Document title	**Clinical Study Report Synopsis**
Study title	**Effects of terutroban versus aspirin on composition of atherosclerotic plaque in patients undergoing a carotid endarterectomy. A multicentre, randomised, double blind, two parallel group study comparing terutroban 30 mg o.d. versus aspirin 100 mg o.d. administered orally.**
Study drug	**S 18886 (Terutroban)**
Studied indication	**Atherothrombosis**
Development phase	**Phase II**
Protocol code	**CL2-18886-026**
Study initiation date	**16 April 2008**
Study completion date	**20 February 2009**
Main coordinator	[redacted]
Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 Rue Carnot** **92284 Suresnes Cedex - France**
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 23 March 2010**

~~**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: Effects of terutroban versus aspirin on composition of atherosclerotic plaque in patients undergoing a carotid endarterectomy. A multicentre, randomised, double blind, two parallel group study comparing terutroban 30 mg o.d. versus aspirin 100 mg o.d. administered orally.
Protocol No.: CL2 - 18886 - 026

Investigator: [redacted] Cedex

Study centre: Total number of centres: 3 centres in France

Publication (reference): NA

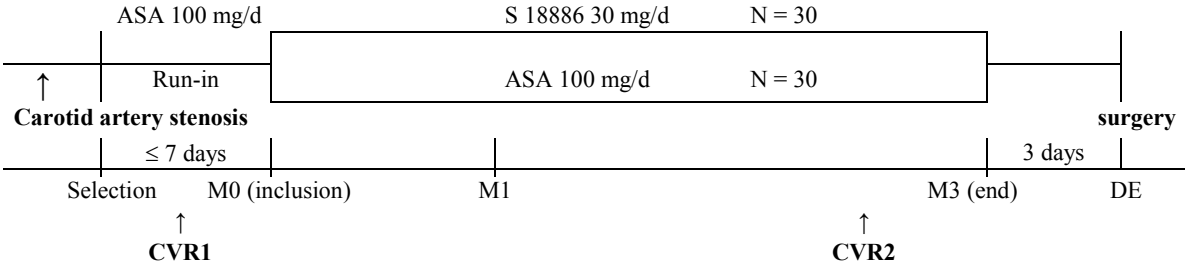
Studied period:	**Phase of development of the study:**
Initiation date: 16 April 2008 Completion date: 20 February 2009 (premature termination)	Phase II study

Objective:
Primary objective: to evaluate the effects of a 3-month treatment with S 18886 30 mg o.d. *versus* aspirin (ASA) 100 mg o.d. in patients undergoing a carotid endarterectomy on the expression of atherosclerosis markers in carotid plaque removed during endarterectomy.
Secondary objectives:

- To assess the effects of S 18886 on morphology of the carotid plaque.
- To evaluate the effects of S 18886 on blood atherosclerosis markers.
- To assess the cerebral vasoreactivity in this population.

Tolerance and safety were evaluated during the whole study duration.

Methodology: A multicentre, randomised, double-blind, two parallel groups, controlled versus aspirin study



M: month; CVR: Cerebral VasoReactivity; DE = Day of endarterectomy

Number of patients:
Planned: 60
Included: 7

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Diagnosis and main criteria for inclusion:

- Age ≥ 18 years.
- Men and post-menopausal women or with effective contraception.
- Patients with planned, non-urgent endarterectomy for clinically asymptomatic carotid artery stenosis (usually ≥ 70%).
- Without personal haemorrhagic history.
- Platelet count ≥ 120 G/L.
- Calculated creatinine clearance ≥ 30 mL/min according to the Cockroft-Gault formula.
- ASAT or ALAT < 3 x Upper Normal Limit.
- Having given informed consent.

Study drug:
S 18886 – Tablets – 30 mg – per os – once a day - Batch No's. L0010044, L0018961

Reference product: Aspirin – Enteric coated tablets – 100 mg – per os – once a day

Duration of treatment: Treatment of run-in period: 1 week. Treatment of blind period: 3 months

Criteria for evaluation:

Efficacy evaluation:

Main criterion:

Expression of biochemical markers of inflammation: Glycoprotein V (GPV), Myeloperoxydase (MOP), CD40 Ligand (CD-40L) in carotid plaque, removed during endarterectomy after a 3-month treatment.

Secondary criteria:

- Assessment of other biochemical markers of atherosclerotic plaque after a 3-month treatment.
- Morphological assessment of carotid plaque after a 3-month treatment.
- Blood atherosclerosis markers at CVR1 and CVR2.
- Cerebral Vasoreactivity (CVR) assessed by Mean Flow Velocity at CVR1 and CVR2 visits.

Safety evaluation:

- Adverse events.
- Vital signs (Systolic and Diastolic Blood Pressure (SBP, DBP), and Heart Rate (HR).
- ECG abnormalities.
- Haematology/Biochemistry abnormalities.

Statistical methods:

Efficacy analysis:

The following analyses were to be performed:

Main criterion: S 18886 group was to be compared with Aspirin group on biochemical markers of inflammation in carotid plaque using a Student t-test for independent sample.

Secondary criteria: the treatment groups were to be compared using a Student t-test for independent sample for other biochemical markers of inflammation in carotid plaque and using a Mantel-Haenszel Chi-square test for morphological assessment of carotid plaque

An analysis of covariance with treatment factor and baseline as a covariate was planned on atherosclerosis markers in plasma and CVR, considering the change from CVR1 to CVR2, in order to provide an estimate of the difference between the treatments and the associated 95% confidence interval.

Safety analysis: descriptive analyses were planned.

Due to the premature termination of the study, no statistical analyses were performed.

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SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

Out of 60 scheduled patients, 9 patients were screened, 8 were selected and 7 were included in the study. The reason for non selection was intake of clopidogrel and the reason for non inclusion was anaemia. The poor recruitment (rate less than one patient by month requiring 5 years to reach the target number) led to the premature termination of the study on 7 April 2009.

Three patients were randomised in the S 18886 group: 2 males (61 and 64 years old) and a female (70 years old). Four patients were randomised in the ASA group, all males, 66, 70, 71 and 77 years old, respectively.
Six patients were ex-smokers and one patient was a smoker. Medical history reported in more than one patient was hypertension (6 patients), dyslipidaemia (3 patients), hypercholesterolaemia (2 patients), diabetes (2 patients) and cataract (2 patients). Most frequent concomitant treatments at inclusion and on-going during the study were in relation with the medical history: anti-hypertensive drugs, cholesterol-lowering drugs (statins) and glucose- lowering drugs (gliclazide and repaglinide). Six patients were treated with platelet aggregation inhibitors (aspirin or clopidogrel) as previous treatment and stopped this treatment before or at selection. Relevant surgical history included a coronary artery bypass and a coronary arterial stent insertion (patient No. 026 250 0001 00072), and a previous carotid endarterectomy (patient No. 026 250 0002 00068). All patients had a planned endarterectomy within 4 months for clinically asymptomatic carotid artery stenosis: at CVR1, all patients had a stenosis of the left or right internal common artery of at least 70%.
The patients' characteristics were in accordance with the inclusion criteria of the study protocol.
Patients No. 026 250 0002 00066 (S 18886 group) prematurely discontinued the treatment due to a serious adverse event after 59 days of treatment (see safety results below). Treatment durations were 92 days in the two other patients of the S 18886 group. Treatment durations in the ASA group were 90, 86, 38 and 95 days, respectively. Compliance to treatment was 49%, 98% and 101% in the S 18886 group and 100%, 100%, 74% and 99% in the ASA group.

EFFICACY RESULTS

As the study was prematurely interrupted, no statistical analysis of the efficacy results was performed.

SAFETY RESULTS

Two serious adverse events leading to premature treatment discontinuation were reported in the same patient (No. 026 250 0002 00066, S 18886 group):

- Skin ulcer (ulcer of the right big toe with right iliac artery occlusion), which occurred in the month following the first drug intake (exact date unknown) and was considered unrelated to the study drug. The patient was recovering at the end of the follow-up.
- Peripheral arterial disease (obstructive arteriopathy of the lower limbs (stage IV)/ischaemia of the right two first toes - severe intermittent claudication and severe ulcer of the right big toe), which occurred about 2 months (exact date unknown) after the first study drug intake. The event was considered unrelated to the study drug by the investigator and related to the medical history. The patient underwent a transmetatarsus amputation and recovered with sequelae.

One non-serious adverse event was reported in patient No. 026 250 0001 00073 (S 18886 group): pustular rash. This event occurred about 1 month after the first study drug intake (exact date unknown) and was considered related to the study drug according to the investigator. It was rated as mild in intensity and recovered before the end of the study despite treatment continuation.

No effects of S 18886 were detected on laboratory results or in clinical examination parameters.

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CONCLUSION

This pilot open non-comparative study was stopped prematurely because of poor recruitment. Seven patients (instead of 60 planned patients) were randomised and received either S 18886 30 mg/day (3 patients) or aspirin 100 mg/day (4 patients). No unexpected adverse events or bleeding appeared to be associated with S 18886 treatment. No effect of S 18886 was detected on clinical examination and laboratory testing.

Date of the report: 23 March 2010