Document title	**Clinical Study Report Synopsis**
Study title	**Efficacy of 15 mg and 50 mg of S 18986 on cognitive symptoms in Mild Cognitive Impairment patients treated over a 12-month oral administration period. An international multicentre, 3 parallel groups, randomised, double blind, placebo-controlled phase II study.**
Study drug	**S 18986**
Indication	**Mild Cognitive Impairment**
Development phase	**II**
Protocol code	**CL2-18986-009**
Study initiation date	**22 June 2005**
Study completion date	**16 March 2006**
Main coordinator	[redacted] **France**
Company / Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 Rue Carnot** **92284 Suresnes Cedex - France** **Servier Canada Inc.** **235 Armand-Frappier Blvd** **Laval - Quebec - Canada** **International Centre for Therapeutics Research (I.C.T.R.)** **Gallions Wexham Springs** **Framewood Road - 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 13 April 2007**

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:
Efficacy of 15 mg and 50 mg of S 18986 on cognitive symptoms in Mild Cognitive Impairment patients treated over a 12-month oral administration period. An international multicentre, 3 parallel groups, randomised, double blind, placebo-controlled phase II study.
Protocol No.: CL2-18986-009.

Main coordinator: [redacted], France).
National coordinators: [redacted] Australia), [redacted] Belgium), [redacted] Canada), [redacted] Germany), [redacted], The Netherlands), [redacted] The United Kingdom).

Study centres: Multicentre study involving 15 active centres (38 included patients): 1 centre in Australia (2 included patients), 1 centre in Belgium (2 included patients), 3 centres in France (4 included patients), 6 centres in Germany (9 included patients), 1 centre in New Zealand (1 included patient) and 3 centres in the United Kingdom (20 included patients).

Publication (reference): Not applicable.

Studied period: Initiation date: 22 June 2005. Completion date: 11 October 2005 (study suspension), 16 March 2006 (last follow-up visit) and 29 March 2006 (study stop). **The study was prematurely stopped due to safety concerns.**	**Phase of development of the study:** II

Objectives:
Main objective: To demonstrate a superiority of at least one dose of S 18986 *versus* placebo on verbal episodic memory performance in Mild Cognitive Impairment (MCI) patients over 12 months.
Secondary objectives:

- To demonstrate a superiority of at least one dose of S 18986 *versus* placebo on visual episodic memory and other cognitive domains performance in patients with MCI over 12 months.
- To demonstrate a superiority of at least one dose of S 18986 *versus* placebo in the activities of daily living, the patient self-perception of his/her memory impairment and the clinician global impression of change in patients with MCI over 12 months.
- To show a reduction or a stabilisation in hippocampal and whole brain atrophy using Magnetic Resonance Imaging (MRI) in patients with MCI treated with S 18986 *versus* patients with MCI receiving placebo for 12 months.
- To show a lower number of conversion to Alzheimer's disease with S 18986 *versus* placebo over 12 months.
- To assess safety and acceptability of S 18986 in patients with MCI over 12 months.
- To collect plasma concentrations of S 18986 and its metabolite Y 1255 to compare the level with previous studies.

Methodology: Multicentre, multinational, randomised, double-blind, 3 parallel groups, placebo-controlled study. The randomisation was centralised, balanced, non-adaptative, stratified on centre and on Apolipoprotein E allel 4 presence (ApoE ε4). Patients referred for memory complaint expressed by himself or herself and/or informant with a decline for at least the last 6 months prior to selection.

Number of patients:
Planned: 450 (150 per group).
Included: 38 (12 in the S 18986 15 mg group, 10 in the S 18986 50 mg group and 16 in the placebo group).

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Diagnosis and main criteria for inclusion:
Age ≥ 55 years, 7 years of education at least, LM II of WMS-Revised with 1.5 SD below norm as function of age, MMSE ≥ 24, global CDR = 0.5 (memory box ≥ 0.5), not sufficiently impaired to meet dementia (DSM IV).
Ach EI were to be stopped at least 3 months before selection. SSRI or SNRI for depressive symptoms and low dose of anxiolytic or hypnotic, used as sleep aid accepted if stabilized symptoms for at least 3 consecutive months before selection.

Study drug:
S 18986 capsules, 15 mg and 50 mg, oral route, one capsule once daily.
Batch Nos.: L 0004434 (S 18985 15 mg), L 0004519 (S 18986 50 mg).

Reference product:
Placebo capsules, oral route, one capsule once daily.

Duration of treatment:
Planned: Run-in period without any treatment: from 2 weeks up to 6 weeks (Selection visit).
Active treatment period with placebo or S 18986: 12 months (Inclusion visit at D0, D15, M1, M2, M3, M6, M9 and M12 visits).
Follow-up period with no study treatment: 1 month (follow-up visit).
Due to the premature study end, no planned visit was performed after M3 but follow-up visits were organised until the resolution of any symptom and/or biological abnormality observed after inclusion on S 18986.

Criteria for evaluation:
Efficacy measurements:
Primary efficacy criterion:
Trial I-V total score (maximum score: 75, delta = 4 words) of the Rey Auditory Verbal Learning Test (RAVLT) at D0, M6 and M12 visits.
Secondary efficacy criteria:
RAVLT (other criteria than the primary), Paired Associate Learning (PAL) and Pattern Recognition Memory (PRM) from the Cambridge Neuropsychological Test Automated Battery (CANTAB), category fluency test (3 categories comprising animal), symbol digit test, stroop test, trail making tests A & B, ADCS ADL-PI informant, cognitive difficulties scale, Clinician's Global Impression of Change (MCI-CGIC) at D0, M6 and M12 visits.
ADCS-MCI ADAS-Cog at selection and M12 visits.
Conversion to AD at D15, M1, M3, M6, M9, M12, Mend.
Measure of MRI hippocampal, ventricular and whole brain volumes at selection and M12 visits.
Safety measurements:
- Collection of adverse events and concomitant treatments at each visit.
- Clinical examination: blood pressure, heart rate, weight, temperature, neurological examination at selection, D0, D15, M1, M3, M6, M9, M12 and Mend visits.
- Biological examinations at selection, D0, D15, M1, M3, M6, M9, M12 and Mend visits.
- ECG at selection, D0, M1, M3, M6, M12 and Mend visits.

Pharmacokinetic measurements:
- Plasma concentrations of S 18986 and its metabolite Y 1255 at D0, D15, M1, M3, M6, M9 and M12 visits.

Statistical methods:
Because of treatment-related clinical adverse events and biological abnormalities reported among the first included patients, the study was stopped. Consequently, the statistical analyses were performed on the included patients, on all performed visits and were descriptive only. PK analysis was not performed.
Efficacy analysis: No post-baseline efficacy value was collected. No analysis was performed.
Safety analysis: Descriptive analyses were performed in the Safety Set: in each treatment group, on each dose of S 18986 and on pooled doses of S 18986.

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SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

Due to safety concerns, the study was prematurely suspended on 11 October 2005 and terminated on 29 March 2006. Only, 38 patients were included: 12 in the S 18986 15 mg group, 10 in the S 18986 50 mg group and 16 in the placebo group. All patients had taken at least one dose of treatment.

Disposition of patients

	S 18986 15 mg	**S 18986 50 mg**	**Placebo**	**All**
Included (randomised)	**12**	**10**	**16**	**38**
Withdrawn due to adverse event	1	6	0	7
Study stop due to sponsor's decision	11	4	16	31
Safety set	12	10	16	38

Overall, 17 women and 21 men were randomised in the study, mainly in the United Kingdom (20 patients). The mean ± SD age was 66.7 ± 6.6 years. Patients had an average memory decline duration of 3.9 ± 3.6 years and 71.1% of them were not previously treated with a central nervous system treatment. About 60% of the patients, equally distributed in the treatment groups, were ApoE ε4 carriers. All patients had a normal neurological examination at baseline except 2 patients in the S 18986 15 mg group (motor strength abnormality and cranial nerves abnormality). The neuropsychological evaluation was similar in the 3 treatment groups. All the patients had a total mini mental score ≥ 24.

Treatment duration was similar in the 3 groups (on average 25.3 ± 15.7 days). The longest treatment duration was 61 days in the S 18986 15 mg group, 68 days in the S 18986 50 mg group and 52 days in the placebo group. All patients had a compliance between 70 and 130% except one in the S 18986 15 mg group (2.6%).

Overall, 7 patients withdrew due to adverse events (1 in the S 18986 15 mg group and 6 in the S 18986 50 mg group). For 4/7 patients, this event was serious. Withdrawals occurred between D15 and M3. Following the safety problems, the treatment and the study were stopped for the 31 on-going patients. Follow-up visits were planned to collect safety information until patients' recovery.

EFFICACY RESULTS

No post-baseline efficacy value was collected.

SAFETY RESULTS

After the first inclusions, emergent adverse events described as flu-type symptoms, and hepatic enzyme increases and/or platelet decreases were observed in different centres. Most concerned patients were included in centres 903 and 904 in the United Kingdom which had a high recruitment rate. Out of a total of 19 included patients in these centres, 9 patients reported emergent adverse events (mostly influenza like illness without fever), of moderate and severe intensity requiring the patient's hospitalisation in 3 cases (influenza like illness associated with atrial fibrillation in one patient, myalgia and malaise in one patient; and radiculopathy in one patient). Among them, 6/8 patients withdrew due to these adverse events between 1 and 16 days of treatment. The events were considered to be related to the study treatment by the investigator. The events were associated with hepatic enzymes increase in 7/8 patients and with platelet decrease in 5/8 patients.

These events led to a biological and clinical review of all events in the active centres.

In Australia, one patient had pyrexia 6 days after the first intake which led to her hospitalization and her withdrawal from the study. She had also hepatic enzyme increase and platelet decrease. In France, one patient presented with a transient hepatic enzyme increase and platelet decrease, spontaneously normalized on treatment. In Germany, one patient had platelet decrease.

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SUMMARY - CONCLUSIONS (Cont'd)

These observations are summarized in the table below:

Alerting events

	Emergent flu-type symptoms	**Hospitalisation**	**Withdrawal due to AE**	**Platelet decrease**	**Hepatic enzymes increase**
S 18986 15 mg (n = 4)					
Centre 903: n = 1	Migraine NOS, sweating increased, rigors	-	-	-	X
Centre 904: n = 3	Influenza like illness	-	-	-	X
	Influenza like illness	-	X	X	X
	-	-	-	X	-
S 18986 50 mg (n = 8)					
Centre 903: n = 1	**Influenza like illness, atrial fibrillation**	X	X	-	-
Centre 904: n = 4	Influenza like illness	-	X	X	X
	Influenza like illness	-	X	X	X
	Myalgia, malaise	X	X	X	X
	Radiculopathy NOS	X	X	X	X
Centre 102: n = 1	**Pyrexia**	X	X	X	X
Centre 501: n = 1	-	-	-	X	X
Centre 601: n = 1	-	-	-	X	-

Bold serious adverse event

The Data Monitoring Committee was consulted on these cases. It was decided to break the blind. All patients with flu-type symptoms, platelet decrease and hepatic enzyme increase were on S 18986, mostly on 50 mg. The DMC advised to suspend the study and the treatments were stopped. Patients were followed for any symptoms appeared after treatment intake; then the study was terminated, 5 months later. All the patients recovered at the end of the study, except the patient with radiculopathy who was still recovering after 11 months of follow-up.

Adverse events are summarised in the table below.

Summary of adverse events

Patients having reported		**S 18986 15 mg (N = 12)**	**S 18986 50 mg (N = 10)**	**S 18986 pooled (N = 22)**	**Placebo (N = 16)**
At least one emergent adverse event	n (%)	7 (58.3)	9 (90.0)	16 (72.7)	9 (56.3)
At least one occurrence of influenza like illness	n (%)	2 (16.7)	3 (30.0)	5 (22.7)	-
At least one treatment-related emergent adverse event	n (%)	4 (33.3)	8 (80.0)	12 (54.5)	3 (18.8)
At least one serious adverse event	n (%)	1 (8.3)	5 (50.0)	6 (27.3)	1 (6.3)
At least one adverse event leading to patient's withdrawal	n (%)	1 (8.3)	6 (60.0)	7 (31.8)	-

The percentage of patients with an emergent adverse event was greater in the S 18986 groups (72.7%) than in the placebo group (56.3%). As regard S 18986 doses, the emergence of adverse events increased with the dose: 58.3% at 15 mg and 90.0% at 50 mg.

The most frequently reported system organ classes in the S 18986 pooled group were: general disorders and administration site conditions (25.0% in the S 18986 15 mg group, 50.0% in the S 18986 50 mg group *versus* none in the placebo group), investigations (16.7%, 30.0% *versus* 6.3%, respectively) and nervous system disorders (25.0%, 20.0% *versus* 12.5%, respectively).

For the first two system organ classes, the higher incidence on S 18986 were mainly due to influenza like illness and liver function tests NOS abnormal. C-reactive protein increase was reported in 1 patient on S 18986 15 mg and 2 on S 18986 50 mg.

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SUMMARY - CONCLUSIONS (Cont'd)

For the third most frequently reported system organ class, the between-group difference compared to placebo were due to headaches (grouping together tension headaches, headache and migraine NOS). They were reported in 3 patients on S 18986 15 mg, 1 on S 18986 50 mg *versus* none in the placebo group.

Overall, 7 patients reported 9 serious adverse events. All but one (dizziness) were in S 18986-treated patients: 1 patient in the S 18986 15 mg group (stress symptoms), and 5 patients in the S 18986 50 mg group (pyrexia, urinary tract infection, influenza like illness and atrial fibrillation, myalgia and malaise, radiculopathy). All but one (stress symptoms) were emergent. In addition, one serious urinary tract infection NOS was reported in the S 18986 50 mg group. The serious emergent adverse events occurred from 3 to 10 days after the study drug intake. All but one (urinary tract infection NOS) were considered by the investigator to be related to treatment.

Overall, 7 patients withdrew from the study due to adverse events which were serious in 4 patients.

Clinical laboratory evaluation

Biochemical abnormalities were more frequently reported in the S 18986 pooled group than in the placebo group. Abnormalities were more encountered at the highest dose of S 18986.

Hepatic parameters were elevated in 5 patients in the S 18986 15 mg, 6 patients in the S 18986 50 mg and 3 patients in the placebo group. In the S 18986 groups, the disorders concerned several hepatic parameters (ASAT, ALAT, GGT, alkaline phosphatase, bilirubin and LDH). These disturbances were considered clinically significant by the investigator in 1 patient in the S 18986 15 mg group, 3 in the S 18986 50 mg group. They were transient and followed by normal value at the following visits after treatment stop.

A decrease in electrolytes was observed in the S 18986 pooled group only: sodium, potassium, chloride, and calcium (in all 5 patients concerned).

Low emergent out-of-reference-range abnormalities for total proteins were more frequent in the S 18986 pooled group than in the placebo group (31.8% *versus* 18.8%, respectively). CPK were elevated in 2 patients in the S 18986 50 mg group *versus* none in the placebo group, and CRP, measured for safety reasons, was elevated in 4 patients in the S 18986 groups.

Concerning haematological parameters, a platelet decrease was observed in the S 18986 groups in 9 patients whereas no decrease was encountered in the placebo group. These decreases occurred rapidly after the first intake (all but one reported at D15). Emergent values below the reference range were reported in 1 patient in the S 18986 15 mg group and 7 patients in the S 18986 50 mg group. They were potentially clinically significant for the 7 patients on 50 mg. All patients had normalisation of their platelet counts on treatment except for 2 patients normalised 18, and 23 days after the last study drug intake. Moreover, low emergent out-of-reference-range values were reported in the S 18986 pooled group only for white blood cells (4 patients) and lymphocytes (3 patients). These abnormalities were transient and patients returned to normal values after treatment stop.

Vital signs

No changes over time were observed in weight, blood pressures and heart rate.

Electrocardiogram

No difference between groups was observed.

Neurological examination

1 patient in the S 18986 50 mg group reported 3 emergent neurological abnormalities considered by the investigator clinically significant. This patient had a radiculopathy during the study which was recovering/improving at the end of the study after 11 months of follow-up.

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CONCLUSION

This phase II study was prematurely stopped (38 patients included, 450 planned) due to the emergence of particular adverse events on S 18986. The adverse events consisted of a flu-type syndrome without fever in all but one case, frequently associated with liver enzyme increase and/or platelet decrease. Clinical and biological acceptability was dose dependent. For most patients, clinical symptoms as well as the biological abnormalities were resolved within a few days after discontinuing the study treatment. All S 18986-treated patients recovered but one was still recovering after 11 months of follow-up (radiculopathy). Due to this major safety concern, the clinical study was stopped.

Date of the report: 13 April 2007