This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2 SYNOPSIS

Title of Study:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety of SCH 530348 in Subjects Undergoing Non-Emergent Percutaneous Coronary Intervention (**T**hrombin **R**eceptor **A**ntagonist in **PCI** [TRA^{SM}-PCI]) (Protocol P03573).	
Investigators:	Multicenter	
Study Centers:	Multicenter study in the USA, Canada, Germany, Sweden, The Netherlands, Belgium, Italy, New Zealand	
Publications:	none at the time of this report	
Studied Period:	30 AUG 2005 to 28 JAN 2007	**Clinical Phase:** 2

Objectives: The primary objective was to evaluate the safety of SCH 530348 with respect to the incidence of major and minor bleeding events, as assessed by the TIMI (**T**hrombolysis **I**n **M**yocardial **I**nfarction Study Group) system of classification, in addition to the standard of care in subjects undergoing non-emergent PCI, and as maintenance therapy after the procedure.

Secondary objectives included evaluation of SCH 530348 in addition to the standard of care in general terms of:

- nonTIMI bleeding, and other measures of blood loss;
- incidence of various component combinations of death, major adverse cardiac events (MACE; any of non-fatal myocardial infarction [MI], ischemia requiring rehospitalization, or coronary revascularization with either coronary artery bypass grafting [CABG] or subsequent PCI), and stroke, as measures of potential clinical benefit;
- inhibition of platelet aggregation induced by various appropriate agonists, as an indicator of the desired pharmacodynamic effect; and
- effect on expression of markers of inflammation and of platelet release and activation (ie, hs-CRP [high-sensitivity C-reactive protein], CD40 ligand [CD40L], and membrane-bound P-selectin).

Methodology: Double-blind, randomized, placebo-controlled, fixed-dose, sequential-parallel-groups comparison conducted in conformance with Good Clinical Practice. Investigational treatment was to be administered in addition to the standard of care. All subjects were to receive a loading dose of SCH 530348 – 10, 20, or 40 mg – or placebo in a 3:1 ratio on the day of procedure; this was to be followed by daily maintenance dosing with SCH 530348 – 0.5, 1, or 2.5 mg within each loading dose – or continued placebo for total of 60 days of investigational treatment if PCI commenced (PCI cohort), or no further investigational treatment beyond the loading dose if PCI did not commence (nonPCI cohort). Telephone follow-up contact was to be made with all subjects, PCI and nonPCI cohorts, at 30 and 60 days after the last dose. Sequential groups were defined by the loading dose of SCH 530348; safety at each loading-dose level was determined by a Safety Review Committee before proceeding to the next level.

Death, MACE, stroke, and TIMI bleeding were adjudicated by an independent Clinical Events Committee (CEC).

Number of Subjects: 1030 enrolled; 773 SCH 530348 and 257 placebo; 573 in the PCI cohort (422 SCH 530348 and 151 placebo) and 457 in the nonPCI cohort (351 SCH 530348 and 106 placebo).

Diagnosis and Criteria for Inclusion: Adults ≥45 years old with atherosclerosis and previously documented symptoms of coronary artery disease who were scheduled to undergo non-emergent PCI, or non-emergent cardiac catheterization with the intent to undergo PCI.

Test Product, Dose, Mode of Administration, Batch Nos.: Single loading dose: SCH 530348 oral 10-mg tablet; 1 x 10 mg for 10-mg dose, 2 x 10 mg for 20-mg dose, and 4 x 10 mg for 40-mg dose; taken at least 1 hour before initiation of anticipated PCI. Batch nos. [redacted] and [redacted]

Daily Maintenance Doses: SCH 530348 oral tablets 0.5 mg, 1 mg, and 2.5 mg of identical size and appearance; taken in AM after overnight fast at least 30 min before AM meal. Batch nos.: 0.5 mg = [redacted] 1 mg = [redacted] 2.5 mg = [redacted]

Duration of Treatment: 60 days if PCI commenced, ie, guide wire crossed the lesion (PCI cohort); 1 day if guide wire did not cross the lesion (nonPCI cohort).

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Reference Therapy, Dose, Mode of Administration, Batch Nos.: Single loading dose: oral placebo tablet to match SCH 530348 10 mg; 1 tablet for 10-mg dose, 2 tablets for 20-mg dose, and 4 tablets for 40-mg dose; taken as for SCH 530348. Batch Nos. [redacted] and [redacted]

Daily Maintenance Doses: Oral placebo tablet to match SCH 530348 0.5, 1, and 2.5 mg; taken as for SCH 530348. Batch No. [redacted]

Criteria for Evaluation: Primary endpoint was occurrence of TIMI Major plus Minor bleeding in the PCI cohort at the end of the protocol-specified treatment phase. Secondary endpoints included:

- occurrence of TIMI Major bleeding, TIMI Minor bleeding, nonTIMI bleeding and other indicators of blood loss, death/MACE and various combinations of components, and adverse events in the PCI and nonPCI cohorts at the end of the protocol-specified treatment phase and during the protocol-specified follow-up phase;
- inhibition of platelet aggregation induced by various appropriate agonists within 2 hours after the loading dose in the PCI and nonPCI cohorts, and 30 and 60 days after PCI in the PCI cohort; and
- effect on expression of markers of inflammation and of platelet release and activation immediately after catheterization/PCI in the PCI and nonPCI cohorts, and 60 days after PCI in the PCI cohort.

Statistical Methods: The differences in incidences between SCH 530348 and placebo, and corresponding 95% confidence intervals, were calculated for TIMI Major plus Minor bleeding through the end of the protocol-specified treatment phase among subjects who underwent PCI for:

- all SCH 530348 treatment arms pooled across the three sequential groups versus all placebo, and
- SCH 530348 treatment arms pooled within each of the three sequential groups versus all placebo.

SUMMARY-CONCLUSIONS:

RESULTS:

Efficacy: Clinical outcomes during treatment in the PCI cohort are summarized briefly in **Table 1**. Many of the events recorded occurred on the day of randomized treatment assignment, the day of PCI per protocol, and almost all occurred within the first week after randomized treatment assignment; periprocedural MI was the most common event. Although the study was neither designed nor powered to assess differences between treatments in incidence of outcomes (eg, MACE), the results suggest a numerically smaller proportion of SCH 530348-treated than placebo-treated subjects with outcomes, with an apparent drug-associated trend, during the protocol-specified treatment phase. Relatively few outcomes were recorded during follow-up in the PCI cohort, or during the study in the nonPCI cohort.

Inhibition of platelet aggregation was investigated in a subset of participating study sites. SCH 530348 inhibited thrombin-receptor-agonist-peptide(TRAP)-induced platelet aggregation in dose-dependent fashion after the initial loading dose (**Table 2**). The results show that at 2 hours, 96% of subjects who received 40 mg had platelet aggregation inhibited by ≥80%, compared with 53% with 20 mg and 43% with 10 mg. All three maintenance doses maintained clinically relevant inhibition of TRAP-induced platelet aggregation at the 30-day and 60-day visits in the PCI cohort, and 1 and 2.5 mg maintained ≥80% inhibition in all subjects at both visits. SCH 530348 did not affect platelet aggregation induced by adenosine diphosphate, arachidonic acid, or collagen.

No meaningful change from baseline was observed in concentrations of the three biomarkers assayed – hs-CRP, CD40L, and membrane-bound P-selectin – over the course of the study.

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Table 1 Number (%) of Subjects in the PCI (Primary) Cohort Who Died, Had a Non-Fatal MACE, or Non-Fatal Stroke During Treatment

Events Adjudicated by the Clinical Events Committee	All Subjects in All Three Sequential Groups		From Sequential Group 3[a]	
				TRA
	Placebo (n = 151)	TRA (n = 422)	Placebo (n = 63)	40/2.5 mg[b] (n = 58)
Subjects Who Died or Had any Non-Fatal MACE or Stroke	13 (9)	25 (6)	6 (10)	4 (7)
Death	0	1 (<1)	0	0
Any Non-Fatal MACE	13 (9)	24 (6)	6 (10)	4 (7)
Peri-PCI Myocardial Infarction	10 (7)	13 (3)	5 (8)	3 (5)
Non-Fatal Stroke	0	1 (<1)	0	0

Abbreviations: MACE = major adverse cardiac event; PCI = percutaneous coronary intervention; TRA = thrombin-receptor antagonist, SCH 530348.

a: Does not include subjects who did not receive randomized assignment of a maintenance dose.

b: 40-mg loading dose followed by 2.5-mg maintenance dosing.

Table 2 Percentage of Subjects With Greater Than or Equal to 80% Inhibition of TRAP-Induced Platelet Aggregation Relative to Baseline After the Loading Dose: PCI and Non-PCI Cohorts Combined

Time	Placebo	SCH 530348		
		10 mg	20 mg	40 mg
0.5 h	0.0 (0/16)	0.0 (0/14)	6.3 (1/16)	28.6 (6/21)
1 h	0.0 (0/18)	0.0 (0/14)	53.8 (7/13)	67.9 (19/28)
1.5 h	0.0 (0/16)	21.4 (3/14)	46.2 (6/13)	82.1 (23/28)
2 h	0.0 (0/17)	42.9 (6/14)	52.9 (9/17)	96.3 (26/27)

Note: Final concentration of TRAP = 15 μM.

Abbreviations: PCI = percutaneous coronary intervention; TRAP = thrombin-receptor agonist peptide.

The results of pharmacokinetic analysis demonstrated that a two-compartment model with first-order absorption and elimination could adequately describe the pharmacokinetics of SCH 530348 in these subjects with atherosclerosis. The pharmacokinetic parameters were well estimated (coefficients of variation ≤25%) and consistent with those derived from non-compartmental analysis of Phase 1 studies with normal volunteers. In general: Cmax and AUC were inversely related to body mass index; women had greater exposure (AUC) than men; and Cmax was inversely related to age.

Safety: Results of the primary endpoint analysis in the PCI cohort are summarized in **Table 3**. SCH 530348 was not associated with an increase in occurrence of TIMI Major plus Minor bleeding compared with placebo during the protocol-specified treatment phase. Similarly, no difference between placebo and SCH 530348 was indicated during the protocol-specified follow-up phase.

All bleeding in the PCI cohort is summarized briefly in Table 4. The occurrence of bleeding that did not meet criteria for TIMI Major or Minor bleeding – nonTIMI bleeding – was numerically greater with SCH 530348 than with placebo. Most of the events seen comprised bleeding from arterial access sites, and contusions and bruising. Other forms of nonTIMI bleeding, including from accidental nicks and cuts, gingival bleeding, gastrointestinal bleeding, genitourinary bleeding (including hematuria), epistaxis, and other incidental causes were not different in occurrence between placebo and SCH 530348. The proportions of subjects who discontinued either treatment or the study as a result of nonTIMI bleeding were low (~1%) and not different between placebo and SCH 530348. During follow-up, occurrences of bleeding were much lower, and there was little difference between placebo and SCH 530348. Overall, contusions/bruises was the only bleeding type that may have been reported for more SCH 530348-treated (3%) than placebo-treated (1%) subjects.

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Table 3 Occurrence of CEC-Adjudicated TIMI Major Plus Minor Bleeding During Treatment in the PCI Cohort

All Placebo	SCH 530348		
	Percentage	SCH 530348 - Placebo	
		Point[a]	95% CI
3.3 (5/151)	**All SCH 530348**		
	2.8 (12/422)	All SCH 530348 - Placebo	
		-0.5	(-3.7, 2.8)
	SCH 530348 10 mg		
	1.6 (2/129)	10 mg - Placebo	
		-1.8	(-5.3, 1.8)
	SCH 530348 20 mg		
	2.5 (3/120)	20 mg - Placebo	
		-0.8	(-4.8, 3.2)
	SCH 530348 40 mg		
	4.0 (7/173)	40 mg - Placebo	
		0.7	(-3.4, 4.8)

Abbreviations: CEC = Clinical Events Committee; CI = confidence interval; PCI = percutaneous coronary intervention; TIMI = Thrombolysis in Myocardial Infarction Study Group.

a: Point estimate of the difference between SCH 530348 and placebo.

Table 4 Number (%) of Subjects in the PCI Cohort With Bleeding During Treatment

CEC-Adjudicated Bleeding Category	All Subjects in All Three Sequential Groups		From Sequential Group 3[a]	
				TRA
	Placebo (n = 151)	TRA (n = 422)	Placebo (n = 63)	40/2.5 mg[b] (n = 58)
TIMI MAJOR or MINOR	5 (3)	12 (3)	1 (2)	2 (3)
NON-TIMI	48 (32)	169 (40)	19 (30)	29 (50)

Abbreviations: CEC = Clinical Events Committee; PCI = percutaneous coronary intervention; TIMI = Thrombolysis in Myocardial Infarction Study Group; TRA = thrombin-receptor antagonist, SCH 530348.

a: Does not include subjects who did not receive randomized assignment of a maintenance dose.

b: 40-mg loading dose followed by 2.5-mg maintenance dosing.

Review of results for other adverse events, laboratory test data, vital signs, and electrocardiograms failed to yield any convincing indication of a specific safety risk associated with treatment with SCH 530348.

CONCLUSIONS: The overall conclusions of the study are as follows. Safety conclusions are presented first because the study was designed primarily to evaluate the safety of SCH 530348.

- Overall, administration of SCH 530348 was not associated with a demonstrable increase in TIMI or nonTIMI bleeding.
- Administration of SCH 530348 was not associated with any specific identifiable risk among other indicators of safety.
- Although the study was not designed to be able to make inferences about clinical outcomes, the numerically favorable results for SCH 530348 compared with placebo for MACE, predominantly periprocedural MI, warrant further study in an expanded Phase 3 program.

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- Administration of the loading dose of SCH 530348 caused dose-related inhibition of platelet aggregation stimulated by 15 μM TRAP for the first 2 hours after dosing. The 40-mg dose was most effective in producing ≥80% inhibition in 1 to 2 hours after dosing.

- Administration of SCH 530348 in a daily maintenance dose of 1 or 2.5 mg sustained near-complete inhibition of platelet aggregation in all subjects after 1 and 2 months.

Date of the Report: 28 JAN 2008