



<i>Document title</i>	Clinical Study Report Synopsis
<i>Study title</i>	Prevention of cerebrovascular and cardiovascular Events of ischaemic origin with teRutroban in patients with history of strOke or tRansient ischaeMic attack. The PERFORM Study. An international, randomised, double-blind, two parallel group study comparing terutroban 30 mg o.d. versus aspirin 100 mg o.d. administered orally for a 3-year mean duration (event driven trial).
<i>Study drug</i>	S 18886 (Terutroban)
<i>Studied indication</i>	Atherothrombosis
<i>Development phase</i>	Phase III
<i>Protocol code</i>	CL3-18886-012
<i>Study initiation date</i>	22 February 2006
<i>Study completion date</i>	31 March 2010
<i>Main coordinator</i>	[REDACTED] France
<i>Sponsors</i>	Institut de Recherches Internationales Servier (I.R.I.S.) 50 Rue Carnot 92284 Suresnes Cedex - France Laboratorios Servier, S.L. Avenida de los Madronos, 33 28043 Madrid - Spain SERVIER CANADA Inc. 235, Armand-Frappier Blvd Laval H7V 4A7 - Québec - Canada SERVIER UK Gallios, Wexham Springs, Framewood Road Wexham, Slough SL3 6RJ - United Kingdom
<i>Responsible medical officer</i>	[REDACTED]
<i>GCP</i>	This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.
<i>Date of the report</i>	Final version of 17 May 2011

CONFIDENTIAL

2. SYNOPSIS

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<p>Title of study: Prevention of cerebrovascular and cardiovascular Events of ischaemic origin with teRutroban in patients with a history of ischaemic strOke or tRansient ischaeMic attack. The PERFORM Study. An international, randomised, double-blind, two parallel group study comparing terutroban 30 mg o.d. <i>versus</i> aspirin 100 mg o.d. administered orally for a 3-year mean duration (event driven trial). Protocol No.: CL3-18886-012 The PERFORM Study is registered with www.controlled-trials.com, registration number ISRCTN66157730.</p>		
<p>International coordinator, Chairman of the Executive Committee: [REDACTED] (France)</p>		
<p>Study centres International, multicentre study with 802 centres in 46 countries having randomised at least one patient: Argentina: (23 centres – 463 patients), Australia (24 centres – 494 patients), Austria (16 centres – 191 patients), Belgium (22 centres – 564 patients), Brazil (22 centres – 1022 patients), Bulgaria (10 centres – 468 patients), Canada (32 centres – 483 patients), Chile (11 centres – 165 patients), China (21 centres – 468 patients), Croatia (6 centres – 190 patients), Czech Republic (10 centres – 789 patients), Finland (9 centres – 245 patients), France (56 centres – 797 patients), Germany (66 centres – 1482 patients), Greece (5 centres – 29 patients), Hong-Kong (4 centres – 224 patients), Hungary (22 centres – 767 patients), India (14 centres – 277 patients), Ireland (6 centres – 25 patients), Italy (61 centres - 1099 patients), Lithuania (6 centres – 193 patients), Luxembourg (1 centre – 17 patients), Malaysia (2 centres – 61 patients), Mexico (12 centres – 119 patients), Morocco (5 centres - 117 patients), Netherlands (19 centres – 469 patients), New Zeland (7 centres – 83 patients), Norway (5 centres – 99 patients), Poland (24 centres – 384 patients), Portugal (6 centres – 262 patients), Republic of Korea (11 centres – 377 patients), Romania (15 centres – 810 patients), Russian Federation (56 centres – 1596 patients), Singapore (3 centres – 173 patients), Slovakia (14 centres – 533 patients), Slovenia (4 centres - 157 patients), South Africa (10 centres – 130 patients), Spain (53 centres – 1079 patients), Sweden (8 centres – 128 patients), Switzerland (9 centres – 204 patients), Taiwan (8 centres – 256 patients), Thailand (8 centres – 343 patients), Tunisia (7 centres – 151 patients), Turkey (10 centres – 78 patients), Ukraine (7 centres – 213 patients), United Kingdom (52 centres – 865 patients).</p>		
<p>Publications: [REDACTED]</p>		
<p>Studied period: Initiation date: 22 February 2006 Completion date: 31 March 2010* <i>*additional patients data were obtained up to 17 June 2010</i></p>		<p>Phase of development of the study: Phase III</p>

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<p>Objectives: The primary objective was to demonstrate the superiority of S 18886 30 mg o.d. over aspirin 100 mg o.d., in reducing cerebrovascular and cardiovascular events of ischaemic origin (<i>primary efficacy end point</i>: composite of ischaemic stroke [fatal or non-fatal], myocardial infarction [fatal or non-fatal], other vascular death from non-haemorrhagic origin) in patients with a history of ischaemic stroke or transient ischaemic attack. The secondary objectives were to assess the effect of S 18886 on the other efficacy endpoints and its safety. Five substudies were conducted in subgroups of the overall population to evaluate the effects of S 18886 in comparison with aspirin:</p> <ul style="list-style-type: none"> - On the carotid intima media thickness (IMT) change (PERFORM vascular project). - On markers of platelet activation, inflammation, oxidative stress and endothelial dysfunction (PERFORM Biomarkers project). - On the evolution of cerebral atherothrombotic processes and their consequences (PERFORM Magnetic Resonance Imaging (MRI) project). - On the health-related quality of life (PERFORM Quality of life project). - On pharmacokinetic parameters of S 18886 for which a report will be presented apart. 		
<p>Methodology: This was an international, randomised, double-blind, with two parallel and balanced groups, controlled study <i>versus</i> aspirin. Randomisation was stratified by country. The study was event driven and designed to terminate after at least 2340 primary endpoints had occurred.</p>		
<p>Number of patients: Planned: 18000 patients (9000 per treatment group) Analysed (Randomised Set): 19100 (9556 patients in the S 18886 group and 9544 in the aspirin group)</p>		
<p>Diagnosis and main criteria for selection/inclusion:</p> <ul style="list-style-type: none"> - Women or men, age ≥ 55 years, with: - An history of Ischaemic stroke (IS) or arterial retinal ischaemic event (ARIE) confirmed by an ophtalmologist > 48 hours and ≤ 3 months before randomisation, or transient ischaemic attack (TIA) with at least symptoms of motor weakness in the limbs and/or aphasia within 8 days before randomisation. - Neurologically, clinically and haemodynamically stable at inclusion. - A Computerised Tomography-scan (CT-scan) or a Magnetic Resonance Imaging (MRI) ruling out intracranial haemorrhage or any non-ischaemic neurological disease. 		
<p>Study drug: S 18886 (terutroban) 30 mg given orally as one tablet/day. Batch Nos.: L0009329; L0009335; L0009635; L0010044; L0010048; L0010052; L0012351; L0012355; L0015928; L0015930; L0017144; L0017148; L0018957; L0018961; L0019954; L0019958; L0020830; L0020834; L0022502; L0022890; L0022894; L0023811; L0023815; L0024139; L0024144; L0025095; L0025097; L0027086; L0029387.</p>		
<p>Reference product: Aspirin 100 mg given orally as one tablet/day.</p>		
<p>Duration of treatment: Selection visit: was to be either the same day or less than 7 days before the inclusion visit. Active treatment period: planned from a minimum of 2 years to a maximum of 4 years with a mean duration of 3 years, and that could be extended up to 5 years, depending on the number of primary events observed in the study (event-driven trial). However, the study was prematurely stopped for futility. The mean follow-up duration was 2.4 years.</p>		

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<p>Criteria for evaluation: An independent Critical Event Committee (CEC), blinded to treatment group, adjudicated the critical events related to endpoints occurring in the study population. The results of these adjudications were used for the efficacy analyses. A general safety evaluation was performed throughout the study by the Data Monitoring Committee.</p> <p>Efficacy endpoints</p> <p>Primary efficacy endpoint First occurrence of an event in the composite of ischaemic stroke [fatal or non-fatal], myocardial infarction [fatal or non-fatal], other vascular death (excluding haemorrhagic death of any origin).</p> <p>Secondary efficacy endpoints</p> <ul style="list-style-type: none"> - First occurrence of: <ul style="list-style-type: none"> • An event in the composite of any stroke [fatal or non-fatal], myocardial infarction [fatal or non-fatal], other vascular death (excluding haemorrhagic death of any origin). • Ischaemic stroke (fatal or non-fatal). • Myocardial infarction (fatal or non-fatal). • Other vascular death (excluding haemorrhagic death of any origin). • Non-fatal ischaemic stroke. • Fatal ischaemic stroke. • Non-fatal myocardial infarction. • Fatal myocardial infarction. • Any death. • Any stroke (ischaemic stroke or haemorrhagic stroke or unknown type, fatal or non-fatal). • Any fatal stroke. • Disabling stroke. - Cognitive decline. - Incidence of dementia. <p>Tertiary efficacy endpoints</p> <ul style="list-style-type: none"> - First occurrence of: <ul style="list-style-type: none"> • Any cardiac cause leading to hospitalisation (or prolongation of hospitalisation): myocardial infarction, unstable angina, heart failure, and other cardiac cause. • Death due to cardiac cause. • Revascularisation (Coronary Arterial Bypass Graft (CABG), PCI (percutaneous coronary intervention), lower limb revascularisation, carotid endarterectomy or angioplasty), • Carotid endarterectomy or angioplasty. • Major lower limb amputation (at the ankle level or higher, non traumatic and non malignant). • Either fatal or disabling stroke. - Disability. - Dependency. 		

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<p>Criteria for evaluation (Cont'd)</p> <p>Safety measurements:</p> <ul style="list-style-type: none"> - Events related to safety criteria: <ul style="list-style-type: none"> • Haemorrhagic stroke (fatal or non-fatal) <i>i.e.</i> intracerebral haemorrhage. • All bleedings. • Life-threatening bleedings. • Major bleedings. • Minor bleedings. • Symptomatic intracranial haemorrhages (fatal or non-fatal). • Fatal intracranial haemorrhages. • Gastro-intestinal bleedings. • Gastro-intestinal tolerability. • Non vascular death. - Other adverse events. - Vital signs: systolic and diastolic blood pressure, heart rate (measured at each visit from M0 in supine position), weight. - ECG abnormalities: standard 12-lead ECG performed at inclusion (M0 or within 7 days before M0) and then every 12 months (M12 up to Final visit). - Laboratory test: biochemistry (sodium, potassium, chloride, creatinine, total proteins, fasting glucose, uric acid, GGT, total bilirubin, alkaline phosphatase, ALAT, ASAT, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, C-reactive protein (at inclusion only) and haematology parameters (red blood cell count, haemoglobin, haematocrit, mean cell volume, white blood cell count, differential white blood cell count, platelet count) were assessed at inclusion (M0), M1, M3, M12, and then every 12 months up to Final visit (except total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides not assessed at M1) and analysed in a Central Laboratory. Urinalysis (albumin/creatinine) was only assessed at inclusion. <p>Ancillary projects criteria:</p> <ul style="list-style-type: none"> - PERFORM vascular project: The rate of mean carotid IMT change (mm by year) was based on assessments by central reading of carotid ultrasonography at M0, M12, M24 (if applicable), M36 or final visit. - PERFORM biomarkers project: The evolution over time of markers of platelet activation (sP-selectin, sCD40L, urinary 11-dehydro-TXB₂), inflammation (hs-CRP and IL-6), oxidative stress (myeloperoxidase (MP0)) and endothelial dysfunction (sICAM-1, albuminuria) was assessed. - PERFORM Magnetic Resonance Imaging (MRI) project: The efficacy criteria were the mean change in brain, hippocampal and Fluid-Attenuated Inversion-Recovery (FLAIR) lesions volumes from M1 to M24. The safety criterion was the microbleeds. - PERFORM Quality of life project: The quality of life was assessed through the EuroQoL (EQ-5D) questionnaire, a self-administered questionnaire composed of 5 items and a Visual Analog Scale (VAS) where the patient evaluates his health state. The primary criterion was the rating of the EuroQoL Visual Analog Scale (EQ-5D VAS) assessed at M0, M1, M6, M12, M24, M36 and M48/final visit. - PERFORM pharmacokinetics project: presented in a separate report. 		

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<p>Statistical methods: The main Sets for the statistical analysis were:</p> <ul style="list-style-type: none"> - The Randomised Set (RS), based on the intention-to-treat principle, defined as all patients with a randomisation number allocated by the IRS. - The Safety Set (SS) defined as all patients who received at least one dose of the study drug. <p>Study outcome: descriptive statistics were provided in the Randomised Set.</p> <p>Efficacy analysis: Most efficacy analyses were provided in the Randomised Set.</p> <ul style="list-style-type: none"> - Primary composite endpoint The main analysis of the primary composite endpoint was the evaluation of the treatment effect using a survival analysis conducted on a time-to-first-event basis. The treatment effect was estimated using a Cox's proportional hazards model adjusted for country. The superiority p-value was to be provided if the non-inferiority was achieved. Estimate of the treatment effect (S 18886/aspirin) was performed in predefined subgroups of patients from the RS based on a Cox's proportional hazard model adjusted for country. Interaction between treatment groups and the subgroup was tested using a likelihood ratio test. Subgroups were defined according to: age (< 75 or ≥ 75 years), sex (male/female), diabetes (yes/no), subtype of qualifying event (atherothrombotic or likely atherothrombotic, lacunar, or other ischaemic stroke subtype), previous ischaemic stroke (with/without), previous coronary artery disease (with/without), history of arterial hypertension (with/without), use of statins and use of ACE-inhibitor (with/without). - Secondary endpoints <i>Secondary endpoints:</i> same analyses as for the primary composite endpoint <i>Dementia and cognitive decline:</i> the estimate of the treatment effect on occurrence of events and on change of score from baseline was provided. - Tertiary endpoints <i>Medical procedures and events due to cardiac cause:</i> same analyses as for the primary composite endpoint. <i>Dependency and disability:</i> the estimate of the treatment effect on occurrence of events was provided. <p>Safety analysis: descriptive statistics were provided in the Safety Set. For gastrointestinal tolerability, estimate of the treatment effect was provided based on a Cox's proportional hazard model adjusted for country.</p> <p>The independent Data Monitoring Committee performed two interim efficacy analyses. The first one dedicated only to detect a premature efficacy, the second one to investigate both premature efficacy and futility. The type I error rate was fixed at 0.01% for the first interim efficacy analysis and at 0.1% for the second one.</p>		
<p>SUMMARY - CONCLUSIONS STUDY POPULATION AND OUTCOME On 12 October 2009, the Data Monitoring Committee recommended the PERFORM trial to be stopped on the grounds that the study was most unlikely to demonstrate any benefit of the study drug compared with aspirin, and that the continuation of the study was futile. This recommendation was ratified by the Executive Committee on 23 October 2009, whereupon, between November 2009 and March 2010, the investigators recalled patients for the final end-of-study visit. A total of 19100 patients were retained in the Randomised Set: 9556 patients in the S 18886 group and 9544 patients in the aspirin group. During the study, 1179 patients (6.2%) died, 382 patients (2.0%) refused to provide additional information and 58 patients (0.3%) were lost to follow-up. A total of 17474 patients (91.5% of the randomised patients) completed the study: 8749 patients (91.6%) in the S 18886 group and 8725 patients (91.4%) in the aspirin group. Most of the patients who completed the study (81.3%) were still on study drug treatment at the time of completion.</p>		

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SUMMARY - CONCLUSIONS (Cont'd)				
STUDY POPULATION AND OUTCOME (Cont'd)				
Patient status at the end of the study is indicated in Table 1. Premature study drug withdrawal was reported in 22.2% of the patients, with a similar rate in both groups, mainly due to adverse events (10.1% of the patients), mostly cardiac disorders (2.6% in the S 18886 group and 2.5% in the aspirin group), critical events (6.4%) and non-medical reason (6.3%).				
Table 1: Disposition of patients				
Status		S 18886	Aspirin	All
Randomised Set	n	9556	9544	19100
Lost to follow-up	n (%)	25 (0.3)	33 (0.4)	58 (0.3)
Death	n (%)	593 (6.2)	586 (6.1)	1179 (6.2)
Patient refusal to provide additional information	n (%)	187 (2.0)	195 (2.0)	382 (2.0)
No follow-up ¹	n (%)	2 (< 0.1)	5 (0.1)	7 (< 0.1)
Completed	n (%)	8749 (91.6)	8725 (91.4)	17474 (91.5)
With study treatment ²	n (%)	7116 (81.3)	7088 (81.2)	14204 (81.3)
Without study treatment ²	n (%)	1633 (18.7)	1637 (18.8)	3270 (18.7)
Reasons for premature study drug withdrawal	n (%)	2120 (22.2)	2124 (22.3)	4244 (22.2)
Adverse event	n (%)	952 (10.0)	972 (10.2)	1924 (10.0)
Critical event	n (%)	622 (6.5)	606 (6.3)	1228 (6.4)
Non medical reason	n (%)	593 (6.2)	602 (6.3)	1195 (6.3)
Safety Set	n (%)	9479 (99.2)	9466 (99.2)	18945 (99.2)
<i>n</i> number of patients				
<i>%</i> Calculated as percentage of patients from the Randomised Set				
¹ Patients having a randomisation number attributed but not included (having not received any study drug)				
² % calculated as percentage of the completed patients				
Demographic and baseline characteristics				
No relevant difference between the two groups was observed regarding demographic and baseline characteristics. In the Randomised Set, patients were in average 67.2 ± 7.9 years old, and 20.1% were ≥ 75 years. All patients had a qualifying event before randomisation including: ischaemic stroke (IS) (89.5%), Transient Ischaemic Attack (TIA) (10.1%) or Arterial Retinal Ischaemic Event (ARIE) (0.4%). The mean time between the occurrence of the qualifying event and the randomisation was 26.9 ± 23.9 days for IS or ARIE, and 5.8 ± 5.3 days for TIA. Medical history including mostly arterial hypertension (83.6%), dyslipidaemia (55.8%), family history of atherothrombotic disease (43.7%), type II diabetes (27.2%), cerebral ischaemia (24.4%) including ischaemic stroke (15.2%) and TIA (7.5%), and coronary artery disease (21.6%), including myocardial infarction (8%). Most of the patients (83.0%) had no or slight disability (modified Rankin Scale ≤ 2). Patients had a preserved cognitive function with a mean Mini-Mental State Examination (MMSE) = 27.6 ± 3.3. Main concomitant treatments received between qualifying event and randomisation were antithrombotic treatments (92.9% of the patients) mostly aspirin (86.3%), statins (57.9%), and ACE inhibitors (54.6%).				
Concomitant treatments during the study				
During the study, statins were received by 72.4% of the patients and angiotensin-converting enzyme inhibitors by 64.7% of the patients.				
Follow-up and treatment duration				
The mean follow-up duration was 28.3 ± 7.7 months <i>i.e.</i> about 2 years (ranging from 0 to 48 months) and mean treatment duration was 25.0 ± 10.4 months (ranging from 0 to 48 months). Most of the patients (64.4%) were treated for at least 2 years.				

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SUMMARY - CONCLUSIONS (Cont'd)**EFFICACY RESULTS****Primary composite endpoint****- Main analysis**

The primary composite endpoint occurred in 2153 patients (*i.e.* 92% of the target number): 1091 patients, 11.4%, 5.1%PY in the S 18886 group and 1062 patients, 11.1%, 5.0%PY in the aspirin group, without significant difference (Hazard Ratio (HR): 1.02, 95% CI [0.94 ; 1.12]). No treatment effect of S 18886 *versus* aspirin was found regarding each of the components.

The Kaplan-Meier curves of the time to first event of primary composite endpoint are presented in Figure 1.

The results of the components as secondary endpoints are described afterwards in Table 2.

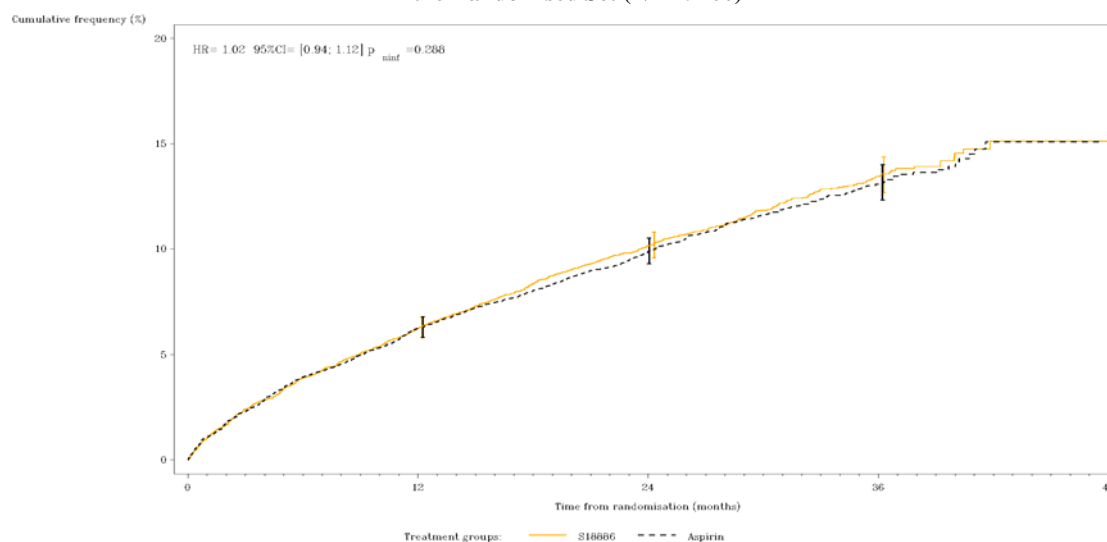
Table 2: Primary composite endpoint and selected secondary endpoints - Estimate of the treatment effect in the Randomised Set (N = 19100)

	S 18886 (N = 9556)			Aspirin (N = 9544)			Hazard ratio			p value ⁽¹⁾
	n	%	PY	n	%	PY	E	SE	95% CI	
Primary composite endpoint	1091	11.4	5.1	1062	11.1	5.0	1.02	0.04	[0.94 ; 1.12]	0.288
Selected secondary endpoints										
Ischaemic stroke (fatal or not)	781	8.2	3.6	763	8.0	3.6	1.02	0.05	[0.92 ; 1.13]	0.285
Myocardial infarction (fatal or not)	159	1.7	0.7	129	1.4	0.6	1.23	0.15	[0.98 ; 1.56]	0.914
Other vascular death ⁽²⁾	215	2.3	1.0	224	2.4	1.0	0.95	0.09	[0.79 ; 1.15]	0.158

Tests of S 18886 as compared to aspirin. Non inferiority one-sided type I error rate 0.025, non inferiority margin 1.05;

N number of randomised patients ; n number of patients having experienced the endpoint; % global incidence rate; n/Nx100; PY annual incidence rate, number of patients having experienced the endpoint on the whole study for 100 patient-years at risk; E estimate of the hazard ratio between treatment groups (S 18886/aspirin) based on a Cox's proportional hazards model adjusted for country; SE standard error of the hazard ratio; 95% CI 95% Confidence Interval of the estimate (two-sided); 1 Non-inferiority p-value non-inferiority Wald test from Cox's proportional hazards model adjusted for country; 2 excluding haemorrhagic death of any origin)

Figure 1: Primary composite endpoints - Kaplan Meier curve - Time to first event in the Randomised Set (N = 19100)



Nber of patients at risk*	9551/9534	8779/8732	6256/6226	1335/1356	0/0
Cumul. nber of endpoints*	0/0	588/588	943/912	1079/1048	1091/1062
Cumul. frequency (%)*	0/0	6.22/6.24	10.15/9.87	13.43/13.0	

*S18886/Aspirin

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SUMMARY - CONCLUSIONS (Cont'd)**EFFICACY RESULTS (Cont'd)****- Primary composite endpoint in subgroups of the Randomised Set**

No treatment effect of S 18886 *versus* aspirin was detected in any pre-specified subgroup of the Randomised Set, except in patients with a previous ischaemic stroke having occurred before the qualifying event. In this subgroup, patients treated with S 18886 group were less frequently affected by the primary composite endpoint than patients treated with aspirin: 214 patients (7.3%PY) *versus* 263 patients (8.9%PY), respectively, HR:0.78, 95% CI [0.65 ; 0.94].

- Secondary and tertiary endpoints

No statistically significant treatment effect of S 18886 *versus* aspirin was detected.

- Perform Ancillary projects (vascular, biomarkers, MRI, quality of life) did not show any clinically relevant change over time nor between-group differences whatever the parameter considered.

SAFETY RESULTS**Emergent adverse events:**

The main focus on the presentation of emergent adverse events was on the clinical events that occurred on treatment (adverse event which occurred, worsened or became serious between the first study drug intake and the last drug intake + 10 days). These results are summarised in Table 3.

Table 3: Summary of safety results (Safety Set)

		S 18886 (N = 9479)	Aspirin (N = 9466)
Patients having reported at least one			
Emergent adverse event	n (%)	7947 (83.8)	7940 (83.9)
Treatment-related emergent adverse event	n (%)	1103 (11.6)	1142 (12.1)
Serious emergent adverse event (including death)	n (%)	2975 (31.4)	3126 (33.0)
Premature study withdrawal			
Due to an emergent adverse event	n (%)	911 (9.6)	901 (9.5)
Deaths	n (%)	605 (6.4)	592 (6.3)

The frequency of patients affected by emergent adverse events (EAEs) on treatment was similar in both treatment groups: 7947 patients (83.8%) in the S 18886 group *versus* 7940 (83.9%) in the aspirin group. They affected mainly the following SOCs: metabolism and nutrition disorders (27.2% in the S 18886 group *versus* 26.6% in the aspirin group), infestations (26.4% *versus* 25.2%, respectively), nervous system disorders (26.1% *versus* 26.5%, respectively), and vascular disorders (26.1% *versus* 25.9%, respectively). The most frequently reported EAEs were blood pressure inadequately controlled (16.6% *versus* 16.7%, respectively), hypercholesterolemia (7.8% *versus* 7.3%, respectively), depression (6.7% *versus* 7.5%, respectively), diabetes mellitus inadequate control (6.4% *versus* 6.3%, respectively), and fall (6.4% *versus* 7.2%, respectively). No relevant difference between-group was observed in the nature and the frequency of the EAEs.

Treatment-related EAEs (according to the investigator opinion) were reported in 11.6% of the patients in the S 18886 group *versus* 12.1% in the aspirin group. These events were principally gastrointestinal disorders (4.4% *versus* 4.7%, respectively), and nervous system disorders (1.7% *versus* 1.2%, respectively).

EAEs leading to premature study drug withdrawal were similar in both treatment groups: 9.6% and 9.5%, respectively. The most frequently affected SOCs were cardiac disorders (2.4% *versus* 2.2%, respectively), including mainly atrial fibrillation (1.8% *versus* 1.7%, respectively), gastrointestinal disorders (1.3% *versus* 1.6%, respectively), and neoplasm benign, malignant and unspecified (1.2% in both groups).

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<p>SUMMARY - CONCLUSIONS (Cont'd) SAFETY RESULTS (Cont'd)</p> <p>Serious EAEs on treatment were reported in 31.4% of the patients in the S 18886 group and 33.0% in the aspirin group. The most frequently affected SOCs were nervous system disorders (7.4% in the S 18886 group <i>versus</i> 7.8% in the aspirin group), mainly transient ischaemic attack (2.0% <i>versus</i> 2.2%, respectively) and infections and infestations (5.0% <i>versus</i> 4.8%, respectively). There were 1197 deaths : 605 patients (6.4%) in the S 18886 group <i>versus</i> 592 patients (6.3%) in the aspirin group.</p> <p>Emergent bleedings: The rate of patients affected by emergent bleeding events on treatment (confirmed by the CEC) was higher in the S 18886 group than in the aspirin group: 15.4% <i>versus</i> 14.4%, respectively (HR: 1.09, 95% CI [1.01 ; 1.17]). Most of these events were classified as minor with a significantly higher frequency in the S 18886 group than in the aspirin group: 12.1% <i>versus</i> 11.0%, respectively (HR:1.11; 95% CI [1.02 ; 1.21]). Gastrointestinal bleedings were similarly reported in both groups (3%).</p> <p>Gastrointestinal tolerability was similar in both treatment groups: 12.9% of the patients reported gastrointestinal emergent events on treatment in the S 18886 group <i>versus</i> 13.7% in the aspirin group.</p> <p>Vital signs No relevant change over time or between-group difference were detected for vital signs (body mass index, systolic and diastolic blood pressure and heart rate).</p> <p>Laboratory test Biochemical and haematological parameters (including hepatic and renal parameters) did not show any differences between groups.</p>		
<p>CONCLUSION</p> <p>The PERFORM study was designed to demonstrate the superiority of S 18886 over aspirin in reducing cerebrovascular and cardiovascular events in patients with a history of ischaemic stroke or transient ischaemic attack. The study was prematurely stopped for futility based on the recommendation of the Data Monitoring Committee. No evidence for a difference between S 18886 over aspirin in reducing the incidence of the primary composite endpoint (fatal or non-fatal ischaemic stroke, fatal or non-fatal myocardial infarction, or other vascular death from non-haemorrhagic origin) was demonstrated. Results were consistent across all specified subgroups except in the subgroup of patients having a previous ischaemic stroke occurred before the qualifying event, with more favourable results under S 18886. No statistically significant between-group difference was detected regarding secondary or tertiary endpoints. The safety profile was similar in both groups, at the exception of bleeding events increased in the S 18886 group compared to aspirin group, mainly due to minor bleedings.</p>		
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