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 co-administration with donepezil (10 mg/day) in patients with moderate Alzheimer's Disease.** **A 24-week international, multi-centre, randomised, double-blind, placebo-controlled phase IIb study.**
Test drug code	**S 38093**
Indication	**Alzheimer's disease**
Development phase	**Phase IIb**
Protocol code	**CL2-38093-012**
Study initiation date	**04 October 2012**
Study completion date	**29 January 2015**
Main coordinator	[redacted]
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - France** **Laboratorios Servier S.L.** **Departamiento de Investigacion y Desarrollo** **Avenida de los Madronos 33, 28043 Madrid - Spain** **Servier Research and Development Ltd.** **Rowley, Wexham Springs, Framewood Road** **Wexham, Slough SL3 6PJ - United Kingdom** **Servier Canada Inc.** **235, Armand Frappier Blvd.** **Laval, Quebec, Canada H7V 4A7**
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	**22 December 2015**
Version of the report	**Final version**
	~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Sponsor: **I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex – France** **Servier Canada Inc. Laval – Quebec, H7V 4A7 – Canada** **Servier R&D Ltd. Wexham, Slough SL3 6PJ - United Kingdom** **Laboratorios Servier S.L. Avd De los Madronos 33, 28043 Madrid – Spain**		*(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 co-administration with donepezil (10 mg/day) in patients with moderate Alzheimer's Disease.
A 24-week international, multi-centre, randomised, double-blind, placebo-controlled phase IIb study.

Protocol No.: CL2-38093-012
EudraCT No.: 2011-005862-40
The description of the study protocol given hereafter includes the modifications of the amendments to the protocol (amendments Nos. 1, 2, 3, 4, 5, 6, 7 and 8).

International coordinator: [redacted]

Study centres:
127 centres located in 15 countries included 806 patients: 8 centres in Argentina (44 patients included), 11 centres in Australia (52 patients included), 2 centres in Austria (7 patients included), 6 centres in Brazil (41 patients included), 8 centres in Canada (35 patients included), 4 centres in Finland (15 patients included), 10 centres in Germany (63 patients included), 16 centres in Italy (76 patients included), 5 centres in Mexico (48 patients included), 11 centres in Poland (130 patients included), 7 centres in Portugal (42 patients included), 8 centres in Slovakia (60 patients included), 15 centres in Spain (115 patients included), 4 centres in Sweden (11 patients included) and 12 centres in United Kingdom (67 patients included).

Publication (reference): Not Applicable

Studied period:	**Phase of development of the study:**
Initiation date: 04 October 2012 (date of first visit first patient) Completion date: 29 January 2015 (date of last visit last patient)	phase IIb

Objectives:
The purpose of the study was to assess the efficacy and the safety of S 38093 *versus* placebo, in combination with donepezil, after 24 weeks of co-administration in patients with moderate Alzheimer's Disease (AD).
The primary objective of this study was to assess the efficacy of 3 fixed doses of S 38093 (2, 5 and 20 mg/day) *versus* placebo, in co-administration with donepezil 10 mg/day, after 24 weeks of treatment, on cognitive performance measured with the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) 11-items in patients with moderate AD.
The key secondary objective was to assess the efficacy of the 3 fixed doses of S 38093 *versus* placebo, in co-administration with donepezil 10 mg/day, after 24 weeks of treatment, on activities of daily living assessed by the Disability Assessment for Dementia (DAD) in patients with moderate AD.
The secondary objectives were to assess:

- The efficacy of the 3 fixed doses of S 38093 versus placebo, in co-administration with donepezil 10 mg/day after 24 weeks of treatment on other criteria assessing cognitive performance (Mini Mental State Examination (MMSE)), clinical global impression of change (Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC)), neuropsychiatric symptoms (Neuropsychiatric Inventory (NPI)) and informant burden (Zarit Burden Inventory), in patients with moderate AD.
- The safety of the 3 fixed doses of S 38093 versus placebo, in co-administration with donepezil 10 mg/day after 24 weeks of treatment.
- The pharmacokinetics of S 38093.

Methodology:
This was a phase IIb, international, multi-centre, randomised, double-blind, placebo-controlled in co-administration with donepezil (10 mg/day) study, with 4 parallel groups (S 38093 2 mg, S 38093 5 mg, S 38093 20 mg and placebo). The randomisation was balanced, non-adaptive, with stratification by country.
This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.
As primary and key secondary endpoints were not met in both the S38093 study in monotherapy (CL2-38093-011, EudraCT No.: 2010-024626-37) and the S38093 study in co-administration with donepezil (CL2-38093-012 subject of the present report), the development of S38093 in Alzheimer's disease was stopped in June 2015. For this reason, the results of the present study are the subject of an abbreviated report.

Number of patients:
Planned: 700 patients (175 per group) (instead of 1000 patients initially planned, *i.e.* 250 per group modified by Amendment No. 7).
Included: 806 patients (201 in S 38093 2 mg group, 202 in S 38093 5 mg group, 203 in S 38093 20 mg group, and 200 in placebo group).

Diagnosis and main criteria for inclusion:
The main inclusion criteria were out-patients aged 55-90 years (as per amendment No. 6), school education ≥ 4 years, with memory impairment (DSM-IV-TR criteria for dementia of AD type and NINCDS/ADRDA criteria for probable AD), MMSE at selection visit (ASSE) = 12-20 inclusive, brain Magnetic Resonance Imaging (MRI) at selection, identified informant to accompany the patient to all study visits, and donepezil treatment for at least 4 months before selection visit, with a stable dose of 10 mg/day for at least 3 months before the selection visit.

Test drug:
S38093: 1 tablet (2 mg, 5 mg or 20 mg) to be taken orally once daily, upon waking in the morning, starting the day after the inclusion visit up to the day of the visit W24.
Batch No.: L0042471, L0046037, L0051267, L0042483, L0046039, L0051269, L0042485, L0046041, L0051273, L0039229, L0046035, L0051238.
In addition, the patients had to take 1 tablet of donepezil (10mg) orally once daily.

Comparator (Reference product and/or placebo):
Placebo: 1 tablet to be taken orally once daily, upon waking in the morning, starting the day after the inclusion visit up to the day of the visit W24.
In addition, the patients had to take 1 tablet of donepezil (10mg) orally once daily.

Duration of treatment:
Run-in period: 2-6 weeks, only donepezil 10 mg / day was administered.
Treatment period: 24 weeks, with double-blind treatment in addition to donepezil.
Wash-out / follow-up period: 2 weeks, only donepezil 10 mg / day was administered.

Criteria for evaluation:
Efficacy measurements:

- *Primary criterion:* Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) 11-item administered at inclusion, week 12 (W12) and week 24 (W24) 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 and W24 or in case of premature withdrawal.

Criteria for evaluation: (Cont'd)

Safety measurements:

- *Adverse events:* At each visit from ASSE or in case of premature withdrawal.
- *Physical examination including neurological examination:* At each on-site visit from ASSE or in case of premature withdrawal.
- *Vital signs (blood pressure, heart rate and body temperature), height, weight, and body mass index:* At each on-site visit from ASSE or in case of premature withdrawal except height at selection only and weight not measured at W4.
- *12 lead-ECG (centralised):* At each on-site visit from ASSE or in case of premature withdrawal.
- *Laboratory examinations including biochemistry, haematology, prolactin and urinalysis (centralised):* At each on-site visit from ASSE or in case of premature withdrawal for all parameters except for thyroid hormones, serology for hepatitis B and C, vitamin B12 and HbA1C at selection only.

Statistical methods:

Efficacy analysis

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, in co-administration with donepezil 10 mg/day, after 24 weeks of treatment was assessed from the 11-item ADAS-Cog total score expressed in terms of change from baseline at 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.

Key secondary analysis (key secondary criterion): The superiority of at least one dose of S 38093 as compared to placebo on activities of daily living, in co-administration with donepezil 10 mg/day, after 24 weeks of treatment was 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, the MMRM approach could not be considered and an analysis of covariance (ANCOVA) model with the Last Observation Carried Forward (LOCF) method for handling missing data was used.
In order to take into account the multiplicity of comparisons associated with the primary objective of the study, as well as to continue to control the type I error of the comparisons associated to the key secondary objective of the study, a Bonferroni-based sequentially rejective multiple test procedure 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 analyses and using two single two-way ANCOVA models (one for each of the studied criteria) on the factors treatment and country with baseline as covariate and no interaction.

In addition, descriptive statistics by treatment group were provided.

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.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

A total of 1456 patients were screened and 1323 were selected for the study. Of them, 806 patients were included and randomised: 201 patients in the S 38093 2 mg group, 202 patients in the S 38093 5 mg group, 203 patients in the S 38093 20 mg group, and 200 patients in the placebo group. A well-balanced distribution was achieved.

713 out of all the 806 randomised patients (88.5%) completed the study, and 93 patients (11.5%) withdrew prematurely. The most frequent reasons for withdrawal were adverse event (5.7%, 46 patients), followed by non-medical reason (2.9%, 23 patients) and protocol deviation (2.6%, 21 patients). All were more frequent in the S 38093 20 mg group, leading to a higher withdrawal rate (14.8%) than in the S 38093 2 mg (10.0%), 5 mg (11.9%) and placebo groups (9.5%). No patient was lost to follow up during the study. Patient status during the study is indicated in Table 1.

SUMMARY – CONCLUSIONS (Cont'd)

DISPOSITION OF PATIENTS AND ANALYSIS SETS

Table 1 - Disposition of patients

		S 38093 2mg N = 201	S 38093 5mg N = 202	S 38093 20mg N = 203	Placebo N = 200	All N =806
Included (Randomised)	**N**	**201**	**202**	**203**	**200**	**806**
Withdrawn due to	**n (%)**	**20 (10.0)**	**24 (11.9)**	**30 (14.8)**	**19 (9.5)**	**93 (11.5)**
adverse event	n (%)	9 (4.5)	13 (6.4)	14 (6.9)	10 (5.0)	46 (5.7)
non-medical reason	n (%)	6 (3.0)	6 (3.0)	8 (3.9)	3 (1.5)	23 (2.9)
protocol deviation	n (%)	3 (1.5)	5 (2.5)	7 (3.4)	6 (3.0)	21 (2.6)
lack of efficacy	n (%)	2 (1.0)	-	1 (0.5)	-	3 (0.4)
Completed the W0-W24 period	**n (%)**	**181 (90.1)**	**178 (88.1)**	**173 (85.2)**	**181(90.5)**	**713 (88.5)**
Randomised Set (RS)	n	**201**	**202**	**203**	**200**	**806**
Full Analysis Set	n (%)	199 (99.0)	200 (99.0)	202 (99.5)	199 (99.5)	800 (99.3)
Safety set	n (%)	191 (95.0)	192 (95.0)	193 (95.1)	189 (94.5)	765 (94.9)

N: Total patients of included (randomised)
%: n/N x 100

BASELINE CHARACTERISTICS

In the RS, the mean age (± standard deviation (SD)) was 72.6 ± 7.7 years, most were of Caucasian origin (92.4%) and 62.5% were female. Overall, patients had an average educational level of 9.8 ± 4.0 years, ranging from 4 to 24 years. No relevant between-group difference was observed for demographic characteristics.

Weight ranged between 37.6 kg and 123.0 kg with a mean of 69.0 ± 13.0 kg at baseline and the mean BMI was 26.1 ± 4.2 kg/m^2. Mean supine BP (SBP/DBP) was 133.8 ± 16.8 mmHg / 76.6 ± 9.3 mmHg and the mean heart rate was 62.3 ± 9.3 bpm. Measured orthostatic hypotension without symptoms was observed in 82 patients (10.2%) at baseline.

At inclusion, the mean MMSE total score was 17.5 ± 3.3, at selection, the mean Modified Hachinski Ischemic score was 0.7 ± 0.8 and the mean Geriatric Depression Rating Scale-15 (GDS) total score was 1.7 ± 1.4, without relevant difference between groups. These parameters fulfilled inclusion criteria for all patients.

The average duration of Alzheimer's was 3.5 ± 2.3 years (median 3.0 years). All patients took donepezil for the treatment of Alzheimer's disease before study for 1.5 ±1.4 years (median 1.0), mainly in the evening (62.4%).

In the RS, the mean total score of ADAS-Cog was 26. 4 ± 9.0 (median = 25.5), ranging from 8.7 to 56.3, and the total DAD score ranged from 10.0% to 100.0%, with a mean score of 69.1 ± 19.9% (median = 70.0%). No clinically relevant differences between treatment groups were observed for ADAS-Cog and DAD total scores at baseline.

Baseline characteristics in the FAS (N = 765, 94.9% of the RS) were similar to those observed in the Randomised Set.

EXTENT OF EXPOSURE

In the RS, during the 24-week treatment period, the overall mean study drug duration was 157.2 ± 35.4 days (median of 168.0 days), and the mean donepezil duration was 158.1 ± 33.7 days (median of 168.0 days). The global compliance was good as 96.7% and 97.8% of patients, respectively for the study drug and donepezil, had compliance between 70% and 130%. No relevant difference was observed between groups.

SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS

Primary efficacy criterion

- Table 2 summarises the comparison of the mean change of ADAS-Cog total score from baseline to W24 between each S 38093 dose and placebo in the FAS.

Table 2 - ADAS-Cog total score - Change from baseline to W12 and W24
Comparison to placebo at W24 in the FAS

		S 38093 2 mg (N = 191)	S 38093 5 mg (N = 192)	S 38093 20 mg (N = 193)	Placebo (N = 189)
Baseline (W0)	n	191	192	193	189
	Mean ± SD	27.24 ± 9.74	25.98 ± 7.90	25.85 ± 9.27	26.33 ± 8.94
Change from baseline to W12	n	191	192	192	185
	Mean ± SD	1.56 ± 4.74	0.80 ± 4.54	0.36 ± 4.98	-0.16 ± 4.64
Change from baseline to W24	n	178	176	172	178
	Mean ± SD	1.08 ± 5.07	1.08 ± 5.93	0.48 ± 6.26	0.52 ± 6.00
Statistical analysis[(1)]	E (SE) [(2)]	0.72 (0.61)	0.49 (0.61)	-0.04 (0.61)	
	95% CI [(3)]	[-0.48 ; 1.91]	[-0.70 ; 1.69]	[-1.24 ; 1.16]	
	p-value [(4)]	1.000	1.000	1.000	

*(1) Mixed-effects Model for Repeated Measures including terms for fixed categorical effects of treatment, pooled country, 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) One-sided adjusted p-value (to be compared to 0.025), taking into account a Bonferroni-based sequentially rejective multiple test procedure for multiplicity adjustment.

- In the FAS, no statistically significant superiority was demonstrated between any S 38093 dose group and the placebo group on the mean change of ADAS-Cog total score from baseline to W24. Results were confirmed by the sensitivity analyses to the method of handling missing data.

Key secondary efficacy criterion

- Table 3 gives the comparison of the mean change of DAD total score from baseline to W24 between each S 38093 dose and placebo in the FAS.

Table 3 - DAD total score (%) - Change from baseline to W24(*)
Comparison to placebo in the FAS

		S 38093 2 mg (N = 191)	S 38093 5 mg (N = 192)	S 38093 20 mg (N = 193)	Placebo (N = 189)
Baseline (W0)	n	189	189	190	186
	Mean ± SD	69.42 ± 20.74	70.07 ± 16.93	70.75 ± 20.82	67.79 ± 19.66
W24(*)	n	189	189	190	186
	Mean ± SD	65.39 ± 20.52	67.26 ± 19.89	65.09 ± 24.22	64.44 ± 21.97
Change from baseline to W24(*)	n	189	189	190	186
	Mean ± SD	-4.03 ± 13.28	-2.81 ± 12.30	-5.66 ± 15.54	-3.35 ± 12.40
Statistical analysis[(1)]	E (SE) [(2)]	-0.54 (1.35)	0.70 (1.35)	-1.88 (1.35)	
	95% CI [(3)]	[-3.20 ; 2.12]	[-1.96 ; 3.36]	[-4.53 ; 0.78]	
	p-value [(4)]	1.000	1.000	1.000	

(*) After LOCF imputation
(1)Analysis of covariance model on factors treatment, and pooled country 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 value. Due to only one post-baseline assessment of the key secondary criterion, the MMRM approach cannot be considered.
(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)One-sided adjusted p-value (to be compared to 0.025), taking into account a Bonferroni-based sequentially rejective multiple test procedure for multiplicity adjustment

- In the FAS, no statistically significant superiority was demonstrated between any S 38093 dose group and the placebo group on the mean change of DAD total score from baseline to W24. Results were confirmed by the sensitivity analyses to the method of handling missing data.

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS

Emergent adverse events

Table 4 - Overall summary for adverse events in the Safety Set

		S 38093 2 mg (N = 199)	S 38093 5 mg (N = 200)	S 38093 20 mg (N = 202)	Placebo (N = 199)
Patients having reported					
at least one emergent adverse event	n (%)	103 (51.8)	109 (54.5)	106 (52.5)	118 (59.3)
at least one treatment-related emergent adverse event	n (%)	15 (7.5)	21 (10.5)	18 (8.9)	12 (6.0)
Patients having experienced					
at least one serious adverse event (including death)	n (%)	15 (7.5)	20 (10.0)	22 (10.9)	26 (13.1)
at least one serious emergent event (including death)	n (%)	12 (6.0)	15 (7.5)	19 (9.4)	23 (11.6)
at least one treatment-related serious adverse event	n (%)	2 (1.0)	3 (1.5)	2 (1.0)	1 (0.5)
Patients with treatment withdrawal					
due to emergent adverse event	n (%)	9 (4.5)	13 (6.5)	15 (7.4)	9 (4.5)
due to serious emergent adverse event	n (%)	2 (1.0)	6 (3.0)	7 (3.5)	6 (3.0)
due to treatment-related EAE	n (%)	7 (3.5)	7 (3.5)	5 (2.5)	2 (1.0)
due to a treatment-related serious EAE	n (%)	2 (1.0)	3 (1.5)	2 (1.0)	-
Patients who died	n (%)	1 (0.5)	2 (1.0)	2 (1.0)	2 (1.0)

N: Total number of patients in the considered treatment group
n: Number of affected patients
*%: n/N*100*

- During the treatment period, the percentage of patients with at least one emergent adverse event (EAEs) was slightly lower in the 3 S 38093 dose groups (51.8%, 54.5% and 52.5%, respectively in the S 38093 2 mg, 5 mg and 20 mg groups) than in the placebo group (59.3%).
- Among the most frequently affected (≥ 10% of patients in any group) system organ classes (SOCs), higher frequencies on S 38093 than on placebo were observed for nervous system disorders (14.9% in the S 38093 20 mg group *versus* 10.1% in the placebo group) and injury, poisoning and procedural complications (10.5% in the S 38093 5 mg group *versus* 6.5% in the placebo group).
- Among the EAEs reported at least once by at least 3% of patients on any dose of S 38093, the following were more frequently reported in S 38093 groups than in the placebo group: fall (8.0% and 6.4%, respectively in the S 38093 5 mg and 20 mg groups *versus* 4.5% in the placebo group), urinary tract infection (6.5% in the S 38093 2 mg group and 5% in the 5 mg group *versus* 4.5% in the placebo group), diarrhoea (4.5% in the S 38093 2 mg group *versus* 2.5% in the placebo group), nausea (4.0% in the S 38093 20 mg group *versus* 1.5% in the placebo placebo), aggression (4.0% in the S 38093 2 mg group *versus* 2.0% in the placebo group), upper respiratory tract infection (3.0% in the S 38093 20 mg group *versus* 0.5% in the placebo group), depression (3.0% in the S 38093 2 mg group *versus* 0.5% in the placebo group) and fatigue (3.0% in the S 38093 20 mg group *versus* none in the placebo group).
- In the Safety Set, a total of 5 patients reported orthostatic hypotension (5 EAEs in 5 patients), with 2 patients in both S 38093 5 mg and 20 mg groups and one in the placebo group. Three (3) EAEs in the S 38093 groups and one in the placebo group were symptomatic orthostatic hypotension, and one orthostatic hypotension in the 5 mg group was asymptomatic. When calculated based on the change of SBP and DBP, the incidence of emergent orthostatic hypotension was higher in the S 38093 20 mg group (43 patients, 23.8%) than in the placebo group (36 patients, 20.7%), while lower than placebo in the S 38093 2 mg group (29, 16.2%) and 5 mg group (28, 15.8%).
- The severe EAEs were rare and less frequently reported in the 3 S 38093 dose groups than in the placebo group. As regards S 38093 doses, the severe EAEs were more frequent in the S 38093 20 mg group than in the other 2 dose groups (2.3%, 2.4%, and 4.4% of EAEs respectively in the S 38093 2 mg, 5 mg and 20 mg groups *versus* 5.6% in the placebo group).
- The treatment-related EAEs tended to be reported in more patients in the S 38093 groups (7.5%, 10.5%, and 8.9% in the S 38093 2 mg, 5 mg and 20 mg groups, respectively) than in the placebo group (6.0%). No event was more frequently reported (at least 4 patients) in any S 38093 dose group than in the placebo group, except for dizziness with 4 patients (2.0%) in the S 38093 20 mg group *versus* none in the placebo group.

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Emergent adverse events (Cont'd)

- Overall, 71 EAEs leading to study drug withdrawal were reported in 46 patients (5.8%), slightly more frequent in the S 38093 5 mg and 20mg groups (6.5% and 7.4%, respectively) than in the placebo group (4.5%), and the same as placebo in the S 38093 2 mg group (4.5%). The slight imbalance between groups was mainly due to the following preferred terms, all of which were only reported on S 38093: dizziness (1.5% in the S 38093 5 mg group), agitation (1.5% in the S 38093 20 mg group), nausea (1.5% in the S 38093 20 mg group) delusion (1.0% in the S 38093 2 mg group) and dementia (1.0% in the S 38093 20 mg group).

In all 7 patients (0.9%) died during the study, 1 (0.5%) in the S 38093 2 mg group, 2 (1.0%) in the S 38093 5 mg group, 2 (1.0%) in the S 38093 20 mg group, and 2 (1.0%) in the placebo group:

- 5 patients died on treatment with 2 patients due to sudden death (one in the S 38093 2 mg group and the other in the placebo group), 1 patient due to post procedural sepsis in the S 38093 5 mg group, 1 due to pneumonia in the S 38093 20 mg group and 1 due to cardiogenic shock with acute coronary syndrome in the placebo group.
- 2 patients died after the treatment period due to events occurring on treatment, with 1 patient in the S 38093 5 mg group (herpes simplex encephalitis) and 1 in the S 38093 20 mg group (postoperative wound infection).
- A total of 69 patients (8.6%) experienced 140 serious emergent adverse events (including death) during the treatment period. The highest rate was observed in the placebo group (6.0% in the S 38093 2 mg, 7.5% in the 5 mg group 9.4% in the 20 mg group, and 11.6% in the placebo group). The most frequently reported preferred terms were fall in 12 patients overall including the placebo group with no relevant difference between groups (2 patients (1.0%), 3 patients (1.5%), 3 patients (1.5%), respectively in the S 38093 2 mg, 5 mg, 20 mg groups *versus* 4 patients (2.0%) in the placebo group), and syncope in 6 patients overall, with 1 patient (0.5%) in the S 38093 5 mg group and 5 (2.5%) in the S 38093 20 mg group, *versus* none on placebo.
- A total of 17 Serious EAEs were considered as treatment-related in 8 patients: 2 patients (1.0%) in S 38093 2 mg group, 3 patients (1.5%) in S 38093 5 mg group, 2 patients (1.0%) in S 38093 20 mg group and 1 patient (0.5%) in the placebo group.

Laboratory parameters

- In the Safety Set, neither clinically relevant changes from baseline to last post-baseline value on treatment nor differences between groups were detected in biochemical and haematological parameters over the 24-week treatment period. The prolactin level over the 24-week treatment period increased with the 3 doses of S 38093 compared to the placebo, especially for the 20 mg dose, with mean increases of 0.8 ± 5.7 µg/L, 0.2 ± 9.0 µg/L and 1.2 ± 16.0 µg/L in the S 38093 2 mg, 5 mg, and 20 mg groups *versus* 0.1 ± 11.8 µg/L in the placebo group.
- The emergent potentially clinically significant abnormal (PCSA) biochemical and haematological values on treatment were sparse for each parameter in all groups, except for high triglycerides without difference with the placebo group (8.2% of patients had at least one PCSA value on treatment in the S 38093 5 mg group *versus* 8.6% in the placebo group).

Vital signs and clinical examination

- Neither clinically relevant changes from baseline to last post-baseline value on treatment nor differences between groups were detected in vital signs except for supine SBP and DBP, both of which decreased more in all S 38093 groups than in the placebo group (mean changes in SBP/DBP: -3.1 ± 15.4 / -1.6 ± 10.0 mmHg, -2.3 ± 15.3 / -0.9 ± 9.1 mmHg, -2.6 ± 16.3 / -1.9 ± 9.8 mmHg in the S 38093 2 mg, 5 mg and 20 mg groups *versus* -0.5 ± 16.7/-0.3 ± 9.9 mmHg in the placebo group).
- Neither clinically relevant mean changes nor differences between treatment groups were detected on ECG parameters. Few patients were detected with at least one emergent ECG abnormality during the treatment period, with no relevant difference between groups (7.0% in the S 38093 2 mg group, 4.0% in the S 38093 5 mg group, 5.5% in the S 38093 20 mg group *versus* 6.5% in the placebo group).

CONCLUSION

This international, multi-centre, randomised, double-blind, placebo-controlled, in co-administration with donepezil (10 mg/day), phase IIb study conducted in patients suffering from moderate Alzheimer's disease did not show any statistically or clinically significant effect of S 38093 after 24 weeks of treatment at any dose (2 mg, 5 mg and 20 mg) on cognitive functions (ADAS-Cog 11-items), functional ability (DAD), and other secondary endpoints.

Regarding the safety profile, fall was the most common EAE on S 38093, occurring more frequently in the S 38093 5 mg and 20 mg group than in the placebo group. Regarding biological safety, S 38093 was well tolerated. A slight prolactin increase was observed on S 38093 compared to placebo, especially with S 38093 20 mg. Supine SBP and DBP tended to decrease more with S 38093 than with placebo. No other safety concerns were raised in this study, and in particular, there were no concerns regarding orthostatic hypotension or ECG abnormalities.

Date of the report: 22 December 2015

Version of the report: Final version