2.3 Availability of Proposed Active Ingredient in the United States

Prasugrel has not been previously marketed in the United States.

2.4 Important Issues With Pharmacologically Related Products

Other ADP receptor antagonists such as ticlopidine hydrochloride and clopidogrel bisulfate can be associated with neutropenia, agranulocytosis, thrombotic thrombocytopenic purpura (TTP), aplastic anemia, and bleeding.

2.5 Presubmission Regulatory Activity

Prasugrel was initially developed with free base, but the sponsor subsequently switched to the HCl salt, citing advantages such as increased bioavailability and solubility at higher pHs.

2.6 Other Relevant Background Information N/A

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

b(4)

The Chemistry division has asked the sponsor to provide a comprehensive analysis of all such compounds that could be present in the drug substance or drug product. Please refer to the CMC review which will be completed at a later date.

3.2 Animal Pharmacology/Toxicology

Two carcinogenicity studies in the rat and in the mouse were reviewed. In the rat, survival analysis showed no statistically significant dose response relationship or differences in survival between prasugrel treatment groups and control in either sex. Additionally, tumor data analysis was not statistically significant.[6]

In the mouse, pairwise comparisons showed a statistically significantly increased incidence of hepatocellular adenoma and combined incidences of hepatocellular adenoma and hepatocellular carcinoma in the high dose (300 mg/kg/d) prasugrel treatment group in males, and in the medium (100 mg/kg/d) and high dose (300 mg/kg/d) prasugrel treatment groups in females, compared to controls.[7]

The Executive Carcinogenicity Advisory Committee met on February 26, 2008 and concluded that the rat study was adequate and was negative for drug-related tumors. Additionally, the mouse study was adequate and was positive for hepatocellular adenomas in both sexes.

[6]**Analysis by Mohammad Atiar Rahman, Ph.D., Division of Biometrics, FDA (Review dated 2/19/2008)**
7**Analysis by Mohammad Atiar Rahman, Ph.D., Division of Biometrics, FDA (Review dated 2/19/2008)**

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sponsor submitted an electronic NDA which can be found at the following link:
\\CDSESUB1\EVSPROD\NDA022307\022307.enx

4.2 Tables of Clinical Studies

The current submission includes Clinical Study Reports for TAAL, TABL, TAAH, and approximately 47 other clinical, pharmacokinetic, or pharmacodynamic studies. A summary of the pivotal phase 2 and phase 3 studies is displayed in Table 7.

Table 7. Summary of the Pivotal Phase 3 and Phase 2 Studies

Study ID (total randomized)	Study Title	Study Dates	Number of Subjects Randomized in Each Treatment Arm	Sex (F=Female; M=Male)
H7T-MC-TAAL (n=13,608)	A Comparison of CS-747 and Clopidogrel in Acute Coronary Syndrome Subjects who are to Undergo Percutaneous Coronary Intervention/TIMI 38 (Date of Report: November 28, 2007)	November 5, 2004 – July 22, 2007	Prasugrel (60 mg LD/ 10 mg MD): 6813 Clopidogrel (300 mg LD/ 75 mg MD): 6795	Prasugrel: (1705 F, 5108 M) Clopidogrel: (1818 F, 4977 M)
H7T-MC-TABL (n=201)	PRasugrel IN Comparison to Clopidogrel for Inhibition of Platelet Activation and AggrEgation (PRINCIPLE) – TIMI 44 (Date of Report: October 1, 2007)	August 24, 2006 – June 20, 2007	Prasugrel (60 mg LD/10 mg MD x 14 days then Clopidogrel 600/150 mg x 14 days): 102 Clopidogrel (600 mg LD/150 mg MD x 14 days then Prasugrel 60mg LD/10 mg MD x 14 days): 99	Prasugrel/Clopidogrel: (29 F, 73 M) Clopidogrel/Prasugrel: (22 F, 77 M)
H7T-MC-TAAH (n=904)	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) (Date of Report: June 24, 2005)	April 15, 2003 - January 6, 2004	Prasugrel 40/7.5 mg: 199 Prasugrel 60/10 mg: 200 Prasugrel 60/15 mg: 251 Clopidogrel 300/75 mg: 254	Prasugrel 40/7.5: (47 F, 152 M) Prasugrel 60/10: (49 F, 151 M) Prasugrel 60/15: (53F, 198 M) Clopidogrel 300/75: (59 F, 195 M)
LD: loading dose; MD: maintenance dose				

4.3 Review Strategy

In the Appendix, please see reviews for each individual study. TAAL is the sole study submitted for efficacy and is also summarized in the Integrated Summary of Efficacy and Safety. All available studies were used for the Integrated Summary of Safety. Additionally, FDA conducted analyses of neoplasms and bleeding.

4.4 Data Quality and Integrity

There were data quality and integrity issues in this application. The sponsor submitted an adverse events data set that had preexisting conditions included with treatment emergent adverse events. As a result, we requested numerous case report forms to determine timing of events, especially related to malignancy and bleeding. In the review process, it also became apparent that the verbatim terms we had requested for the adverse event data set were not included and that some preexisting condition information was replaced by subsequent adverse event information. When we asked the sponsor to submit changes from original to final terms for the adverse event data set, we

discovered that approximately 19,000 lines out of the original 155,619 lines of the adverse event data set had been modified. While most of these changes were not important, and predominantly represented changes in spelling, some of the changes were important. However, given the size of the adverse event data set, the information in question represented 2% of the entire adverse data set, and we did not think it would substantially change the results of our analyses. Nevertheless, we have requested additional information from the sponsor for clarification purposes.

Lastly, there were instances of suboptimal adjudication by the Clinical Events Committee, as demonstrated in the following examples:

1. Subject 27094118600 (53 yo female) (UA/NSTEMI) (clopidogrel): This subject had a history of thyroid cancer (1986), hypertension, hypercholesterolemia, and diabetes mellitus. On [redacted], she underwent index PCI with placement of a 3.0 x 16 mm Liberte stent placement in the proximal left anterior descending artery (deployed with 2 inflations at 12 atmospheres for 22 and 30 seconds, respectively). She also underwent PTCA of the diagonal artery (1.5 x 15 mm Maverick balloon with 2 inflations at 16 atmospheres for 29 and 26 seconds, respectively). On [redacted], she "was found dead in her bed at home. A diagnosis of organ failure was made by the doctor. No autopsy was performed." The initial CEC cause of death was cardiovascular (sudden or unwitnessed death), and the box for possible stent thrombosis fulfilling the Academic Research Consortium definition was checked. There was no angiographic or pathologic determination of the culprit lesion. Clinical stent thrombosis was thought to have occurred (unexplained cardiovascular death defined as either sudden or unwitnessed death without clear non-cardiovascular cause) in the late (> 30 days – 1 year post stent) time-frame. However, on the **Endpoint Reporting of Death form** (page 900), the **primary cause of death checked was "Non-Cardiovascular" and "Other Non-Cardiovascular—organ failure."** Instead of being coded as a "non-cardiovascular death, this event should have been coded as a cardiovascular death and a possible late stent thrombosis. b(6)

2. Subject 33058616068 (82 yo male) (STEMI) (clopidogrel): This subject had a history of diabetes mellitus, peripheral vascular disease. and lung cancer. He was status post a left lobectomy on some unknown date. He underwent index PCI on [redacted] and received overlapping stents in the mid left anterior descending artery (predilated with Viva 2.0 x 20 mm balloon; placement of Cypher 2.5 x 23 mm stent in the distal part of the lesion and 2.5 x 33 mm Cypher stent in the proximal area of the lesion). Length of stented segment was 56 mm and maximum inflation pressure was 14 atmospheres. Study adverse events included bronchopneumopathy on [redacted] and third degree AV block on [redacted] for which acebutolol was subsequently discontinued. He underwent pacemaker implantation on [redacted] The last day of study drug was on 6/7/2006. The patient died at home on [redacted] According to the spouse, the patient had symptoms for several days and did not feel well. The patient's physician thought the cause of death was "probably from a new infarct." Initially, the CEC adjudicated cause of death was "cardiovascular," and the "sudden or unwitnessed death" box was checked. The CEC adjudicated this case as a "possible" stent thrombosis, defined as any unexplained death from 30 days following intracoronary stenting until end of trial follow-up (i.e. late stent thrombosis). There was also thought to be stent thrombosis fulfilling the TIMI definition, since the "clinical" box was checked as well as the "unexplained cardiovascular death defined as either sudden or unwitnessed death without clear non-cardiovascular cause." However, on the **Endpoint Reporting of Death form** (page 900), the **primary cause of death was checked "uncertain."** This death should have been coded as a cardiovascular death and a possible late stent thrombosis. The subject was on omeprazole at the time of his death. b(6)

3. Subject 48046511535 (64 yo female) (STEMI) (prasugrel): This subject had a past medical history of hypertension, diabetes, obesity, and cataracts. On [redacted] she underwent PCI with placement of a bare metal stent. On 9/13/2005, she experienced gastrointestinal bleeding adjudicated as a TIMI minor bleed. On 9/13/2005, her physician stopped coumadin for her paroxysmal atrial fibrillation and aspirin. On [redacted] she was hospitalized and underwent endoscopy of the rectum and colon which revealed multiple polyps with no active bleeding. Histopathology result of colon polyps was adenocarcinoma. Her last dose of study drug was on 9/16/2005. On [redacted] she experienced a stroke confirmed on CT, and died on [redacted] Initially, the CEC adjudicated her death as "cardiovascular" and "non-hemorrhagic stroke." However, on the **Endpoint Reporting form (page 900), the final cause of death was checked as "non-cardiovascular" due to "stroke."** Clearly, non-hemorrhagic stroke should have been listed as a cardiovascular cause of death. b(6)

- In the setting of lansoprazole, the Cmax of prasugrel.HCl decreased by 30% but AUC(0-∞) and AUC(0-t_{last}) were not significantly changed.
- The administration of oral ranitidine (coadministration of 150 mg ranitidine with 60 mg prasugrel on Day 1 and 7 days of coadministration of 150 mg ranitidine with 10 mg prasugrel from Days 2 to 8) did not significantly affect the pharmacokinetics of prasugrel.
- The pharmacokinetics of prasugrel is best described by a three-compartment model.
- The active metabolite of prasugrel is R-138727.
- The Tmax of prasugrel ranges from 0.25 hours to 2.25 hours and for the metabolites ranges from 0.5 – 1 hour. The terminal t1/2 of the active metabolite is 7.4 hours.
- Prasugrel is hydrolyzed to a pharmacologically inactive thiolactone, R-95913, which is metabolized to the active metabolite, R-138727 through the action of several CYPs including CYP3A4>CYP2B6>CYP2C9~CYP2C19>CYP2D6. CYP3A is the major enzyme responsible for active metabolite formation.
- Prasugrel weakly inhibits CYP2B6.
- Ketoconazole decreased the Cmax of R-138727 by 46% after the loading dose but did not affect $AUC_{(0-24)}$ or T_{max}.
- Rifampicin (600 mg once daily) did not affect the pharmacokinetics of R-138727.
- Following co-administration of prasugrel (60 mg LD/10 mg MD x 10 days) and single dose warfarin (15 mg) on Day 6, there was a prolongation in bleeding time at 12, 24, and 48 hours postdose compared to predose on Day 1, with bleeding time being approximately 47%, 71%, and 104% longer, respectively.
- Following coadministration of prasugrel (60 mg LD, 10 mg MD) and aspirin (900 mg single dose, 150 mg daily dose), there was a 43% increase in bleeding time ratio.
- A high fat meal decreased Cmax by 49%, but did not affect the AUC of R-138727. In a fed state, the Tmax was delayed from 0.5 to 1.5 hours. Prasugrel may be taken with or without food.
- The absolute bioavailability of prasugrel has not yet been determined. Based on a ^{14}C study, at least 79% of the prasugrel dose was absorbed.
- Since the active metabolite of prasugrel is unstable in plasma, its binding to plasma proteins could not be determined. However, binding was 98% in a 4% human serum albumin solution in phosphate buffer at pH 7.4.
- Approximately 95% of a [^{14}C] prasugrel dose was recovered after oral administration. About 68% and 27% of the dose was recovered in urine and feces, respectively, suggesting that urinary excretion is the major pathway for the elimination of prasugrel metabolites.
- In vivo, prasugrel does not significantly affect P-glycoprotein activity.
- Following a single dose of prasugrel (60 mg), there was a 12% lower Cmax and 22% lower $AUC_{(0-last)}$ in subjects with mild to moderate hepatic impairment.
- In a multiple dose study in subjects with stable Child-Pugh Class B cirrhosis, the pharmacokinetics of prasugrel were not significantly affected.
- In subjects with end stage renal disease, the active metabolite AUC (0-t_{last}) was 47% lower than in matching healthy subjects.
- In subjects with moderate renal impairment, the pharmacokinetics of prasugrel were not significantly affected.

5.1.1 Salt to Base Conversion

In Study TACS, the objective was to determine the effect of salt conversion to base during storage of prasugrel tablets on the pharmacokinetics of prasugrel's active metabolite in healthy subjects taking a proton pump inhibitor (lansoprazole 30 mg once daily). Prasugrel was administered orally as a single 60 mg dose provided as 10 mg tablets with high surface area (SA-H) of [redacted] Lansoprazole was administered orally as daily 30 mg doses provided as 30 mg capsules extent of conversion of prasugrel.HCl low (5%), intermediate (58%), or high extent of conversion (70%). b(4)

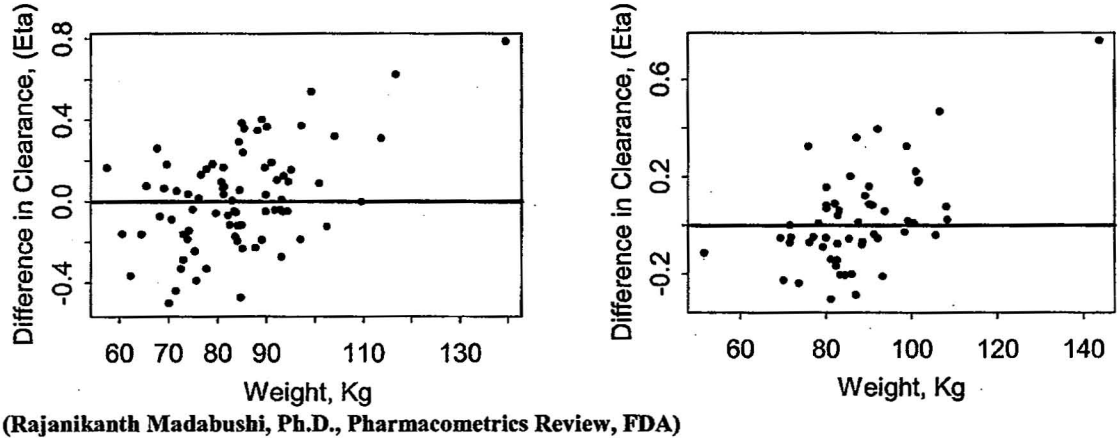
Results demonstrated that after pre-treatment with 30 mg lansoprazole, the low, intermediate, and high rate of conversion tablets were not bioequivalent to each other since the Cmax failed to meet the 90% confidence interval

criteria of 80-125. Furthermore, the difference in plasma levels translated into differences in maximum platelet aggregation which could be clinically significant.

5.1.2 Relationship Between Body Weight and Exposure

In Studies TAAD and TABR, population pharmacokinetic analyses demonstrated that the clearance of the active metabolite, R-138727, increased with an increase in body weight as seen in Figure 2. Therefore, patients with decreased body weight would have decreased clearance of the active metabolite R-138727 and increased exposure.

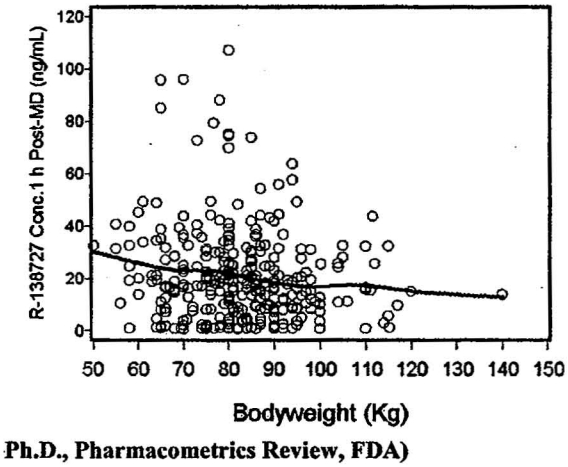
Figure 2. Clearance of R-138727 Increases with Increase in body weight



(Rajanikanth Madabushi, Ph.D., Pharmacometrics Review, FDA)

Increased exposures of R-138727 in patients with decreased body weight were seen in Study TAAL, as shown in Figure 3.

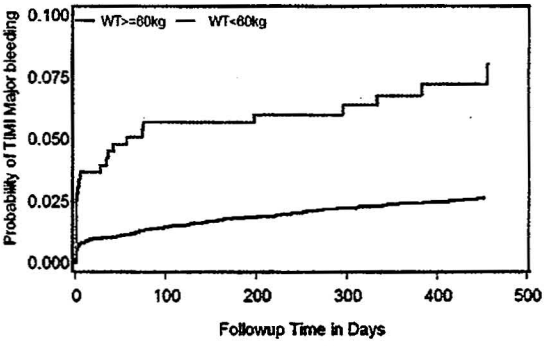
Figure 3. Increased Exposures of R-138727 with Decreased Body Weight (TAAL)



(Rajanikanth Madabushi, Ph.D., Pharmacometrics Review, FDA)

In patients with lower body weight, increased exposure to the active metabolite was associated with an increased risk for TIMI major bleeding, as shown in Figure 4.

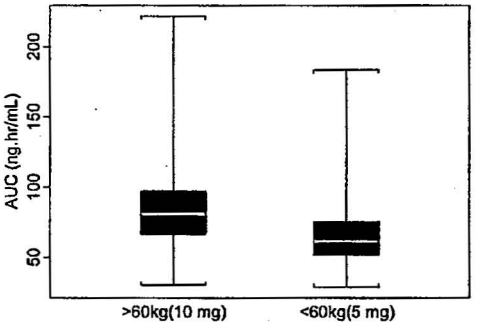
Figure 4. Risk for TIMI Major Bleeding is Higher in Patients with Body Weight < 60 kg



(Rajanikanth Madabushi, Ph.D., Pharmacometrics Review, FDA)

Therefore, the sponsor recommends reducing the maintenance dose of prasugrel from 10 mg to 5 mg daily in patients weighing < 60 kg, and we agree. In the simulation displayed in Figure 5, the 5 mg maintenance dose in patients weighing < 60 kg would result in exposures predominantly corresponding to the lower two quartiles of those expected with the 10 mg maintenance dose in patients weighing > 60 kg.

Figure 5. Simulation (N=2000) of the Proposed 5 mg Maintenance Dose in Patients with Body Weight < 60 kg ((CL = 123 x (WT/85)$^{0.798}$; Between-subject variability (%CV) = 24%) (Study TABR)



(POPPK Analysis of Study TABR by Rajanikanth Madabushi, Ph.D., Pharmacometrics Review, FDA)

5.2 Pharmacodynamics

The effect of prasugrel on blood pressure, heart rate, and QT interval are discussed in the Integrated Summary of Safety in Section 7. The effect of prasugrel on platelet aggregation is further discussed in Study TABL in Section 9.2 of the Appendix.

5.3 Exposure-Response Relationships

Exposure-response analyses with respect to efficacy and safety are presented in various parts of this review.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor's proposed indication is for "the reduction of atherothrombotic events and the reduction of stent thrombosis in acute coronary syndromes (ACS) as follows:

- "patients with unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI) who are managed with percutaneous coronary intervention (PCI)
- "patients with ST-segment elevation myocardial infarction (STEMI) who are managed with primary or delayed PCI.

"Prasugrel has been shown to reduce the rate of a combined endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke."

6.1.1 Methods

The sponsor submitted one trial, H7-MC-TAAL TRITON TIMI 38, for the efficacy claim.

6.1.2 General Discussion of Endpoints

In TAAL, the primary efficacy endpoint was a composite of cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal stroke at a median of 12 months follow-up.

Secondary endpoints included the following
- CV death, nonfatal MI, or nonfatal stroke at 90 days post randomization
- CV death, nonfatal MI, or nonfatal stroke at 30 days post randomization
- CV death, nonfatal MI, or urgent target vessel revascularization (UTVR) at 90 days post randomization
- CV death, nonfatal MI, or UTVR at 30 days post randomization
- All-cause death, nonfatal MI, or nonfatal stroke at study end (after a median follow-up of at least 1 year post randomization)
- CV death, nonfatal MI, nonfatal stroke, or rehospitalization for cardiac ischemic events at study end
- Definite or probable (ARC definition[8]) stent thrombosis

Please see Section 9.1.10.2 in the Appendix under Study TAAL for a complete discussion of the statistical methods.

6.1.3 Study Design

This was a Phase 3, multicenter, randomized, parallel-group, double-blind, double-dummy, active-controlled study in 13,608 subjects with acute coronary syndrome. Acute coronary syndrome (ACS) included subjects with unstable angina and non-ST-segment elevation myocardial infarction (UA/NSTEMI) with TIMI risk score ≥ 3 or ST-segment elevation myocardial infarction (STEMI) who were to undergo percutaneous coronary intervention (PCI).

[8]**Cutlip DE, S Windecker, R Mehran, A Boam, DJ Cohen, G-A van Es, PG Steg, M-A Morel, L Mauri, P Vranckx, E McFadden, A Lansky, M Hamon, MW Krucoff, PW Serruys and on behalf of the Academic Research Consortium, 2007, Clinical End Points in Coronary Stent Trials: A Case for Standardized Definitions, Circulation, 115:2344-2351.**

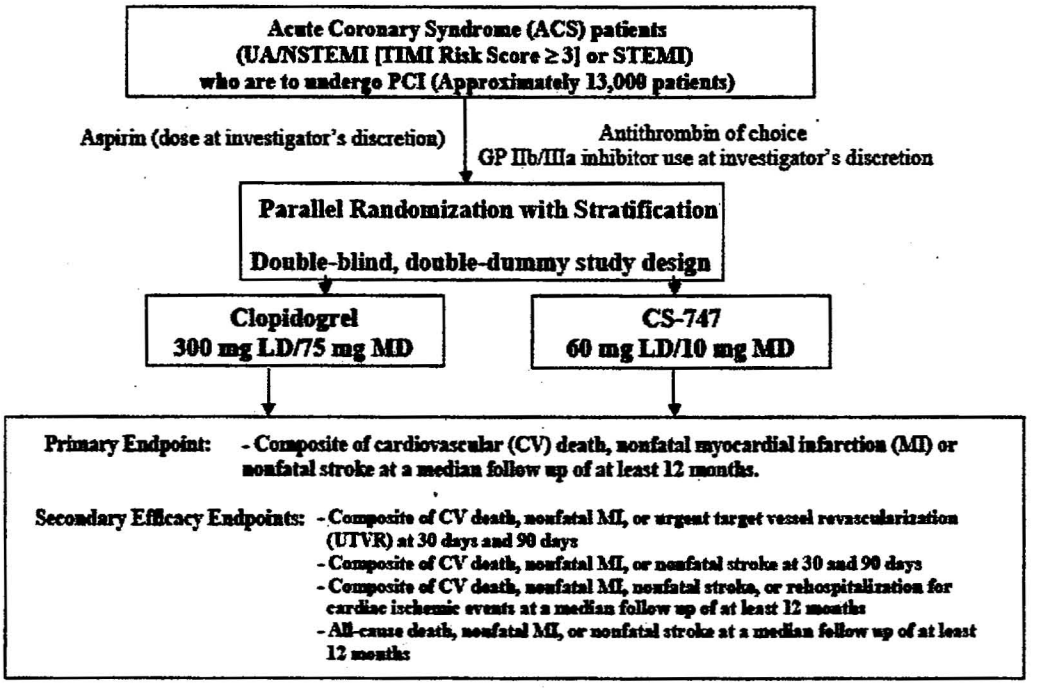
Following screening and informed consent, subjects underwent parallel randomization with stratification as follows:

- Subjects presenting with UA/NSTEMI and those presenting with STEMI > 12 hours after symptom onset were randomized and loaded with study drug after diagnostic angiography confirmed anatomy suitable for PCI only
- Subjects presenting with STEMI ≤ 12 hours after symptom onset (those undergoing primary PCI) were randomized and loaded with study drug at the time of diagnosis and prior to diagnostic angiography

Through an interactive voice response system (IVRS), subjects were randomized in a 1:1 fashion to receive either CS-747 (prasugrel: 60 mg oral loading dose followed by 10 mg daily oral maintenance dose) or clopidogrel (300 mg oral loading dose followed by 75 mg daily oral maintenance dose) using a double-dummy design. The study design is described in Figure 6 and the study treatment plan is displayed in Figure 7.

Additionally, subjects were to receive ASA during the 24 hours prior to PCI (75 to 325 mg oral or 250 to 500 mg intravenous) and for the duration of the study (between 75 mg and 325 mg oral).

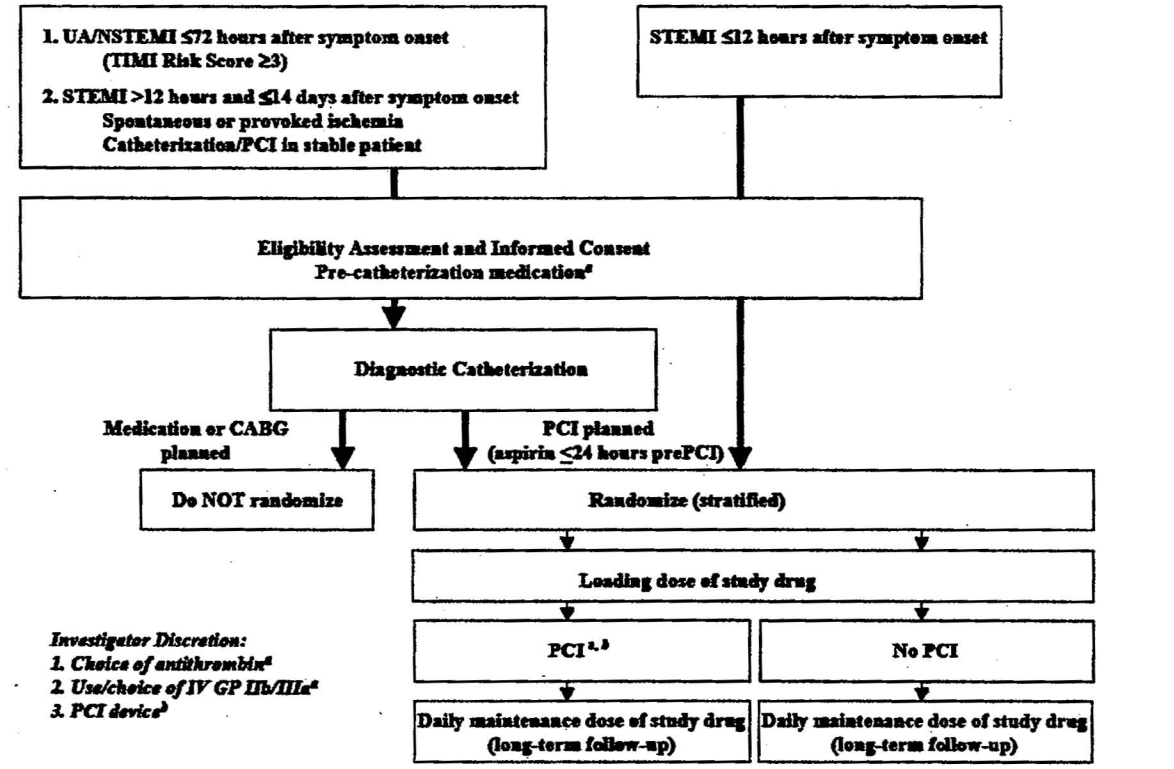
Figure 6. Study H7T-MC-TAAL Study Design



Abbreviations: ACS=acute coronary syndrome; CV=cardiovascular; GP=glycoprotein; LD=loading dose; MD=maintenance dose; MI=myocardial infarction; NSTEMI=non-ST-segment elevation myocardial infarction; PCI=percutaneous coronary intervention; STEMI=ST-segment elevation myocardial infarction; TIMI=The TIMI Study Group; UA=unstable angina; UTVR=urgent target vessel revascularization

(Reproduced from Sponsor, TAAL Clinical Study Report, Figure TAAL.9.1, page 86 of 27024)

Figure 7. Study H7T-MC-TAAL Treatment Plan



Abbreviations: ACS=acute coronary syndrome; CV=cardiovascular; GP=glycoprotein; LD=loading dose; MD=maintenance dose; MI=myocardial infarction; NSTEMI=non-ST-segment elevation myocardial infarction; PCI=percutaneous coronary intervention; STEMI=ST-segment elevation myocardial infarction; TIMI=The TIMI Study Group; UA=unstable angina; UTVR=urgent target vessel revascularization

(Reproduced from Sponsor, Protocol dated January 10, 2006, page 2676)

Subjects were to receive the loading dose of study drug at any time between randomization and the completion of the PCI procedure, defined as ≤ 1 hour of the subject leaving the cardiac catheterization laboratory.

The first maintenance dose was to be administered 20 to 28 hours after the loading dose and subsequent maintenance doses were to be taken in a fed or fasting state.

PCI was to be performed immediately following randomization or at any time within the first 24 hours (maximum of 28 hours) after the loading dose, and prior to the first maintenance dose. At the investigator's discretion, the activated clotting time (ACT) could be used to monitor unfractionated heparin (UFH). If UFH was used with GPIIb/IIIa inhibition, the recommended maximal ACT during PCI was 200 to 250 seconds. If UFH was used with GP IIb/IIIa inhibition, the recommended maximal ACT was 350 seconds.

The choice of antithrombin and dose administered, use and choice of GP IIb/IIIa inhibitors, and choice of device(s) used for PCI were at the discretion of the investigators. Investigational devices were not to be used during PCI. Use of approved closure devices was permissible. It was recommended that intravenous antithrombin therapy be discontinued on completion of the PCI procedure and not restarted. Specific therapy for bleeding, including transfusion with platelets and/or other blood products or discontinuation of concomitant therapy was also at the