9.3 Study H7T-MC-TAAH (Clinical Study Report: "A Double-Blind, Randomized, Multicenter, Dose-Ranging Trial of CS-747 (LY640315) Compared With Clopidogrel in Subjects Undergoing Percutaneous Coronary Intervention (Joint Utilization of Medications to Block Platelets Optimally) (JUMBO-TIMI 26)") (Study Dates: April 15, 2003 – January 6, 2004) (Date of Report: June 24, 2005)

9.3.1 Protocol, Amendment, and Post Hoc Changes

The study description was based on the original protocol dated January 31, 2003 and Protocol Amendment (a) dated October 2, 2003.

Protocol Amendment (a) included the following changes:

- Modification of heparin dosing to allow additional boluses
- Clarification of medications excluded during study participation
- Correction of hemoglobin drop for major and minor bleeding as defined by the TIMI hemorrhage criteria
- Modification of confidence intervals (CI) from 95% to 90% because the study was nonpivotal and powered for one-sided 0.05 tests, which roughly correspond to making decisions based on 90% CIs.
- Minor changes to the Schedule of Events, including the requirement that a baseline CK-MB was to be performed in addition to cardiac troponin
- Clarification of the collection process for clinical endpoints and serious adverse events to prevent unblinding of outcomes unless appropriate to do so

9.3.2 Study Design

This was a multicenter, randomized, parallel, double-blind, double-dummy, active comparator-controlled trial.

9.3.3 Study Population

The study population included subjects undergoing elective or urgent PCI with coronary stenting.

9.3.4 Objectives

Primary Objectives:
The primary objectives of the study were

- To evaluate the safety of increasing doses of CS-747 (a loading dose during PCI and 29 to 34 days of once-daily maintenance dosing) by observing the rate of noncoronary artery bypass graft (non-CABG)-associated significant bleeding (that is, major plus minor bleeding) at 30 to 35 days after PCI
- To compare the safety of CS-747 to a standard regimen of clopidogrel (a 300 mg loading dose during PCI and 29 to 34 days of a 75 mg once-daily maintenance dose) by observing the rate of non-CABG associated significant bleeding at 30 to 35 days after PCI.

Secondary Objectives:
The secondary objectives of the study were

- To evaluate the safety and efficacy of increasing doses (loading dose and 29 to 34 days of once-daily maintenance dosing) of CS-747 by observing the following endpoints at 30 to 35 days after PCI:
    - Non-CABG-associated major bleeding
    - Major adverse cardiovascular events (MACE)
    - Non-CABG major plus minor bleeding plus MACE
- To compare the effect of CS-747 versus a standard regimen of clopidogrel (loading dose, 300 mg; maintenance dose, 75 mg per day) on the following endpoints at 30 to 35 days after PCI:

- Non-CABG-associated major bleeding
- MACE
- Non-CABG-associated significant bleeding (that is, major plus minor bleeding) plus MACE

9.3.5 Inclusion/Exclusion Criteria

Inclusion Criteria (Reproduced from Sponsor, page 11 of 48)
Subjects were eligible to be entered in the study if they met **all** of the following criteria:

1. were candidates for elective or urgent PCI with intended coronary stenting
2. had a native target coronary artery stenosis > 60% (by visual estimation) that was amenable to stenting with ≤ 2 coronary stents that were approved for use by regulatory authorities (multilesion or multivessel stenting was acceptable provided all lesions were treated in a single non-staged procedure)
3. were men or nonpregnant women (that is, postmenopausal women, women who were surgically sterile, or women of childbearing potential who had a negative urine or serum pregnancy test) who were ≥ 18 and ≤ 75 years of age
4. provided written informed consent before entering the study

Exclusion Criteria (Reproduced from Sponsor, page 11 of 48)
Subjects were excluded from the study if they met **any** of the following criteria:

Cardiovascular Exclusion Criteria

5. have a planned PCI procedure as initial treatment for an acute ST-elevation acute myocardial infarction (STEMI)
6. have a planned PCI within 24 hours of fibrinolytic therapy for STEMI
7. have left main stenosis ≥ 50% (by visual estimation), unless the left coronary system is protected by at least one patent bypass graft
8. have a target lesion in a saphenous vein graft or arterial conduit graft (Note that PCI with stenting of a native vessel lesion performed via a venous or arterial graft approach is not an exclusion)
9. have a target lesion that cannot be covered by ≤ 2 approved coronary stents
10. have a left ventricular ejection fraction known to be < 30% by any imaging technique or have symptoms of New York Heart Association (NYHA) Class III or IV congestive heart failure (that is, congestive heart failure symptoms with minimal activity or at rest)
11. have a planned brachytherapy (intracoronary artery radiation therapy) for in-stent restenosis or use any investigational coronary device (including nonapproved coronary stents)
12. have a planned, staged, multivessel PCI procedure (as noted in Inclusion Criterion [2], multilesion or multivessel PCI in the same setting is not an exclusion as long as each native vessel lesion can be covered by ≤2 approved coronary stents)
13. have cardiogenic shock (systolic blood pressure < 90 mm Hg or requiring pressors to maintain pressure over 90 mm Hg and associated with clinical evidence of end-organ hypoperfusion)

Bleeding Risk Exclusion Criteria

14. have active internal bleeding or history of bleeding diathesis
15. have had major surgery or significant trauma within 3 months before entering the study
16. have had clinically evident gastrointestinal or genitourinary bleeding within 3 months before entering the study
17. have any of the following manifestations of neurologic disease:
    a. prior history of hemorrhagic cerebrovascular accident (CVA)
    b. Nonhemorrhagic CVA within 2 years before enrollment
    c. Prior CVA with residual neurologic deficit
    d. Intracranial neoplasm, arteriovenous malformation, or aneurysm
18. have uncontrolled hypertension, defined as a systolic blood pressure > 180 mm Hg or diastolic blood pressure > 110 mm Hg at the time of enrollment

Prior/Concomitant Therapy Exclusion Criteria

19. are receiving or will receive oral anticoagulation therapy that cannot be safely discontinued for the duration of the study
20. have an INR known to be > 1.5
21. have received treatment with a thienopyridine (ticlopidine or clopidogrel) within the preceding 5 days prior to enrollment
22. have received subcutaneous low-molecular-weight heparin (for example, Enoxaparin or dalteparin) within 8 hours prior to PCI
23. have received intravenous bivalirudin at any time prior to PCI
24. have received a proton pump inhibitor (PPI) within 12 hours prior to PCI or are scheduled to receive a PPI following PCI (The use of a PPI pre- or post-PCI is not allowed during the study period.)
25. have been treated with an oral or intravenous H_2 antagonist (for example, cimetidine, ranitidine, famotidine, nizatidine) within 2 hours before PCI (The use of an H_2 antagonist following PCI is allowed)

General Exclusion Criteria

26. are investigator site personnel directly affiliated with the study, or are immediate family of investigator site personnel directly affiliated with the study. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
27. are employed by either Eli Lilly or Sankyo (that is, employees, temporary contract workers, or designees responsible for the conduct of the study). Immediate family of Lilly employees may participate in Lilly-sponsored clinical trials, but are not permitted to participate at a Lilly facility. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted
28. have received an investigational drug or have undergone implantation of an investigational device within the previous 30 days
29. have previously completed or withdrawn from this study or any other study investigating CS-747
30. are women who have given birth within the past 90 days or who are breastfeeding
31. have a concomitant medical illness (for example, malignancy, uncontrolled diabetes, or hepatic, pulmonary, or renal disease) that in the opinion of the investigator precludes participation in the study
32. have renal insufficiency (creatinine > 2.0 mg/dL) or require renal dialysis
33. have a condition associated with poor treatment compliance, including alcoholism, mental illness, or drug dependence
34. may be unable to cooperate with protocol requirements and follow-up
35. have a platelet count prior to PCI of < 100,000/mm^3
36. have a history of intolerance or allergy to aspirin (ASA) or approved thienopyridines (ticlopidine or clopidogrel)
37. have anemia (Hgb < 10 gm/dL)

9.3.6 Study Plan

Approximately 900 subjects were to be randomized through an interactive voice response system to one of the three dosing regimens of CS-747 (prasugrel) plus aspirin or to clopidogrel plus aspirin described in Table 70. Subjects were to receive the loading dose at the time of PCI followed by 29-34 days of once daily maintenance dosing.

Table 70. Treatment Regimen (TAAH)

Treatment	Regimen
Prasugrel	40 mg loading dose ; 7.5 mg maintenance dose x 29-34 days
Prasugrel	60 mg loading dose; 10 mg maintenance dose x 29-34 days
Prasugrel	60 mg loading dose; 15 mg maintenance dose x 29-34 days
Clopidogrel	300 mg loading dose; 75 mg maintenance dose x 29-34 days

Procedural anticoagulation was to include unfractionated heparin(UFH) therapy only.

- If the subject was receiving an intravenous GP IIb/IIIa inhibitor, UFH was to be provided as a bolus of 50 U/kg (not to exceed 5000 U) with a target activated clotting time (ACT) of 200 to 250 seconds.

- If the subject was not receiving an intravenous GP IIb/IIIa inhibitor, provide UFH as a bolus of 60 U/kg (not to exceed 5000 U) with a target ACT of 250 to 300 seconds.

Excluded treatments included proton pump inhibitors, intravenous H_2 antagonists, bivalirudin (any time before or during PCI), and low-molecular-weight heparin (administered either subcutaneously within 8 hours before PCI or intravenously during PCI).

Clinical endpoints were to be determined at hospital discharge and after 30 to 35 days of treatment.

The study design is described in Figure 32.

Figure 32. H7T-MC-TAAH Study Design

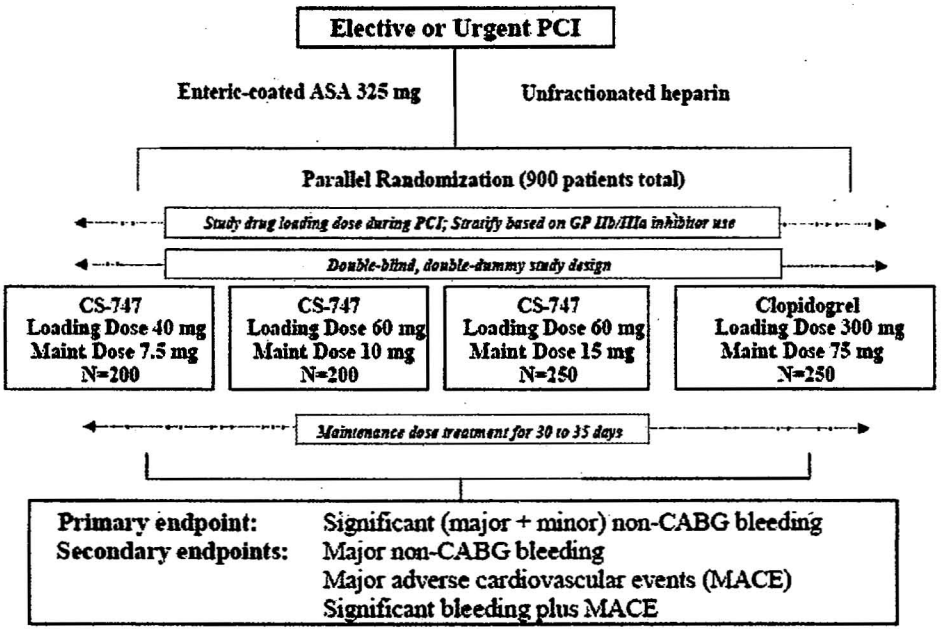

Figure TAAH.1. H7T-MC-TAAH study design.

Abbreviations: ASA = aspirin; CABG = coronary artery bypass grafting; GP = glycoprotein; MACE = major adverse cardiovascular events; maint. = maintenance; PCI = percutaneous coronary intervention.

(Reproduced from Sponsor, Figure TAAH.1, Original Protocol, page 9 of 48)

Subjects discontinuing the study drug and/or the study early were to undergo end-of-therapy and/or end-of-study procedures and were to be switched to open-label clopidogrel unless clinically contraindicated.

9.3.7 Schedule of Evaluations and Procedures

The study schedule is displayed in Table 71.

Table 71. Study Schedule (TAAH)

	Visit 1		Visit 2					Visit 3
	Screening	Enrollment (Day 0)	PCI (Day 1)	4-8 h (post-LD)	12-24 h (post-LD)	Daily (in hospital)	Hospital Discharge[c]	Visit at Day 30 to Day 35
Screen and obtain signed consent	X							
Randomization			X					
Medical history	X							
Physical exam and vital signs	X (Complete)						X (no VS)	X (no VS)
Assess for AEs	X							
12-lead ECG[a]		X (pre-PCI)	X (post-PCI)				X	X
Medications:								
ECASA 325 mg	X		X			X	X	X[d]
Study Drug			Loading dose (during PCI)		Daily Maintenance Therapy			
Labs:								
CBC w/ Diff and Plt Ct	X					X		X
PT and INR	X							
CK-MB[a]	X			X	X			
Clinical chemistry[b]	X							X
Pregnancy test	X							

Abbreviations: AE = adverse event; CK-MB = creatine kinase–MB isoform; ECG = electrocardiogram; ECASA = enteric-coated aspirin; CBC w/ Diff = complete blood count with differential; INR = international normalized ratio; PCI = percutaneous coronary intervention; Plt Ct = platelet count; post-LD = post-loading dose; PT = prothrombin time; VS = vital signs.

a Obtain serial CK-MB measurements (and/or cardiac troponin levels) and serial ECGs for recurrent ischemic chest pain at rest lasting >10 minutes post-PCI.

b Clinical chemistry sample is sent to central lab (all other lab tests are performed locally).

c Hospital discharge or Day 4 post-PCI, whichever comes first.

d Subject receives daily ECASA 325 mg from hospital discharge to Visit 3 at Day 30 to Day 35.

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(Reproduced from Sponsor, page 40 of 48)

9.3.8 Endpoints

9.3.8.1 Primary Safety Measure

The primary safety measure was a comparison between treatment groups of the development of significant non-CABG-associated bleeding complications through 30 to 35 days after PCI. Significant bleeding was defined as the composite of TIMI major and minor bleeding.

The TIMI definitions of major and minor bleeding are displayed in Table 72.

Table 72. TIMI Hemorrhage Criteria

	TIMI Hemorrhage Criteria[a]		
	ICH	**Clinically Overt (including imaging)**	**Hgb Drop[b] (g/dL)**
Major Bleeding	×	×	≥5
Minor Bleeding	-	×	3 to <5
Minimal Bleeding	-	×	<3

Abbreviations: Hct = Hematocrit; Hgb = hemoglobin; ICH = Intracranial hemorrhage.

[a] Accounting for the effect of transfusions on change in Hgb as described in footnote b.

[b] One unit packed red blood cells = 1 g Hgb = 3% Hct.

(Reproduced from Sponsor, Original Protocol, page 26 of 48)

9.3.8.2 Secondary Safety and Efficacy Measures

The secondary safety and efficacy measures include major adverse cardiovascular events (MACE), defined as any one of the following, up to 30 to 35 days after PCI:

1. Death (all cause mortality)
2. Nonfatal myocardial infarction
3. Stroke
4. Recurrent myocardial ischemia requiring rehospitalization
5. Total or subtotal occlusion of the target vessel documented angiographically and occurring ≥ 2 hours after the loading dose of study drug
6. Urgent target vessel revascularization (any PCI or CABG performed in response to ischemic symptoms involving the epicardial coronary artery that was the target vessel for the index procedure)

The subset of MACE elements (5) and (6) were to be referred to as "Clinical Target Vessel Thrombosis" for the purposes of interim safety monitoring.

9.3.9 Statistical Considerations

9.3.9.1 Sample Size

The sponsor estimated that by enrolling 250 subjects in the clopidogrel arm and 200 to 250 subjects in each of the three prasugrel arms there would be at least 80% power to detect a 2.5-fold increase in the risk of significant non-CABG-associated bleeding. The sample size also would provide > 80% power to detect a 2-fold increase in the risk

of significant non-CABG-associated bleeding, but only if the event rate for the dosing regimens with lower-risk was sufficiently high.

9.3.9.2 Statistical and Analytical Plans

Per the Statistical Analysis Plan, since there were minimal differences between the analysis sets, the evaluable set was used. The evaluable set (n=904 total) was defined as all subjects who received at least one dose of study drug.

The primary analyses were a comparison among CS-747 doses and between the combined CS-848 group and the clopidogrel group of the development of significant non-CABG-associated bleeding. All statistical analyses were performed using a two-sided test with a significance level of 0.05.

All primary and some secondary analyses were based on clinical events committee (CEC)-adjudicated endpoints (significant bleeding, myocardial infarction [MI], clinical target vessel thrombosis [CTVT], and stroke). Death and recurrent ischemia was not adjudicated by the CEC.

The key comparisons of interest were described as follows:

- Between prasugrel and clopidogrel
  1. All Prasugrel arms combined versus the Clopidogrel arm (that is, the Prasugrel 40-mg LD/7.5-mg MD **AND** Prasugrel 60-mg LD/10-mg MD **AND** Prasugrel 60-mg LD/15-mg MD arms versus the Clopidogrel 300-mg LD/75-mg MD arm)
  2. Prasugrel 60-mg LD/15-mg MD arm versus the Clopidogrel arm
  3. Prasugrel 40-mg LD/7.5-mg MD arm **AND** 60-mg LD/10-mg MD arm combined versus the Clopidogrel arm
  4. Prasugrel 40-mg LD/7.5 mg MD arm **OR** 60-mg LD/10-mg MD arm alone versus the Clopidogrel arm

- Among the prasugrel treatment arms
  5. Prasugrel 60-mg LD/15-mg MD arm versus Prasugrel 40-mg LD/7.5 mg MD AND CS-747 60-mg LD/10-mg MD arms combined
  6. Prasugrel 60-mg LD/15-mg MD arm versus Prasugrel 40-mg LD/7.5 mg MD arm OR Prasugrel 60-mg LD/10-mg MD arm alone
  7. Prasugrel 40-mg LD/7.5 mg MD arm versus Prasugrel 60-mg LD/10-mg MD arm

There were no corrections for multiple comparisons.

The rate of significant bleeding and the rate of MACE was to be analyzed in the following subgroups:

- Body size (BMI $\leq$ 20 or BMI $\geq$ 25 versus BMI between 20 and 25)
- Male versus female
- Age (< 65 years versus $\geq$ 65 years)
- Use of any GP IIb/IIIa inhibitor
- TIMI Risk Score (TIMI score $\leq$ 2 or TIMI score > 2)

9.3.9.3 Interim Analyses

Two interim analyses were planned that would analyze data from the first 150 and 450 evaluable subjects across the three prasugrel treatment arms. Evaluable subjects were defined as those who received the loading dose of study drug.

The Data Safety Monitoring Board (DSMB) would decide whether or not to reduce the prasugrel loading dose or to discontinued a prasugrel dosing group is the DSMB-unblinded data demonstrated a statistically significant event rate of > 3% for major bleeding or >2% for clinical target vessel thrombosis (that is, the lower bound of the 95% confidence interval exceeded 3% for major bleeding or 2% for clinical target vessel thrombosis).

9.3.10 Results

9.3.10.1 Sites, Investigators, and Study Dates

The study was conducted from April 15, 2003 to January 6, 2004 at 75 study centers in the United States and 13 in Canada. Nine of the 75 study centers in the United States did not enroll subjects. Three principal investigators had two sites each.

9.3.10.2 Good Practice, Monitoring, and Protocol Deviations

The study was conducted in accordance with Good Clinical Practices and the Declaration of Helsinki. There were numerous protocol deviations; however, these deviations were distributed across all treatment groups. Approximately 102 subjects were categorized into the following categories:

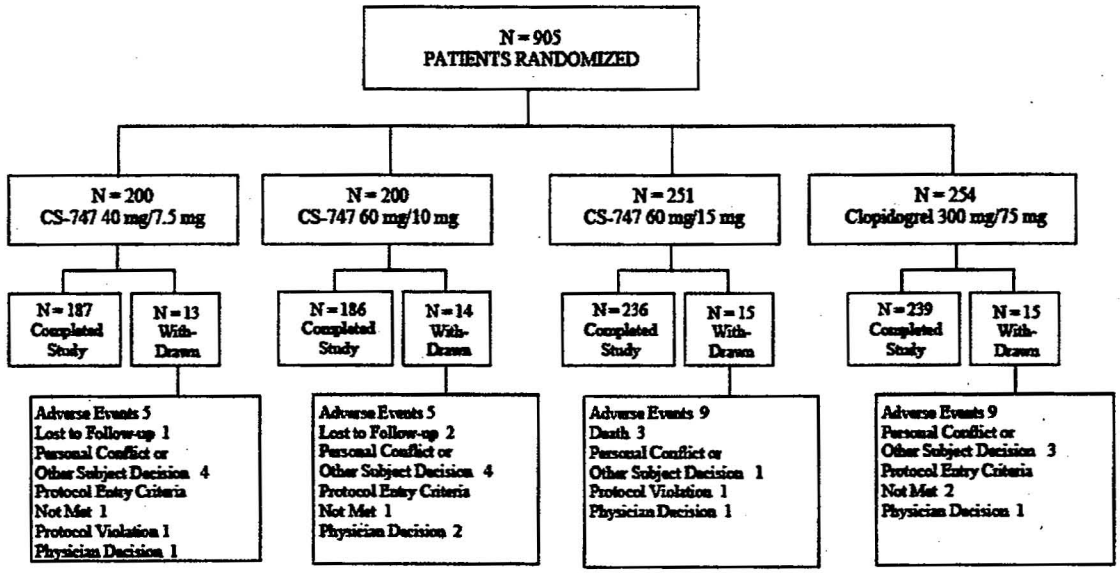
- Those who entered the study even though they did not satisfy the entry criteria (23 subjects)
- Those who developed withdrawal criteria during the study but were not withdrawn (37 subjects)
- Those who received the wrong treatment or dose (2 subjects) or
- Those who received an excluded concomitant medication (40 subjects)

The majority of subjects who received an excluded concomitant medication had received proton pump inhibitors.

9.3.10.3 Disposition of Subjects

Subject disposition is displayed in Figure 33.

Figure 33. Subject Disposition (All Randomized Set) (TAAH)



Source of Information: Table TAAH 14.1

(Reproduced from sponsor, Clinical Study Report, Figure TAAH.10.1, page 100 of 8860)

9.3.10.4 Subject Demographics and Baseline Characteristics

Subject demographics and baseline characteristics are presented in Table 73.

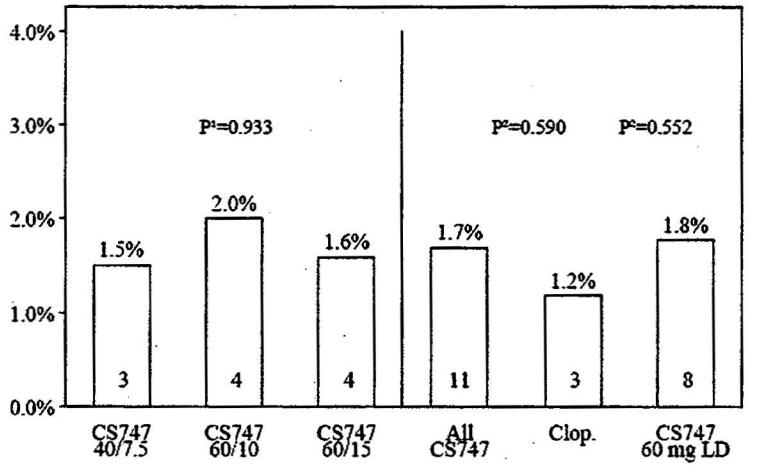
Table 73. Subject Demographics and Baseline Characteristics (Evaluable Set)

	CS-747				Clopidogrel	Total
	40/7.5 mg N=199	60/10 mg N=200	60/15 N=251	Subtotal N=650	300/75 mg N=254	N=904
Age (years)						
No. Subjects	199	200	251	650	254	904
>65	70 (35.2)	48 (24.0)	66 (26.3)	184 (28.3)	59 (23.2)	243 (26.9)
Mean (SD)	60.4 (8.72)	58.7 (9.15)	59.4 (8.97)	59.5 (8.96)	58.4 (9.17)	59.2 (9.03)
Sex						
Male	152 (76.4)	151 (75.5)	198 (78.9)	501 (77.1)	195 (76.8)	696 (77.0)
Ethnicity						
Caucasian	180 (90.5)	180 (90.0)	226 (90.0)	586 (90.2)	238 (93.7)	824 (91.2)
TIMI Risk Score, n (%)						
Median	2.0	2.0	2.0	2.0	3.0	2.0
History of CVA	**2 (1.0)**	**0**	**2 (0.8)**	**4 (0.6)**	**5 (2.0)9**	**9 (1.0)**
Reproduced from Sponsor, Clinical Study Report, Table TAAH.11.3, pages 118-124.						

9.3.10.5 Safety Endpoints

Although the percentage of subjects experiencing significant (TIMI non-CABG Major and Minor) bleeding at the 30-day visit was higher in all CS-747 treatment groups, compared to clopidogrel, this difference was not statistically significant, as seen in Figure 34.

Figure 34. Significant (TIMI non-CABG Major + Minor) Bleeding at 30-Day Visit (%)



P¹: Fisher's exact p-value
P²: Log-rank p-value

Abbreviations: CABG = coronary artery bypass graft; Clop = clopidogrel; LD = loading dose; TIMI = Thrombolysis in Myocardial Infarction.

P¹ = comparison among CS-747 groups, p=0.933.

P² (left) = comparison between combined CS-747 groups versus clopidogrel, p = 0.590.

P² (right) = comparison of combined 60 mg CS-747 LD versus clopidogrel, p = 0.552.

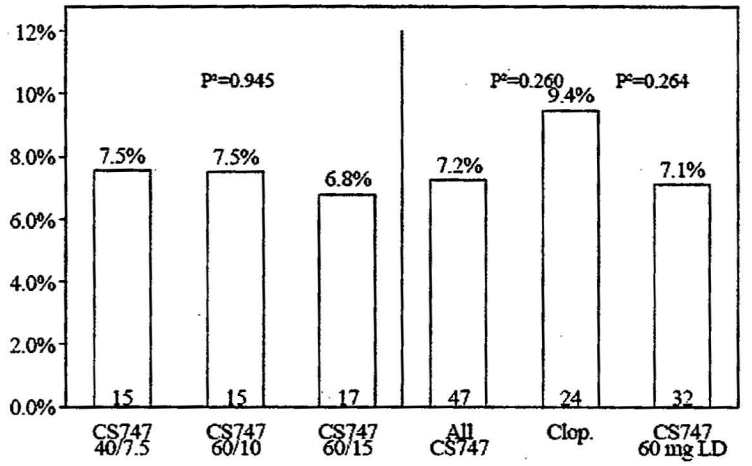
(Reproduced from Sponsor, Clinical Study Report, Figure TAAH.11.1, page 154)

9.3.10.6 Major Adverse Cardiovascular Events (MACE)

Three subjects in the CS-747 60/15 mg group died during the study due to sudden death, circulatory collapse, and decreased cardiac output, respectively. Two subjects in the CS-747 60/10 mg treatment group experienced a non-hemorrhagic stroke and one subject in the CS-747 60/15 mg treatment group experienced a hemorrhagic stroke.

MACE was highest in the clopidogrel treatment group and was lowest in the CS-747 60/15 mg treatment group. Overall, there was no statistically significant difference in MACE between treatment groups, as demonstrated in .

Figure 35. MACE (Death + MI + Stroke +CTVT + Recurrent Ischemia) at 30-Day Visit (%) (TAAH)



P¹: Fisher's exact p-value
P²: Log-rank p-value
Abbreviations: MACE = major adverse cardiovascular event; D = death; MI = myocardial infarction; CTVT = clinical target vessel revascularization; Clop = clopidogrel; LD = loading dose.
P¹ = comparison among CS-747 groups, p=0.945.
P² (left) = comparison between combined CS-747 groups versus clopidogrel, p = 0.260.
P² (right) = comparison of combined 60 mg CS-747 LD versus clopidogrel, p = 0.264.

(Reproduced from Sponsor, Clinical Study Report, Figure TAAH.11.18, page 173)

9.3.10.7 Summary

The CS-747 40/7.5 mg regimen had a lower incidence of significant bleeding and a similar incidence of MACE compared to the CS-747 60/10 mg regimen.

9.4 Line-by-Line Labeling Review

Completed and circulating to review team via email.

10 REFERENCES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Karen Hicks
4/28/2008 10:39:20 AM
MEDICAL OFFICER