **Alzheimer's Disease Cooperative Study Unit Clinician's Global Impression of Change (ADCS-CGIC)**

Over the W0-W12 period in the FAS, no relevant difference between groups was observed in mean ADCS-CGIC scores which remained stable at each visit and at last assessment in all groups. Results in the OCS were similar to those observed in the FAS.

- **Neuropsychiatric inventory (NPI)**

Over the W0-W12 period in the FAS, the mean and median decrease from baseline to last post-baseline assessment was slightly greater (difference ≥ 1.0) in the S 38093 5 mg group than in the placebo group for the NPI 12-items total score as well as frequency and caregiver's distress scores: it is to note that scores at baseline were higher in all the S 38093 dose groups (especially S 38093 5 mg) than in the placebo group, which puts in question the comparability between groups.

Similar results were observed for the NPI 10-items scores.

**NPI 12-item total scores - Change from baseline to last post-baseline value W0-W12 period in FAS**

| | | **S 38093 5 mg (N = 51)** | **S 38093 20 mg (N = 52)** | **S 38093 50 mg (N = 50)** | **Placebo (N = 53)** |
|---|---|---|---|---|---|
| **12-item total score** | | | | | |
| Baseline | n | 51 | 50 | 47 | 52 |
| | Mean ± SD | 11.0 ± 12.7 | 9.3 ± 12.9 | 8.7 ± 10.7 | 7.2 ± 8.7 |
| | Median | 6.0 | 4.0 | 4.0 | 2.5 |
| | Q1 ; Q3 | 2.0 ; 15 | 1.0 ; 13.0 | 2.0 ; 12 | 0.5 ; 11.5 |
| | Min ; Max | 0 ; 53 | 0 ; 56 | 0 ; 53 | 0 ; 29 |
| Last post-baseline assessment | n | 48 | 51 | 48 | 51 |
| | Mean ± SD | 7.8 ± 11.0 | 8.7 ± 11.9 | 8.8 ± 11.2 | 6.5 ± 8.3 |
| | Median | 4.5 | 4.0 | 4.0 | 3.0 |
| | Q1 ; Q3 | 1.0 ; 10.0 | 0 ; 14.0 | 1.0 ; 13.0 | 0 ; 8.0 |
| | Min ; Max | 0 ; 62 | 0 ; 60 | 0 ; 47 | 0 ; 30 |
| Change from baseline* | n | 48 | 49 | 46 | 51 |
| | Mean ± SD | -3.5 ± 8.6 | -1.0 ± 11.9 | 0.0 ± 10.3 | -0.8 ± 7.2 |
| | Median | -1.0 | 0.0 | 0.0 | 0.0 |
| | Q1 ; Q3 | -8.5 ; 1.5 | -5.0 ; 4.0 | -2.0 ; 1.0 | -4.0 ; 2.0 |
| | Min ; Max | -33 ; 13 | -52 ; 32 | -27 ; 31 | -22 ; 17 |
| **12-item frequency total score** | | | | | |
| Baseline | n | 51 | 50 | 47 | 52 |
| | Mean ± SD | 7.3 ± 7.0 | 5.7 ± 6.0 | 6.0 ± 6.4 | 5.2 ± 5.6 |
| | Median | 5.0 | 4.0 | 4.0 | 2.5 |
| | Q1 ; Q3 | 2.0 ; 11.0 | 1.0 ; 8.0 | 1.0 ; 8.0 | 0.5 ; 9.0 |
| | Min ; Max | 0 ; 32 | 0 ; 23 | 0 ; 26 | 0 ; 19 |
| Last post-baseline assessment | n | 48 | 51 | 48 | 51 |
| | Mean ± SD | 5.0 ± 5.4 | 5.5 ± 6.8 | 5.6 ± 6.4 | 4.8 ± 5.4 |
| | Median | 4.0 | 4.0 | 4.0 | 3.0 |
| | Q1 ; Q3 | 1.0 ; 7.0 | 0 ; 9.0 | 1.0 ; 7.0 | 0 ; 8.0 |
| | Min ; Max | 0 ; 27 | 0 ; 32 | 0 ; 27 | 0 ; 18 |
| Change from baseline* | n | 48 | 49 | 46 | 51 |
| | Mean ± SD | -2.4 ± 5.0 | -0.4 ± 6.0 | -0.3 ± 6.2 | -0.4 ± 4.5 |
| | Median | -1.0 | 0.0 | 0.0 | 0.0 |
| | Q1 ; Q3 | -5.0 ; 1.0 | -3.0 ; 4.0 | -2.0 ; 2.0 | -2.0 ; 1.0 |
| | Min ; Max | -15 ; 5 | -20 ; 16 | -18 ; 16 | -15 ; 16 |

** to last post-baseline ~~assessment~~*

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**SUMMARY – CONCLUSIONS (Cont'd)**
EFFICACY RESULTS (Cont'd)

**NPI 12-item total scores - Change from baseline to last post-baseline value W0-W12 period in FAS (Cont'd)**

| | | S 38093 5 mg (N = 51) | S 38093 20 mg (N = 52) | S 38093 50 mg (N = 50) | Placebo (N = 53) |
|---|---|---|---|---|---|
| **12-item severity total score** | | | | | |
| Baseline | n | 51 | 50 | 47 | 52 |
| | Mean ± SD | 4.0 ± 4.0 | 3.6 ± 3.9 | 3.4 ± 3.6 | 3.0 ± 3.0 |
| | Median | 2.0 | 2.0 | 2.0 | 2.0 |
| | Q1 ; Q3 | 1.0 ; 5.0 | 1 ; 6.0 | 1.0 ; 5.0 | 0.5 ; 4.5 |
| | Min ; Max | 0 ; 16 | 0 ; 17 | 0 ; 18 | 0 ; 10 |
| Last post-baseline assessment | n | 48 | 51 | 48 | 51 |
| | Mean ± SD | 2.8 ± 3.2 | 3.1 ± 3.6 | 3.3 ± 3.7 | 2.6 ± 2.9 |
| | Median | 2.0 | 2.0 | 2.0 | 2.0 |
| | Q1 ; Q3 | 1.0 ; 3.5 | 0.0 ; 5.0 | 1.0 ; 4.5 | 0.0 ; 4.0 |
| | Min ; Max | 0 ; 16 | 0 ; 15 | 0 ; 16 | 0 ; 10 |
| Change from baseline* | n | 48 | 49 | 46 | 51 |
| | Mean ± SD | -1.4 ± 2.8 | -0.7 ± 3.8 | -0.1 ± 3.5 | -0.4 ± 2.5 |
| | Median | -1.0 | 0.0 | 0.0 | -1.0 |
| | Q1 ; Q3 | -3.0 ; 1.0 | -2.0 ; 1.0 | -1.0 ; 1.0 | -2.0 ; 1.0 |
| | Min ; Max | -10 ; 3 | -15 ; 8 | -10 ; 10 | -8 ; 7 |
| **12-item caregiver's distress total score** | | | | | |
| Baseline | n | 51 | 50 | 47 | 52 |
| | Mean ± SD | 5.7 ± 6.4 | 5.3 ± 6.5 | 4.8 ± 6.3 | 4.3 ± 5.4 |
| | Median | 4.0 | 3.0 | 3.0 | 2.0 |
| | Q1 ; Q3 | 1.0 ; 8.0 | 1.0 ; 8.0 | 0.0 ; 6.0 | 0.0 ; 7.5 |
| | Min ; Max | 0 ; 25 | 0 ; 26 | 0 ; 30 | 0 ; 24 |
| Last post-baseline assessment | n | 48 | 51 | 48 | 51 |
| | Mean ± SD | 4.5 ± 5.3 | 5.1 ± 7.2 | 4.0 ± 5.3 | 4.0 ± 4.5 |
| | Median | 3.0 | 2.0 | 2.0 | 3.0 |
| | Q1 ; Q3 | 0.0 ; 7.0 | 0.0 ; 7.0 | 0.5 ; 6.0 | 0.0 ; 7.0 |
| | Min ; Max | 0 ; 27 | 0 ; 31 | 0 ; 25 | 0 ; 15 |
| Change from baseline* | n | 48 | 49 | 46 | 51 |
| | Mean ± SD | -1.5 ± 4.7 | -0.7 ± 5.9 | -0.7 ± 6.1 | -0.3 ± 3.8 |
| | Median | -1.0 | 0.0 | 0.0 | 0.0 |
| | Q1 ; Q3 | -2.5 ; 1.0 | -3.0 ; 1.0 | -2.0 ; 2.0 | -3.0 ; 1.0 |
| | Min ; Max | -21 ; 5 | -23 ; 12 | -24 ; 16 | -9 ; 11 |

** to last post-baseline assessment*

Regarding NPI, results in the OCS were similar to those observed in the FAS.

- **Apathy Evaluation Scale (AES)**

No relevant difference was observed on the mean and median changes from baseline to last post-baseline value between S 38093 groups and placebo group in the FAS: -0.3 ± 7.5 (median 0.5), 2.3 ± 7.1 (median 2.5), 3.8 ± 9.0 (median 3.0) and 2.7 ± 8.1 (median 0.5) in the S 38093 5 mg, 20 mg, 50 mg and placebo groups, respectively.
Results in the OCS were similar to those observed in the FAS.

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**SUMMARY – CONCLUSIONS (Cont'd)**

EFFICACY RESULTS (Cont'd)

- **Epworth Sleepiness Scale (ESS)**

No relevant difference was observed on the mean changes (median = 0) from baseline to last post-baseline value between S 38093 dose groups and placebo group in the FAS: -0.3 ± 3.8, 0.2 ± 3.5, 0.8 ± 3.4 and -0.4 ± 3.1 in the S 38093 5 mg, 20 mg, 50 mg and placebo groups, respectively).
Results were in the same line in the OCS.

Results in patients with positive ApoE e4 genotype were in line with those in patients with negative ApoE e4 genotype for efficacy criteria: however, due to the low number of patients by groups, results should be interpreted with caution. Regarding 12-item NPI analyis according to the genotype, the low number of patients by group and the differences between groups observed at baseline made the interpretation difficult and did not allow to conclude.

SAFETY RESULTS

**Summary of safety results – Safety Set**

| | | **S 38093 5 mg (N = 52)** | **S 38093 20 mg (N = 52)** | **S 38093 50 mg (N = 52)** | **Placebo (N = 53)** |
|---|---|---|---|---|---|
| Patients having reported | | | | | |
| at least one emergent adverse event | n (%) | 33 (63.5) | 31 (59.6) | 41 (78.8) | 25 (47.2) |
| at least one treatment-related emergent adverse event | n (%) | 17 (32.7) | 14 (26.9) | 20 (38.5) | 10 (18.9) |
| Patients having experienced | | | | | |
| at least one serious adverse event | n (%) | 5 (9.6) | 2 (3.8) | 4 (7.7) | 4 (7.5) |
| at least one treatment-related serious adverse event | n (%) | - | 1 (1.9) | - | - |
| Patients withdrawn | | | | | |
| due to emergent adverse event | n (%) | - | 1 (1.9) | 5 (9.6) | 1 (1.9) |
| due to serious emergent adverse event | n (%) | - | - | 1 (1.9) | 1 (1.9) |
| due to treatment-related EAE | n (%) | - | - | 4 (7.7) | - |
| due to a treatment-related serious EAE | n (%) | - | - | - | - |
| Patients who died* | n (%) | - | - | - | - |

*N Total number of patients in the considered treatment group*
*n Number of affected patients*
*% n/N*100*
**One non-included patient (No. 005 276 0511 05627) died during the selection period*

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**SUMMARY – CONCLUSIONS (Cont'd)**
SAFETY RESULTS (Cont'd)

**Adverse events**
Overall, during the double-blind treatment period, the percentage of patients who experienced at least one emergent adverse event (EAE) was higher in the S 38093 groups (63.5%, 59.6% and 78.8% in the S 38093 5 mg, 20 mg and 50 mg dose group, respectively) than in the placebo group (47.2%), especially in the S 38093 50 mg dose group.
The most frequent system organ classes affected (> 10% of patients) in any of the S 38093 dose groups were psychiatric disorders (32.7% in the S 38093 50 mg dose group *versus* 9.4% in the placebo group), nervous system disorders (17.3% in the S 38093 20 mg dose group and 26.9% in the S 38093 50 mg dose group *versus* 9.4% in the placebo group), infections and infestations (21.2% in the S 38093 5 mg dose group and 17.3% in the S 38093 50 mg dose group *versus* 17.0% in the placebo group), gastrointestinal disorders (19.2% in the S 38093 50 mg dose group *versus* 1.9% in the placebo group), investigations (13.5% in both S 38093 5 and 50 mg dose groups *versus* 3.8% in the placebo group), general disorders and administration site conditions (13.5% in the S 38093 50 mg dose group *versus* 5.7% in the placebo group) and injury, poisoning and procedural complications (11.5% in the S 38093 5 mg dose group *versus* 1.9% in the placebo group). The incidence of nervous system disorders and gastrointestinal disorders was higher in all S 38093 dose groups than in the placebo group. The incidence of psychiatric disorders and of general disorders and administration site conditions was higher in the S 38093 50 mg dose group than in the placebo group. The incidence of infections and infestations was higher in the S 38093 5 mg dose group than in the placebo group. The incidence of investigations and of injury, poisoning and procedural complications was higher in the S 38093 5 and 50 mg dose groups than in the placebo group.

Among EAE reported by at least 6% of the patients in the S 38093 dose groups, the following ones were more frequent (more than 5% between-group difference) in one (or more) of the S 38093 dose groups than in the placebo group: depression (11.5% in the S 38093 50 mg group *versus* none in the placebo group), fall (7.7% in both S 38093 5 mg and 50 mg groups *versus* 1.9% in the placebo group), dizziness (7.7% in the S 38093 50 mg group *versus* 1.9% in the placebo group), fatigue (7.7% in the S 38093 50 mg group *versus* 1.9% in the placebo group), vertigo (7.7% in the S 38093 5 mg group *versus* none in the placebo group). The incidence increased with the S 38093 dose for depression (3.8%, 1.9% and 11.5% in respectively S 38093 5 mg, 20 mg and 50 mg dose groups), dizziness (3.8%, 5.8%, 7.7% in respectively S 38093 5 mg, 20 mg and 50 mg dose groups) as well as for fatigue (1.9%, 3.8%, 7.7% in respectively S 38093 5 mg, 20 mg and 50 mg dose groups).
The following EAE were reported in one (or more) of the S 38093 dose groups by at least 3 patients *versus* none in the placebo group: confusional state, tremor and vomiting reported only in the S 38093 50 mg dose group (5.8%); back pain and blood urea increased (5.8% in the S 38093 20 mg dose group for both events and 1.9% in the 5 mg dose group for back pain); cystitis and hypercholesterolaemia (5.8% in the S 38093 5 mg dose group for both events and 1.9% in the 50 mg dose group for hypercholesterolaemia).
Overall 5 EAE were rated as severe with a higher number in the S 38093 50 mg group (3 events: hand fracture, prostate cancer and erectile dysfunction) than in the placebo group (one herpes zoster).
The percentage of patients with at least one treatment-related EAE was higher in S 38093 groups (32.7%, 26.9% and 38.5% in the S 38093 5 mg, 20 mg and 50 mg groups, respectively) than in the placebo group (18.9%). The most frequent treatment-related EAE in the S 38093 groups were vomiting (5.8% in the S 38093 50 mg group), tremor (5.8% in the S 38093 50 mg group) and vertigo (7.7% in the S 38093 5 mg group): none of them was reported in the placebo group.
One patient (in the S 38093 20 mg group) had an EAE subsequent to study drug discontinuation: "disinhibition" (psychiatric disorders) not recovered at the end of the study.
In the Safety Set, most of the EAE completely recovered (270 emergent adverse events, 82.3%) with a lower rate in the S 38093 groups (83.8% in the S 38093 20 mg dose group and 75.0% in the S 38093 50 mg dose group) than in the placebo group (88.2%).

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**SUMMARY – CONCLUSIONS (Cont'd)**

SAFETY RESULTS (Cont'd)

The most frequent not recovered EAE in the S 38093 groups were hypercholesterolaemia (2 events in the S 38093 5 mg dose group), depression, tremor and confusional state (2 events for each in the S 38093 50 mg dose group): none of these events were reported in the placebo group.

No death occurred during the study in included patients; one non-included patient died during the selection period, the day after a fall with trochanteric femoral fracture. Overall, 12 patients (5.7%) reported 12 serious emergent adverse events (SEAE) during the double-blind treatment period without relevant difference between groups: 5.8% in the S 38093 5 mg group, 3.8% in the S 38093 20 mg group, 7.7% in the S 38093 50 mg and 5.7% in the placebo group. None of the SEAE was reported more than once: angina unstable and hyponatraemia in the S 38093 5 mg group, simple partial seizure, subarachnoid haemorrhage and renal failure in the S 38093 20 mg group, asthenia, chest pain, prostate cancer and peripheral arterial occlusive disease in the S 38093 50 mg group and aortic valve stenosis, sinus bradycardia and melaena in the placebo group.
One serious emergent adverse event was considered as related to the study treatment (simple partial seizures in the S 38093 20 mg group in patient with medical history of temporal lobe epilepsy); this event did not lead to treatment withdrawal.
EAE led to treatment withdrawal in 7 patients (3.3%): they were serious in 2 patients (one prostate cancer in the S 38093 50 mg group and one sinus bradycardia in the placebo group) and non-serious in 5 patients (one in the S 38093 20 mg [dementia Alzheimer's type] and 4 in the S 38093 50 mg [nausea (2 patients), vomiting and nightmare (one patient for each)].

**Biology**

Neither clinically relevant changes from baseline to last post-baseline value on treatment nor differences between groups over the selection-W12/Wend period were detected for biochemical and haematological parameters.

Emergent potentially clinically significant abnormal biochemical values were sparse in all groups, except for the following parameters more frequently reported in some S 38093 groups than in the placebo group: high phosphorus and high glucose (4.2% in the S 38093 50 mg groups *versus* none in the placebo group) as well as high urea (7.8% in the S 38093 20 mg groups *versus* 3.9% in the placebo group). The emergent PCSA values were a worsening of abnormal baseline value except one hyperglycaemia (with however known medical history of hyperglycaemia) and one hyperphosphoraemia in the S 38093 50 mg dose group; in the 20 mg dose group one patient had an hyperuraemia at W002 with a normal baseline value at W000 but an already high value at selection. Overall 3 haematological emergent PCSA values were reported: low haematocrit in both S 38093 20 mg group (value already low at baseline) and placebo group, low white blood cells in the S 38093 20 mg group.

Regarding endocrinological results, an increase with the dose was observed from baseline in S 38093 groups for prolactin: 0.1 ± 8.9 µg/L, 3.9 ± 4.8 µg /L and 11.3 ± 13.8 µg /L in the S 38093 5 mg, 20 mg and 50 mg groups, respectively *versus* –0.3 ± 2.4 µg /L in the placebo group. Emergent high out-of-reference range prolactin values were more frequent in the S 38093 groups (5.8%, 31.4% and 72.9% in 5 mg, 20 mg and 50 mg dose groups) than in the placebo group (3.9%). There was no emergent endocrinological PCSA value.

As regards urinalysis, no clinically relevant difference between S 38093 and placebo groups was observed at last post baseline assessment: it is to note a higher number of patients with positive proteinuria in the S 38093 20 mg group (5 patients) than in the placebo group (1 patient).

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**SUMMARY – CONCLUSIONS (Cont'd)**
**SAFETY RESULTS (Cont'd)**

**Vital signs, clinical examination and ECG**

Neither clinically relevant changes nor differences between treatment groups were detected over time in vital signs or clinical examination.

Regarding ECG, 3 patients in both S 38093 5 mg and 50 mg groups had a QTcF interval switching from normal baseline value to a value in ]450 ms; 480 ms] range at the last post-baseline assessment on treatment *versus* none in the placebo group. One patient (in the S 38093 50 mg dose group) had a QTcF interval switching from a value ≤ 480 ms at baseline to a value in ]480 ms; 500 ms] range at last post-baseline assessment on treatment.

The percentage of patients with at least one emergent ECG abnormality under treatment was higher in S 38093 groups (44.2%, 43.1% and 43.8% in the S 38093 5 mg, 20 mg and 50 mg dose groups, respectively) than in the placebo group (32.7%): at baseline, ECG abnormalities were also more frequent in S 38093 groups than in the placebo group. The emergent ECG abnormalities more frequently reported in S 38093 groups than in the placebo group were: sinus bradycardia (18.8% in the S 38093 50 mg groups *versus* 9.6% in the placebo group), atrio-ventricular block first degree (5.9% and 6.3% in S 38093 20 mg and 50 mg dose groups respectively, *versus* 1.9% in the placebo group), QT prolonged (3.8%, 5.9% and 4.2% in the S 38093 5 mg, 20 mg and 50 mg dose groups, respectively, *versus* none in the placebo group), QRS complex prolonged (5.9% in the S 38093 20 mg group *versus* none in the placebo group) and supraventricular extrasystoles (5.8% in the S 38093 5 mg dose group *versus* 1.9% in the placebo group).

Neither clinically relevant changes nor differences between treatment groups were detected over time regarding other quantitative ECG parameters.

PHARMACOKINETIC RESULTS

[redacted]

**CONCLUSION**

**This international, multi-centre, randomised, double-blind, placebo-controlled phase II study conducted in patients suffering from mild to moderate Alzheimer's Disease over 12 weeks did not show any significant effect of S 38093 on cognitive functions, Clinical Global Impression of Change, Sleepiness or Apathy in the overall population (FAS) at the 5 mg, 20 mg or 50 mg doses vs placebo (nevertheless, this exploratory study was not designed to show statistical difference). However, in the subset of patients with moderate stage of AD in the 20 mg dose group, a strong favourable trend in efficacy was observed on working memory and psychomotor speed tasks. Emergent adverse events were more frequent with S 38093 than with placebo especially with 50 mg dose, the most frequent being depression. Regarding biological safety, S 38093 was well tolerated. A slight expected dose-dependant prolactinaemia increase was observed. Some differences between S 38093 groups and placebo group were observed regarding ECG abnormalities. No concerns were observed regarding other safety assessments.**

**Date of the report: 1 March 2012**