SYNOPSIS

Title of the study: A randomized dose ranging study of hexadecasaccharide including active control, in patients with unstable angina or non-ST-segment elevation myocardial infarction scheduled to undergo percutaneous coronary intervention (SHINE; DRI5228)

Investigator(s): [redacted]

Study center(s): Patients were enrolled at 141 centers in 18 countries in Europe, North America, South America, Asia and Australia

Publications (reference): Lincoff AM, Caramori P, Armstrong PW, Cura FA, Hochman JS, Kleiman NS, Van de Werf F, Carreras LO, Bash DL, Galla JM, Topol EJ. SR123781A, a synthetic antithrombin-dependent thrombin and factor Xa inhibitor, in patients with non-ST-segment elevation acute coronary syndromes (NSTEACS): Results of an active-controlled, dose-ranging study. J Am Coll Cardiol. 2008;51(suppl A):A211.

Study period: Date first patient enrolled: 14-Dec-2004 Date last patient completed: 21-May-2007

Phase of development: Dose-ranging

Objectives:

Primary objective

To evaluate the dose effect of hexadecasaccharide (HDS) and select the dose in patients with unstable angina or non-ST-segment elevation myocardial infarction (NSTEMI) who are scheduled to undergo percutaneous coronary intervention (PCI) within 48 hours.

Secondary objectives

To compare the efficacy and safety of each dose of HDS with an active control of unfractionated heparin (UFH) and abciximab.
To evaluate the effect of HDS on the following markers: post-PCI cardiac markers, coagulation activation markers, inflammatory markers, coagulation tests.

Methodology: This was a dose-ranging, multicenter, multinational, randomized, parallel-group study of the use of HDS versus UFH plus abciximab in patients with unstable angina or NSTEMI scheduled to undergo PCI in the index hospitalization and within 48 hours of randomization. Eligible patients were randomized (1:1:1:1:1:1) via an interactive voice response system to 1 of 5 HDS double-blind dose regimens (0.25, 0.5, 1.0, 2.0, and 4.0 mg) or open-label therapy with UFH plus abciximab. The study treatments were to be given in addition to aspirin and clopidogrel as recommended in American Heart Association/American College of Cardiology and European Society of Cardiology guidelines for the management of patients with acute coronary syndrome. Patients were to be followed up for 90 days (changed to 180 days or until the last patient had been followed for 90 days, whichever occurred earlier, as specified by Amendment No. 1). The 0.25, 0.5 and 1.0 mg HDS dose groups were discontinued during the study due to an observed increased risk of catheter-related thrombotic events in these groups (Amendment No. 3).

Number of patients:
Planned: 1800 (300 per group) in original protocol
Randomized: 1257 Treated: 1243
Evaluated: Efficacy: Intent-to-treat (ITT) 1243, PCI 775 Safety: Safety 1243, Safety PCI 775

Diagnosis and criteria for inclusion: Men and women older than 21 years with a diagnosis of unstable angina or NSTEMI presenting with an episode of angina within the preceding 24 hours, with new electrocardiogram (ECG) changes and/or elevated troponin, for whom coronary angiography is planned and PCI is anticipated to occur in the index hospitalization and within 48 hours of randomization, and in whom upfront use of glycoprotein IIb/IIIa inhibitors (tirofiban or eptifibatide) before angiography is not deemed necessary.

Investigational product:	Hexadecasaccharide (HDS, SR123781A)
Dose:	0.25, 0.5, 1.0, 2.0, and 4.0 mg: one subcutaneous dose once daily and one single intravenous (IV) dose within 5–30 minutes before the start of the procedure on the day of PCI and at least 5 minutes before administration of IV bolus of UFH (clarified by Amendments Nos. 2 and 3).
Administration:	Subcutaneous and IV injection (1 mL of solution)
Batch number(s):	[redacted]
Duration of treatment:	
HDS dose groups:	From Day 1 to Day 5 (or until hospital discharge, if earlier)
UFH plus abciximab group:	UFH from Day 1; abciximab on day of procedure, ending 12 hours after completion of intervention
Duration of observation:	Original protocol: 90 days per patient. Amendment No.1: 180 days per patient or until the last patient had been followed up for 90 days, whichever occurred first.
Reference therapy:	Unfractionated heparin (UFH) plus abciximab
Dose:	UFH: IV bolus of 60-70 units/kg (maximum 5000 units) followed by IV infusion of 12-15 units/kg/h (maximum 1000 units/h) titrated to an activated partial thromboplastin time 1.5-2.5 times the control immediately after randomization. Administration prior to and during PCI: to achieve and maintain a target activated clotting time of ≥200 seconds. Abciximab: IV bolus of 0.25 mg/kg body weight within 10 to 60 minutes prior to intervention, followed by continuous IV infusion of 0.125 μg/kg/min (maximum of 10 μg/min), ending 12 hours after completion of intervention.
Administration:	IV in accordance with recommendations in package insert
Batch number(s):	Not applicable (UFH and abciximab dispensed from the local pharmacy)

Criteria for evaluation:

The current report is an abbreviated report, and as such, only the safety results are being presented in full. The following safety criteria were evaluated: Major bleeding according to the criteria of the Thrombolysis In Myocardial Infarction (TIMI) study group (adjudicated by the Clinical Events Adjudication Committee, CEAC), minor bleeding (TIMI criteria, CEAC-adjudicated), adverse events (AEs) with focus on treatment-emergent AEs (TEAEs), laboratory safety parameters (hematology, biochemistry), stroke, vital signs and ECG.

Statistical methods:

Primary analysis of primary efficacy variable: The primary analysis of the primary endpoint (the composite of all-cause death, new myocardial infarction (MI), or recurrent episode of severe myocardial ischemia requiring urgent repeat target vessel revascularization, from randomization through Day 7) was performed on data that were adjudicated by the CEAC using the ITT population (all randomized patients who received at least 1 dose of study drug whether they underwent PCI or not; patients analyzed as randomized). The dose response relationship was assessed by analyzing the crude rate of patients with a primary efficacy outcome across HDS groups using a logistic regression model with the logarithmic HDS dose levels as the only independent variable. For each of the 6 treatment groups, the number of patients who reached the primary endpoint was summarized using counts and percentages at Day 7 with exact 95% confidence intervals (CI).

Secondary analyses of primary efficacy variable: Secondary analyses of the primary endpoint were performed using the ITT and PCI populations (the subpopulation of the ITT population who underwent the index PCI between randomization and Day 5; patients analyzed as randomized). The primary endpoint was further analyzed for the HDS 2 mg and 4 mg groups to evaluate the impact of the systemic UFH that was added by Amendment No. 3, using logistic regression incorporating a term for treatment group, a term indicating whether patients were randomized before or after implementation of Amendment No. 3, and a term corresponding to the appropriate interaction between the 2 factors. The addition of UFH was considered to have no impact on the treatment effect if the interaction p-value was ≥0.15. When the addition of UFH had no impact, the Fisher exact test (HDS 2 mg, 4 mg versus UFH) was performed. The primary analysis was repeated on the PCI population.

Analyses of secondary efficacy variables: The first occurrence of the primary endpoint was analyzed using the nonparametric Kaplan-Meier method up to the planned end of the study. The incidence of the components of the primary endpoint up to Day 7 and the incidence of procedural complications were summarized using counts, percentages and exact 95% CI.

Safety analyses: The safety population comprised all randomized patients who received at least 1 dose of study drug whether they underwent PCI or not. The safety PCI population comprised all randomized patients who received at least 1 dose of study drug and underwent the index PCI between randomization and Day 5. Patients were analyzed as treated.

Bleeding analyses were performed with CEAC-adjudicated data (TIMI score). Major and any (minor and/or major) bleedings up to Day 7 were analyzed using the same methodology described for the primary efficacy endpoint. In addition, the first occurrence of a bleeding event (major or minor) up to Day 30 was analyzed using the nonparametric Kaplan-Meier method.

Stroke analyses were performed with CEAC-adjudicated data. Patients with stroke events from first administration of study drug up to the end of exposure were summarized using counts, percentages and exact 95% CI. The first occurrence of stroke was described using the nonparametric Kaplan-Meier method.

Adverse events, laboratory safety parameters, vital signs and ECG were summarized using descriptive statistics.

Interim analyses: No formal interim analysis for efficacy was planned. However, both blinded and unblinded data were reviewed by the Data Monitoring Committee on several occasions during the study, resulting in formal recommendations to the Steering Committee that led in some cases to specific action taken to modify the conduct of the study.

Summary:

Efficacy results:

No dose response relationship among the HDS dose groups was demonstrated in the primary analysis. The overall event rate for the primary variable was lower than expected.

Primary analysis: All-cause death, new MI or urgent repeat target vessel revascularization up to Day 7 - Number (%) of patients and dose response relationship among HDS groups - Logistic regression - ITT population

	Treatment group					
	HDS 0.25mg (N=115)	HDS 0.5mg (N=122)	HDS 1mg (N=116)	HDS 2mg (N=298)	HDS 4mg (N=305)	UFH/abciximab (N=287)
Number of patients with endpoint	6 (5.2%)	5 (4.1%)	4 (3.4%)	11 (3.7%)	13 (4.3%)	11 (3.8%)
95% CI [a]	1.9% to 11.0%	1.3% to 9.3%	0.9% to 8.6%	1.9% to 6.5%	2.3% to 7.2%	1.9% to 6.8%
Logistic regression p-value [b]	0.7478					
Hosmer-Lemeshow test [c]	0.9152					

Note: Only patients with events occurring from randomization up to Day 7 are considered
[a] 95% CIs are computed using exact method
[b] logistic regression model with log HDS dose as covariable
[c] goodness of fit test for the logistic regression model

There was no statistically significant effect on the primary event rate in the HDS 2 mg and 4 mg groups following the administration of systemic UFH during PCI (implemented by Amendment No. 3). Sequential pairwise comparisons (Fisher exact test) showed no statistically significant differences between HDS doses (HDS 2 mg and HDS 4 mg) and the comparator UFH/abciximab for the primary efficacy variable.

No dose response relationship was demonstrated for the triple composite efficacy endpoint up to Day 30, Day 90 and Day 180 (Kaplan-Meier) or for any of the individual components of the primary efficacy variable up to Day 7.

PCI complications occurred more frequently with HDS (13.5% to 17.5%) than with UFH/abciximab (7.1%), with a trend toward more thrombotic complications (abrupt closure, new angiographic thrombus, thrombus in catheter or distal embolization) occurring at lower doses (HDS 0.25 mg and 0.5 mg). Following implementation of Amendment No. 3, the rate of thrombotic PCI complications was not higher with HDS 2 mg and HDS 4 mg than with UFH/abciximab (3.0% and 1.7% respectively versus 3.6% for UFH/abciximab).

Safety results:

Bleeding: The frequency of patients with TIMI major bleeding up to Day 7 ranged from 1.6% to 2.6% in the HDS groups compared to 1.0% in the UFH/abciximab group. The frequency of patients with any (major and/or minor) bleeding up to Day 7 ranged from 3.4% to 6.0% in the HDS groups compared to 4.9% in the UFH/abciximab group. Although there was a tendency to more bleeding (any and major) in the HDS groups than the UFH/abciximab group up to Day 7, differences among the treatment groups (HDS 2 mg and 4 mg versus UFH) were not statistically significant. Statistical testing demonstrated no dose response relationship among the HDS dose groups, no influence of HDS dose, and no effect of the additional UFH bolus (comparison between before and after Amendment No. 3) on major or any bleeding. No relationship was observable between major or any bleeding occurrence and concomitant treatment with aspirin and/or clopidogrel. No relevant differences were observed between treatment groups for the frequency of minor bleeding.

Adverse events: In the HDS groups, the overall frequency of any TEAEs ranged from 34.1% to 45.7%, as compared to 36.1% in the UFH/abciximab group. With the exception of the HDS 0.5 mg group (34.1%), the overall frequency of TEAEs was higher in each HDS group than in the UFH/abciximab group. Moreover, the overall frequencies of serious TEAEs and TEAEs leading to discontinuation of study medication were higher in all HDS groups than in the UFH/abciximab group. However, no dose relationship was observable across the HDS groups for any of these categories of TEAE.

The overall frequency of TEAEs leading to death in the HDS 2 mg group (1.7%) and HDS 4 mg group (1.3%) was comparable to that in the UFH/abciximab group (1.7%). In the lowest HDS groups, a slightly higher percentage of patients experienced TEAEs leading to death (HDS 0.25 mg: 3.4%; HDS 0.5 mg: 2.4%). No deaths occurred in the HDS 1 mg group.

Of all the treatment groups, the HDS 0.25 mg group had the highest frequency of serious TEAEs (14.5%), TEAEs leading to death (3.4%), and TEAEs leading to discontinuation of study medication (7.7%).

As expected for the patient population and interventional setting, the majority of TEAEs were cardiac disorders or administration site conditions such as hemorrhage, hematoma or other symptoms at vessel puncture sites. The most frequent individual TEAEs were coronary artery disease, headache and back pain.

The frequency of hemorrhage as a TEAE increased with HDS dose. The frequency of hemorrhagic TEAEs in the HDS 1 mg and HDS 2 mg groups (11.2% in both cases) was similar to that in the UFH/abciximab group (9.7%), but the frequency in the HDS 4 mg group was notably higher (17.1%). The frequency of hemorrhage as a TEAE in the HDS 0.25 mg and HDS 0.5 mg groups was lower and comparable at 5.1% and 4.9%, respectively. The most common types of hemorrhagic TEAE were administration site related, particularly hemorrhages and hematomas at the vessel puncture site or catheter site. The rates of such events were higher in the higher HDS dose groups and the UFH/abciximab group.

Few cerebrovascular disorders were observed during exposure to study medication (1 to 3 patients per treatment group). One patient in the HDS 0.5 mg group experienced a hemorrhagic stroke on Day 2 of the study (1 day after a single injection of HDS was administered) and died on Day 3.

The overall frequency of AEs up to the planned end of study was the same for the HDS 2 mg, HDS 4 mg and UFH/abciximab groups (55.6% in each group), but was slightly higher in the lower HDS groups (0.25 mg: 58.1%, 0.5 mg: 58.5%, 1 mg: 62.9%). No important new patterns or consistent trends could be detected in the AE data up to the planned end of study that were not already identified in the TEAE data.

Laboratory safety: Analyses of laboratory safety data showed a tendency to a higher frequency of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations in the HDS 2 mg group (ALT >2 upper limit of normal [ULN]: 3.2%, AST >2 ULN: 3.1%), but the frequency of such elevations in the HDS 4 mg group was comparable to or lower than that in the UFH/abciximab group (ALT >2 ULN: 1.2% for HDS 4 mg, 1.9% for UFH/abciximab; AST >2 ULN: 1.2% for HDS 4 mg, 2.3% for UFH/abciximab). No other notable findings were observed for any of the other laboratory parameters analyzed.

Other safety: No clinically relevant treatment differences were found in the analyses of vital signs or ECG.

Conclusions: [redacted]

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