



Questions

Prasugrel for ACS

February 3, 2009

DEPARTMENT OF HEALTH AND HUMAN
SERVICES
Public Health Service
Food and Drug Administration

The Advisory Committee is requested to opine on the approvability of prasugrel for the treatment of acute coronary syndromes.

Prasugrel is a thienopyridine that irreversibly blocks P2Y₁₂ receptors that mediate ADP-dependent platelet activation. Its structure and mechanism of action are similar to those of clopidogrel, with which it was compared in the TRITON study.

TRITON was a double-blind study in which 13,608 subjects with acute coronary syndrome (ACS), 10,074 with unstable angina or non-ST elevation myocardial infarction (UA/NSTEMI) and 3534 with ST-elevation myocardial infarction (STEMI), were, at the time of diagnostic percutaneous coronary intervention (PCI), randomized evenly to clopidogrel (300 mg followed by 75 mg per day) or to prasugrel (60 mg followed by 10 mg/day) and followed for a median of 12 months. Subjects all received aspirin.

The primary end point was an intent-to-treat analysis of time to first event of cardiovascular death, MI, or stroke in the UA/NSTEMI group followed by the overall population.

MI, which accounted for most of the end point events, were blindly and centrally adjudicated with triggers from investigator reports, algorithmic searches of biomarker data and adverse events, and the committee's review of source documents.

1. Benefit

Prasugrel was associated with an 18% reduction in the hazard ratio ($p=0.002$) for the primary end point in the UA/NSTEMI population, a 19% reduction in the all ACS population ($p=0.0004$), and a 21% reduction in the STEMI population ($p=0.019$). Half or more of the events occurred within the first few days, and the difference between groups was evident within the first day and either maintained (STEMI) or widened progressively (UA/NSTEMI) through more than a year of follow-up. Most of the first events were MI (77%), and that is where the difference between the groups was most clear, but CV death (20% of events) trended in favor of prasugrel (as did all-cause mortality). Strokes (3% of events) were 0.9% in both groups.

1.1. Was the primary end point reasonable? In particular, comment on the strategy for assessing MI. Ordinarily, the investigator-reported events and the adjudicated events differed little, but, in

TRITON, only about half of the events were identified by investigators. Is there a concern that the additional events, generally asymptomatic peri-procedural MIs, lack clinical significance? What are the long-term consequences of non-fatal myocardial infarction?

- 1.2. Clopidogrel is believed to have benefits on these events compared with placebo. Based on the results of TRITON, can we infer that prasugrel would also be superior to placebo?
- 1.3. Prasugrel was superior to clopidogrel in both UA/NSTEMI and STEMI populations.
 - 1.3.1. Does the Committee agree that these findings are sufficiently robust and the two populations are sufficiently related to support an overall claim for the ACS patient population?
 - 1.3.2. Do the results support a superiority claim for prasugrel to the approved regimen of clopidogrel?
- 1.4. Ninety-four percent of subjects in TRITON received a stent during the index PCI. Definite or probable stent thrombosis was reported for bare metal stents was 1.9% on clopidogrel and 1.1% on prasugrel (40% reduction; $p=0.01$), and for drug-eluting stents, it was 2.0% on clopidogrel and 0.8% on prasugrel (62% reduction; $p<0.001$).
 - 1.4.1. Is the Committee concerned about potential bias in the manner of determining stent thrombosis in TRITON?
 - 1.4.2. Is reduction in stent thrombosis compared to placebo a reasonable claim based on TRITON?
 - 1.4.3. Is reduction in stent thrombosis compared with clopidogrel a reasonable claim based on TRITON?

2. Risk

- 2.1. The primary risk was bleeding, clearly worse on prasugrel.

Hemorrhages in TRITON (All ACS; Kaplan-Meier estimates)

	Prasugrel	Clopidogrel
Fatal	0.36%	0.09%
Life-threatening (including fatal)	1.44%	0.94%
TIMI Major (including life-threatening)	2.43%	1.84%

- 2.1.1. What are the long-term consequences of non-fatal hemorrhage?
- 2.1.2. In both treatment groups, bleeding was most frequent around the time of the index PCI, and much more frequent following CABG. All types of bleeding were more frequent on prasugrel than clopidogrel. Can patients at high risk of requiring CABG be identified prior to dosing? If so, should prasugrel be withheld in such patients?
- After CABG, the major risk factors for major bleeding were prior TIA/stroke ($p=0.0016$), weight <60 kg ($p=0.0027$), treatment with prasugrel ($p=0.0106$), use of GPIIb/IIIa inhibitors ($p=0.0298$), and age >75 ($p=0.0464$).
- 2.1.3. Fewer than 4% of subjects enrolled with prior stroke/TIA. Those randomized to clopidogrel had primary end point events about as often as did clopidogrel subjects with no such history. However, prasugrel subjects with a history of stroke/TIA had primary end point events nearly twice as often as other prasugrel subjects. Should labeling discourage use of prasugrel in patients with a history of stroke/TIA or in whom stroke/TIA develop during treatment with prasugrel?
- 2.1.4. Quintile analyses of primary end point events reveal a fairly uniform advantage of prasugrel over clopidogrel regardless of weight, and suggest no strong relationship between weight and bleeding risk. In contrast, a dichotomous analysis demonstrates a statistically significant increase in bleeding risk for patients <60 kg. What, if anything, should labeling say about use of prasugrel in patients according to weight?
- 2.1.5. GPIIb/IIIa inhibitors were used by about half of all ACS subjects in TRITON. The clinical benefit of prasugrel on the primary end point was similar regardless of GPIIb/IIIa inhibitor use. What, if anything, should labeling say about use of prasugrel in patients according to concomitant GPIIb/IIIa inhibitor?
- 2.1.6. For patients in older age strata, prasugrel showed less benefit over clopidogrel. In addition, older ACS patients in the Study CURE received less benefit from clopidogrel over placebo. What, if anything, should labeling say about use of prasugrel in patients according to age?

2.2. Cancer was somewhat more commonly reported in the prasugrel group than in the clopidogrel group. The strength of association depends largely on whether or not non-melanoma skin cancers are included in the analyses. The pharmacologist and the Carcinogenicity Assessment Committee interpret the preclinical data as not indicative of carcinogenic or tumor growth enhancement. The Division of Oncology Drug Products consultative review concludes that the trend in TRITON was probably spurious.

2.2.1. How strong does the Committee believe the association with cancer to be?

2.2.2. What should labeling say about cancers? Does this merit...

- ...a restriction on use for a limited time?
- ...a box warning?
- ...a section in Warnings and Precautions?
- ...periodic screening?
- ...special mention in adverse events?

2.2.3. What, if any, post-marketing action does the Committee recommend to follow up on the cancer issue?

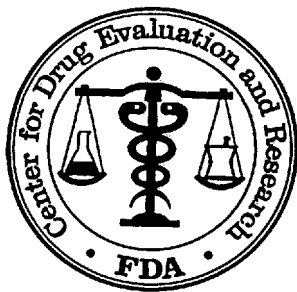
2.3. The prasugrel batches used in TRITON contained varying ratios of salt to free base. In subjects not taking a proton pump inhibitor (PPI), salt and base produce the same exposure. However, at high gastric pH (as on a PPI), prasugrel base produces a lower maximum exposure to its active metabolite. In TRITON, about 41% of subjects were on a PPI at some time, and the benefit of prasugrel was similar in strata using and never using a PPI. Bleeding risk was somewhat higher in subjects on a PPI in both treatment groups, but the relative risk for bleeding on prasugrel compared with clopidogrel was similar in subjects taking a PPI (HR=1.1) and in those never taking a PPI (HR=1.2). To-be-marketed prasugrel is expected to contain no more than 25% base, compared with the 42 to 87% estimated base in batches used in TRITON. What, if anything, should labeling say about this formulation issue?

3. Risk-benefit

3.1. The primary end point results can be described as a net reduction of 22 events (20 MIs and 2 cardiovascular deaths) per 1000 ACS patients treated with prasugrel instead of clopidogrel.

The price in bleeding corresponds to 2 fatal bleeding events, 4 TIMI life-threatening events and an overall excess of 5 TIMI major bleeding events per 1000 ACS patients treated. Even if the risks of hemorrhage could not be mitigated, does the Committee believe that this represents a favorable benefit to risk?

- 3.2. Does the Committee believe that the following restrictions are likely to improve the benefit to risk:
 - 3.2.1. Use around CABG procedures
 - 3.2.2. Patients with prior stroke/TIA
 - 3.2.3. Elderly patients?
- 3.3. VOTE: Should prasugrel be approved to treat patients with acute coronary syndromes, presenting with either UA/NSTEMI or STEMI? After the vote, please comment.
- 3.4. VOTE: Should prasugrel be approved to reduce the incidence of stent thrombosis? After the vote, please comment.



DIVISION OF CARDIOVASCULAR and RENAL PRODUCTS
Revised Secondary CDTL Review

Date: January 9, 2009

NDA: 22-307
EFFIENT™ (prasugrel hydrochloride) Tablets
Eli Lilly and Company

Status: Priority

Submitted: 26 December 2007

Goal Date: 26 June 2008

Reviewer: Ellis F. Unger, M.D.
Deputy Director
Division of Cardiovascular and Renal Products

Through: Norman Stockbridge, M.D., Ph.D.
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To: The File

This secondary review is based, in part, on the primary reviews of:

- Chemistry (Sharmista Chatterjee, Zhengfang Ge, and Kasturi Srinivasachar), May 14, 2008, and August 29, 2008
- Preclinical Pharmacology and Toxicology (Belay Tesfamariam and Albert DeFelice), April 26, 2008
- Clinical Pharmacology and Biopharmaceutics, (Elena V. Mishina, Sripal Mada, Patrick Marroum, Raj Madabushi, Yaning Wang), May 23, 2008
- QT (Suchitra Balakrishnan, Yeh-Fong Chen, Joanne Zhang, Nitin Mehrotra, and Christine Garnett), April 9, 2008
- Clinical (Karen A. Hicks), April 28, 2008
- Clinical Team Leader (Thomas A. Marciniak), December 31, 2008
- Biostatistics (Ququan Liu), April 29, 2008

The legal basis for submission is 505(b)(1).

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1. Background and Introduction

1.1. Background

Prasugrel is a thienopyridine adenosine diphosphate (ADP) receptor antagonist that irreversibly inhibits the platelet P2Y₁₂ receptor, inhibiting platelet activation and aggregation. Prasugrel is a pro-drug that undergoes deacetylation by esterases to form an inactive thiolactone, that is then converted to the active moiety, R-138727, through the cytochrome P450 system. The active metabolites of prasugrel irreversibly inhibit the P2Y₁₂ ADP receptor for the entire lifespan of the platelet (approximately 10 days).

1.2. Indication Sought by Sponsor

“Acute Coronary Syndromes

[Trade Name] (prasugrel hydrochloride) is indicated 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.

[Trade Name] has been shown to reduce the rate of a combined endpoint of cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal stroke.”

1.3. Currently Available Related Drugs for Indication

Clopidogrel bisulfate (PLAVIX and generic) and ticlopidine hydrochloride (TICLID and generic) are ADP receptor antagonists of the thienopyridine class that inhibit platelet activation and aggregation and carry cardiovascular claims:

1. Clopidogrel is indicated for the reduction of atherothrombotic events as follows:

Recent MI, Recent Stroke or Established Peripheral Arterial Disease

For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease...to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.

Acute Coronary Syndrome

For patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-Q-wave MI) including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (with or without stent) or CABG...to decrease the rate of a combined endpoint of cardiovascular death, MI, or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.

For patients with ST-segment elevation acute myocardial infarction, PLAVIX has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction or stroke. This benefit is not known to pertain to patients who receive primary angioplasty.

2. Ticlopidine is indicated:

- To reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke.
- As adjunctive therapy with aspirin to reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation

Ticlopidine carries box warnings for thrombotic thrombocytopenic purpura (TTP), neutropenia/agranulocytosis, and aplastic anemia, and the indication states that the drug “...should be reserved for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy.”

2. Regulatory History and Status

The data submitted in support of the safety and efficacy of prasugrel were developed from studies conducted under IND 63,449, held by Eli Lilly and Company.

The original application was filed December 26, 2007. The important regulatory history has been summarized by others.

(b) (4)

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4. Nonclinical Pharmacology/Toxicology

4.1. Pharmacokinetics and Metabolism

Prasugrel's metabolic pathways are similar in mice, rats, dogs, and humans. Following oral administration, the drug is rapidly absorbed, hydrolyzed by esterases, and metabolized by cytochrome P450 enzymes to form the active metabolite, R-138727. Protein binding of metabolites was high (>80%) in rats and dogs, and binding of the active metabolite was estimated to be 98% in human serum albumin (HSA) solution *in vitro*. Biliary excretion was the major route for elimination of prasugrel and its metabolites in rats and dogs; in mice, elimination was primarily in the urine.

Prasugrel causes induction of cytochrome P450 of phase I and phase II drug metabolizing enzymes, which is consistent with observed decreases in exposure to prasugrel metabolites

after multiple dosing. No specific animal studies were conducted on the effects of induction of drug metabolizing enzymes and interaction with other drugs metabolized via CYP2B and CYP3A.

4.2. Safety Pharmacology

Prasugrel is a prodrug whose active metabolite irreversibly inhibits the platelet P2Y₁₂ receptor, inhibiting ADP-mediated platelet activation and aggregation. Prasugrel is approximately 10- and 100-fold more potent than clopidogrel or ticlopidine, respectively, in inhibiting platelet aggregation, inhibiting thrombus formation, and prolonging bleeding times. The antiplatelet effects of the active metabolites of prasugrel and clopidogrel are approximately equipotent *in vitro*, implying that prasugrel's greater pharmacodynamic effect is related to more extensive formation of its active metabolite, compared to clopidogrel.

Compared with the free base form, oral administration of the prasugrel HCl salt form is associated with approximately 20-30% higher exposure to active metabolites.

Gastric pH is an important determinant of prasugrel absorption after oral administration, and this is particularly true for the free base form. Concomitant administration of PPIs (which increase gastric pH) reduced plasma concentrations of metabolites following oral administration of both forms. Concomitant administration of ranitidine, a histamine H₂ receptor blocker, reduced plasma concentrations of prasugrel metabolites by 30% and 65%, respectively, for the HCl salt and free base forms. Because the gastric pH effects were less pronounced for the HCl salt form, it was selected for further development. The review teams opined that the data suggest that dose adjustment may be warranted during treatment with PPI or H₂ receptor blockers.

Additive or synergistic platelet inhibitory effects that result from co-administration of prasugrel and aspirin were demonstrated in several studies of platelet aggregation (*ex vivo*), thrombus formation (*in vivo*), and bleeding times.

4.3. Genetic Toxicity

No evidence of prasugrel-induced genetic toxicity was observed in standard tests for mutagenicity or clastogenicity that included an *in vitro* bacterial mutation (Ames) test, Chinese hamster lung chromosomal aberration assay, and an *in vivo* mouse micronucleus assay for clastogenicity.

4.4. Carcinogenicity

Carcinogenicity studies in the rat and in the mouse were reviewed by the Pharmacology/ Toxicology Review team, the Executive Carcinogenicity Advisory Committee, and the Medical Team Leader.

4.4.1. Rat

In a 24-month carcinogenicity study in rats, doses as high as 100 mg/kg were administered, and associated with systemic R-138727 and R-106583 exposure up to 1000- and 50-fold higher than the anticipated human exposures, respectively. The highest dose was associated with decreases in body weight, and was considered the maximally tolerated dose (MTD). There was no overall difference in survival between prasugrel and controls in either sex, and no apparent dose-response in terms of excess tumors. Diffuse hepatocyte hypertrophy was observed in both sexes at the high dose (100 mg/kg), as well as increased severity of hepatic eosinophilic foci (in males). These foci were thought to be secondary to induction of drug-metabolizing enzymes. Although such foci are considered to be progenitor lesions from which hepatocellular

neoplasia might arise, there was no evidence of malignant tumors in the 2-year lifetime rat studies. The primary pharmacology/toxicology reviewer, Carcinogenicity Assessment Committee (CAC), and Medical Team Leader agreed with this interpretation.

4.4.2. Mouse

Prasugrel doses up to 300 mg/kg were administered in the 24-month carcinogenicity study in mice, yielding systemic exposures of R-138727 and R-106583 about 500-fold greater than the anticipated human exposures. The highest dose was associated with body weight decreases, and considered the MTD. An increased incidence of hepatocellular adenoma was observed in males in the high-dose group (300 mg/kg) and in females in the mid- and high-dose groups (100 and 300 mg/kg), exposures approximately 190-fold greater than the anticipated human exposure levels. The dose-response relationship for the incidence of hepatocellular adenoma was statistically significant, as was the dose-response relationship for the combined incidences of hepatocellular adenoma and hepatocellular carcinoma. Pairwise comparisons showed statistically significant increases in the incidence of hepatocellular adenoma and combined incidences of hepatocellular adenoma and hepatocellular carcinoma for the high-dose group in males, as well as the mid- and high-dose groups in females, compared to respective controls. Combining male and female groups, the numbers of hepatic adenomas (per 110 animals in each group) were 25 in the control group, versus 16, 46, and 83 in the prasugrel 50, 100, and 300 mg/kg/day groups, respectively. The numbers of hepatocellular carcinomas were 12 in the control group, versus 16, 15, and 21 in the prasugrel 50, 100, and 300 mg/kg/day groups, respectively. The Executive Carcinogenicity Advisory Committee concluded that the mouse study was adequate, and positive for hepatocellular adenomas in both sexes. In their minutes, the Committee did not comment on the trend for increased hepatocellular carcinomas in the high-dose group. The Medical Team Leader also noted weak associations between prasugrel exposure and both intestinal and lung cancers in the mouse study.

4.5. Reproductive Toxicology

There was no significant effect of prasugrel on male or female fertility or on early embryonic development at oral doses up to 100 mg/kg (30 times human exposure). At doses ≥ 100 mg/kg, decreases in adrenal gland, seminal vesicle/prostate gland, and epididymal weights were observed, as well as a reduction in mean fetal weight. Dose-associated maternal toxicity and decreases in fetal weight were observed; however, there were no adverse effects on *in utero* survival or morphological development of the conceptus at 100 mg/kg dose. There was no evidence of teratogenicity, based on the absence of changes in the frequency of external, visceral, and skeletal anomalies (100 times human exposure). Placental transfer of prasugrel metabolites to the fetus of pregnant rats was low. However, ^{14}C -prasugrel was excreted in the milk of lactating rats.

4.6. Summary of Major Pharmacology-Toxicology Issues

Toxicology studies identified the liver as a target organ, with increases in liver mass, hepatocellular hypertrophy, elevations of alkaline phosphatase, and proliferation of smooth endoplasmic reticulum. There were tendencies for increased incidence of eosinophilic altered cell foci in the higher dose groups, thought to be consequence of induction of hepatic drug-metabolizing enzymes. Such altered cell foci are progenitor lesions that are thought to have the potential to lead to hepatocellular neoplasia. In the mouse, at exposures approximately 190 times higher than those anticipated in humans, there was, in fact, a statistically significant dose-response relationship for hepatocellular adenoma. Though not statistically significant, there was a trend in favor of increased hepatocellular carcinomas at the highest dose, with 12 in the

control group, and 16, 15, and 21 in the prasugrel 50, 100, and 300 mg/kg/day groups, respectively (per 110 animals in each group).

The Pharmacology/Toxicology Team and the Executive Carcinogenicity Advisory Committee concluded that the 2-year rat and mouse studies were reassuring, and found no evidence of a prasugrel-associated increase in malignant tumors in either species. Overall, although inconclusive, they regarded the hepatic findings to be consistent with induction of hepatic drug metabolizing enzymes.

No genetic toxicity was observed for prasugrel in standard tests that included an *in vitro* bacterial mutation test, Chinese hamster lung chromosomal aberration assay, and *in vivo* mouse micronucleus test.

Prasugrel did not cause any significant effects on fertility, early embryonic development, embryo-fetal development, or pre-/postnatal development in the rat or rabbit (approximately 30 times human exposure). At doses high enough to cause effects on maternal body weight and/or food consumption, there was a slight decrease in offspring body weight relative to controls. Placental transfer of prasugrel metabolites to the fetus of pregnant rats was low. ¹⁴C-prasugrel was excreted in the milk of lactating rats.

4.7. Pharmacology Toxicology Reviewer's Recommendations

"The extent and scope of the pharmacological and toxicological documentation provided are appropriate to support the clinical use of prasugrel at daily oral dose of 10 mg.

Adequate exposure was obtained in the toxicology studies, and all circulating metabolites in humans occurred in the circulation of species used in the non-clinical toxicity studies. The non-clinical studies adequately address the safety of prasugrel.

The proposed prescribing information includes an appropriate description of the genotoxicity, animal carcinogenicity studies, developmental and reproductive studies, and appropriate advice on breast feeding."

5. Clinical Pharmacology/Biopharmaceutics

5.1. Absorption, Distribution, Metabolism, Excretion

More than 79% of an oral dose of prasugrel is absorbed. The pro-drug is rapidly hydrolyzed by intestinal hydroxysterases to a thiolactone, which is then converted to the active metabolite by a single step, primarily by CYP3A4 and CYP2B6, and to a lesser extent by CYP2C9 and CYP2C19. The parent drug cannot be detected in plasma. Absorption and metabolism are both rapid; peak plasma concentrations of the active metabolite are reached approximately 30 minutes after administration. Exposure to the active metabolites increases slightly more than proportionally over the therapeutic dose range. The administration of repeated doses of 10 mg does not lead to the accumulation of the active metabolite.

In subjects with stable atherosclerosis, estimates of the apparent volume of distribution of prasugrel's active metabolite ranged from 30-84 L, and estimates of apparent clearance ranged from 73-266 L/hr.

Binding of the active metabolite to plasma proteins was not determined *in vivo*, but was highly bound *in vitro*. The inactive metabolites are also highly bound to human plasma proteins.

Prasugrel is cleared both by the liver and the kidney: about 68% of the prasugrel dose is excreted in the urine and 27% in the feces, as inactive metabolites. The active metabolite R-138727 has an elimination half life of about 7.4 hours (range 2 to 15 hours).

The active metabolite contains 2 chiral centers; therefore, there are 4 enantiomers: (R,S), (R,R), (S,R), and (S,S). The R- and S-configurations at the 1' position interconvert *in vivo*. Thus, the 4 enantiomers of R-138727 can be considered to be 2 pairs: (R,S)/(R,R) and (S,R)/(S,S). Each possesses different activity towards the platelet P2Y₁₂ ADP receptor; however, the ratio of enantiomers was consistent across subjects. Thus, variation in enantiomeric ratios is not important in interpreting the clinical data. The (R,R)/(R,S) pair comprises about 84% of the total active metabolite, and is the most potent.

5.2. Demographic Interactions/Special Populations

5.2.1. Body Weight

Exposure of R-138727 increased with decreasing body weight. Major bleeding (Thrombolysis in Myocardial Infarction [TIMI] major bleeding - any intracranial hemorrhage, or bleeding requiring intervention associated with a decrease in hemoglobin [Hgb] ≥ 5 g/dL) was 2-fold higher in subjects weighing less than 60 kg, but efficacy was similar across body weight groups. The sponsor proposes a reduction in the maintenance dose from 10 mg to 5 mg in subjects weighing less than 60 kg, and the Clinical Pharmacology team concurs with this recommendation.

5.2.2. Gender

The data do not support a rationale for dose adjustment based on sex, and none is recommended.

5.2.3. Pediatric Patients

The pharmacokinetics of prasugrel were not studied in pediatric subjects, and no recommendations are supported.

5.2.4. Advanced Age

Advanced age is an important predictor of morbidity and mortality in the ACS patient population. Likewise, age is an important predictor of bleeding in this patient population. The sponsor proposed prasugrel dose reduction in patients over the age of 75. The Clinical Pharmacology review team does not agree with this plan.

Whereas the hazard ratio (HR) was 0.78 in favor of prasugrel (versus clopidogrel) in preventing the primary triple endpoint in subjects less than 75 years of age, efficacy of the two drugs was similar (HR statistically indistinguishable from 1) for subjects over 75. For TIMI Major bleeding, the HR favored clopidogrel, and was similar for subjects less than and greater than age 75 years (hazard ratios of 1.47 and 1.23, respectively). Thus, a reduction in dose might lessen bleeding in patients over 75 years of age, the impact of dose reduction on efficacy is unknown, and could be unfavorable. Therefore, the Clinical Pharmacology team opined against a dose reduction for patients over the age of 75.

5.2.5. Race

Exposure to prasugrel's active metabolite in Caucasian, African, and Hispanic subjects was similar; however, exposure was approximately 40-45% higher in Asian versus Caucasian subjects. After adjusting for body weight and other covariates, C_{\max} and $AUC(0-t_{\text{last}})$ were still

20% higher in Asians than in Caucasians. Although there was considerable variability in the IPA response, IPA was generally higher in Asian subjects than in Caucasians. Consistent with these disparities in pharmacokinetics and pharmacodynamics, the highest incidence of bleeding-related adverse events was reported for Korean subjects. In light of the above, the Clinical Pharmacology team recommended advice in labeling to the effect that prasugrel should be administered with caution in patients of Asian descent.

5.2.6. Renal Impairment

There were too few subjects in the development program with end-stage renal disease (ESRD) to draw firm conclusions regarding pharmacokinetics or pharmacodynamics in this patient population. After 60 and 10 mg doses of prasugrel, the exposure to R-138727 (both C_{max} and $AUC[0-t_{last}]$) decreased by half in subjects with ESRD compared to that in healthy controls and subjects with moderate renal impairment. The sponsor concluded that the differences in platelet aggregation between subjects with renal impairment and healthy matched subjects at each time point were not statistically significant. However, given the limited sample size, it is difficult to draw conclusions regarding platelet aggregation in patients with ESRD. Bleeding events were not assessed in these studies. The Clinical Pharmacology Review team recommended a contraindication for prasugrel in patients with ESRD. Of note, a contraindication in this patient population would be unusual. More typically, the package insert would note that experience is limited in this patient population.

5.2.7. Hepatic Impairment

The PK parameters estimated for the active metabolite were similar in healthy subjects and subjects with moderate hepatic impairment. The pharmacodynamic response measured as maximum platelet aggregation to 20 mcM ADP was similar as well.

A dose adjustment is not required for the patients with mild and moderate hepatic impairment.

The Clinical Pharmacology/Biopharmaceutics review team opined that prasugrel should be contraindicated in patients with severe hepatic impairment due to the potential risk of bleeding.

5.3. Extrinsic Factors

5.3.1. Food Effects

In Study TAAF, when a single 15-mg prasugrel dose was co-administered with a high-fat high-calorie meal, C_{max} of the active metabolite was reduced by nearly half (49%), and T_{max} was delayed from 0.5 to 1.5 hours. The extent of absorption (AUC) was unaffected. Because patients undergoing PCI are generally fasting, the review team opined that prasugrel can be administered without regard to food. More properly, the label should state that the drug should be administered in the fasting state.

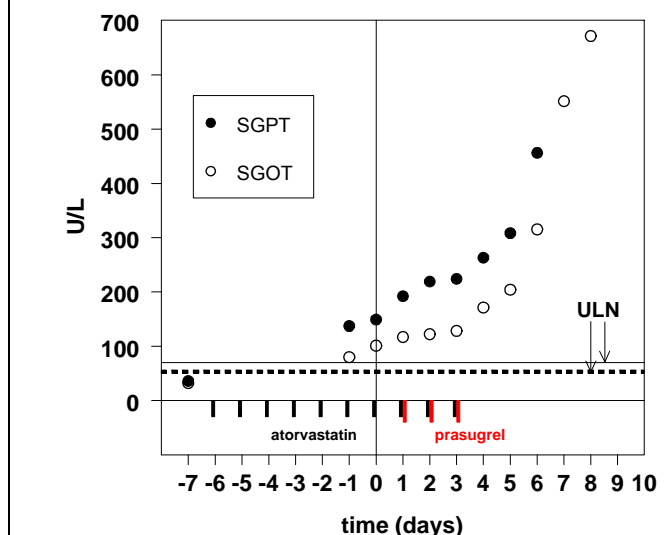
5.3.2. Drug-Drug Interaction Information

There were no clinically important drug-drug interactions with a CYP3A4 inhibitor (ketoconazole), a CYP3A4 inducer (rifampicin), or a CYP2B6 substrate (bupropion). Conversely, a clinically significant pharmacodynamic drug-drug interaction, prolongation of the bleeding time, was observed when prasugrel was co-administered with aspirin, heparin, and warfarin. Caution should be exercised when these drugs are co-administered with prasugrel.

Although the pharmacokinetic interactions between atorvastatin and prasugrel are limited, acute liver failure was reported in one subject who received prasugrel and atorvastatin in a PK study.

Subject 115, a 59 year-old male in the 2-period PK study TAAV, received prasugrel alone in a Period 1 without untoward effects. In Period 2, he received atorvastatin 80 mg QD, day -6 to 3, per protocol. Hepatic transaminases were elevated to 2-3X ULN on Day -1, after receipt of 5 doses of atorvastatin, and prior to receiving his initial dose of prasugrel (Figure 1). A 60-mg LD of prasugrel was administered on Day 1, and MDs of 10-mg were administered on Days 2 and 3. Upon receipt of the serum biochemistry results on Day 3, a further increase in the subject's liver enzymes was evident and both drugs were discontinued. The increases in liver enzymes resolved after approximately 56 days (not shown).

Figure 1: Transaminase Elevations in TAAV Subject 115



In this subject, the transaminases were moderately elevated on Days -1 and 0. The additional increase observed on Days 1, 2, and 3 occurred before administration of prasugrel (the Day 1 sample was obtained in the early morning hours, and so could not have been affected by the initial prasugrel LD, administered that day). The more striking increases in transaminases (Day 4 and beyond) might have occurred as a result of atorvastatin alone, even in the absence of prasugrel. Thus, given this uncertainty, and given that this occurred in only a single subject, this secondary reviewer does not believe that any specific advice is appropriate or necessary for labeling.

The potential role of prasugrel as a Pgp substrate was not evaluated in this NDA. Co-administration of prasugrel with digoxin reveals that prasugrel is not an inhibitor of Pgp. Digoxin clearance was not affected by prasugrel co-administration, and no dose adjustment is needed for digoxin when co-administered with prasugrel.

5.4. Exposure-Response Relationships

The sponsor based dose selection for the pivotal trial primarily on the effect of prasugrel on the inhibition of platelet aggregation (IPA) and bleeding, compared to clopidogrel, in subjects with stable atherosclerosis. In Study TAAV, 4 prasugrel regimens were compared with the approved clopidogrel regimen: prasugrel 40-mg loading dose (LD)/5-mg maintenance dose (MD); 40-mg LD/7.5-mg MD; 60-mg LD/10-mg MD; 60-mg LD/15-mg MD; clopidogrel 300-mg LD/75-mg MD. Both the 40-mg and 60-mg prasugrel LDs resulted in more rapid onset with significantly greater IPA than the 300-mg LD of clopidogrel. The 60-mg prasugrel LD consistently achieved the highest IPA. Both the 10- and 15-mg prasugrel MDs achieved consistent and significantly greater IPA than the 75-mg clopidogrel MD. However, the 15-mg MD was associated with more bleeding.

The phase 2 Study TAAH assessed bleeding events associated with three regimens of prasugrel (40 mg LD + 7.5 mg daily MD, 60 mg LD + 10 mg daily MD, or 60 mg LD + 15 mg daily MD), versus a standard regimen of clopidogrel (300 mg LD + 75 mg daily MD) in subjects undergoing urgent or elective PCI. The results of the study are described in Section 6, below.

5.5. Form Conversion from Salt to Base

5.5.1. Bioequivalence of Prasugrel – Low, Medium, and High Salt-to-Base Conversion

The sponsor conducted two bioequivalence studies wherein they compared the bioavailability of lots with low (5%), intermediate (58%), and high (70%) degrees of conversion to base, with and without co-administration of a PPI (lansoprazole) to raise gastric pH. The sponsor concluded that up to 70% conversion from salt to free base was clinically acceptable in patients, both with and without concomitant PPI use; however, the agency's clinical pharmacology reviewer did not concur.

- When prasugrel 60-mg was administered without a PPI:
Prasugrel lots with low, intermediate, and high salt to base conversion were bioequivalent with respect to R-138727, prasugrel's active moiety. This was true with respect to both C_{max} and area under the curve (AUC).
- When prasugrel 60-mg was administered on a background of lansoprazole:
Prasugrel lots with low, intermediate, and high salt to base conversion were still bioequivalent for R-138727 with respect to AUC, but *were not bio-equivalent with respect to C_{max}* (Table 1). The mean difference in C_{max} between the low and the high conversion lots was 29% (90% confidence interval [C.I.] 17%, 38%), and there was a 20% difference in C_{max} between the medium and high conversion lots (90% C.I. 8%, 31%). There was no statistically significant difference in C_{max} for the low and medium conversion lots.

Table 1: Relative Bioavailability of R-138727, the Active Moiety of Prasugrel – Comparison of Low, Medium, and High Extents of Conversion with Background 30-mg Lansoprazole (sponsor's table TACS 7.2)

Geometric least square means (90% CI)			Ratio of means (90% CI)		
prasugrel-LC	prasugrel-MC	prasugrel-HC	M-C/LC	H-C/L-C	H-C/M-C
AUC(0-t_{last}) (ng•h/mL)					
470 (424, 522)	467 (421, 518)	409 (368, 454)	0.99 (0.93, 1.06)	0.87 (0.82, 0.93)	0.88 (0.82, 0.93)
C_{max} (ng/mL)					
331 (285, 384)	297 (257, 344)	236 (204, 274)	0.90 (0.77, 1.04)	0.71 (0.62, 0.83)	0.80 (0.69, 0.92)

LC ≡ low conversion; MC ≡ medium conversion; HC ≡ high conversion

5.5.2. Pharmacodynamics of Prasugrel – Low, Medium, and High Salt-to-Base Conversion

Analysis of the pharmacodynamics of prasugrel in the presence and absence of PPI provides insight into the potential consequences of these differences in C_{max} . The effects of thienopyridines on platelet aggregation last for the life of a platelet and are concentration-dependent. A delay in reaching C_{max} , i.e., a lengthened T_{max} or a lower C_{max} , could delay the full effect of the drug on platelet aggregation. For the 60-mg prasugrel loading dose, these differences translated into absolute disparities in inhibition of platelet aggregation (IPA) of

approximately 20% at 0.5 hours post-dose (high versus low- or medium-salt-to-base conversion) and 12% at 1 hour post-dose, when prasugrel is given on a background of lansoprazole (Figure 2). Thus, at the time points that bracket T_{max} , the high salt-to-base conversion lots are not bio-equivalent to lots with medium or low conversion. However, at subsequent time points (2, 4, and 24 hours post-dose), inhibition of platelet aggregation continued to increase, such that IPA was virtually identical with lots of all degrees of conversion by two hours (Figure 2). In essence, therefore, the bioinequivalence results in a delay of perhaps 20 minutes in achieving maximal inhibition of platelet aggregation. This is manifested only with the high salt-to-base conversion product, and only in the presence of PPI or H2 receptor antagonists.

5.5.3. Relevance of Altered Pharmacodynamics of High Salt-to-Base Conversion

Because PCI may precipitate periprocedural myocardial infarction, a considerable number of events occur very soon after PCI. As a case in point, in TAAL, of all the non-fatal myocardial infarctions recorded during the course of the 15-month study, *30% of them occurred within the first hour of the study!* Clearly, therefore, rapid inhibition of platelet aggregation may be important in preventing periprocedural MIs, and the delay in achieving inhibition of platelet aggregation resulting from use of the high salt-to-base conversion product in the presence of PPIs or H2 receptor blockers has at least the potential to be clinically meaningful.

However, to understand fully the significance of the delay, it is important to contrast the prasugrel's overall IPA activity to that of clopidogrel. Figure 3 shows the IPA in response to 20 μ M ADP for subjects who received prasugrel versus clopidogrel from Study TAAJ (loading and daily maintenance doses). Although prasugrel lots with high salt-to-base conversion exhibit delayed inhibition of platelet aggregation in the presence of high gastric pH, the difference seems negligible when placed into context with the effect of clopidogrel, at least on a population basis. Prasugrel has a markedly higher IPA than clopidogrel at all time points following administration.

Figure 2: Inhibition of Platelet Aggregation (IPA) to 20 μ M ADP, Following 60-mg Prasugrel: Lots with Low, Medium, and High Extents of Salt-to-Base Conversion on Background of Lansoprazole 30-mg (* $p < 0.01$, high conversion versus low or medium conversion, mean \pm SD; calculated by CDER, Study TACS)

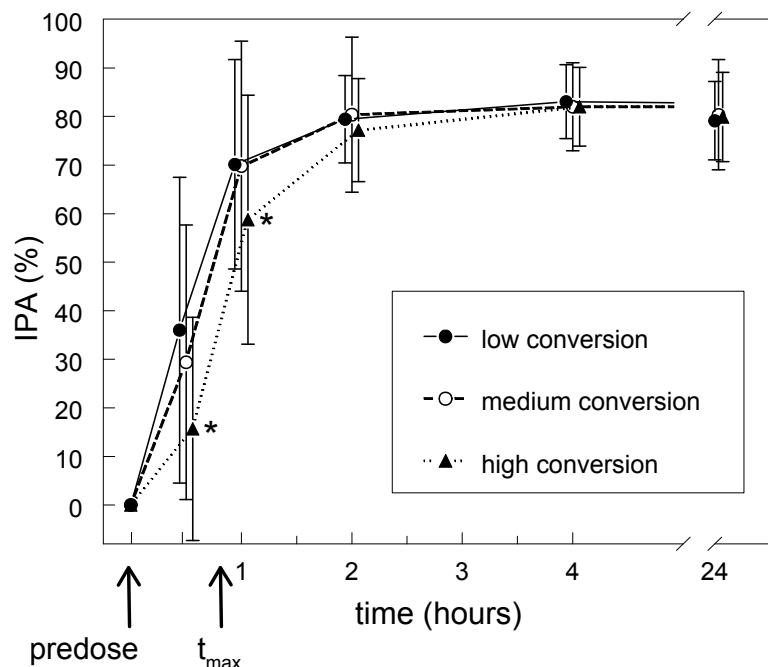
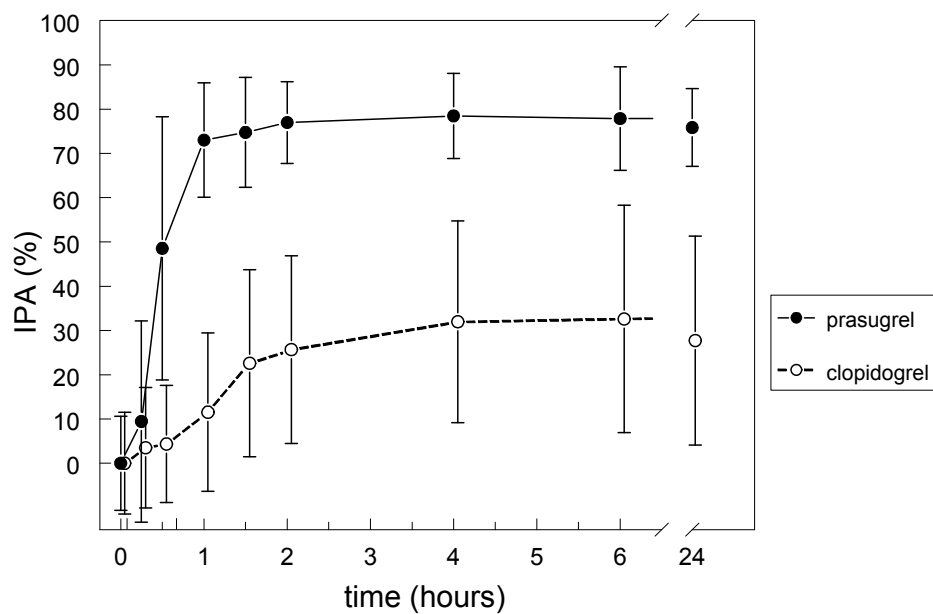


Figure 3: Inhibition of Platelet Aggregation (IPA) to 20 μ M ADP, Following Loading Doses of Prasugrel 60 mg or Clopidogrel 300 mg (from Study TAAJ, mean \pm SD)



6. Dose Identification/Selection and Limitations

In retrospect, the rationale for dose selection for the phase 3 study seems only questionably adequate. Although the tested prasugrel regimen proved superior to clopidogrel in terms of endpoint events in the phase 3 study, it is unknown whether a lower dose would have achieved a more favorable risk-benefit profile, with similar efficacy but lower rates of bleeding.

The identification for dose selection for the phase 3 study was largely accomplished through a small study of IPA (Study TAAD, see 5.4, described above), and a medium-sized phase 2 study (TAAH).

Study TAAH, “A Double-Blind, Randomized, Multicenter, Dose-Ranging Trial of CS-747 (LY640315) Compared With Clopidogrel in Subjects Undergoing Percutaneous Coronary Intervention” assessed the bleeding events associated with three regimens of prasugrel. Subjects undergoing urgent or elective PCI were randomized to receive prasugrel 40 mg LD + 7.5 mg daily MD, prasugrel 60 mg LD + 10 mg daily MD, prasugrel 60 mg LD + 15 mg daily MD, or a standard regimen of clopidogrel (300 mg LD + 75 mg daily MD). Subjects were treated for one month, and the study was powered to detect two-fold increases in the risk of bleeding, assuming that the bleeding rate in the clopidogrel group would be >5%.

Rates of significant (TIMI major + TIMI minor) bleeding were much lower than anticipated, and statistically indistinguishable between the treatment groups. The rates at Day 30 were 1.5%, 2.0%, 1.6%, and 1.2% in the prasugrel 40/7.5, 60/10, 60/15, and clopidogrel 300/75 groups, respectively. (These percentages reflect only 3 or 4 events in each group). In terms of effect, rates of major adverse cardiac events (MACE) were similar in all prasugrel groups: 7.5% in the 40/75 and 60/10 groups; 6.8% in the 60/15 group. The rate of MACE was 9.4% in the clopidogrel group (P=NS versus pooled prasugrel). In short, neither bleeding rates nor MACE rates provided a firm foundation for dose selection.

The sponsor’s rationale behind dose selection for the phase 3 study is paraphrased from the TAAL study protocol:

- In TAAH, prasugrel 60/10 or 60/15 resulted in a consistent trend towards reduced 30-day MACE compared with clopidogrel.
- In TAAH, the prasugrel 60/10 or 60/15 regimens were not associated with significant increases in 30-day bleeding rates compared with clopidogrel.
- Based on dose-ranging studies in subjects with stable coronary disease and subjects undergoing elective or urgent PCI, the 10-mg MD of prasugrel did not result in higher rates of TIMI Minimal bleeding and/or non-TIMI bleeding episodes (for example, no increase in epistaxis or oral bleeding) compared with the 75-mg MD of clopidogrel.

Thus, a 60-mg LD followed by a 10-mg once-daily MD was selected for the registrational trial (TAAL) based on the results of TAAH and TAAD. Importantly, however, the sponsor’s decision was based on weak trends in the data and a handful of events, rather than statistical certainty. It is possible that a lower prasugrel dose would have resulted in similar efficacy with less risk of bleeding, but the development program does not assess this possibility.

7. Clinical/Statistical – Phase 3 Clinical Study Essential to Regulatory Decision

Study TAAL: “A Comparison of CS-747 and Clopidogrel in Acute Coronary Syndrome Subjects who are to Undergo Percutaneous Coronary Intervention/TIMI 38.”

7.1. Design/Protocol Study TAAL

Study TAAL was a Phase 3, multinational, randomized, double-blind, double-dummy, active-controlled study in subjects with acute coronary syndrome (ACS), who were scheduled to undergo PCI. The primary objective of the study was to test the hypothesis that prasugrel plus aspirin is superior to clopidogrel plus aspirin in the treatment of these subjects, as measured by a reduction in the composite endpoint of cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal stroke (to be referred to as the “triple endpoint” in this review document), at a median follow-up of ≥ 12 months. The study involved 717 principal investigators at 725 study centers (8 investigators oversaw 2 study sites, each) in 30 countries.

The 1^o endpoint (triple endpoint) was to be analyzed first in subjects with unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI), followed by the entire group of ACS subjects (UA/NSTEMI and ST-segment elevation myocardial infarction [STEMI]).

7.1.1. Study population

For inclusion, subjects must have presented with ACS (based on the disease diagnostic criteria, below), and have been scheduled to undergo PCI.

Disease Diagnostic Criteria:

ACS was to include: 1) moderate to high risk UA and NSTEMI; and 2) STEMI, as follows:

- Moderate to high risk UA \equiv history of chest discomfort or ischemic symptoms of ≥ 10 minutes duration at rest ≤ 72 hours prior to randomization, with persistent or transient ST-segment deviation ≥ 1 mm in one or more electrocardiogram (ECG) leads without elevation of creatine kinase muscle-brain (CK-MB) or troponin T or I but with a TIMI Study Group (TIMI) risk score ≥ 3
- Moderate to high-risk NSTEMI \equiv history of chest discomfort or ischemic symptoms of ≥ 10 minutes duration at rest ≤ 72 hours prior to randomization with no evidence of persistent ST-segment elevation. Subjects must also have CK-MB or troponin T or I greater than the upper limit of normal (ULN) and a TIMI risk score ≥ 3 . If neither CK-MB nor troponin were available, total CK $> 2 \times$ ULN was acceptable.
- STEMI \equiv history of chest discomfort or ischemic symptoms of >20 minutes duration at rest ≤ 14 days prior to randomization with one of the following present on at least one ECG prior to randomization: a) ST-segment elevation ≥ 1 mm in two or more contiguous ECG leads; b) new or presumably new left bundle branch block (LBBB); c) ST-segment depression ≥ 1 mm in two anterior precordial leads (V1 through V4) with clinical history and evidence suggestive of true posterior infarction.

Subjects receiving alteplase, reteplase, or tenecteplase could have been randomized ≥ 24 hours after completion of infusion; subjects receiving streptokinase (no longer marketed in the US) could have been randomized ≥ 48 hours after completion of infusion.

Key exclusion criteria (subjects must have met none):

- Cardiovascular:
 - cardiogenic shock
 - refractory ventricular arrhythmias
 - New York Heart Association (NYHA) Class IV congestive heart failure (CHF)
- Bleeding:
 - Receipt of alteplase, reteplase, or tenecteplase < 24 hours prior to randomization (study entry ≥ 24 hours after completion of infusion allowed)
 - Receipt of streptokinase (no longer marketed in the US) < 48 hours prior to randomization (study entry ≥ 48 hours after completion of infusion allowed)
 - active internal bleeding or history of bleeding diathesis
 - history of hemorrhagic stroke, ischemic stroke ≤ 3 months prior to screening, intracranial neoplasm, arteriovenous malformation, or aneurysm
 - International Normalized Ratio (INR) > 1.5
 - platelet count < 100,000/mm³
 - anemia (hemoglobin [Hgb] < 10 gm/dL)
- Prior/Concomitant Therapy
 - Receipt of a thienopyridine (ticlopidine or clopidogrel) ≤ 5 days prior to PCI
 - Receipt of oral anticoagulation or other antiplatelet therapy that cannot be safely discontinued for the duration of the study
 - Receipt of daily nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX2) inhibitors that cannot be discontinued, or anticipated to require > 2 weeks of daily treatment during the study.
- General
 - Females known to be pregnant, ≤ 90 days post-partum, or breastfeeding
 - Severe hepatic dysfunction (i.e., cirrhosis or portal hypertension)

7.1.2. Randomization

Subjects were randomized 1:1 to either prasugrel (60-mg load; 10-mg daily maintenance) or clopidogrel (300-mg load; 75 mg daily maintenance) via an interactive voice response system (IVRS). Randomization was carried out at the site level and stratified by clinical presentation: UA/NSTEMI versus STEMI. Subjects who presented with STEMI within 12 hours of symptom onset (in whom 1° PCI was planned) could be randomized at the time of diagnosis, prior to diagnostic arteriography. All other subjects could be randomized only after diagnostic coronary arteriography confirmed anatomy suitable for PCI.

The study employed a double-dummy design, with subjects receiving the active formulation of one drug and placebo formulation of the other. The LD of the study drug was to be administered at any time between randomization and completion of the PCI (defined as no more than 1 hour after the subject left the catheterization laboratory). The LD consisted of 10 tablets: either six prasugrel 10-mg tablets and four clopidogrel placebo tablets, or four clopidogrel 75-mg tablets and six prasugrel placebo tablets. The subject and all site personnel were blinded to identity of the study drug and placebo. Clopidogrel was supplied as Plavix, Sanofi-Synthelabo.

The initial maintenance dose was to be administered within 20 to 28 hours of the LD, with subsequent maintenance doses administered once daily.

7.1.3. Concomitant Therapies

- Aspirin was to be administered (75-325 mg PO or 250-500-mg IV) within 24 hours prior to the index PCI.
- GPIIb/IIIa inhibitors were permitted before randomization, as well as during and after PCI. Decisions regarding use of a GPIIb/IIIa inhibitor, choice of agent, dose, and duration of therapy were left to investigators' discretion, and were to reflect contemporary practice.
- Antithrombin therapy was to be administered to all subjects as part of standard of care, with the choice of specific agent left to the judgment of the investigator. If unfractionated heparin was used without a GPIIb/IIIa inhibitor, the target for maximal activated clotting time (ACT) during PCI was 350 seconds. If unfractionated heparin was given with a GPIIb/IIIa inhibitor, the target ACT was 200-250 seconds.
- Fibrinolytic therapy was permitted for re-infarction or other indications after the index PCI, if deemed necessary by the investigator. Study drug could be temporarily discontinued at the investigator's discretion if thrombolytic therapy was instituted.
- GPIIb/IIIa inhibitors, antithrombin therapy, and fibrinolytic agents could be discontinued for bleeding events. The study drug could be temporarily discontinued for up to 14 days, or longer is necessary.
- Other medications permitted at the discretion of the treating physician included: H2 receptor blockers, PPIs, nitrates, calcium channel blockers, beta blockers, angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), statins, anti-arrhythmic drugs, vasodilators, and intravenous vasopressors.

7.1.4. Monitoring

Subjects were evaluated at 24 hours post-PCI or hospital discharge, Days 30, 90, 180, 270, 360, and 450 (or last visit). At each visit, subjects were queried for adverse events and concomitant medications. In addition, each visit included assessments of vital signs, a targeted physical examination, ECG, complete blood count, platelet count, and clinical chemistries.

Primary efficacy endpoint: was a composite of CV death, nonfatal MI, or nonfatal stroke ("triple endpoint") at a median of 12 months follow-up.

Secondary endpoints: were to compare prasugrel with clopidogrel with respect to:

- Composite of CV death, nonfatal MI, nonfatal stroke or urgent target vessel revascularization (UTVR) at Day 30 (this endpoint per protocol, section 6.1.2.; however, endpoint in Statistical Plan omits nonfatal stroke [section 8.2])
- Composite triple endpoint at Day 30
- Composite of CV death, nonfatal MI, or UTVR at Day 90
- Composite triple endpoint at Day 90
- Composite triple endpoint or re-hospitalization for cardiac ischemic events at a median of ≥ 12 months
- Composite of all-cause mortality, nonfatal MI, or nonfatal stroke at a median of ≥ 12 months

- Definite or probable stent thrombosis per Academic Research Consortium (ARC) definition at study end

The 2° endpoints were to be analyzed in both the UA/NSTEMI and entire ACS populations.

7.1.5. Definitions

- CV death \equiv death due to documented cardiovascular cause. In addition, death not clearly attributable to non-CV causes was considered to be CV death.
- Nonfatal MI: The definition of MI was adapted from the American College of Cardiology (ACC) definition and dependent on the timing of the event in relation to the presenting syndrome and cardiovascular procedures.

Peri-procedural events must have been temporally distinct from the index event. If cardiac biomarkers were elevated at the onset of a suspected event, there must have been evidence of a falling biomarker level prior to the event, and the subsequent peak must have exceeded 1.5 times the value prior to the event.

The biomarker levels required for the diagnosis of MI were dependent on the temporal relationship to cardiac procedures:

- If the suspected event was within 48 hours of a PCI, the CK-MB value must have been $> 3X$ the ULN on ≥ 2 samples; symptoms were not required. A January 10, 2006 amendment extended the definition of peri-procedural MI to include a CK-MB $> 5X$ ULN on one sample if it was the last available sample and was drawn ≥ 12 hours after PCI.
- If the suspected event was within 48 hours of a CABG, the CK-MB value (on a single measure) must have been $> 10X$ the upper limit of normal; no symptoms were required.
- If the suspected event was not within 48 hours of a PCI or CABG, the diagnostic criteria for MI were met if the subject had CK-MB or cardiac troponin $> ULN$ and the presence of either chest pain ≥ 20 minutes in duration or ST-segment deviation $\geq 1mm$.

The appearance of new Q-waves distinct from a prior event (including the presenting event) or pathologic evidence (such as autopsy) showing a new MI thought to be distinct from a prior event was considered evidence for MI, as was ST segment elevation (meeting enrollment criteria) lasting for at least 20 minutes and accompanied by ischemic chest pain or hemodynamic decompensation.

Five major sets of criteria were used for diagnosis of nonfatal MI:

1. ST elevation or re-elevation, and either ischemic chest pain ≥ 20 minutes in duration or hemodynamic decompensation.
2. Spontaneous CK-MB or troponin $> ULN$, and ischemic chest pain (or anginal equivalent) ≥ 20 minutes in duration or ST segment deviation ≥ 1 mm in one or more leads
3. CK-MB $> 3X$ ULN on ≥ 2 samples following PCI
4. CK-MB $> 10X$ ULN on one sample following CABG

5. New Q waves ≥ 0.04 seconds, or pathology distinct from prior MI

ECGs and other supporting clinical tests and evaluations were to be centrally adjudicated by a Clinical Endpoints Committee (CEC).

- Nonfatal Stroke \equiv the acute onset of new-persistent neurologic deficit lasting >24 hours. Head computed tomography (CT) or magnetic resonance imaging (MRI) scan imaging was strongly recommended. CT or MRI scans were to be considered by the CEC to support the clinical impression. Nonfatal stroke was to be classified as either ischemic or hemorrhagic based on imaging data, if available, or uncertain cause if imaging data were not available.
- Urgent target vessel revascularization (UTVR) \equiv PCI or CABG for recurrent ischemia that, in the investigator's opinion, is non-elective and cannot be delayed for more than 24 hours. UTVR must include the vessel(s) dilated at initial PCI.

Safety objectives were primarily focused on bleeding, designed to compare prasugrel with clopidogrel with respect to:

- TIMI Study Group (TIMI) major bleeding \equiv any intracranial hemorrhage (ICH) or overt bleeding associated with a hemoglobin (Hgb) decrease ≥ 5 g/dL from baseline
- TIMI life-threatening bleeding (a subset of the above). "Life-threatening" \equiv fatal, causes hypotension that requires IV inotropic agents, surgical intervention, ≥ 4 units blood or packed RBCs within 48 hours, or symptomatic ICH.
- TIMI minor bleeding \equiv clinically overt bleeding associated with a decrease in Hgb of ≥ 3 g/dL but < 5 g/dL from baseline

Bleeding was categorized as related to, or not related to, coronary artery bypass graft (CABG) surgery.

- assessments of clinical findings, laboratory values, and adverse events (AEs)

7.1.6. Safety Endpoints

- Non-CABG related TIMI major bleeding
- Non-CABG-related TIMI life-threatening bleeding (any non-CABG-related TIMI major bleeding that is fatal, leads to hypotension, requires surgical intervention, or necessitates transfusion of ≥ 4 units blood products over a 48-hour period; or any symptomatic ICH)
- Non-CABG-related fatal bleeding
- Non-CABG-related TIMI minor bleeding (clinically overt bleeding associated with a fall in Hgb of ≥ 3 g/dL but < 5 g/dL)
- CABG related bleeding

Analytic Methodology:

The statistical analysis plan was finalized on September 18, 2007. The analyses of the primary and secondary endpoints are discussed below.

7.1.7. Efficacy Endpoints

An independent CEC performed blinded adjudicated all efficacy events reported by investigators. Per protocol, the 1°, 2°, and other efficacy endpoint analyses were based on the determinations of events as adjudicated by the CEC.

Primary endpoint: Due to a potentially varying hazard ratio, the analysis for the 1° efficacy endpoint was based on the time from randomization to the first primary outcome using the Gehan-Wilcoxon test. Primary analyses were carried out in a hierarchical manner. At the first step, time-to-first primary outcome was carried out at a one-sided significance level of 0.025 (equivalent to a two-sided test at 0.05) in the UA/NSTEMI subject population. If superiority of prasugrel was established in the UA/NSTEMI population, then time-to-first primary outcome was to be carried out at a one-sided significance level of 0.025 in the All ACS population. For the latter analysis, ACS classification (UA/NSTEMI or STEMI) was to be used as a stratification factor. No adjustment for multiplicity was applied, because of the closed nature of hypothesis testing.

Secondary endpoints:

- Plan for evaluating secondary endpoints in UA/NSTEMI subject population

Following the establishment of the superiority of prasugrel over clopidogrel relative to the primary endpoint, additional analyses for secondary efficacy endpoints were performed using the log-rank test. Per agreement with FDA, the secondary endpoints were comprised of two groups: the first (Group 1) are those endpoints that do not require adjustment for multiplicity; the second (Group 2) are those that need to be predefined in a hierarchical manner (see Figure 4).

Group 1 secondary endpoints were each evaluated at a one-sided 0.025 alpha level (i.e., equivalent to a two-sided 0.05 level).

- Triple endpoint at Day 90
- Triple endpoint at Day 30

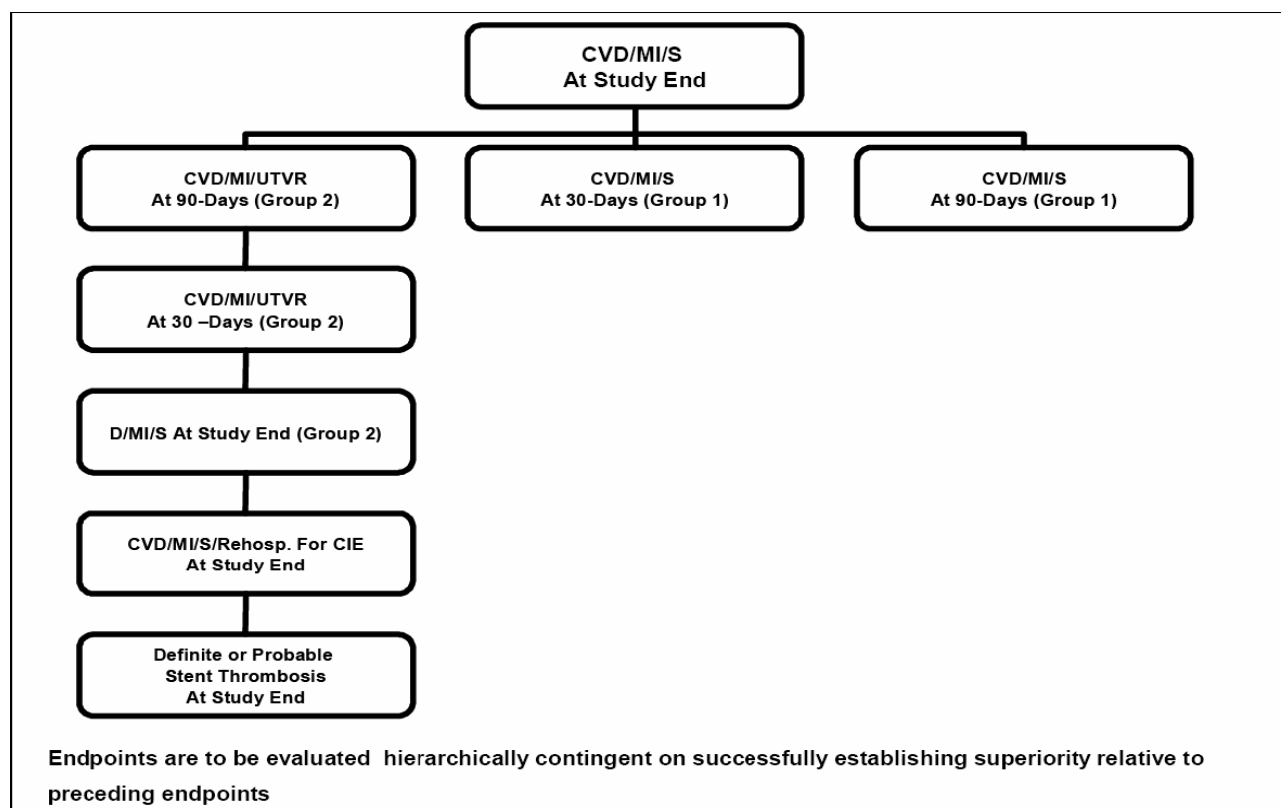
Both 2° endpoints in Group 1 were to be eligible for inclusion in labeling if the results were statistically significant.

The evaluations of Group 2 endpoints were dependent on demonstration of superiority of prasugrel on the 1° endpoint in the UA/NSTEMI population. To protect the overall type 1 error rate at a level of 0.05, the 5 remaining secondary endpoints were evaluated hierarchically, each at a one-sided 0.025 alpha level:

- CVD, nonfatal MI, or UTVR at 90 days post-randomization
- CVD, nonfatal MI, or UTVR at 30 days post-randomization
- All cause mortality, nonfatal MI, or nonfatal stroke at study end
- CVD, nonfatal MI, nonfatal stroke, or rehospitalization for cardiac ischemic event at study end
- Definite or probable stent thrombosis.

Numerous exploratory endpoints included components of the above composite endpoints at various timepoints.

Figure 4: Hierarchical plan for secondary endpoints



(Source: Sponsor's Figure 9.2, page 9169 of H7T-MC-TAAL Study Report. Abbreviations: CVD = cardiovascular death, D = death, Rehosp. = rehospitalization, S = stroke)

- Plan for evaluating secondary endpoints in All ACS subject population

Contingent on a demonstration of superiority of prasugrel for the 1^o endpoint in the All ACS population, each of the 7 secondary endpoints was evaluated in the hierarchical method described above in All ACS population. The log-rank test was used for each analysis at a one-sided 0.025 significance level. The clinical presentation (UA/NSTEMI or STEMI) was used as the stratification factor in these analyses.

7.1.8. Power and Sample Size

For UA/NSTEMI subjects, the study was planned to provide 90% power to establish superiority on the triple endpoint based on the following assumptions:

- 10.5% of subjects in the clopidogrel group would reach the triple endpoint within 1 year of PCI, based on event rates of the "Clopidogrel in Unstable Angina to Prevent Recurrent Events" (CURE) trial, for the subset of subjects with a TIMI risk score ≥ 3
- A mean hazard ratio of 0.80 for prasugrel versus clopidogrel relative to the primary endpoint, and
- The time-to-first event analysis based on a two-sided log-rank test used a two-sided significance level (alpha) of 0.05 to assess superiority relative to the triple endpoint.

The proposed sample size was 13,000 subjects, assuming that $\geq 95\%$ of subjects would be evaluable for the primary endpoint and that STEMI subjects would comprise 20 to 30% of the total enrollment (with a cap of 3500 subjects).

The study was to continue until 875 UA/NSTEMI subjects experienced a triple endpoint event, a median duration of therapy of 12 months, and a minimum follow-up of 6 months.

The blinded event rate was to be evaluated when 650 UA/NSTEMI subjects had reached the primary endpoint. However, the Study Operations Committee conducted a blinded review of the aggregated event rate when 589 subjects with UA/NSTEMI reached the primary endpoint and determined there was a slightly lower than anticipated aggregated event rate. Thus, the size of the UA/NSTEMI population was expanded to 10,100 subjects to achieve a target of 875 events.

7.2. General Results

7.2.1. Conduct

TAAL was conducted from November 5, 2004 through July 22, 2007. A total of 13,619 subjects were enrolled over a period of approximately 26 months, with entrance of the final subject on January 14, 2007. The study involved 725 centers in 30 countries, for an overall average of approximately 19 subjects enrolled per site. The database was locked on September 20, 2007.

Reviewer's Comments: In light of the rapid enrollment of the study, and the fact that the study was concluded only within the past year, the data are very much representative of contemporary medical practice. Beyond this, the requirement for all subjects to undergo PCI ensured a fair degree of consistency in medical management of ACS, consistency that could be lacking in studies where PCI is only optional.

Protocol violations, identified from both the clinical database and site monitoring, were relatively unimportant, low in number, and similar in frequency between treatment groups. As such, they are deemed unlikely to influence the study results.

7.2.2. Disposition of Subjects

Overall, 18,357 potential subjects were screened, in order to enroll 13,619 subjects (approximately 25% were screening failures). Of the 13,619 subjects enrolled, 11 had an incomplete informed consent document, and were not included in the analyses. Thus, the intent-to-treat population included 13,608 subjects: 6,813 subjects were randomized to prasugrel and 6,795 subjects were randomized to clopidogrel. Approximately 98.8% of randomized subjects received the study agent (13,457), and comprise the safety population. Median length of follow-up was 450 days (mean 380 ± 121 days). Nineteen percent (19%) of subjects had unstable angina, 55% had NSTEMI, and 26% had STEMI (18% treated within 12 hours, 8% beyond 12 hours).

7.2.3. Baseline Characteristics

As expected in a study of this size, there were no important imbalances in baseline demographic or disease characteristics (Table 2). From the standpoint of generalizability of the results, however, several points are worth noting. Roughly a quarter of the subjects were female; only 3% of subjects were of African ancestry. Approximately 30% of subjects were from the U.S.; eastern and western Europe each accounted for approximately 25% of subjects. The median (and mean) age was 61, with 13% of subjects age 75 or older. Concomitant medical history (Table 3) and pharmacotherapy (Table 4) were typical of an ACS population. The majority of subjects were taking statins and beta blockers; about half of the subjects were taking GPIIb/IIIa inhibitors and ACE inhibitors.

7.2.4. Index Procedure

Essentially all subjects (98.6% in each treatment group) underwent PCI as directed per protocol, and 94% received at least one stent, divided fairly equally between bare metal stents (47%) and drug eluting stents (42%) (Table 5). Of the 1.4% of subjects who did not undergo PCI, one-fourth (0.35% overall) underwent CABG and three-fourths (1.1% overall) were managed medically without revascularization.

Table 2: Demographic Characteristics in TAAL		
	Prasugrel n=6813	Clopidogrel n=6795
Age (years)		
mean ± SD	60.9 ± 11.2	60.9 ± 11.4
median	61	61
25th, 75th percentile	53, 69	53, 70
≥ 75 yrs	13.2	13.4
Female sex	25.0	26.8
Ethnicity		
Caucasian	91.9	92.3
African	3.0	2.8
Hispanic	3.9	3.8
Asian	0.9	0.9
Other	0.2	0.2
Region of enrollment		
U.S.	29.9	29.7
North America, non-U.S.	1.9	1.9
South America	4.0	3.9
Western Europe	26.1	26.1
Eastern Europe	24.3	24.5
Rest of world	13.8	13.9
Body Mass Index (kg/m ²)		
mean ± SD	28.5 ± 5.0	28.5 ± 5.1
median	27.8	27.8
25th, 75th percentile	25.1, 31.1	25.1, 31.1
Weight (kg)		
mean ± SD	83.6 ± 16.8	83.2 ± 16.9
median	82.0	81.0
25th, 75th percentile	72.6, 93.0	72.0, 92.1

7.3. **Primary Efficacy Endpoint**

For the study as a whole (All ACS), 643 subjects (9.4%) in the prasugrel group and 781 subjects (11.5%) in the clopidogrel group experienced a 1° triple endpoint event of cardiovascular death, nonfatal MI, or nonfatal stroke. Treatment with prasugrel was associated with a statistically significant reduction in the triple composite endpoint in the UA/NSTEMI population (Cox proportional hazard ratio in favor of prasugrel 0.82, 95% C.I. 0.73 to 0.93, p=0.002, Table 6, Figure 5, top panel). Therefore, as prospectively specified in the analytic plan, the analysis was carried out in the overall ACS patient population (Figure 6). Prasugrel was associated with a statistically significant treatment effect, with a hazard ratio of 0.81 (95% C.I. 0.73 to 0.90,

Table 3: Medical History (%)

	Prasugrel n=6813	Clopidogrel n=6795
Hypertension	64.1	64.3
Hypercholesterolemia	55.6	55.8
Diabetes	23.1	23.1
treated with insulin	5.6	5.8
not treated with insulin	17.5	17.3
Metabolic syndrome	43.5	43.2
Tobacco use		
ever	65.5	66.1
current	38.3	38.0
Hepatic impairment	0.5	0.6
Renal impairment		
Ccr ≤ 60 mL/min	10.7	11.6
Ccr ≤ 30 mL/min	0.8	0.8
Prior MI	18.0	17.8
Prior PCI	13.3	13.6
Prior CABG	7.9	7.3
History of CHF	3.9	3.6
Atrial fibrillation	3.1	3.1
History of carotid/vertebral artery disease	2.8	2.9
Prior Stroke	2.6	2.4
Prior TIA	1.4	1.7
History of peripheral vascular disease	5.1	5.3
Peptic ulcer disease	5.9	6.1

Table 4: Concomitant Pharmacotherapy (%)

	Prasugrel n=6813	Clopidogrel n=6795
Statins	78.8	78.6
ACE inhibitor	52.0	49.4
Beta blocker	74.0	73.9
Calcium channel blocker	14.7	14.2
Aspirin within 7 days prior to symptom onset	34.1	34.3
GPIIb/IIIa use through 3 days	53.4	54.9

Table 5: Index Procedure (%)

	Prasugrel n=6813	Clopidogrel n=6795
PCI	98.6	98.6
no stent	4.0	3.6
bare metal stent only	46.8	46.9
≥ 1 drug-eluting stent	42.0	42.3
CABG	0.4	0.3
Medically managed	1.1	1.1

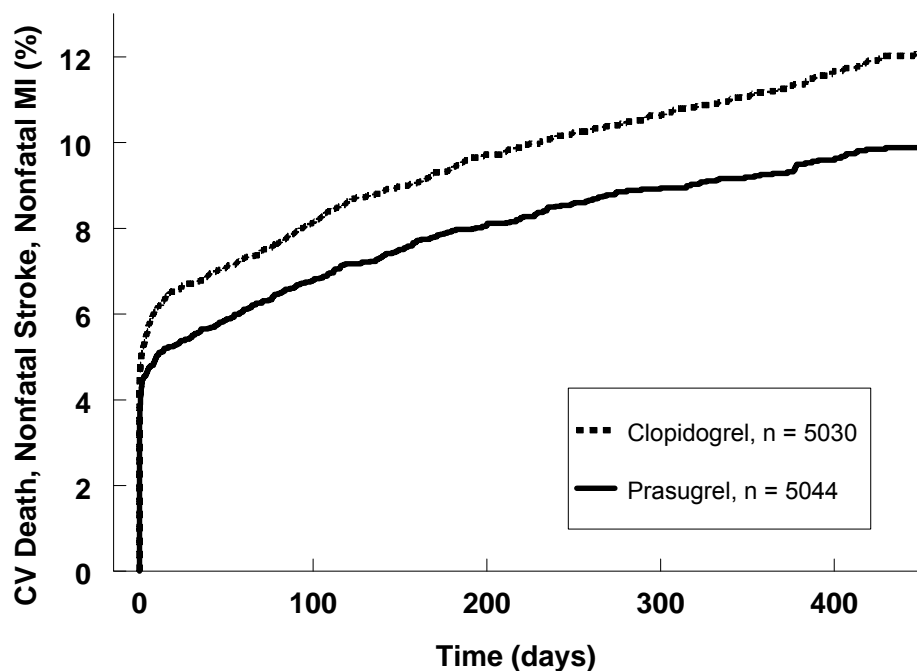
p<0.001, Table 6, Figure 6). Results were also statistically significant for prasugrel in the STEMI population alone (Table 6, Figure 5, bottom panel). The efficacy results for the 1° endpoint were verified by Dr. Ququan Liu in her statistical review.

Table 6: Numbers and Percentages of Subjects Reaching 1° Composite Endpoint								
subject population	Prasugrel			Clopidogrel			Cox Proportional HR (95% C.I.)	p
	N	n	(%)	N	n	(%)		
UA or NSTEMI	5044	469	9.3	5030	565	11.2	0.82 (0.73, 0.93)	0.002
STEMI	1769	174	9.8	1765	216	12.2	0.79 (0.65, 0.97)	0.019
Overall	6813	643	9.4	6795	781	11.5	0.81 (0.73, 0.90)	<0.001

For the entire ACS population, Figure 6 shows the Kaplan-Meier estimates for the composite triple endpoint. The top panel shows the events over the full 450 days; the bottom panel displays the same data but is limited to the first 30 days only. In order to better delineate how prasugrel's treatment advantage is manifested with respect to time, Figure 7 shows the *delta* % with a primary endpoint event as a function of time for both the STEMI and NSTEMI/UA populations. In essence, the Kaplan Meier time-to-event lines in Figure 5 are subtracted to produce Figure 7, and the delta % of Figure 7 represents the distance between the curves in Figure 5, the *cumulative* difference in event rates. For STEMI, the advantage begins immediately, reaches its maximum at 18 days, and remains unchanged thereafter. In the NSTEMI/UA population, approximately 60% of the cumulative treatment advantage occurred within 3 weeks, but the delta continues to increase fairly linearly through 450 days, supporting the concept that prasugrel's treatment advantage persists throughout the entire study.

Figure 5: Kaplan-Meier Estimates of the 1° Efficacy Endpoint CV Death, Nonfatal MI, Nonfatal Stroke

Top Panel: NSTEMI/UA



Bottom Panel: STEMI

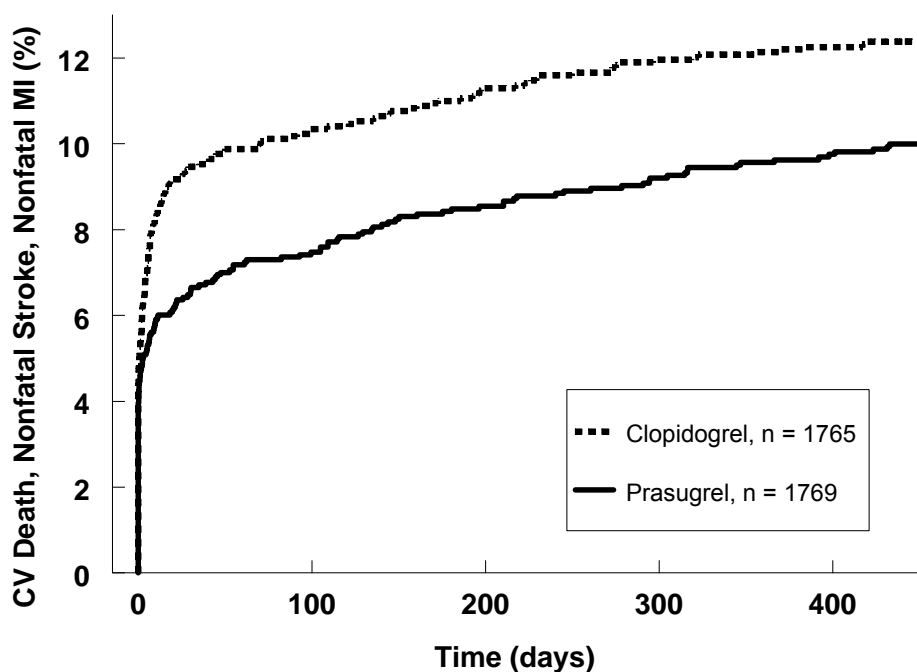
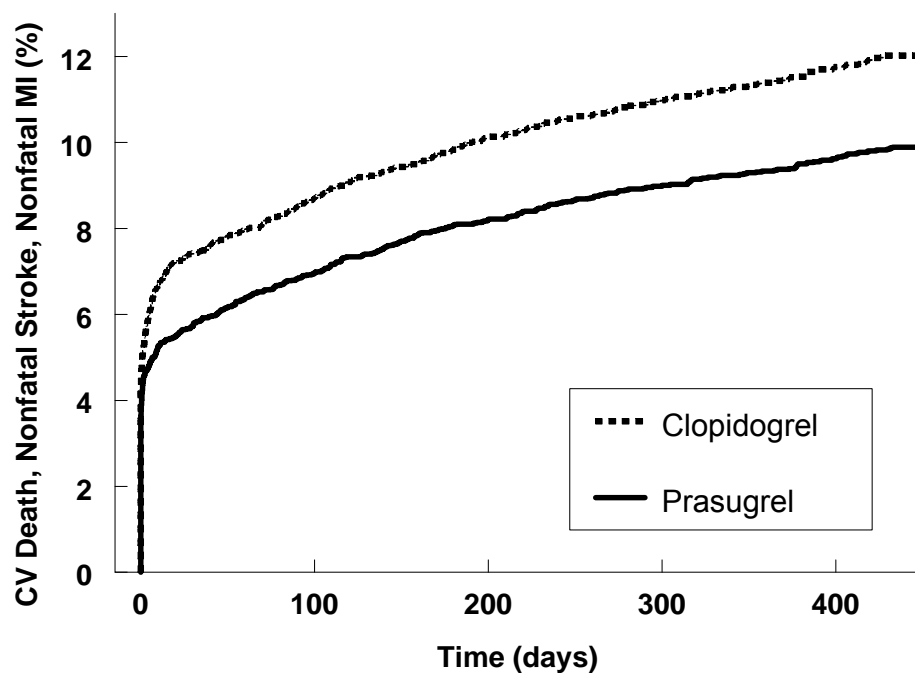


Figure 6: Kaplan-Meier Estimates of the 1° Efficacy Endpoint CV Death, Nonfatal MI, Nonfatal Stroke, All ACS Subjects

Top Panel: 0 – 450 Days;



Bottom Panel: 0 – 30 Days:

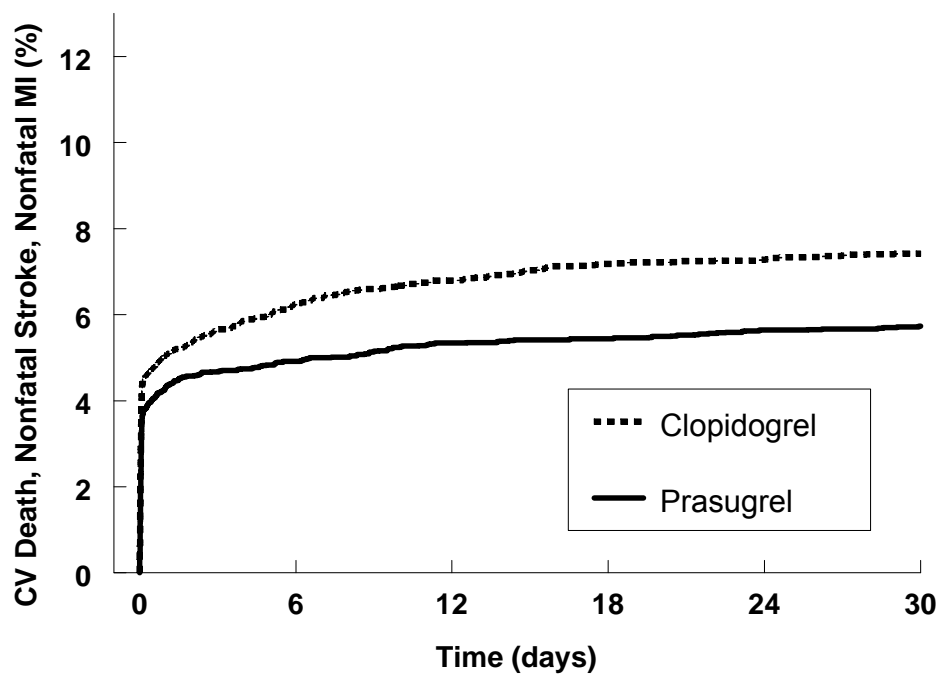
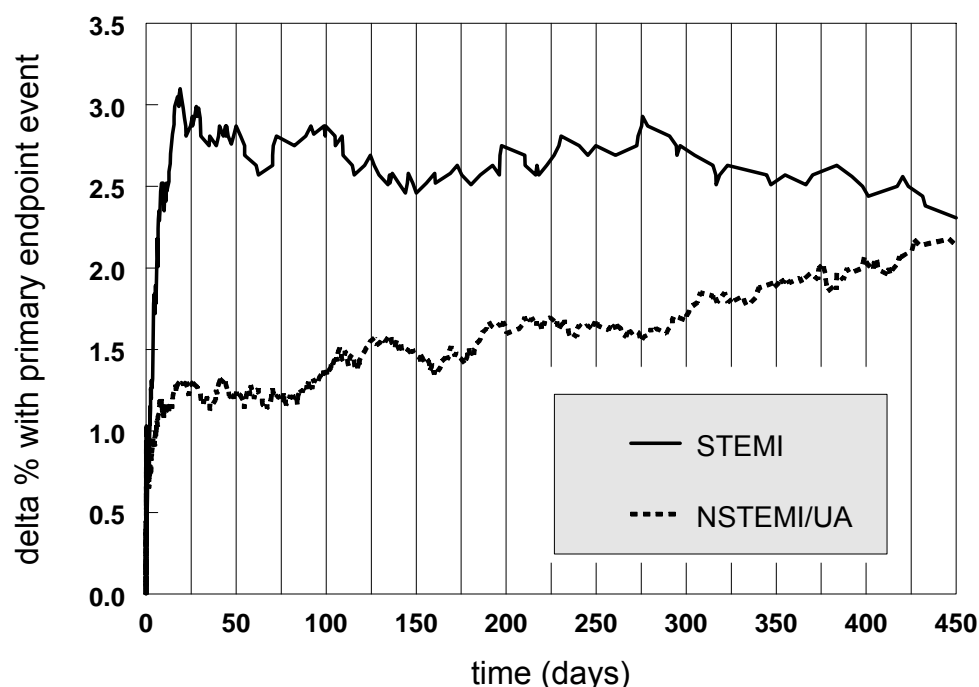


Figure 7: Kaplan-Meier Estimates of the 1° Efficacy Endpoint; Delta between Prasugrel and Clopidogrel, STEMI and NSTEMI/UA Populations



7.3.1. Explorations on the Primary Endpoint

Sponsor's Sensitivity Analyses:

The sponsor conducted sensitivity analyses, restricting the analysis of the 1° endpoint to subjects on treatment, and subjects on treatment and compliant to study drug. For both analyses, the results were consistent with the study results on the whole.

Individual Components of the Endpoint:

The individual components of the 1° endpoint are shown for the UA/NSTEMI, STEMI, and the All ACS populations in Table 7, as reported by the sponsor and confirmed by the statistical reviewer. The incidence of nonfatal MI is statistically significantly lower in the prasugrel group in both the UA/NSTEMI and STEMI populations, and in the ACS population overall; this component of the composite endpoint is what drives the overall study results. The CV death component shows a trend in favor of prasugrel in the STEMI population (hazard ratio = 0.74, $p = 0.13$), and neutrality for the UA/NSTEMI population (representing roughly three-quarters of the overall study population), with only a very weak trend in the overall population ($p=0.307$). The effect of prasugrel on nonfatal stroke was neutral. The statistical reviewer noted that prasugrel was associated with a higher incidence of nonfatal stroke in the All ACS and STEMI populations, but the numbers of events were small, with a hazard ratio fairly close to unity (Table 7).

Table 7: Components of 1° Efficacy Endpoint (from table 11.7 in TAAL Study Report)

endpoint	Patient population	Prasugrel			Clopidogrel			Total			Cox Proportional HR (95% C.I.)	p
		N	n	%	N	n	%	N	n	%		
CV Death	UA/NSTEMI	5044	90	1.8	5030	92	1.8	10074	182	1.8	0.98 (0.73,1.31)	0.885
	STEMI	1769	43	2.4	1765	58	3.3	3534	101	2.9	0.74 (0.50,1.09)	0.129
	All ACS	6813	133	2.0	6795	150	2.2	13608	283	2.1	0.89 (0.70,1.12)	0.307
Nonfatal MI	UA/NSTEMI	5044	357	7.1	5030	464	9.2	10074	821	8.1	0.76 (0.66,0.87)	<0.001
	STEMI	1769	118	6.7	1765	156	8.8	3534	274	7.8	0.75 (0.59,0.95)	0.016
	All ACS	6813	475	7.0	6795	620	9.1	13608	1095	8.0	0.76 (0.67,0.85)	<0.001
Nonfatal Stroke	UA/NSTEMI	5044	40	0.8	5030	41	0.8	10074	81	0.8	0.98 (0.63,1.51)	0.922
	STEMI	1769	21	1.2	1765	19	1.1	3534	40	1.1	1.10 (0.59,2.04)	0.77
	All ACS	6813	61	0.9	6795	60	0.9	13608	121	0.9	1.02 (0.71,1.45)	0.93

Definition of MI:

The protocol's original definition of peri-procedural MI required an elevation of CK-MB to >3X ULN on at least two samples within 48 hours of PCI. A modified definition, specified in protocol amendment "A" dated January 10, 2006, extended the definition of peri-procedural MI to a CK-MB >5X ULN on a single sample if it was the last available sample drawn and obtained ≥12 hours after PCI. This change resulted in the addition of 38 and 44 endpoint events to the prasugrel and clopidogrel groups, respectively, with no substantive change in the overall findings.

Statistical Assumptions of the Cox Model:

Non-informative censoring is a key assumption of the Cox model; the study design must ensure that mechanisms leading to the censoring of subjects are not related to the probability of an event. Dr. Liu, the statistical reviewer, examined the censoring distributions between the two treatment groups in all three subject populations and found them to be similar. Another key assumption of the Cox's regression analysis is the assumption of proportionality of the hazard ratio over time. Dr. Liu created log(-log survivor) plots for the UA/NSTEMI, STEMI, and overall ACS populations. For all 3 populations, the two relations were reasonably parallel over time, supporting the concept that the hazard ratio was fairly constant over time. Thus, the statistical reviewer found no important issues with the statistical assumptions of the Cox Model.

Landmark Analyses:

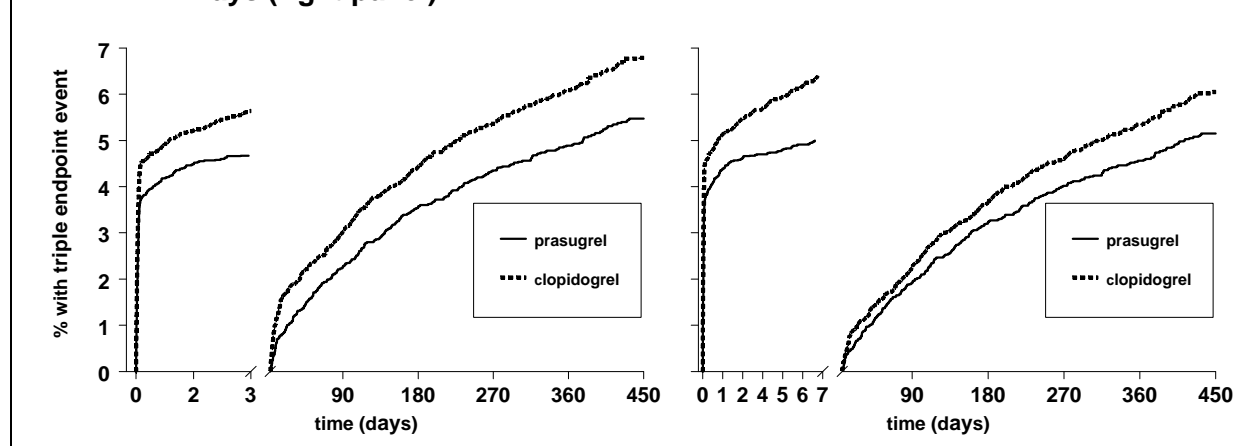
There is support for the concept that a clopidogrel LD of 600-mg is associated with more rapid inhibition of platelet aggregation than the standard LD of 300-mg (used in TAAL), and OASIS7 is being conducted to examine this hypothesis in a randomized controlled trial (ClinicalTrials.gov Identifier: NCT00335452). Thus, some have argued that in TAAL, an inadequate clopidogrel LD provided prasugrel with an advantage during the initial hours of therapy, during the interval when patients were subjected to PCI and at risk of peri-procedural myocardial infarctions.¹

This reviewer conducted landmark analyses, in essence time-to-event analyses before and after cut-points of 3 days (Figure 8, left panel) and 7 days (Figure 8, right panel). These consider event-free survival beginning at points in time beyond which the adequacy of the LD would be

¹ *N Engl J Med.* 2008;358:1298-9

expected to influence events, and beyond which peri-procedural events are likely to occur. The landmark analyses have limitations in that the original randomization is not preserved; therefore, the analyses are somewhat observational in nature. The point can also be argued that events occurring at the beginning of the study might influence events later on; however, it is also true that subjects at the highest risk experience events early in the study. As such, the clopidogrel group is “de-enriched” through removal of subjects at highest risk. Although interpretation is not straightforward, the analyses show a treatment effect of prasugrel from both Day 3 and Day 7 forward, and are consistent with the concept that the superiority of prasugrel is not merely a function of the LD, or simply a reduction in early peri-procedural events.

Figure 8: Landmark Analyses on the 1° Efficacy Endpoint: 3 Days (left panel); 7 Days (right panel)



Multiplicity:

Given the nature and interrelations of the indications supported by the study, multiplicity is a complex issue. Although the statistical reviewer noted that a number of reviewers had comments on multiplicity in their reviews of the study protocol, she opined that the pre-specified strategy for dealing with multiplicity was reasonable. She noted also that adjustment of multiplicity is a moot issue, given the very small nominal p-values for the 1° composite endpoint and the pre-specified 2° endpoints.

Site-Reported Endpoint Events:

Dr. Marciniak performed a number of exploratory analyses to assess the robustness of the 1° efficacy endpoints. In light of his concerns regarding neoplasia (see section 7.4.15), the strength of the efficacy findings are particularly important to the risk-benefit profile.

In TAAL, events could be referred to the CEC by site, or triggered by a review of laboratory values. Dr. Marciniak noted (page 28 of his review): “The CEC adjudicated higher percentages of clopidogrel events as MIs than prasugrel events, as shown in Table 19.” (reproduced here):

Table 19: CEC MI Adjudications by Type of Referring Event

referring event	clopidogrel		prasugrel	
	n	% MI	n	% MI
site MI event	303	80%	180	76%
site other ischemic event	984	19%	903	15%
triggered PPMI*	1022	21%	1049	19%

*PPMI = peri-procedural myocardial infarction

He concluded that site reported MI's appear to be better predictors of death than the CEC-adjudicated MI's, and noted, therefore, that site-reported events are clinically more important than those that are not site-reported. He went on to assess the efficacy endpoint (death, non-fatal MI, non-fatal stroke) in the UA/NSTEMI, STEMI, and overall ACS populations, counting only site-reported events. (Site-reported events represented approximately 60-70% of the total events; therefore, some 30-40% of events were not included in his sensitivity analyses.) With omission of these events, results were not statistically significant. He also noted that there is no substantial treatment effect after 30 days, when considering site-reported events. This is essentially in line with the standard analysis, where the treatment effect waned after 18 days (in STEMI subjects), and waned more gradually in STEMI subjects (Figure 7). Dr. Marciniak has also emphasized that the numbers of events decrease greatly after 30 days. Thus, if there is ongoing risk, it must be considered against a background of diminishing benefit.

This reviewer strongly agrees with the latter point, that is, that the treatment effect is front-loaded. In the opinion of this reviewer, however, these sensitivity analyses do not raise important questions regarding the validity or persuasiveness of the results. My rationale can be summarized as follows:

- 1) Based on Table 19, above, there was essentially no evidence of differential reporting or biased adjudication for the two treatment groups.
- 2) "Enzyme leaks" are widely believed to be of clinical importance. TAAL was designed with the knowledge that many non-fatal myocardial infarctions would be asymptomatic, manifested only as "chemical MIs" or "enzyme leaks." However, because these "events" are believed to have clinical significance,² the trial was designed in such a way as to attempt to ensure that they would be detected and included in efficacy analyses.
- 3) The Division prospectively agreed with the protocol design, to ensure that these events would be counted.

In some clinical trials, it can be important to assess the adjudication of events by a central committee. This is particularly true in studies where there is the potential for unblinding of subjects or investigators (e.g., because of side effects, changes in laboratory values, injection site reactions, etc.), and ascertainment bias is suspected or possible. In such cases, a disparity between treatment groups in terms of the percentages of events adjudicated as positive (versus negative) might suggest that bias was operational. In TAAL, adjudication seems less critical, considering that unblinding would be unlikely, and given that strict criteria were used to analyze laboratory data. (Although these criteria were revised at one point during the study, there is no reason to suspect a differential effect by treatment group.)

² *Eur Heart J.* 2004;25:313-21

Results of the Study by Half:

This reviewer assessed the overall study results by median time of enrollment (first and second halves of study). A trend in favor of a more robust treatment effect in the second half of a study versus the first half would support (but by no means prove) the concept that knowledge gained during the course of the study was used improperly as a basis to alter the study design, enrollment pattern, or analytic plan, in order to increase the apparent (or real) treatment effect. In TAAL, the opposite trend occurred. That is, for the triple composite endpoint over the entire ACS population, the log-rank for prasugrel versus clopidogrel was 0.0013 for the first study half (subjects enrolled through December 20, 2005), and 0.0213 for the second. The less robust treatment effect in the second half of the study suggests that the study was “honest:” that is, there is no suggestion that knowledge gained during the conduct of the study was used improperly to influence study conduct or analysis.

In summary, the results for the 1° efficacy endpoint are persuasive and robust to exploration. The overall treatment effect was driven by nonfatal MI. The CV death component shows a trend in favor of prasugrel in the STEMI population, but only a very weak trend in the overall population. The effect of prasugrel versus clopidogrel on nonfatal stroke was neutral. In light of these findings, the indication in labeling should be restricted to prevention of MI.

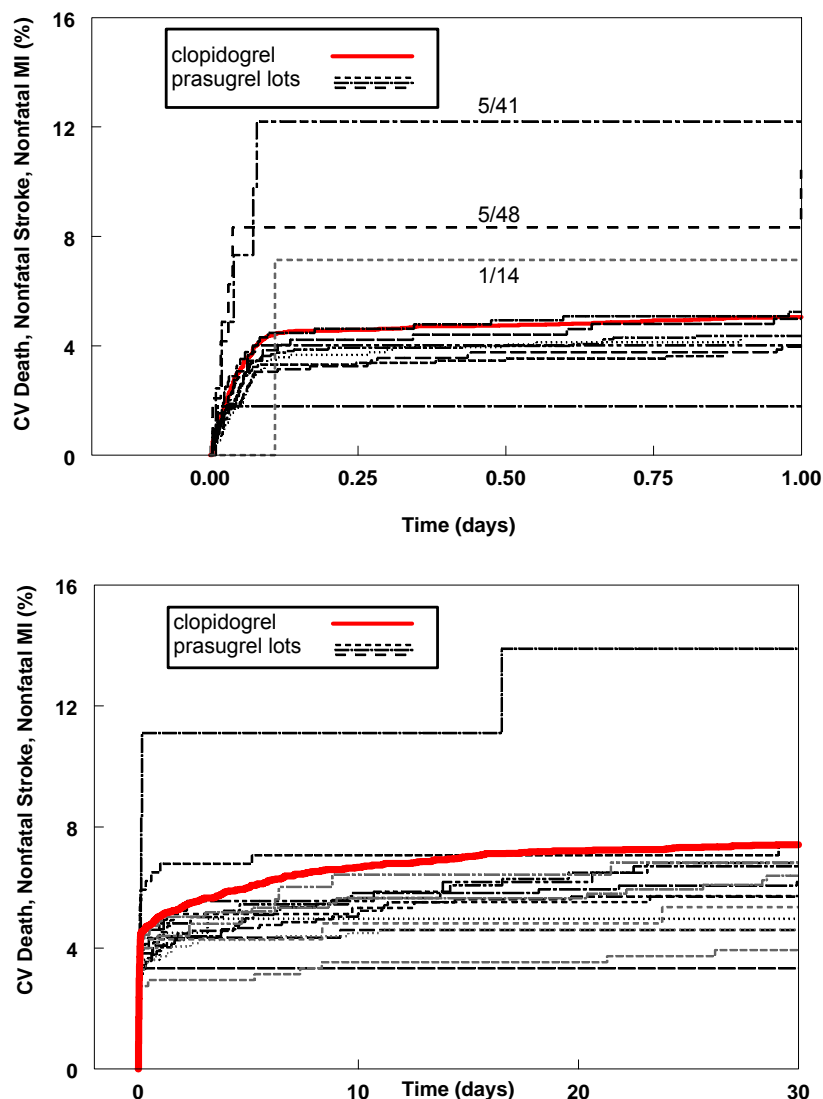
Drug Quality:

The sponsor initiated drug development using the free base of the drug substance, but switched to a hydrochloride (HCl) salt because of greater bioavailability in patients with higher gastric pH. Near the time when TAAL completed enrollment, the sponsor discovered a reaction between the HCl salt and an excipient that converted up to 86% of the salt to the free base. Although lots with low, intermediate, and high conversion to base were found to be bioequivalent at normal gastric pH, prasugrel lots with differing salt to base conversion were bio-inequivalent when administered in the presence of PPI. This is salient because PPI use is common in patients with ACS.

Ideally, one might estimate the clinical importance of salt-to-base conversion by estimating efficacy (and safety) in TAAL by the extent of salt-to-base conversion for the prasugrel administered to each subject. Practically speaking, however, this was problematic for two reasons: First, the lots were batch-tested for salt-to-base conversion at only a few points in time. Conversion was not assessed near the time of administration, and was not assessed serially (serial data might have been used to estimate the extent of conversion at the time of administration). Second, subjects obtained prasugrel from several lots during the course of TAAL.

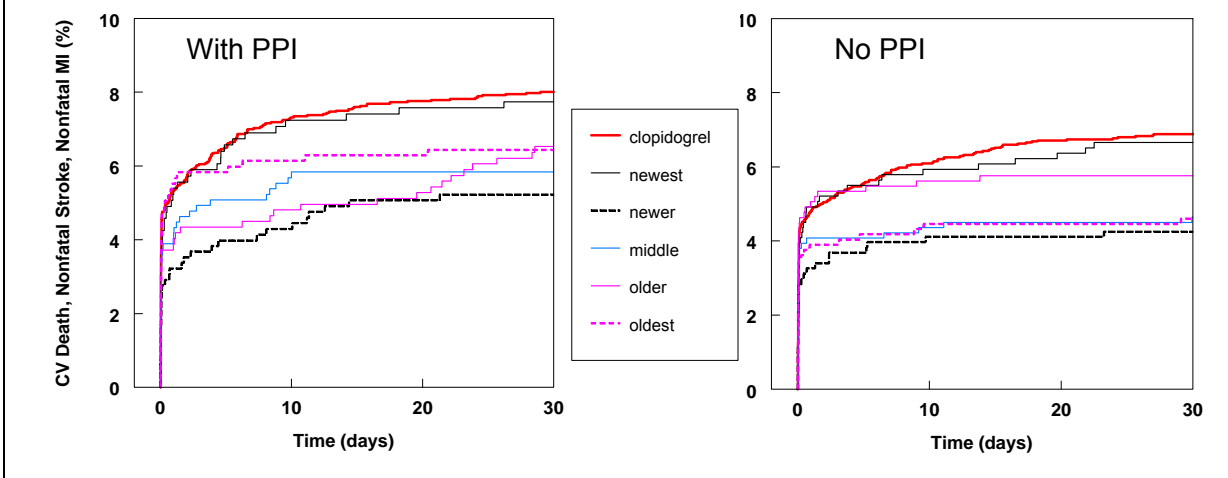
These issues notwithstanding, some estimate of the clinical importance of conversion can be gleaned through the following analyses: Although subjects obtained prasugrel from several lots during the course of the study, the loading dose (6 pills) was obtained from a single lot, and the initial month's supply (Days 2-30) was obtained from a single (but generally different) lot as well. Because more than half of all events occurred between Days 0 and 30, and because the majority of prasugrel's treatment effect was evident during this period, this reviewer analyzed efficacy on the triple composite endpoint as a function of prasugrel lot used for the loading dose (Figure 9, top) and the lot administered Day 2 to 30 (Figure 9, bottom). Although the salt-to-base conversion at the time of actual use cannot be estimated for the disparate prasugrel lots, it is difficult to interpret event-free survival as importantly different from clopidogrel for any prasugrel lot subgroup with a sizable number of subjects. (Note that the subgroups associated with higher event rates tend to be small in size; fractions indicate N with events/ N at risk.)

**Figure 9: 1° Efficacy Endpoint by Prasugrel Lot Administered Through Day 30:
Top – Loading Dose Through Day 1; Bottom – Maintenance Dose Through Day 30**



Because the sponsor asserts that there was at least some conversion of salt to base during storage, this reviewer also assessed efficacy as a function of the age of the prasugrel lot used to supply each subject with their initial 30 day supply, in the presence and absence of PPI use (age = date administered minus date of manufacture). Of note, use of PPIs was transient or intermittent in some subjects; subjects with recorded PPI use at any time were considered PPI users for the purpose of this analysis. In both the presence and absence of PPIs, there was no relation between age of lot administered during the initial 30 days and efficacy (Figure 10).

Figure 10: 1° Efficacy Endpoint by Age of Prasugrel Lot Administered Through Day 30



These analyses suggest that prasugrel's efficacy was at least similar to clopidogrel for the vast majority of lots, and efficacy was not importantly affected by pill age. (The lot with the highest event rate included only 36 subjects.)

Both of these analyses support the concept that neither disparate salt to base conversion nor pill age had an important bearing on efficacy.

7.3.2. Subgroup Analyses

Body Weight:

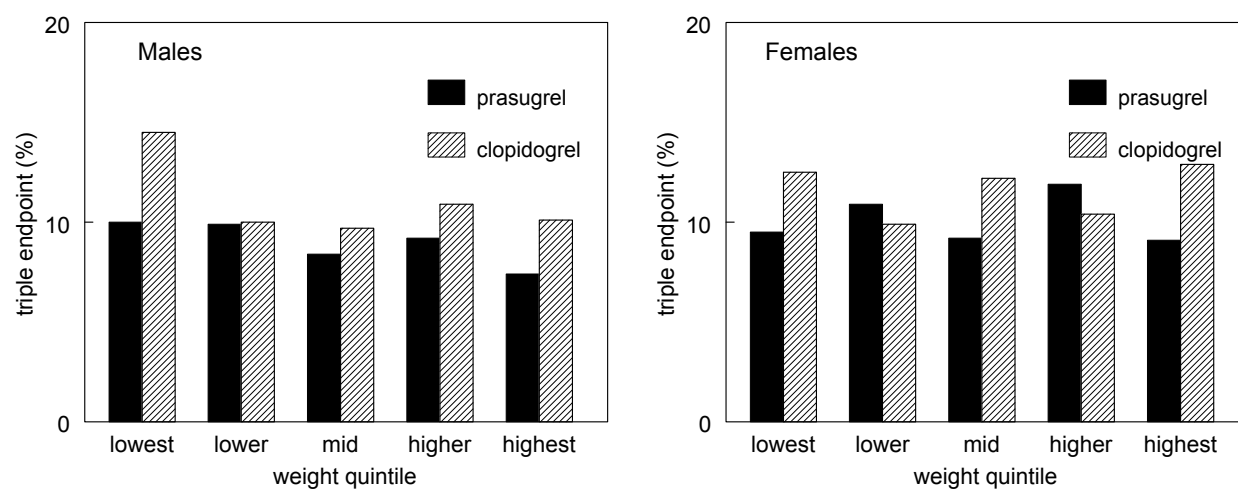
Given that the study employed a fixed dosing regimen (non-weight-adjusted), there is concern that subjects at higher weights may have received an insufficient dose of prasugrel. (There is also the concern that subjects at the lower fringes of weight may have received excess drug, but this is more an issue for safety.) The Clinical Pharmacology Review considered the relationship between body weight and efficacy. Using an exploratory univariate Cox model, the results were inconsistent for the impact of body weight on efficacy, depending on whether it was used as a continuous or categorical variable. Multivariate analyses did not show body weight to be a significant predictor of efficacy.

Dr. Liu, the statistical reviewer, provided a number of analyses of the 1° endpoint by patient weight. The odds ratio was statistically significantly <1 for subjects in the ≥ 50 to <70 kg weight group, as well as for subjects in the ≥ 70 kg, 70-90 kg, and <60 kg weight groups. Only for subjects weighing <50 kg ($n=50$ for the entire study, or 0.4% of the study population) was the odds ratio >1 (1.05; with 95% C.I. 0.60 – 1.82).

Because weight is confounded by sex, this reviewer assessed the 1° efficacy endpoint by weight quintiles, for male and female subjects separately (Figure 11). No trends emerged to suggest that subjects with higher body weights received insufficient drug. The probability of experiencing an endpoint event did not tend to increase with increasing subject weight.

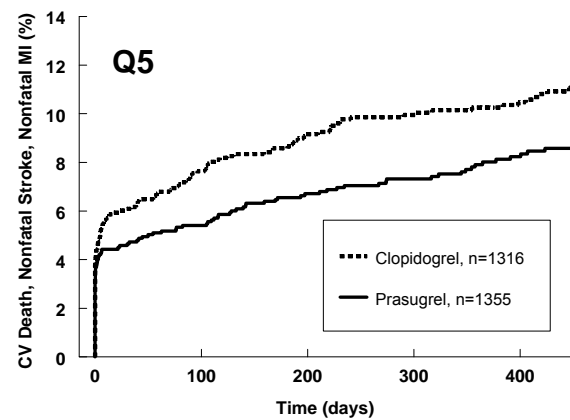
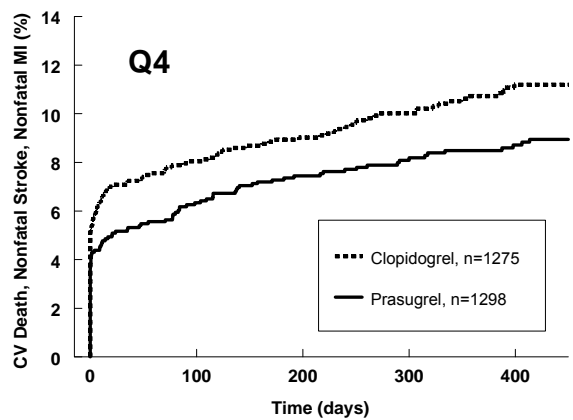
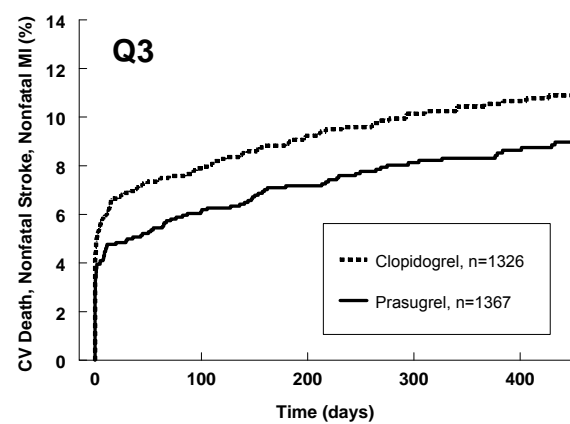
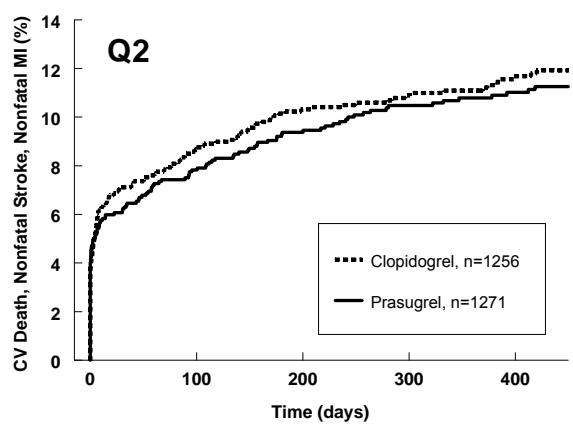
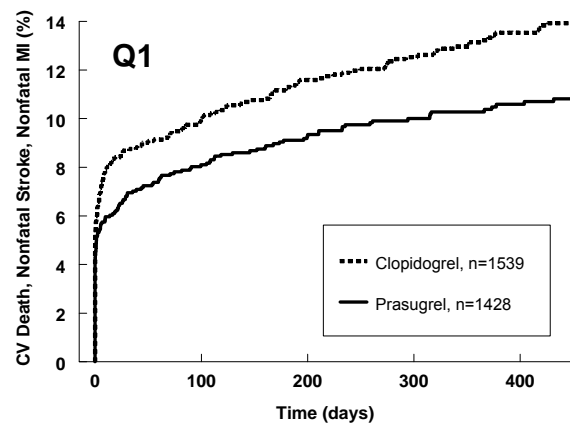
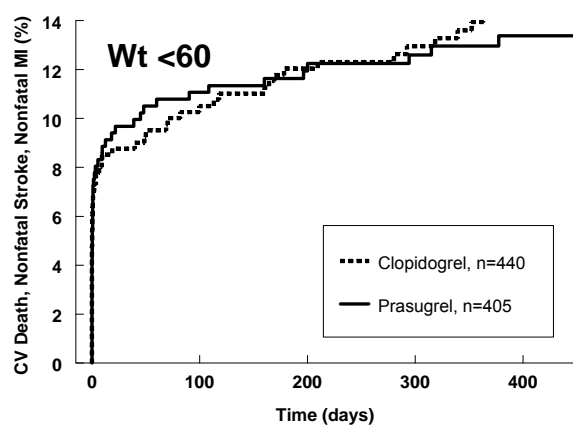
Figure 12 shows the results on the 1° endpoint for the overall ACS population by weight. The upper left panel shows the results for subjects weighing <60 kg. The effect of prasugrel was neutral in this small subgroup, comprising 6% of the overall subject population. The remaining panels show results for weight quintiles 1 through 5. Weights for the 5 quintiles broke down as follows: Q1: weight ≤ 70 kg, Q2: >70 to ≤ 78 kg, Q3: >78 to ≤ 85 kg, Q4: >85 to ≤ 95.24 kg, and Q5: >95.24 kg.

Figure 11: Triple Efficacy Endpoint by Weight Quintiles and Sex



In short, prasugrel appears effective over the range of weights studied. For the small subgroup of subjects weighing <60 kg, prasugrel appears similar, and not superior, to the comparator on the 1° efficacy endpoint.

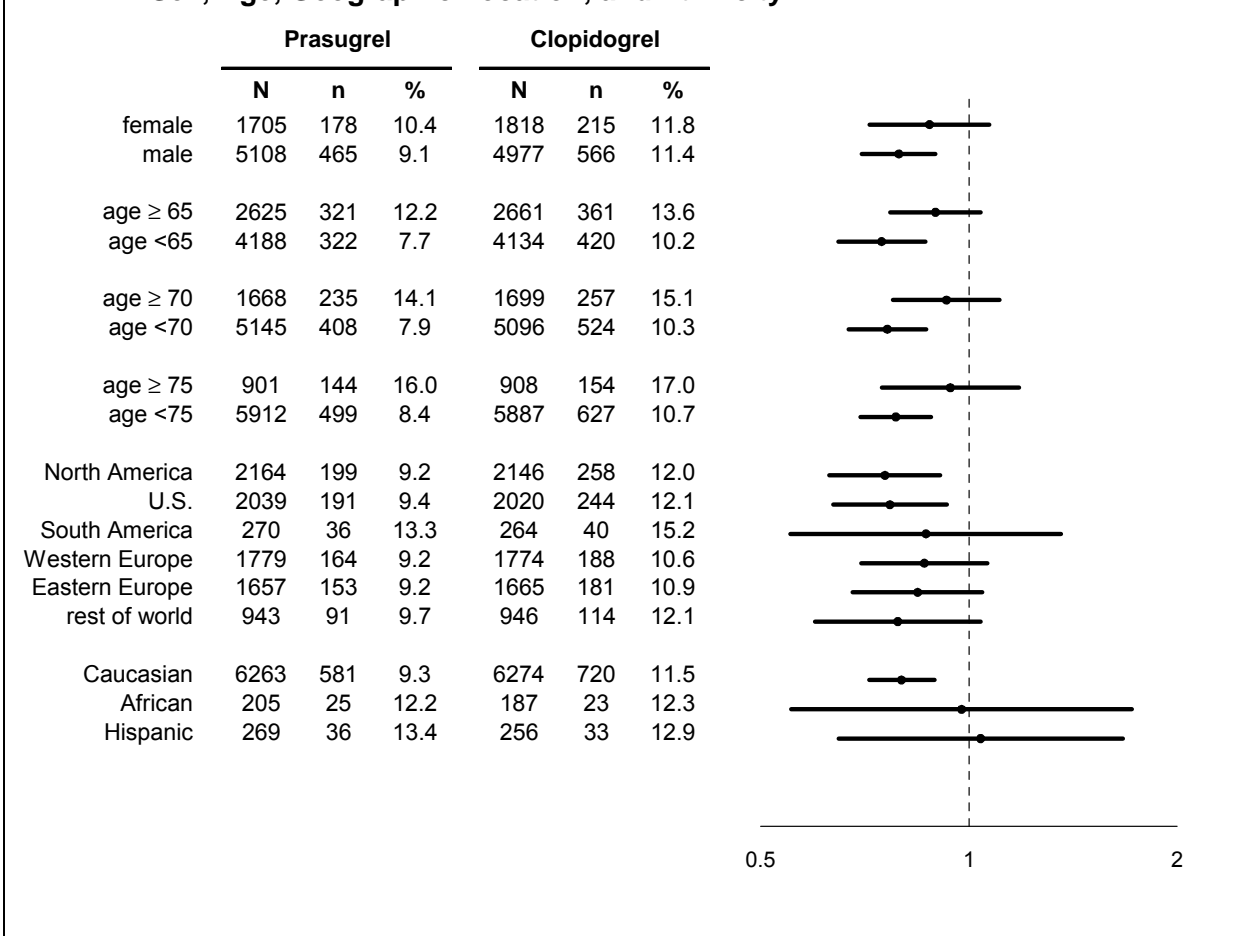
Figure 12: Primary Triple Composite Endpoint by Weight



Subgroups on Sex, Age, and Geographic Location:

Hazard ratios and 95% confidence intervals are shown for the 1° efficacy endpoint for the overall All ACS population across subgroups of sex, age, and geographic location (Figure 13). The treatment benefit of prasugrel tended to be greater in younger versus older populations. Event rates in subjects of African descent tended to be higher than those in Caucasians and the effect of prasugrel was essentially neutral compared to clopidogrel in this population, although the strength of this conclusion is limited given the small number of subjects of African descent studied (less than 3% of the total study population). The numbers of subjects of Asian descent, and numbers of events, were small, and are not shown (1/60 in the prasugrel group; 4/64 in the clopidogrel group). Exposure may be higher in patients of Asian descent (see section 5.2.5).

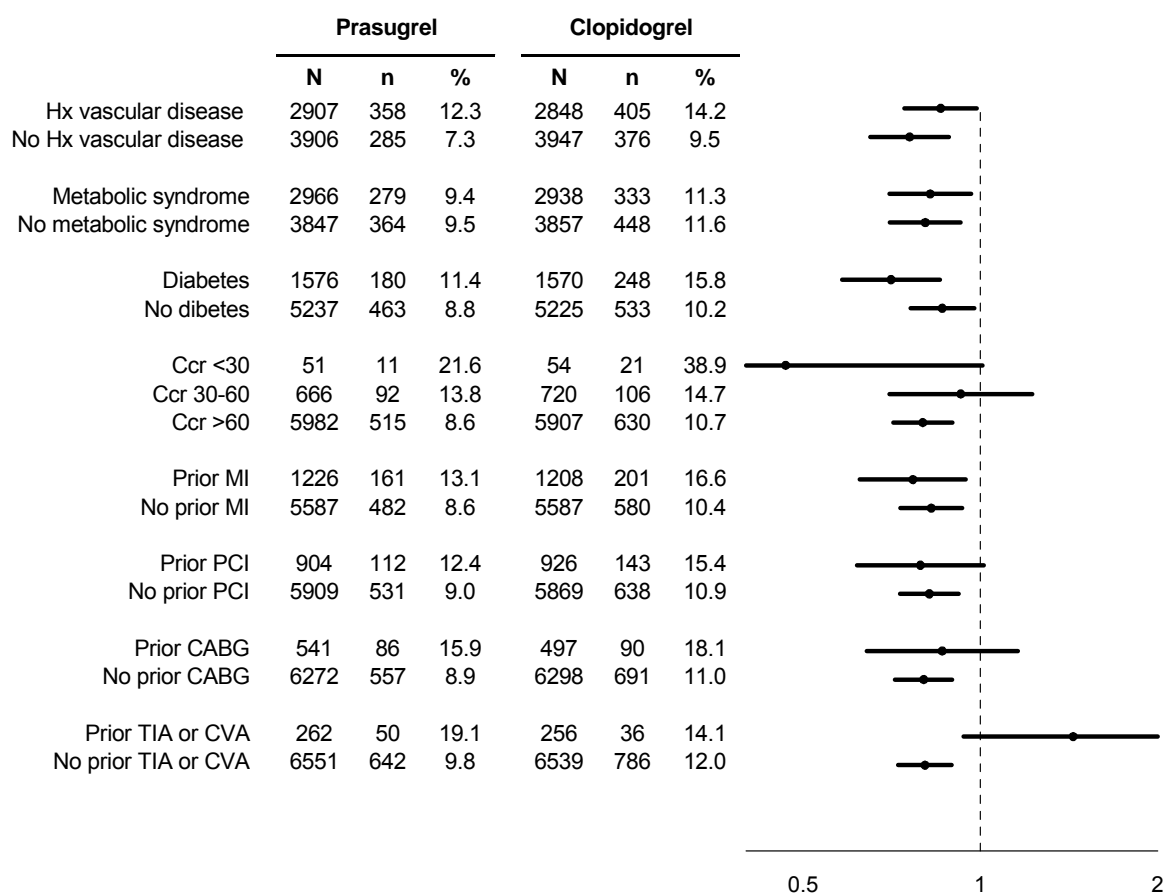
Figure 13: Results for Triple Composite Endpoint – All ACS Population – Subgroups of Sex, Age, Geographic Location, and Ethnicity



Event rates were fairly similar across geographic regions, except for South America, where event rates were higher. There, too, the odds ratio trended favorable for prasugrel.

Figure 14 shows the results for subgroups of prior (known) vascular disease, metabolic syndrome, diabetes, creatinine clearance (Ccr), prior MI, prior PCI, prior CABG, and history of stroke or TIA. The results trend consistently in favor of prasugrel, with the exception of subjects with a prior history of TIA or stroke.

Figure 14: Results for Triple Composite Endpoint – All ACS Population – Subgroups of Preexisting Medical Conditions, Coronary Disease, Procedures, TIA, and CVA



Subjects with Prior History of Transient Ischemic Attack or Stroke:

The clinical outcomes were particularly poor for prasugrel-treated subjects with a prior history of transient ischemic attack (TIA) or non-hemorrhagic stroke. Because of the risk of ICH, potential subjects with a history of hemorrhagic stroke, ischemic stroke ≤ 3 months prior to screening, intracranial neoplasm, arteriovenous malformation, or aneurysm were excluded from participation in TAAL. These criteria allowed entry to patients with a history of ischemic stroke > 3 months prior to screening, as well as patients with a history of TIA.

For subjects with a prior history of TIA or non-hemorrhagic stroke, the HR for the composite efficacy endpoint was unfavorable for prasugrel, going against the grain of the study as a whole. The HR was 1.38 in favor of *clopidogrel*: 47 of 262 prasugrel treated subjects (17.9%) experienced an endpoint event, compared to 35 of 256 clopidogrel-treated subjects (13.7%). Table 8 breaks down the components of the triple endpoint for subjects with and without a prior history of TIA or stroke, and shows "All Stroke" as well. Of note, approximately 1/3 of the endpoint events in the prasugrel group were stroke. Specifically, 6.5% of subjects in the prasugrel treatment group experienced a stroke on study (2.3% ICH; 4.2% thrombotic) compared to 1.2% in the clopidogrel treatment group (0% ICH; 1.2% thrombotic), for a HR of

5.64. In patients with no prior history of TIA or non-hemorrhagic stroke, the incidence of stroke was 0.9% (0.2% ICH) in the prasugrel treatment group and 1.0% (0.3%) in the clopidogrel treatment group.

It is striking that more than one-quarter of the non-fatal strokes in the prasugrel treatment group (17 of 61) occurred in the sub-population of subjects with a history of prior TIA or non-hemorrhagic stroke, a sub-population encompassing only 3.8% of the total subject population. Moreover, it should be re-emphasized that subjects with a history of ischemic stroke within 3 months of randomization, as well as subjects with a history of hemorrhagic stroke at any time, were excluded from the study. (It is possible that such patients would have fared even worse.)

Based on these concerns, the clinical reviewer recommended a contraindication for prasugrel in patients with a prior history of TIA or stroke. This reviewer supports that recommendation.

Table 8: Cardiovascular Death, Nonfatal MI, Nonfatal Stroke, and All Stroke in Subjects With and Without a Prior History of Stroke or TIA

Endpoint	Prior TIA or Stroke?	Prasugrel			Clopidogrel			Cox Proportional HR (95% C.I.)	p
		N	n	%	N	n	%		
Triple Composite	Yes	262	47	17.9	256	35	13.7	1.38 (0.89, 2.13)	0.15
	No	6551	596	9.1	6539	746	11.4	0.79 (0.71, 0.88)	<0.001
CV Death	Yes	262	9	3.4	256	15	5.9	0.63 (0.28, 1.44)	0.27
	No	6551	124	1.9	6539	135	2.1	0.92 (0.72, 1.17)	0.48
Nonfatal MI	Yes	262	29	11.1	256	25	9.8	1.15 (0.67, 1.97)	0.61
	No	6551	446	6.8	6539	595	9.1	0.74 (0.66, 0.84)	<0.001
Nonfatal Stroke	Yes	262	15	5.7	256	2	0.8	7.39 (1.69, 32.3)	0.002
	No	6551	46	0.7	6539	58	0.9	0.79 (0.54, 1.17)	0.23
All Stroke	Yes	262	17	6.5	256	3	1.2	5.64 (1.65, 19.3)	0.002
	No	6551	58	0.9	6539	68	1.0	0.85 (0.60, 1.21)	0.36

Concomitant Therapies:

- Stents

In the All ACS population, the hazard ratio for prasugrel compared to clopidogrel was essentially the same in subjects receiving any stent (0.81), no stent (0.82), any drug-eluting stent (0.79), and any bare metal stent (0.80).

- GPIIb/IIIa Inhibitors

In the All ACS population, the hazard ratio for prasugrel compared to clopidogrel was similar in subjects receiving a GPIIb/IIIa inhibitor during the index procedure (0.79) compared to subjects not receiving a GPIIb/IIIa inhibitor during the index procedure (0.83). A similar pattern was observed for the UA/NSTEMI and STEMI populations.

- Statins

For the overall ACS population, the hazard ratio in favor of prasugrel was similar in subjects treated and not treated with a statin, 0.81 and 0.83, respectively. Hazard ratios were similar for the UA/NSTEMI and STEMI populations.

- Aspirin

According to the sponsor's analyses, the relative risk reduction with prasugrel compared to clopidogrel in the all ACS population was not influenced by the maximum aspirin dose (>0 to <100, 100 to 200, >200-mg/day) administered through 3 days after randomization and more than 3 days from randomization. These observations were similar for the UA/NSTEMI and STEMI populations.

- Proton Pump Inhibitors

If PPI had importantly diminished prasugrel's pharmacodynamic effects in the setting of salt-to-base conversion, one would expect diminished efficacy in subjects who were receiving PPI. Approximately 40% of the subjects in each treatment group reported use of PPI as a concomitant medication. The Cox proportional hazard ratio favored prasugrel over clopidogrel in subsets of subjects who received and did not receive PPI, and was virtually the same in both subsets. Hazard ratios were 0.82 and 0.80 in subjects who reported and did not report use of PPI, respectively.

- CABG

In the All ACS population undergoing CABG, the hazard ratio was favorable for prasugrel (0.71).

Time from First Symptom to Randomization:

For the UA/NSTEMI population, the hazard ratios were favorable for prasugrel in subjects randomized ≤24 hours and >24 hours after symptom onset (hazard ratios 0.75 and 0.87, respectively).

For the STEMI population, the hazard ratios were favorable for prasugrel in subjects randomized >12 hours after symptom onset and ≤12 hours after symptom onset (hazard ratios 0.65 and 0.87, respectively).

Time from Loading Dose to PCI:

Dr. Raj Madabushi explored the relation between the triple-endpoint outcome and the time interval between LD and start of PCI. He divided subjects in octiles based on time between LD and start of PCI, and computed the proportion of triple endpoint events for each octile, by treatment arm. Within each octile, there were fewer numbers of events in prasugrel-treated subjects, demonstrating a consistent advantage of prasugrel over clopidogrel, irrespective of the timing of the LD relative to PCI.

Interestingly, in both treatment arms, the lowest numbers of endpoint events were observed when the loading dose was administered at the start of PCI or within 30 minutes thereof. With increasing time between the LD and start of PCI (earlier or later), the proportion of endpoint events increased. Dr. Madabushi concluded that the LD (for either prasugrel or clopidogrel) should be administered within 30 minutes of the start of PCI.

This conclusion is subject to interpretation. The finding of an association between outcome and timing of the LD relative to PCI does not prove causality. For example, administration of the LD >1 hour after leaving the catheterization laboratory was a protocol violation, and could be related to a subject's medical instability. Prolonged intervals between administration of the LD and subsequent PCI were interpreted as "early" administration of the LD, but may in fact represent delayed PCI, due to difficult vascular access, complex anatomy, clinical instability, etc., which might be associated with worse outcomes. Thus, although these analyses are

interesting and merit consideration, this secondary reviewer is not convinced that the association should be used to provide advice to practitioners in labeling.

7.3.3. Secondary Endpoints

Results from the 2° endpoints are shown in Table 9. The triple composite endpoint was statistically significant in favor of prasugrel at Days 30 and 90. (Although these were denoted as 2° endpoints, they are, in fact, sensitivity analyses on the 1° endpoint.)

The other 2° endpoints were statistically significantly in favor of prasugrel for the All ACS population, and to lesser extents, for the UA/NSTEMI and STEMI populations individually.

The stent thrombosis endpoint is robust (0.49 RR in favor of prasugrel, 95% CI 0.36, 0.68, for the overall ACS population, $p < 0.001$). Initially, the clinical reviewer (Dr. Karen Hicks) raised concerns regarding the validity of the stent thrombosis endpoint, because the CEC review did not meet the diagnostic standards for stent thrombosis developed recently by the Academic Research Consortium (2007). These standards require angiographic confirmation of stent thrombosis, generally determined by an angiographic core laboratory or pathological confirmation: evidence of recent thrombus within the stent or direct examination of tissue retrieved following thrombectomy. In TAAL, there was no review of angiograms by an angiographic core laboratory, and there was limited pathological confirmation; only *reports* of coronary angiograms and other clinical reports were used to make determinations of stent

Table 9: TAAL – Secondary Endpoints

endpoint	Patient population	Cox										p	
		Prasugrel			Clopidogrel			Total			Proportional HR (95% C.I.)		
		N	n	%	N	n	%	N	n	%			
Composite of CV death, nonfatal MI, or UTVR at Day 30													
	UA/NSTEMI	5044	281	5.57	5030	349	6.94	10074	630	6.25	0.80 (0.68, 0.93)	0.005	
	STEMI	1769	118	6.67	1765	155	8.78	3534	273	7.72	0.75 (0.59, 0.96)	0.02	
	All ACS	6813	399	5.86	6795	504	7.42	13608	903	6.64	0.78 (0.69, 0.89)	<0.001	
Composite triple endpoint at Day 30													
	UA/NSTEMI	5044	274	5.43	5030	336	6.68	10074	610	6.06	0.81 (0.69, 0.95)	0.009	
	STEMI	1769	115	6.50	1765	166	9.41	3534	281	7.95	0.68 (0.54, 0.87)	0.002	
	All ACS	6813	389	5.71	6795	502	7.39	13608	891	6.55	0.77 (0.67, 0.88)	<0.001	
Composite of CV death, nonfatal MI, or UTVR at Day 90													
	UA/NSTEMI	5044	345	6.84	5030	420	8.35	10074	765	7.59	0.81 (0.70, 0.94)	0.004	
	STEMI	1769	127	7.18	1765	168	9.52	3534	295	8.35	0.75 (0.59, 0.94)	0.013	
	All ACS	6813	472	6.93	6795	588	8.65	13608	1060	7.79	0.79 (0.70, 0.90)	<0.001	
Composite triple endpoint at Day 90													
	UA/NSTEMI	5044	333	6.60	5030	395	7.85	10074	728	7.23	0.83 (0.72, 0.97)	0.015	
	STEMI	1769	129	7.29	1765	178	10.08	3534	307	8.69	0.72 (0.57, 0.90)	0.004	
	All ACS	6813	462	6.78	6795	573	8.43	13608	1035	7.61	0.80 (0.71, 0.90)	<0.001	
Composite triple endpoint or re-hospitalization for cardiac ischemic events													
	UA/NSTEMI	5044	598	11.86	5030	688	13.68	10074	1286	12.77	0.86 (0.77, 0.96)	0.006	
	STEMI	1769	199	11.25	1765	250	14.16	3534	449	12.71	0.78 (0.65, 0.94)	0.009	
	All ACS	6813	797	11.70	6795	938	13.80	13608	1735	12.75	0.84 (0.76, 0.92)	<0.001	
Composite of all-cause mortality, nonfatal MI, or nonfatal stroke													
	UA/NSTEMI	5044	504	9.99	5030	590	11.73	10074	1094	10.86	0.84 (0.75, 0.95)	0.005	
	STEMI	1769	188	10.63	1765	232	13.14	3534	420	11.88	0.80 (0.66, 0.97)	0.02	
	All ACS	6813	692	10.16	6795	822	12.10	13608	1514	11.13	0.83 (0.75, 0.92)	<0.001	
Definite or probable stent thrombosis per Academic Research Consortium (ARC) definition at study end													
	UA/NSTEMI	4798	39	0.81	4789	80	1.67	9587	119	1.24	0.49 (0.34, 0.72)	<0.001	
	STEMI	1624	19	1.17	1633	40	2.45	3257	59	1.81	0.50 (0.29, 0.87)	0.011	
	All ACS	6422	58	0.90	6422	120	1.87	12844	178	1.39	0.49 (0.36, 0.68)	<0.001	

thrombosis.

The sponsor argued (regulatory response of August 22, 2008) that according to FDA draft guidance, an angiographic core laboratory is not *required*: “FDA strongly recommends that interpretation of data from tests such as angiograms, IVUS, and ECGs be performed by independent core labs and that blinded adjudication of clinical events be conducted by a clinical events committee (CEC Clinical adjudication committees should be independent of core lab analysis centers to avoid potential bias).”³

Ultimately, Dr. Hicks selected a number of cases for review by an independent core laboratory, and requested details regarding the adjudication process. The independent review appeared to support the reliability of the original results.

7.3.4. Efficacy Conclusions

Treatment with prasugrel was associated with a statistically significant reduction in the composite triple endpoint of cardiovascular death, nonfatal MI, and nonfatal stroke. These findings were statistically persuasive across the UA/NSTEMI population, the STEMI population, and the overall ACS population, and robust to exploration. The effect of prasugrel on the 1^o endpoint was evident across the spectrum of subject weight, age, and sex, and in the presence and absence of concomitant diseases and medications that are common in the ACS population. Results were similar whether or not subjects received a stent, and irrespective of whether a bare metal stent or drug-eluting stent was deployed.

Efficacy was driven by a reduction in non-fatal MI, which was statistically significant in both the STEMI and UA/NSTEMI populations. There was a positive trend in mortality in favor of prasugrel in the STEMI population, but not in the larger UA/NSTEMI population. Stroke was similar in the two groups. In exploratory analyses, variability in salt to base conversion had no demonstrable effect on prasugrel's efficacy.

The following weaknesses and concerns have been identified:

1) Prevention of stroke: Importantly, the efficacy of clopidogrel was established in CURE, where clopidogrel was compared to placebo on a background of aspirin in subjects presenting with UA/NSTEMI. The study utilized a triple composite endpoint similar to that used in TAAL. In CURE, clopidogrel was associated with a 20% relative risk reduction on the triple endpoint, but was essentially neutral on the stroke component of the endpoint. Specifically, rates of stroke were 1.2% and 1.4% for the clopidogrel and placebo groups, respectively, for a non-statistically significant relative risk reduction of 14% (95% C.I. -17.7% to 36.6%). In TAAL, prasugrel's effect on stroke was neutral with respect to clopidogrel (hazard ratio 1.02 in favor of clopidogrel, 95% C.I. 0.71 to 1.45). Therefore, in estimating what prasugrel's effect on stroke would have been relative to placebo, the neutral effects in CURE and TAAL are chained, and the evidence of effectiveness is nil.

2) For subjects with a prior history of TIA or stroke, the overall effect of prasugrel was negative, driven by a striking *increase* in strokes (hazard ratio of 5.64, 95% C.I. 1.65 to 19.3). (Of note, subjects with a history of hemorrhagic stroke were excluded from participation, and it is possible that inclusion of such patients might have driven the risk of recurrent stroke even higher.) *Presently, the evidence that prasugrel causes stroke in patients with a prior TIA or*

³ Guidance for Industry: “Coronary Drug-Eluting Stents-Nonclinical and Clinical Studies,” draft, March 2008. <http://www.fda.gov/cdrh/ode/guidance/6255.html>

stroke seems more persuasive than the evidence that prasugrel prevents stroke in those without such a history. As such, it would not be appropriate to give prasugrel an indication for stroke, based on extant data. On the contrary, risk management should include a contraindication for patients with a prior history of TIA or stroke.

3) Subjects of African descent: Subjects of African descent accounted for less than 3% of the subject population in TAAL. At this point, there is no reason to believe that results from Caucasians can not be extrapolated to patients of African descent, but the size of the subgroup was too limited to be very informative in its own right.

7.4. Safety

7.4.1. Exposure

TALL included 6741 subjects in the prasugrel treated population and 6716 subjects in the clopidogrel treated population (13,457 in total). Taking into consideration temporary drug discontinuations, median exposure was 442 days in the prasugrel group and 444 days in the clopidogrel group. Over 4200 subjects in each treatment group were exposed for greater than one year.

Although TAAL was a large cardiovascular outcome study, it was by no means a large “simple” trial. Subjects were evaluated at hospital discharge, Days 30, 90, 180, 270, 360, and 450 (or last visit) for adverse events and concomitant medications. In addition, vital signs, ECG, complete blood count, platelet count, and clinical chemistries were performed at each visit. Thus, the safety database is quite robust.

Because 98.8% of randomized subjects received the study agent, the safety population is not importantly different from the ITT efficacy population. As such, the reader is referred back to Table 2 and Table 3 for a breakdown of demographic and historical characteristics, respectively.

The following weaknesses are identifiable in terms of exposure: the database included few subjects with hepatic and renal impairment. Approximately 0.5% of subjects in each group had pre-existing hepatic impairment; approximately 0.8% had severe renal impairment (calculated creatinine clearance < 30 mL/min). Approximately 10% of subjects had calculated creatinine clearance between 30-60 mL/min. Thus, experience is extremely limited in subjects with severe hepatic and renal dysfunction, and this should be pointed out in labeling.

7.4.2. All-Cause Mortality

Table 10 displays the sponsor’s summary breakdown of deaths in TAAL, adapted from Table TAAL.11.10 of the TAAL study report. The right-most column provides point estimates for the numbers of events that prasugrel would be expected to prevent (if >0) or cause (if <0), relative to clopidogrel, per 1000 patients treated.

There was no significant difference in all-cause death between treatment groups; the frequencies of CEC-adjudicated all-cause mortality were 2.76% and 2.90% in the prasugrel and clopidogrel treatment groups, respectively (p=0.64, Table 10). Differences in mortality in the various categories are not statistically significant, but the most favorable trends for prasugrel (fewer deaths) are in those classified as related to acute MI and sudden/unwitnessed. The most unfavorable trends for prasugrel are in deaths classified as hemorrhagic/non-ICH, ICH, and malignancy.

Deaths due to bleeding and malignancy are addressed more fully in sections below.

	Prasugrel n=6813		Clopidogrel n=6795		delta events per 1000 patients treated (positive = favorable for prasugrel)
	n	%	n	%	
All Cause Death	188	2.76	197	2.9	1.4
Cardiovascular (component of 1° efficacy endpoint)	133	1.95	150	2.21	2.6
atherosclerotic vascular disease (excluding coronary)	0	0	3	0.04	0.4
CHF/cardiogenic shock	31	0.46	30	0.44	-0.1
related to CABG or PCI	15	0.22	16	0.24	0.2
dysrhythmia	4	0.06	7	0.1	0.4
pulmonary embolism	3	0.04	0	0	-0.4
acute MI	24	0.35	36	0.53	1.8
sudden or unwitnessed	36	0.53	42	0.62	0.9
ICH	9	0.13	5	0.07	-0.6
non-hemorrhagic stroke	5	0.07	6	0.09	0.1
other cardiovascular	6	0.09	5	0.07	-0.1
Non-Cardiovascular	55	0.81	47	0.69	-1.2
accident/trauma	4	0.06	4	0.06	0.0
hemorrhage, non-ICH	9	0.13	1	0.01	-1.2
infection	11	0.16	10	0.15	-0.1
malignancy	21	0.31	17	0.25	-0.6
suicide	3	0.04	2	0.03	-0.1
other	7	0.1	13	0.19	0.9

7.4.3. Discontinuations

The most commonly cited reason given for discontinuation was “subject decision,” reported in approximately 9% of subjects in each treatment group. The second most common reason for discontinuation was an adverse event, with 7.2% and 6.3% of subjects discontinuing in the prasugrel and clopidogrel groups, respectively (Table TAAL 12.2, TAAL Clinical Study Report). Hemorrhagic adverse events accounted for essentially all of the disparity: the percentages of subjects discontinuing study drug due to a serious hemorrhagic event were 1.6% and 0.9% in the prasugrel and clopidogrel groups, respectively. For non-serious hemorrhagic events, the respective percentages were 0.9% and 0.5%. The numbers of discontinuations for non-hemorrhagic adverse events were similar in the two groups.

7.4.4. Intracranial Hemorrhage (ICH)

In TAAL, ICH was reported in 20 (0.29%) and 16 (0.24%) subjects in the prasugrel and clopidogrel groups, respectively. In both groups, the majority of events occurred between 30 and 180 days post-randomization. Intracranial hemorrhages in the prasugrel group were more severe and recovery from these events was lower than in the clopidogrel group. Compared to clopidogrel, twice as many prasugrel-treated subjects died from ICH.

7.4.5. Non-ICH Bleeding

The sponsor categorized bleeding events as related or unrelated to coronary artery bypass graft (CABG) surgery. Events within 7 days of completion of the CABG surgery were classified as CABG-related by the central adjudication committee.

7.4.6. Non-CABG-Related Bleeding

The risk of bleeding was well-considered in the review by Dr. Hicks. Prasugrel was associated with excess bleeding relative to clopidogrel, irrespective of bleeding definition, seriousness, or location, and across most subgroups assessed. The time course of CEC-adjudicated TIMI major or minor bleeding is shown Figure 15. Note that approximately one-third of all bleeding events were recorded in the first day; nearly half of all bleeding events were reported in the initial 10 days.

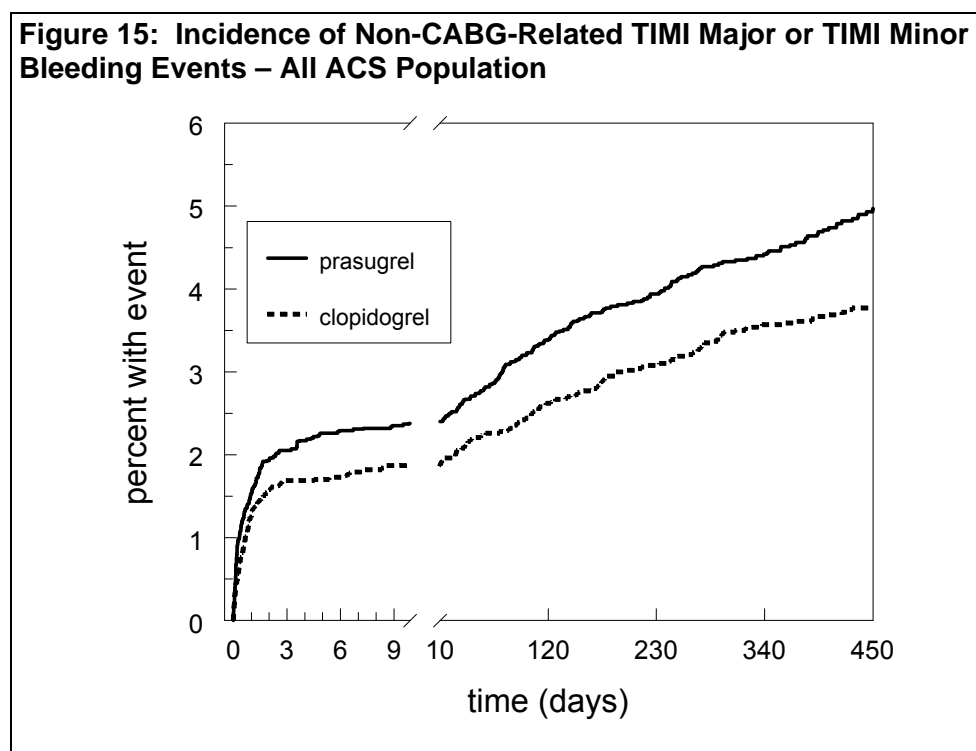


Table 11 summarizes the various categories of bleeding events in TAAL. Because some subjects experienced more than one bleeding event, they appear in more than one category. The last two categories of the upper section, “Worst: TIMI Minor” and “Worst: TIMI Minimal,” represent the subjects in whom the most significant bleeding event was a TIMI minor or TIMI minimal bleeding event, respectively.

There were 21 and 5 fatal bleeding events in the prasugrel and clopidogrel groups, respectively (RR = 4.19, 95% C.I.: 1.58, 11.1, p=0.002), Table 11. All 5 of the fatal bleeding events in the clopidogrel group were intracranial in location. For the prasugrel group, 9 of 21 fatal bleeding events were intracranial, and 12 were not (5 were gastrointestinal [GI], 2 originated from puncture sites, 2 from surgical sites, 2 from retroperitoneal locations, and 1 from an intra-abdominal location). Given that it is generally more feasible to manage bleeding at extra-cranial sites than at intracranial sites, it is worth emphasizing that none of the deaths in the clopidogrel group, but over half the deaths in the prasugrel group, were attributed to extra-cranial sites of

hemorrhage. The disparity in deaths from extracranial hemorrhage between the prasugrel and clopidogrel groups suggests that severe bleeding may be more difficult manage in patients who received prasugrel.

The RR was 1.52 for TIMI life-threatening bleeding events, and this was also statistically significant (Table 11). For TIMI major and TIMI minor bleeding, the relative risks were 1.32 and 1.31, respectively, and the differences were statistically significant.

From these data, it is possible to characterize bleeding in terms of excess bleeding events per 1000 patients treated. Comparing prasugrel to clopidogrel, the absolute risks predict 2.4 additional fatal bleeding events, 4.3 additional TIMI life-threatening bleeds, 5.1 additional TIMI major bleeds (which include fatal and life-threatening bleeds), 5.4 additional TIMI minor bleeds, and 19.4 additional TIMI minimal bleeds per 1000 patients treated. In total, per 1000 patients treated, these calculate to 30 excess TIMI bleeding events of any magnitude, 10.5 bleeding events associated with a decrease in hemoglobin of ≥ 3 g/dL, and 5.1 bleeding events associated with a decrease in hemoglobin of ≥ 5 g/dL.

7.4.7. CABG-Related Bleeding

The prasugrel-associated bleeding risk was particularly malignant in subjects who underwent CABG (Table 11, bottom). In the prasugrel group, there were 24 TIMI major bleeding events in 213 total ACS subjects (11.3%, RR=3.50), of which 2 were fatal (0.9%). In the clopidogrel group, there were 8 TIMI major bleeds, and none were fatal. There are additional analyses of CABG-related bleeding on page 43.

Reviewer's Comments: Prasugrel should not be the drug of choice for patients in whom CABG surgery is anticipated. From a practical standpoint, prasugrel is not well-suited for pre-treatment of patients in whom coronary anatomy is unknown.

CDER undertook independent analyses of bleeding adverse events, characterized as “mild,” “moderate,” or “severe,” as well as those meeting the regulatory definition of a serious adverse event (see primary clinical review). For all categories of bleeding events, the RR was approximately 1.4, and the difference between treatment groups was statistically significant. The frequencies of bleeding events meeting the regulatory definition of a serious adverse event were 5.5 and 3.8% in the prasugrel and clopidogrel groups, respectively (RR 1.46, 95% C.I. 1.25, 1.71).

Table 11: CEC Adjudicated Bleeding**Non-CABG-Related**

bleeding endpoint	Prasugrel			Clopidogrel			HR (95% C.I.)	p
	N	n	%	N	n	%		
TIMI Fatal	6741	21	0.3	6716	5	0.1	4.19 (1.58,11.1)	0.002
TIMI Life-Threatening	6741	85	1.3	6716	56	0.8	1.52 (1.08,2.13)	0.015
TIMI Major	6741	146	2.2	6716	111	1.7	1.32 (1.03,1.68)	0.029
TIMI Minor	6741	164	2.4	6716	125	1.9	1.31 (1.04,1.66)	0.022
TIMI Minimal	6741	460	6.8	6716	314	4.7	1.47 (1.28,1.70)	0.022

CABG-Related

bleeding endpoint	Prasugrel			Clopidogrel			HR (95% C.I.)	p
	N	n	%	N	n	%		
TIMI Fatal	213	2	0.9	224	0	0.0		
TIMI Major	213	24	11.3	224	8	3.6	3.50 (1.53,7.99)	0.002

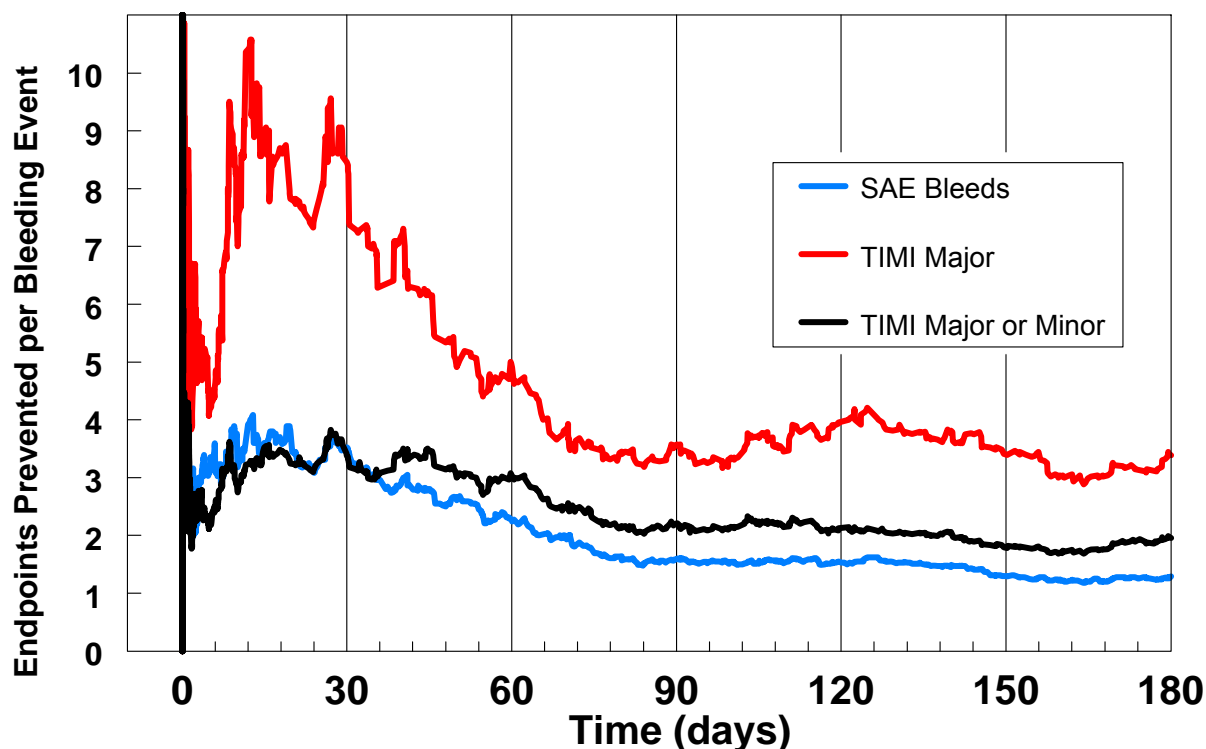
The fatality rate for intracranial hemorrhages was twice as high in the prasugrel treatment group compared to the clopidogrel treatment group.

7.4.8. Risk-Benefit Analysis: Bleeding as a Function of Time

Relative to clopidogrel, the principal risk associated with prasugrel is the risk of bleeding, and the principal benefit is the prevention of non-fatal myocardial infarction. By considering the endpoint events prevented by prasugrel relative to the bleeding events attributed to prasugrel, an actual cumulative benefit-risk *ratio* can be calculated cumulatively over time. The cumulative percentage of endpoint events prevented was calculated by subtracting the event rates for prasugrel and clopidogrel in the Kaplan-Meier analysis for the overall ACS population (i.e., the method used to generate Figure 7). The same approach was used for bleeding events that met the regulatory definition of a serious adverse event (SAE), TIMI major, and TIMI major or minor bleeds. For each bleeding category, the cumulative delta percent was calculated over time. Finally, at each time point, the percentage of endpoint events prevented was divided by the percentage of excess bleeding events. The resulting functions represent the cumulative number of endpoint events prevented per excess bleeding event, as a function of time (Figure 16).

The general shapes of the relations are similar for all the 3 categories of bleeding events. The tradeoff between efficacy and bleeding is most favorable around day 12, exhibits a gentle “plateau” through approximately Day 30, and declines through day 80, as the numbers of attributable bleeding events outpace the number of endpoint events prevented. After day 80, the benefit-risk relation is fairly constant (Figure 16, data shown through Day 180).

Figure 16: Cumulative Benefit-Risk of Prasugrel Compared to Clopidogrel as a Function of Time: All ACS Population



Although the y-axis scaling factor depends on the particular definition of bleeding used for the analysis, it is important to note that the *shape* of the curve is largely independent of the definition of bleeding used, and shows how benefit and risk relate through time. It is also important to emphasize that the relation approximates the benefit-risk for prasugrel relative to clopidogrel, and not to placebo.

7.4.9. Bleeding Events: Subgroup Analyses

Table 12 shows the incidence of non-CABG-related TIMI major or minor bleeding events in subgroups based on demographic characteristics and weight. The data reflect bleeding events while at risk, i.e., events from the first dose of study drug through 7 days after permanent study drug discontinuation. The top portion of the table shows pre-specified subgroups, as adapted from TAAL Table 12.18. The analysis by weight quintiles (bottom) was performed by this reviewer, and is based on the sponsor's CECBLDF.xpt dataset, variable "C_TAIALL."

The sponsor found no significant treatment-by-demographic characteristic interactions. None of the subgroups distinguished themselves as being associated with a particularly high RR for prasugrel, although RR trended slightly higher in females. Relative risk was higher (1.72) for subjects weighing <60 kg; however, this is an arbitrary weight cutoff with relatively few subjects in this subgroup. The overall analysis of RR of bleeding by quintile does not suggest a particular issue with subjects of lower weight. The RR for subjects of African descent was similar to the RR for Caucasians; the RR was less favorable for prasugrel in Hispanic and Asian subjects, although the sample size in both of these subgroups was small. A few other factors deserve special consideration, and they are discussed below.

Table 12: Non-CABG-Related TIMI Major or Minor Bleeding Events by Subgroup

parameter		Prasugrel			Clopidogrel			RR (95% C.I.)	p
		N	n	%	N	n	%		
overall		6741	303	4.5	6716	231	3.4	1.31 (1.11, 1.56)	0.002
sex	female	1684	123	7.3	1798	97	5.4	1.38 (1.06, 1.80)	0.017
	male	5057	180	3.6	4918	134	2.7	1.31 (1.05, 1.64)	0.018
age	<65	4149	141	3.4	4096	99	2.4	1.41 (1.09, 1.83)	0.008
	>=65	2592	162	6.3	2620	132	5.0	1.26 (1.00, 1.59)	0.046
	<70	5095	182	3.6	5041	138	2.7	1.31 (1.05, 1.64)	0.016
	>=70	1646	121	7.4	1675	93	5.6	1.35 (1.03, 1.76)	0.03
	<75	5850	223	3.8	5822	169	2.9	1.32 (1.08, 1.61)	0.006
	>=75	891	80	9.0	894	62	6.9	1.35 (0.97, 1.88)	0.078
ethnicity	Caucasian	6196	281	4.5	6200	217	3.5	1.30 (1.09, 1.56)	0.003
	African	201	10	5.0	185	7	3.8	1.34 (0.51, 3.53)	0.551
	Hispanic	269	10	3.7	255	6	2.4	1.55 (0.56, 4.27)	0.393
	Asian	60	2	3.3	63	1	1.6	-	-
weight quintile; range (kg)	1 (32 - 70)	1416	96	6.8	1526	75	4.9	1.38 (1.03, 1.85)	<0.05
	2 (>70 - 78)	1265	61	4.8	1245	43	3.5	1.40 (0.95, 2.05)	NS
	3 (>78 - 85)	1365	49	3.6	1315	39	3.0	1.21 (0.80, 1.83)	NS
	4 (>85 - 95.2)	1291	50	3.9	1265	42	3.3	1.17 (0.78, 1.75)	NS
	5 (>95.2)	1344	43	3.2	1304	30	2.3	1.39 (0.88, 2.2)	NS
weight unknown		60	4	6.7	61	2	3.3	2.03 (0.39, 10.7)	NS
weight <60 kg *		412	40	9.7	444	25	5.6	1.72 (1.07, 2.79)	<0.05

* Weight <60 kg is a subset of quintile #1.

7.4.10. Bleeding and Advanced Age

For the study overall, there was a striking increase in bleeding with advancing age; however, the HR for prasugrel compared to clopidogrel was consistent across age strata. Specifically, the HR for TIMI Major/Minor bleeding for the overall study was 1.31 (worse for prasugrel). Similarly, the HR for subjects over 70 years of age was 1.35, as was the HR for subjects over 75. Thus, based on a comparison to clopidogrel, prasugrel's risk of bleeding in subjects over 75 seems similar to that in younger patients.

However, the *outcomes* secondary to bleeding in prasugrel-treated subjects over 75 years of age were of particular concern. Specifically, the frequency of fatal hemorrhage was 9/891 (1.0%) for prasugrel-treated subjects, versus 1/894 (0.1%) for clopidogrel-treated subjects. For symptomatic intracranial hemorrhage (ICH), there were 7 (0.8%) versus 3 (0.3%) cases associated with prasugrel and clopidogrel, respectively.

Moreover, prasugrel's efficacy is less certain in patients age 75 or greater. First, In TAAL, the percentages of subjects over the age of 75 experiencing a 1° endpoint event were closer for the prasugrel and clopidogrel groups (16.0% versus 17.0%, respectively) than in the overall study, where the difference was about 2%. Second, the efficacy of *clopidogrel* is less well-established in patients over the age of 75. In CURE, the registrational study of clopidogrel that compared clopidogrel and placebo in the setting of ACS, the frequencies of experiencing the triple endpoint of cardiovascular death, non-fatal MI, or non-fatal stroke were 9.3% and 11.4% for clopidogrel and placebo, respectively. However, in subjects age 75 and over, the respective

frequencies were 17.8% and 19.2%. Thus, efficacy is modest for clopidogrel in the over-75 age group, and by extension, for prasugrel.

In summary, therefore, prasugrel was associated with malignant bleeding outcomes in patients ≥ 75 years of age. Given that prasugrel's efficacy is less clear in this subgroup of patients, the review team opined that use of prasugrel should be discouraged in patients ≥ 75 years of age, and I agree with their reasoning and recommendation.

7.4.11. Concomitant Medication Use

The sponsor conducted subgroup analyses to assess the effects of concomitant medications on the incidence of non-CABG-related bleeding events. The purpose was to investigate the relationship between these medications and the incidence of bleeding during the index hospitalization; therefore, the analysis was limited to medications administered and bleeding events experienced during first 3 days after the LD of study drug.

Medication	Use?	Prasugrel			Clopidogrel			Cox Proportional HR (95% C.I.)
		N	n	%	N	n	%	
Overall		6741		4.5	6716	0	3.4	
GPIIb/IIIa	any	3652	22	0.6	3697	17	0.5	1.31 (0.70, 2.47)
	never	3089	12	0.4	3019	7	0.2	1.68 (0.66, 4.27)
Antithrombin	UFH	3455	21	0.6	3436	9	0.3	2.32 (1.06, 5.07)
	UFH+LMWH	2101	8	0.4	2161	14	0.6	0.58 (0.24, 1.39)
Fibrinolytic	yes	210	0	0.0	218	0	0.0	
	no	6531	34	0.5	6498	24	0.4	1.41 (0.84, 2.38)
Aspirin	>0 - <100 mg	689	7	1.0	672	3	0.4	2.28 (0.59, 8.80)
	100 - 200 mg	1703	10	0.6	1741	8	0.5	1.28 (0.51, 3.24)
	>200 mg	4328	16	0.4	4276	11	0.3	1.44 (0.67, 3.10)
	none	21	1	4.8	27	2	7.4	

Table 13 provides a summary of subgroup analyses of spontaneous (non-instrumented) non-CABG-related TIMI major or minor bleeding events by the use or non-use of a GPIIb/IIIa inhibitor, antithrombin agent, fibrinolytic, and aspirin, from symptom onset through Day 3 (from sponsor's Table 12.24.). For all of these subgroups, the data are somewhat difficult to interpret because the numbers of events are small (the analyses are through Day 3, only). There was a significant treatment-by-subgroup interaction for anti-thrombin monotherapy, unfractionated heparin (UFH), compared to UFH plus low molecular weight heparin (LMWH). In subjects receiving only UFH, the RR for spontaneous non-CABG-related TIMI major or minor bleeding events was 2.32 (worse with prasugrel). Conversely, in subjects receiving UFH plus LMWH, the RR strongly favored prasugrel (RR=0.58). There was higher incidence of bleeding events through 3 days while at risk in subjects receiving a GPIIb/IIIa inhibitor compared to subjects not receiving a GPIIb/IIIa inhibitor in each treatment group. For subjects who received GPIIb/IIIa inhibitors, the RR (1.31, unfavorable for prasugrel) is identical to the RR for the study as a

whole, suggesting that GPIIb/IIIa inhibitors do not pose a particular risk for patients who receive prasugrel.

Proton Pump Inhibitors:

Use of PPI deserves special mention. The clinical pharmacology reviewer (Dr. Mishina) noted that concomitant lansoprazole administration (a PPI) reduced the C_{max} of prasugrel's active metabolite by nearly 30% (Study TAAI). This interaction is thought to be a function of conversion of the product from the hydrochloride salt form to the free base form, i.e., the PPI interaction is important for the free base, but not the salt. The prasugrel used in TAAL was predominantly free base.

Table 14 shows the incidence of TIMI Major and Minor bleeding events through 3 days, dichotomized by PPI use or non-use (top) and H2 receptor antagonist use or non-use (bottom) through 3 days. For both treatment groups, the table also shows the relative risk of using PPI and H2 receptor antagonists, relative to not using them.

Table 14: Non-CABG-Related TIMI Major or Minor Bleeding Events from Symptom Onset Through Day 3, by PPI and H2 Receptor Antagonist Use Through Day 3

Medication	Use?	Prasugrel			Clopidogrel			Cox Proportional HR (95% C.I.)
		N	n	%	N	n	%	
PPI	yes	2760	70	2.5	2719	62	2.3	1.11 (0.79, 1.56)
	no	3981	68	1.7	3997	51	1.3	1.35 (0.94, 1.94)
RR of using PPI:				1.5			1.8	
H2 Antagonist	yes	1027	30	2.9	1017	25	2.5	1.19 (0.70, 2.02)
	no	5714	108	1.9	5699	88	1.5	1.23 (0.93, 1.63)
RR of using H2 Antagonist:				1.5			1.6	

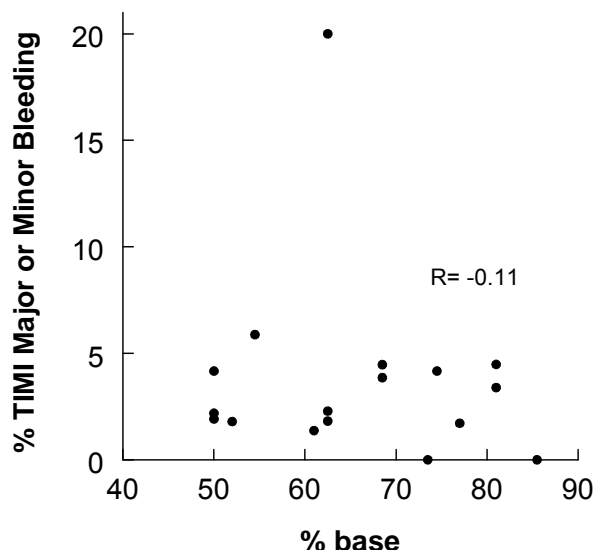
For both treatment groups, the incidence of bleeding was higher in subjects who received gastric pH-raising drugs than in those who did not. This may be related, in part, to the fact that PPI and H2 antagonist use was discretionary, and physicians may have been more willing to prescribe them for patients perceived to be at higher risk of bleeding events.

If prasugrel's salt-to-base conversion led to an important interaction between gastric pH and bleeding (and absent a similar interaction with clopidogrel), use of these medications would be expected to influence prasugrel's bleeding rates to a greater extent than those of clopidogrel. Although this is not a randomized comparison and the numbers of bleeding events are relatively small (through only Day 3), the data do not suggest an interaction that exists for prasugrel but not for clopidogrel. They do suggest that prasugrel's bleeding risk, with or without PPIs or H2 receptor antagonists, is fairly consistent with the study as a whole.

7.4.12. Bleeding by Lot

This reviewer assessed TIMI Major or Minor bleeding rates by lot administered during Days 2-30, and found no relation between salt-to-base conversion and bleeding (Figure 17).

Figure 17: TIMI Major or Minor Bleeding Versus Base Content of Lot Administered Days 2-30



7.4.13. Timing of Drug Discontinuation and CABG-Related Bleeding

Table 15 shows the incidence of TIMI Major/Minor bleeding events as a function of time of discontinuation of study agent relative to subsequent CABG. The frequency of CABG-related bleeding was substantially higher in subjects treated with prasugrel compared to subjects treated with clopidogrel. For prasugrel, the length of time of discontinuation of the drug in advance of CABG was an important determinant of bleeding frequency. When CABG was performed within 3 days of discontinuing prasugrel, the frequency of TIMI Major or Minor bleeding was $12/45 = 27\%$. For clopidogrel, the corresponding frequency was $3/60 = 5\%$. The respective frequencies for discontinuation of prasugrel and clopidogrel >3 to ≤ 7 days prior to CABG were 11% and 3%, respectively. Between 7 and 14 days, the respective frequencies were 10% and 7%. Thus, for prasugrel, it is clear that a longer period of discontinuation will result in less bleeding, and that the risk of bleeding within 3 days of discontinuing prasugrel is particularly high.

The primary clinical reviewer concluded that prasugrel should be discontinued at least 7 days prior to undergoing CABG, if possible. This advice seems reasonable, given that the frequency of TIMI major bleeding was 12.7% when CABG was performed within 7 days of the last dose of prasugrel. However, the risk of bleeding when prasugrel was stopped >7 days prior to surgery is not much lower than 12.7% (it is 8.9%), and is based on only 7 events in 79 subjects.

Figure 18 is adapted from the data at the bottom of Table 15, and shows the cumulative TIMI Major or Minor bleeding frequencies through each day of discontinuation, prior to CABG. Thus, the percentages of events at Day 6 correspond to cumulative bleeding frequencies when the drugs were discontinued ≤ 6 days prior to CABG. For prasugrel, there is little reduction in frequency after Days 7-8. Thus, advice to discontinue prasugrel 7 or more days prior to elective surgery seems fairly reasonable. For clopidogrel, the risk is far lower, and little affected by timing of discontinuation.

Practically speaking, the increased frequency of CABG-related TIMI major bleeding with prasugrel is principally a cause for concern in the setting of urgent CABG, where there is no opportunity to stop the drug. The review team concluded that use of prasugrel should be discouraged when coronary anatomy is unknown and CABG is a possibility. For elective CABG, it seems reasonable to discontinue prasugrel 7 days prior to surgery.

Table 15: CABG-Related TIMI Major or Minor Bleeding Events: Days from Last Dose of Study Drug to CABG

Days from last dose to CABG	Prasugrel			Clopidogrel		
	N	n	%	N	n	%
0	12	1	8.3	22	1	4.5
1	17	6	35.3	12	0	0
2	4	2	50	11	1	9.1
3	12	3	25	15	1	6.7
4	8	1	12.5	14	1	7.1
5	30	3	10	30	2	6.7
6	18	2	11.1	21	0	0
7	24	3	12.5	25	0	0
8	13	1	7.7	10	0	0
9	8	0	0	9	2	22.2
10	10	2	20	5	0	0
11	5	0	0	2	0	0
12	3	0	0	1	0	0
13	1	1	100	2	0	0
14-27	9	0	0	11	0	0
28	1	1	100	1	0	0
29-60	4	0	0	3	0	0
61-341	6	1	16.7	5	0	0

N = numbers of subjects who underwent CABG

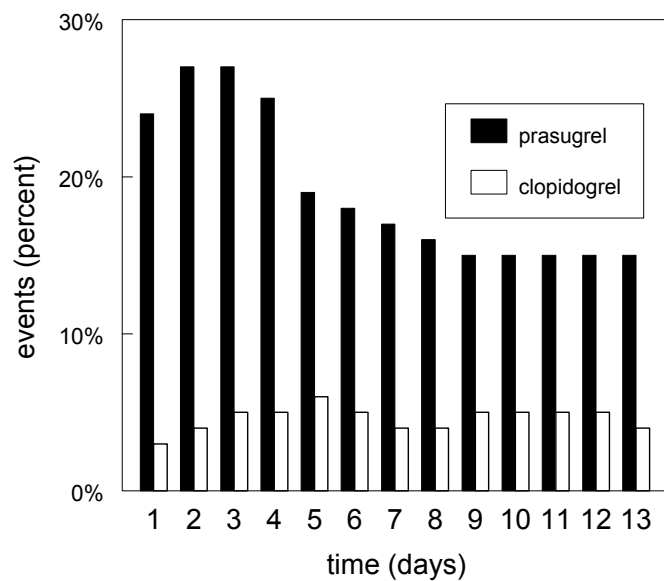
N = numbers of bleeding events

In summary, the review team concluded that the risk of bleeding is clearly higher with prasugrel, and specific information is merited in labeling for:

- patients ≥ 75 years of age (here the greater risk is for fatal and life-threatening bleeding)
- patients with a prior history of a transient ischemic attack or cerebrovascular accident (contraindication)
- patients who undergo CABG, or by extension, probably any surgical procedure

This information appropriate for labeling for patients of low weight is still under discussion.

Figure 18: Cumulative Frequency of TIMI Major or Minor CABG-Related Bleeding, by Day of Discontinuation Prior to Surgery



7.4.14. Non-Hemorrhagic Serious Adverse Events

Respiratory failure, hypotension, colon cancer, and atrial flutter were statistically significantly higher in subjects treated with prasugrel compared to subjects treated with clopidogrel:

- Respiratory failure: 0.22% prasugrel versus 0.09% clopidogrel; $p = 0.050$
- Hypotension: 0.21% prasugrel versus 0.06% clopidogrel; $p = 0.019$
- Atrial flutter: 0.18% prasugrel versus 0.06% clopidogrel; $p = 0.046$

Several of the events of respiratory failure occurred in the setting of TIMI bleeding.

The incidence of cardiac failure was statistically significantly lower in subjects treated with prasugrel than clopidogrel, possibly a dividend from decreasing the frequency of MI.

Clopidogrel carries a warning for thrombotic thrombocytopenia purpura (TTP), which has been reported rarely in association with the drug, and has been fatal in some cases. In the prasugrel development program, there were no reported cases of TTP in prasugrel-treated subjects, versus one case in a clopidogrel-treated subject.

Fifteen (0.22%) subjects in the prasugrel treatment group developed abnormal hepatic function, 8 (0.12%) had abnormal hepatic function reported as a serious adverse event, and 8 (0.12%) developed ALT > 3X ULN and total bilirubin > 1.5X ULN. These compare to 18 (0.27%), 15 (0.22%), and 4 (0.06%) subjects, respectively, in the clopidogrel treatment group. Clopidogrel's labeling does not contain any specific warning or precaution for hepatotoxicity, and based on these data, none seems appropriate for prasugrel.

Twenty-four prasugrel-treated (0.36%) and clopidogrel-treated (0.36%) subjects had allergic reactions reported as serious adverse events. Four (0.06%) prasugrel subjects and 3 (0.04%) clopidogrel subjects had angioedema reported as a serious adverse event. One of the

prasugrel subjects was also receiving an angiotensin converting enzyme inhibitor, begun 5 days earlier.

No adverse events of pancytopenia were reported in any subjects in the development program. Anemia was reported in 2.2% and 2.0% of subjects treated with prasugrel and clopidogrel, respectively. Leukopenia ($< 4 \times 10^9/L$) was reported in 2.8% and 3.5% of prasugrel- and clopidogrel-treated subjects, respectively. There were 4 reported cases (0.06%) of neutropenia in the prasugrel treatment group, compared with 21 cases (0.31%) in the clopidogrel treatment group. The reported frequency of thrombocytopenia was similar between the prasugrel and clopidogrel groups (0.3%). In most of the cases of thrombocytopenia, subjects were also receiving a GPIIb/IIIa inhibitor.

Pyrexia and increased tendency to bruise were reported in at least 1% of prasugrel subjects and the incidence of these adverse events was significantly higher than that in the clopidogrel treatment group. Fever may have been related to bleeding. The sponsor found that subjects treated with prasugrel who had a bleeding event were twice as likely to have fever compared to subjects treated with clopidogrel who had a bleeding event.

7.4.15. Cancer

Proportionally greater numbers of cancers were reported in subjects in the prasugrel treatment group, and much attention was paid to this issue by the Division of Cardiovascular and Renal Products clinical (Dr. K. Hicks) and secondary (Dr. T. Marciniak) reviewers, as well as consultants from the Division of Drug Oncology Products (B. Mann) and the Division of Epidemiology, Office of Surveillance and Epidemiology (Dr. D. Wysowski).

Non-Clinical, In Vitro

Review of the literature finds very little evidence suggesting that prasugrel, clopidogrel, or modulation of the P2Y₁₂ receptor would have important effects on genotoxicity, tumorigenesis, tumor promotion, metastasis, or angiogenesis.

Non-Clinical, In Vivo

To briefly recapitulate the results of the 2-year rodent carcinogenicity studies, the rat data do not suggest increased rates of either benign or malignant neoplasms (see section **Error! Reference source not found.** for details). In the mouse, at high exposures, there was a statistically significant dose-response relationship for hepatocellular adenoma. There was also a non-statistically significant trend in favor of increased hepatocellular carcinomas at the highest dose (300 mg/kg/day). Dr. Marciniak, the Medical Team Leader, expressed concern regarding the findings, in particular the trend for a dose-response in liver carcinomas. He also expressed concern regarding excess cases of lung cancer and intestinal cancer in the prasugrel groups with suggestions of dose-response relationships.

The Pharmacology/Toxicology review team and the Executive Carcinogenicity Advisory Committee opined that there was no evidence of a prasugrel-associated increase in malignant tumors in either species (hepatic or extra-hepatic), and found the results reassuring. Based on classical definitions, they opined that prasugrel is neither a “complete carcinogen” nor a “cancer promoter.”

Clinical

The sponsor’s original tabulation of treatment-emergent serious adverse events, system organ class (SOC) “neoplasms benign, malignant and unspecified (including cysts and polyps),” is

shown in Table 16, as adapted from Table TAAL 14.99. The corresponding tabulation of non-serious adverse events is provided in Table 17, adapted from Table TAAL 14.92.

Colorectal Cancer: The sponsor found 19 colorectal neoplasms in the prasugrel group and 8 in the clopidogrel group (RR=2.4), but found reassurance in the fact that half of cases in the prasugrel group were discovered as a result of an antecedent GI bleed.

Breast Cancer: The sponsor counted 5 cases of breast cancer in the prasugrel group, versus 1 in the clopidogrel group (RR=5.0), but the relatively short time frame between initiation of study drug and diagnosis, for at least some of the cases, assuaged the sponsor's concern.

Lung Cancer: There were 8 and 2 lung cancers reported as adverse events in the prasugrel and clopidogrel groups, respectively (RR=4.0). However, when "lung neoplasms" were added to the cancers, the respective numbers were 12 and 10. The sponsor determined, therefore, that the numbers of subjects with lung neoplasm were not different between treatment groups.

Prostate Cancer: Sixteen subjects in the prasugrel group and 9 in the clopidogrel group experienced an adverse event for prostate cancer or adenoma (RR=1.8). The sponsor took reassurance from the fact that in half of the 16 neoplasms in the prasugrel group, the diagnosis was made within 6 months of starting the study drug, ergo; they considered these unlikely to represent new cancers.

The sponsor was dismissive of these findings in their original summary interpretation:

"Cases of malignancy were reported at a frequency that was higher in the prasugrel than in the clopidogrel group. In some cases, such as prostate cancer, this appears to be a coincidental finding since about half of the cases were reported within 6 months of starting drug. In the case of colon cancer, they were often discovered during a diagnostic procedure following a bleed. In summary, there is no evidence that use of prasugrel is associated with a higher risk of cancer."

Division's Analyses:

The sponsor's initial description and analysis of cancer adverse events was difficult to interpret: 1) the distinction between pre-existing neoplasms and treatment-emergent neoplasms was not always clear; 2) there was little attempt to categorize neoplasms as malignant or non-malignant; and 3) there was little emphasis on categorization of cancers by organ or organ system.

With respect to distinguishing pre-existing from treatment-emergent neoplasms, the case report forms (CRFs) used in TAAL included a "Pre-Existing Conditions" form that was used to "list all ongoing medical conditions at the time of study entry/screening." Confusion arose for two reasons: 1) Each pre-existing condition was recorded as an "event" and given an "event code" numerically continuous with treatment-emergent adverse events recorded on the "Study Adverse Events" CRFs. At times, investigators inadvertently assigned treatment-emergent adverse events to numbers previously allocated to pre-existing conditions, which caused confusion (at times, a pre-existing condition was simply replaced by an adverse event; and 2) There were inconsistencies in recording pre-existing neoplasms, presumably because of investigators' difficulty in deciding whether a prior cancer was "ongoing" if it was not an active medical problem. Finally, for patients in the throes of an acute coronary event, understandably little attention was given to obtaining specific historical information regarding prior cancers.

Table 16: Treatment Emergent Serious Adverse Events from TALL, SOC “Neoplasms, benign, malignant and unspecified...”

Neoplasm as serious adverse event (from TAAL Table 14.99)	Prasugrel n (%)	Clopidogrel n (%)		Prasugrel n (%)	Clopidogrel n (%)
all	87 (1.29)	60 (0.89)	metastases to bone	1 (0.01)	2 (0.03)
colon cancer	10 (0.15)	2 (0.03)	metastases to liver	1 (0.01)	1 (0.01)
gastric cancer	6 (0.09)	7 (0.1)	nasal neoplasm	1 (0.01)	0 (0)
prostate cancer	6 (0.09)	7 (0.1)	oesophageal adenocarcinoma	1 (0.01)	0 (0)
breast cancer	4 (0.06)	1 (0.01)	oesophageal cancer metastatic	1 (0.01)	0 (0)
adenocarcinoma	2 (0.03)	0 (0)	oesophageal carcinoma	1 (0.01)	3 (0.04)
bladder cancer	2 (0.03)	4 (0.06)	ovarian neoplasm	1 (0.01)	0 (0)
brain cancer	2 (0.03)	1 (0.01)	pancreatic carcinoma	1 (0.01)	1 (0.01)
clear cell cancer of kidney	2 (0.03)	0 (0)	papillary thyroid cancer	1 (0.01)	0 (0)
lung neoplasm malignant	2 (0.03)	2 (0.03)	papilloma	1 (0.01)	0 (0)
lung squamous cell carcinoma	2 (0.03)	1 (0.01)	peripheral t-cell lymphoma	1 (0.01)	0 (0)
metastases to lung	2 (0.03)	0 (0)	pituitary tumour benign	1 (0.01)	0 (0)
metastatic neoplasm	2 (0.03)	0 (0)	prostatic adenoma	1 (0.01)	0 (0)
non-small cell lung cancer	2 (0.03)	2 (0.03)	rectal cancer	1 (0.01)	0 (0)
prostate cancer metastatic	2 (0.03)	1 (0.01)	rectal neoplasm	1 (0.01)	0 (0)
renal neoplasm	2 (0.03)	0 (0)	renal cell carcinoma	1 (0.01)	2 (0.03)
squamous cell carcinoma	2 (0.03)	1 (0.01)	salivary gland neoplasm	1 (0.01)	0 (0)
acute myeloid leukaemia	1 (0.01)	0 (0)	sarcoma	1 (0.01)	0 (0)
adenoma benign	1 (0.01)	0 (0)	small cell lung cancer	1 (0.01)	3 (0.04)
basal cell carcinoma	1 (0.01)	1 (0.01)	thyroid cancer	1 (0.01)	0 (0)
benign lung neoplasm	1 (0.01)	0 (0)	transitional cell carcinoma	1 (0.01)	0 (0)
bladder neoplasm	1 (0.01)	1 (0.01)	uterine leiomyoma	1 (0.01)	0 (0)
bladder papilloma	1 (0.01)	0 (0)	adenocarcinoma pancreas	0 (0)	1 (0.01)
bone neoplasm	1 (0.01)	0 (0)	adrenal neoplasm	0 (0)	1 (0.01)
bronchial carcinoma	1 (0.01)	2 (0.03)	bladder transitional cell carcinoma	0 (0)	1 (0.01)
cervix carcinoma	1 (0.01)	0 (0)	carcinoid tumour pulmonary	0 (0)	1 (0.01)
chronic lymphocytic leukaemia	1 (0.01)	0 (0)	chronic myeloid leukaemia	0 (0)	1 (0.01)
colon adenoma	1 (0.01)	1 (0.01)	colon cancer metastatic	0 (0)	1 (0.01)
colon neoplasm	1 (0.01)	0 (0)	gastric neoplasm	0 (0)	1 (0.01)
colorectal cancer	1 (0.01)	0 (0)	hepatic cancer metastatic	0 (0)	1 (0.01)
gallbladder cancer	1 (0.01)	0 (0)	hepatic neoplasm	0 (0)	1 (0.01)
gastrointestinal carcinoma	1 (0.01)	2 (0.03)	lymphocytic leukaemia	0 (0)	1 (0.01)
gastrointestinal tract adenoma	1 (0.01)	0 (0)	malignant melanoma	0 (0)	1 (0.01)
haemangioma	1 (0.01)	0 (0)	metastases to adrenals	0 (0)	1 (0.01)
lung adenocarcinoma	1 (0.01)	0 (0)	myelodysplastic syndrome	0 (0)	1 (0.01)
lung neoplasm	1 (0.01)	1 (0.01)	non-hodgkin's lymphoma	0 (0)	2 (0.03)
malignant ascites	1 (0.01)	0 (0)	small cell lung cancer metastatic	0 (0)	1 (0.01)
mesothelioma malignant	1 (0.01)	0 (0)	thymoma	0 (0)	1 (0.01)

Division's Concerns: The Division expressed its concerns regarding excess neoplasia in the prasugrel group in early communications with the sponsor. The sponsor espoused the view that the observed difference between the prasugrel and clopidogrel groups was due to ascertainment bias, because of increased bleeding associated with prasugrel compared to clopidogrel.

This possibility seemed plausible on its face, and the relative risks of neoplasia and bleeding were quantitatively similar. The Division re-analyzed the cases, excluding cancers where a hemorrhagic adverse event preceded the cancer *in the same organ system as the cancer*, i.e., hemoptysis for lung cancer, hematuria for genitourinary (GU) cancers, GI bleeds for GI cancers, and dysfunctional uterine bleeding for gynecologic cancers. The Division's analysis showed that the between-group difference in neoplasms largely persisted (results not shown).

Table 17: Treatment Emergent Adverse Events from TAAL, SOC “Neoplasms, benign, malignant and unspecified...”

Neoplasm as adverse event (from TAAL Table 14.92)	Prasugrel		Clopidogrel	
	n (%)	n (%)	n (%)	n (%)
all	153 (2.27)	123 (1.83)		
prostate cancer	16 (0.24)	7 (0.1)	metastases to bone	1 (0.01)
colon cancer	11 (0.16)	2 (0.03)	metastases to liver	1 (0.01)
lung neoplasm malignant	8 (0.12)	2 (0.03)	metastases to lymph nodes	1 (0.01)
gastric cancer	6 (0.09)	8 (0.12)	multiple myeloma	1 (0.01)
bladder cancer	5 (0.07)	4 (0.06)	nasal cavity cancer	1 (0.01)
breast cancer	5 (0.07)	1 (0.01)	nasal neoplasm	1 (0.01)
squamous cell carcinoma	5 (0.07)	5 (0.07)	oesophageal adenocarcinoma	1 (0.01)
lung neoplasm	4 (0.06)	8 (0.12)	oesophageal cancer metastatic	1 (0.01)
prostatic adenoma	4 (0.06)	0 (0)	oesophageal carcinoma	1 (0.01)
skin papilloma	4 (0.06)	1 (0.01)	oesophageal neoplasm	1 (0.01)
colon adenoma	3 (0.04)	3 (0.04)	pancreatic carcinoma	1 (0.01)
malignant melanoma	3 (0.04)	3 (0.04)	papillary thyroid cancer	1 (0.01)
metastases to lung	3 (0.04)	0 (0)	papilloma	1 (0.01)
metastatic neoplasm	3 (0.04)	1 (0.01)	peripheral T-cell lymphoma	1 (0.01)
renal neoplasm	3 (0.04)	1 (0.01)	pituitary tumour	1 (0.01)
skin cancer	3 (0.04)	4 (0.06)	pituitary tumour benign	1 (0.01)
adenocarcinoma	2 (0.03)	1 (0.01)	rectal cancer	1 (0.01)
basal cell carcinoma	2 (0.03)	5 (0.07)	rectal neoplasm	1 (0.01)
biliary neoplasm	2 (0.03)	1 (0.01)	renal cell carcinoma	1 (0.01)
brain neoplasm	2 (0.03)	1 (0.01)	salivary gland neoplasm	1 (0.01)
chronic lymphocytic leukaemia	2 (0.03)	1 (0.01)	sarcoma	1 (0.01)
clear cell carcinoma of the kidney	2 (0.03)	0 (0)	small cell lung cancer	1 (0.01)
gastric neoplasm	2 (0.03)	1 (0.01)	thyroid cancer	1 (0.01)
lung squamous cell carcinoma	2 (0.03)	1 (0.01)	transitional cell carcinoma	1 (0.01)
metastasis	2 (0.03)	0 (0)	uterine leiomyoma	1 (0.01)
mycosis fungoides	2 (0.03)	1 (0.01)	xanthoma	1 (0.01)
non-small cell lung cancer	2 (0.03)	2 (0.03)	adenocarcinoma pancreas	0 (0)
ovarian neoplasm	2 (0.03)	0 (0)	adrenal neoplasm	0 (0)
prostate cancer metastatic	2 (0.03)	1 (0.01)	bladder transitional cell carcinoma	0 (0)
thyroid neoplasm	2 (0.03)	2 (0.03)	carcinoid tumour pulmonary	0 (0)
acrochordon	1 (0.01)	1 (0.01)	chronic myeloid leukaemia	0 (0)
acute myeloid leukaemia	1 (0.01)	0 (0)	colon cancer metastatic	0 (0)
adenoma benign	1 (0.01)	1 (0.01)	fibrous histiocytoma	0 (0)
adrenal adenoma	1 (0.01)	0 (0)	haemangioma of liver	0 (0)
benign lung neoplasm	1 (0.01)	0 (0)	hepatic cancer metastatic	0 (0)
bladder neoplasm	1 (0.01)	3 (0.04)	hypergammaglobulinaemia benign	0 (0)
bladder papilloma	1 (0.01)	0 (0)	monoclonal	0 (0)
bladder squamous cell carcinoma	1 (0.01)	0 (0)	laryngeal cancer	0 (0)
bladder transitional cell carcinoma	1 (0.01)	0 (0)	lentigo	0 (0)
bone neoplasm	1 (0.01)	0 (0)	lung carcinoma cell type	0 (0)
bone neoplasm malignant	1 (0.01)	0 (0)	unspecified recurrent	0 (0)
breast cancer recurrent	1 (0.01)	0 (0)	lymphocytic leukaemia	0 (0)
bronchial carcinoma	1 (0.01)	2 (0.03)	melanocytic naevus	0 (0)
cardiac neoplasm	1 (0.01)	0 (0)	metastases to adrenals	0 (0)
cervix carcinoma	1 (0.01)	0 (0)	myelodysplastic syndrome	0 (0)
colon neoplasm	1 (0.01)	0 (0)	myeloproliferative disorder	0 (0)
colorectal cancer	1 (0.01)	0 (0)	nasopharyngeal neoplasm benign	0 (0)
fibroadenoma of breast	1 (0.01)	0 (0)	neoplasm	0 (0)
gallbladder cancer	1 (0.01)	0 (0)	neoplasm malignant	0 (0)
gastrointestinal carcinoma	1 (0.01)	2 (0.03)	non-hodgkin's lymphoma	0 (0)
gastrointestinal tract adenoma	1 (0.01)	0 (0)	ocular neoplasm	0 (0)
haemangioma	1 (0.01)	0 (0)	osteoma cutis	0 (0)
hepatic neoplasm	1 (0.01)	1 (0.01)	pyogenic granuloma	0 (0)
lipoma	1 (0.01)	1 (0.01)	rectal adenoma	0 (0)
lung adenocarcinoma	1 (0.01)	0 (0)	seborrhoeic keratosis	0 (0)
lymphoma	1 (0.01)	1 (0.01)	small cell lung cancer metastatic	0 (0)
malignant ascites	1 (0.01)	0 (0)	squamous cell carcinoma of skin	0 (0)
meso helioma malignant	1 (0.01)	0 (0)	thymoma	0 (0)
			tongue neoplasm malignant	0 (0)

The Division sought additional information from the sponsor, to clarify diagnoses and malignancy status for cases where it was not clear, to distinguish new from pre-existing cancers, to collect investigators' assessment of symptoms, signs, and laboratory studies that led to diagnoses of cancer, and to collect information on long-term vital status. The sponsor developed "Neoplasia" CRFs to capture this information, and sent clinical monitors to the sites to oversee collection of the data. The sites were to complete the CRFs and provide all available source documents supporting the data.

The sponsor provided a regulatory response on 9 May, 2008, wherein they identified 313 subjects reported as having experienced an adverse event within the "Neoplasms Benign, Malignant, and Unspecified" SOC, either as 1) a newly diagnosed adverse event, or 2) a pre-existing condition that increased in severity during the conduct of the trial.⁴ There were 175 prasugrel-treated subjects and 138 clopidogrel-treated subjects who had experienced one or more of these events during the study. Figure 19 and Table 18 show the sponsor's breakdown of non-benign neoplasms, according to their 9 May 2008 submission. (These analyses focus on "non-benign" tumors, including neoplasms characterized as malignant or "unknown.") Once the benign and pre-existing neoplasms were subtracted, the RR was 1.19.

The distribution of tumor types was typical of the patient population, and little affected by prasugrel. According to United States Cancer Statistics, National Program of Cancer Registries, the leading types of cancer by incidence are: prostate, breast, lung/bronchial, and colorectal (<http://apps.nccd.cdc.gov/uscs/>, searched 7/2/08). In TAAL, the numbers of new cancer cases in these categories for prasugrel and clopidogrel were 10 versus 7, 4 versus 1, 18 versus 14, and 20 versus 11, respectively (Table 18). Because females comprised only ~25% of the subjects enrolled in TAAL, the numbers of breast cancer cases would be roughly doubled if extrapolated to a 50% female population.

During the ensuing months, there was much discussion regarding these cases, both internally within the Division/Office, and between the Agency and the sponsor. The sponsor submitted a "Neoplasm White Paper," on September 19, 2008, in response to the Division's ongoing concerns.

Ultimately, there was fair agreement between the Agency and sponsor on categorization of neoplasms in terms of: 1) whether there was substantial evidence of neoplasia; 2) whether a given neoplasm was benign, malignant, or indeterminate; and 3) whether a neoplasm was pre-existing or newly discovered. There was general recognition that newly discovered tumors were in all likelihood extant at the time of study entry, and that the duration of the study was not sufficient to detect tumors that were truly "new," i.e., that might have arisen as a result of carcinogenesis. Thus, the Division and sponsor agreed that the concern is tumor stimulation, and not carcinogenicity.

Two issues have been contentious: 1) the extent to which ascertainment bias played a role in creating the imbalance in malignancies, and 2) whether or not non-melanomatous skin cancers should be considered in the analyses. Non-melanomatous skin cancers have less clinical importance than other solid tumors, and were reported in excess in the clopidogrel group. When they are included in these analyses, the difference between treatment groups is unimpressive (RR = 1.19). Conversely, when non-melanomatous skin cancers are omitted from

⁴ Two subjects were not included, because the sponsor was not able to obtain additional information from the site. Both subjects have been in the prasugrel treatment group, and one was diagnosed with a new "papillary urothelial carcinoma."

Figure 19: Sponsor's May, 2008, Breakdown of Non-Benign Neoplasms

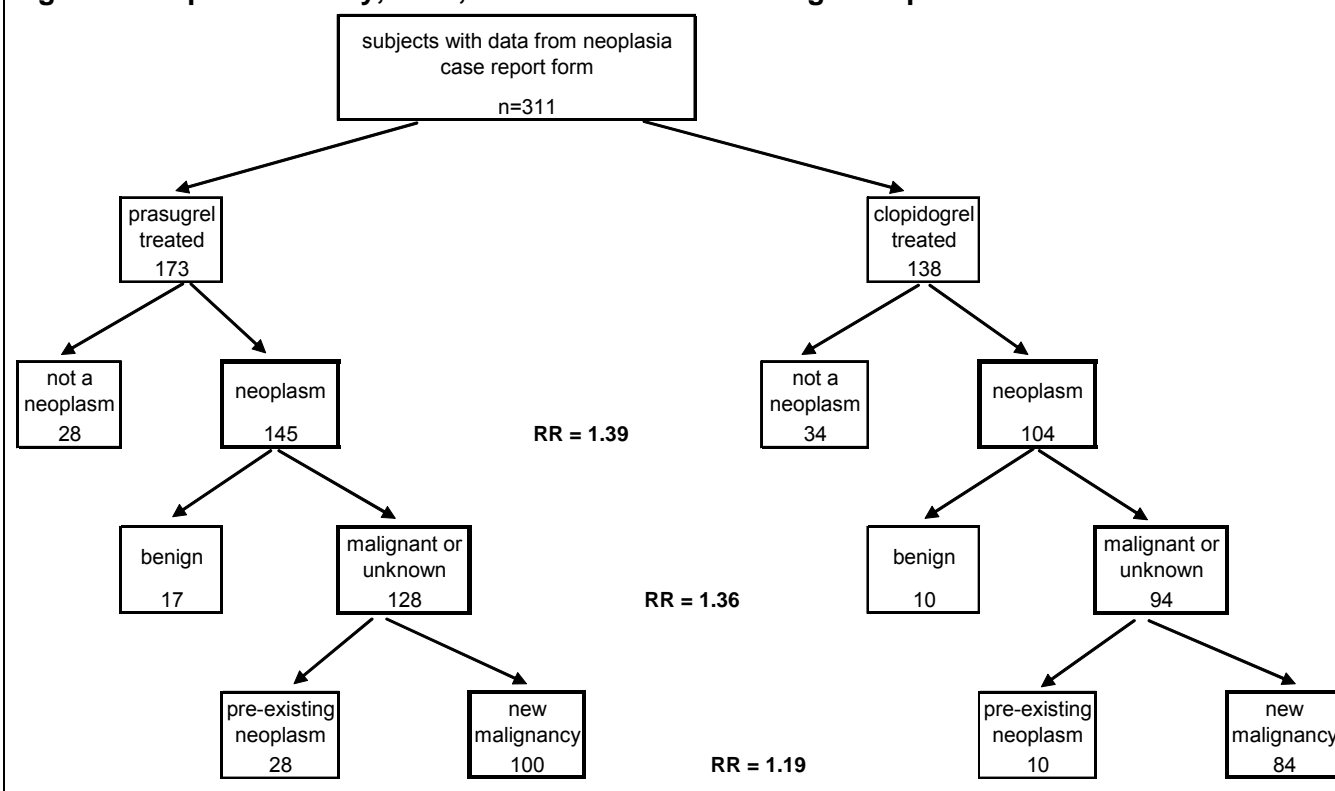


Table 18: Sponsor's May 9, 2008, Analysis of New, Non-Benign Neoplasms

neoplasm location	prasugrel n=6741	clopidogrel n=6716
brain	0	1
eye	0	1
oral cavity and pharynx	1	2
breast	4	1
lung and bronchus	18	14
other respiratory/thoracic	1	0
any GI site	35	25
colorectal, stomach, esophagus	31	21
colorectal	20	11
esophagus	4	3
stomach	7	7
pancreas	2	3
liver	0	1
gallbladder/biliary	2	0
any GU site	20	19
kidney	5	4
bladder	5	8
prostate	10	7
gynecologic	2	1
malignant melanoma	3	2
non-melanomatous skin	6	12
endocrine	2	0
any hematologic	4	4
leukemia	2	1
lymphoma	2	2
other hematologic	0	1
metastasis unknown primary	3	0
other unknown primary	0	1
unknown	1	1
all	100	84

the analyses, the difference between groups can be statistically significant. These two issues are discussed in detail, below.

Ascertainment Bias:

The sponsor's original argument was that neoplasms discovered in subjects with antecedent bleeding events should be excluded from analyses, because they could have been ascertained as a result of the bleeding event, or discovered because of investigator-patient contact, laboratory studies, or imaging investigations initiated in response to the bleeding event. Given that the RR of bleeding was quantitatively similar to the RR of cancer, this was an attractive hypothesis. The Division rejected this argument in favor of a more restricted view: that neoplasms with antecedent bleeding in the same organ system as the tumor (or new or worsened anemia in cases of GI or GU tumors) might be excluded:

1. respiratory (lung and bronchus/other respiratory)
2. GU (kidney and urethral/bladder/gynecologic)
3. GI (colorectal/esophagus/stomach)

The Division extracted all adverse events in subjects with neoplasms, and assessed the temporal sequence of adverse events involving bleeding, anemia, and iron deficiency for each case. Where antecedent bleeding was reported in one of the three organ systems listed above, or when the development or worsening of anemia (or iron deficiency) might lead to a search for occult blood loss (i.e., for the GU and GI systems), the neoplasms were excluded.

The Division and sponsor exchanged interpretations, and the sponsor presented the results of their analysis at a face-to-face meeting on September 24, 2008 (presentation slides were submitted to the dossier on October 3, 2008). Table 19 was developed based on the sponsor's Slide #20, with one difference: the sponsor excluded 5 additional cases with respiratory tumors who had antecedent anemia; for reasons noted above, these cases are restored in Table 19. Irrespective of whether cases with antecedent bleeding or anemia are counted, the RR is 1.4. From these analyses, there is no support for the sponsor's contention that ascertainment bias was responsible for the imbalance in malignancies.

Table 19: Sensitivity Analysis: Effect of Removal of Neoplasia Cases Related to Bleeding or Anemia in the Gastrointestinal, Genitourinary, and Pulmonary Systems

	Prasugrel			Clopidogrel			RR
	N	n	%	N	n	%	
Gastrointestinal (colorectal/ esophagus/ stomach)							
total	6741	32	0.47	6716	19	0.28	1.7
with bleed	6741	25	0.4	6716	14	0.2	1.8
without bleed	6741	7	0.1	6716	5	0.1	1.4
Genitourinary (kidney and urethral/ bladder/ gynecologic)							
total	6741	13	0.2	6716	12	0.2	1.1
with bleed	6741	7	0.1	6716	8	0.1	0.9
without bleed	6741	6	0.1	6716	4	0.1	1.5
Respiratory							
total	6741	16	0.2	6716	13	0.2	1.2
with bleed	6741	3	0.0	6716	3	0.0	1.0
without bleed	6741	13	0.2	6716	10	0.1	1.3
All 3 Systems							
total	6741	61	0.9	6716	44	0.7	1.4
with bleed	6741	35	0.5	6716	25	0.4	1.4
without bleed	6741	26	0.4	6716	19	0.3	1.4

Cancer Mortality: Cancer mortality is another important issue, and one that bears importantly on the question of ascertainment bias. The sponsor's "Supplemental Regulatory Response Concerning Neoplasms" of May 9, 2008 summarized cancer deaths, as follows:

For subjects with pre-existing non-benign neoplasms (n=28 for prasugrel; n=10 for clopidogrel), there were 6 and 2 deaths due to malignancy in the prasugrel and clopidogrel groups, respectively (Table 8 of sponsor's Supplemental Response, shown below in Table 20, top panel). For subjects with non-benign neoplasms that were considered to be new, there were 27 and 19 cancer deaths in the prasugrel and clopidogrel groups, respectively, for a RR of 1.42 (Table 14 of sponsor's Supplemental Response, shown below in Table 20, bottom). Overall, therefore, for subjects with non-benign neoplasms (new or pre-existing), there were 33 and 21 cancer deaths in the prasugrel and clopidogrel groups, respectively (RR=1.57, 95% C.I. 0.91 to 2.71).

Table 20: Sponsor's Accounting of Malignancy Deaths – Top: Subjects with Pre-existing Non-Benign Neoplasms; Bottom: Subjects with New Non-Benign Neoplasm

Table 8. Vital Status of Subjects With a Pre-existing Non-Benign Neoplasm

			Pras	Clop
Total			28	10
Vital Status	Primary Cause of Death	Subcategory		
ALIVE			17	6
DEAD	CARDIOVASCULAR		1	0
	NON-CARDIOVASCULAR	MALIGNANCY	6	2
		OTHER	0	1
	UNKNOWN CAUSE		1	1
	TOTAL DEAD		8	4
UNKNOWN			3	0

Source: l0463_fqvijt11_vital.rtf

Table 14. Vital Status of Subjects With a New Non-Benign Neoplasm

			Pras	Clop
Total			100	84
Vital Status	Primary Cause of Death	Subcategory		
ALIVE			58	54
DEAD	CARDIOVASCULAR		1	3
	NON-CARDIOVASCULAR	MALIGNANCY	27	19
		OTHER	6	2
	UNKNOWN CAUSE		1	1
	TOTAL DEAD		35	25
UNKNOWN			7	5

Source: l0463_fqvijt11_vital.rtf

The sponsor commented as follows:

“The proportion of subjects diagnosed with a new nonbenign neoplasm that died due to malignancy was similar between treatment groups (27 of 100 subjects, 27% prasugrel; 19 of 84 subjects, 23% clopidogrel).”

Although the numbers of events are small, the imbalance in cancer deaths is concerning. The fact that similar proportions of subjects with cancer had a fatal outcome is not reassuring. Moreover, the additional deaths in the prasugrel group argue against the influence of ascertainment bias, given that ascertainment of death should be complete and unbiased.

Reconciled Analyses:

The Division and sponsor reached agreement on the classification of all neoplasia in October, 2008. Table 21 shows the reconciled tabulation of “new” non-benign neoplasms, and is numerically identical to the Sponsor’s Table 7.2 on page 122 of their “Cardiovascular and Renal Drugs Advisory Committee Briefing Document.” Using this categorization, the K-M frequencies of new, non-benign neoplasms were 1.82% versus 1.54% for the prasugrel and clopidogrel groups, respectively, for a RR of 1.18 (log-rank $p = 0.28$). If non-melanomatous skin tumors are excluded, the corresponding frequencies are 1.70% and 1.29%, for a RR of 1.31, log-rank $p = 0.09$. The Kaplan-Meier time-to-event analyses are shown in Figure 20. The top panel shows the results of the analysis that includes all subjects, and the bottom panel shows the results of analyses with clinically less important non-melanomatous skin cancers omitted.

Because of the relatively small numbers of events, the results are sensitive to the categorization of only a few cases. Moreover, some aspects of the categorization, conducted post-hoc and with knowledge of treatment assignment, were extremely difficult. These complexities are exemplified by the following cases, identified by Dr. Marciniak in his December 31, 2008, review:

1. A 68-year-old male in the prasugrel group was hospitalized after more than a year on-study with an enlarged hard, anechoic nodular liver and sepsis. The patient died before a biopsy was done and no autopsy was done. The investigator reported the event as a malignancy and the CEC adjudicated the event as a malignancy death. I believe this case should be classified as a new malignancy while the sponsor proposes to reclassify it as not malignant.
2. A 44-year-old male in the clopidogrel group had an event reported of “recurrent bladder tumor” at about 3 months with a clear history of prior bladder tumors. I believe this case should be classified as a not new, but worse, cancer while the sponsor proposes to reclassify it as new because the initial diagnosis of bladder tumor was six years prior to randomization, although the operative report refers to a “history of superficial bladder tumors” and it is not recorded whether there were any other recurrences. The surgeon gave a clinical diagnosis of “superficial bladder cancer,” although the investigator reported the event and history as histology unknown and a path report was not submitted.
3. A 73-year-old female in the clopidogrel group had a rectal polyp removed that showed high-grade dysplasia. Because all other adenomas with severe dysplasia were classified as not malignant, I believe this case should be classified as not malignant, while at last reconciliation the sponsor classified this case as malignant.
4. A 75-year-old female in the prasugrel group had low back pain at randomization but was not tentatively diagnosed as multiple myeloma until 3 months later. Low back pain is a non-specific symptom, so I believe this case should be classified as a new malignancy.

Table 21: New Non-Benign Neoplasms – Sponsor/FDA Reconciliation 10/08

neoplasm location	prasugrel n=6741	clopidogrel n=6716	
brain	0	1	
endocrine	1	0	
oral cavity and pharynx	1	2	
breast	3	1	
lung and bronchus	16	12	
other respiratory/thoracic	1	0	
any GI site	34	24	
colorectal, stomach, esophagus	30	20	
colorectal	19	10	
esophagus	4	3	
stomach	7	7	
pancreas	2	3	
liver	0	1	
gallbladder/biliary	2	0	
any GU site	19	20	
kidney	6	3	
bladder	5	8	
prostate	8	9	
gynecologic	2	1	
malignant melanoma	3	2	
non-melanomatous skin	6	13	
endocrine	1	0	
any hematologic	3	3	
leukemia	1	1	
lymphoma	2	1	
other hematologic	0	1	
metastasis unknown primary	2	0	
other unknown primary	0	1	
unknown	2	0	
all	94	80	RR = 1.18
all, excluding non-melanomatous skin	88	67	RR = 1.31

Dr. Marciniak analyzed the neoplasia data independently, classifying cases as new or worse based on his review of the case report forms. His Kaplan-Meier incidence plots for new solid tumors and new or worse solid tumors are shown in Figure 21. Note that the analyses exclude non-melanomatous skin cancer, hematological malignancies, and brain tumors. The log-rank p-value for new solid cancers is 0.024; for new or worsened cancers, the p-value is 0.0013.

Dr. Marciniak also reviewed the data from the clopidogrel development program, and found no apparent effect of clopidogrel on cancer rates. CURE showed a doubling in the rate of colorectal cancer with clopidogrel compared to placebo (16 versus 8), but this was not observed in CAPRIE or CHARISMA. Clopidogrel was associated with excess lung cancer in CURE (12 versus 7) and CREDO (5 versus 0), but not in the larger CAPRIE (72 versus 74) or CHARISMA Studies (70 versus 63).

The Division also sought the expertise of the Division of Drug Oncology Products, and their consult team (B. S. Mann, J. R. Johnson, and P. Cortazar) highlighted the following points (paraphrased here):

1. In terms of supporting the concept that prasugrel causes cancer, no analyses based on TAAL can be conclusive:

a. TAAL was not designed to compare the cancer incidences between study arms, so the Type I error rate for this exploratory significance testing is essentially unknown.

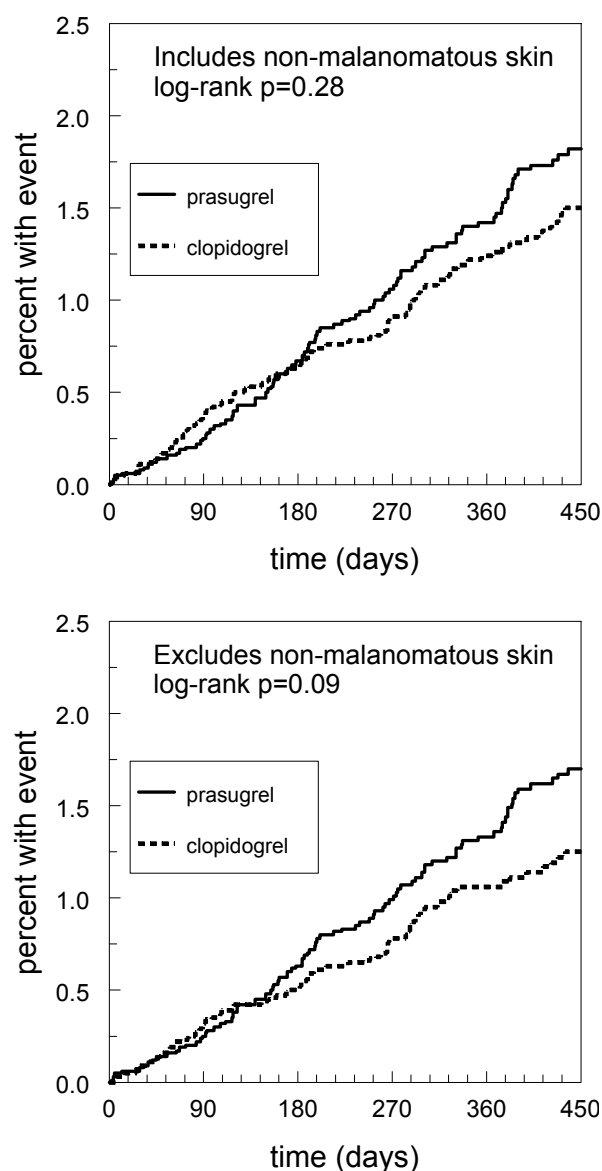
b. The absence of cancer at entry was not a requirement. There was no baseline cancer screening evaluation of study subjects.

c. The clinical significance of the statistical findings obtained by combining of different cancers in the comparisons is hard to interpret given differing etiologies and natural histories of the diverse types of cancers.

2. There are no data in TAAL to support a belief that prasugrel is a “promoter” in humans. Given the absence of a well defined cancer screening at study entry, short drug exposure to the study drugs (6 to 15 months), and no specified follow up to detect specific cancers, the cancers diagnosed on study are more likely to be incidental.

3. To determine whether worsening of cancer was related to study drugs or was spontaneous, one would need to study the progress of known cancers when exposed to study drugs and a placebo to address this issue. Such trials are not possible in humans for clinical, statistical, and ethical reasons.

Figure 20: New, Non-Benign Neoplasms – Top: All; Bottom: Excluding Non-Melanomatous Skin



4. Epidemiologic comparison with the SEER data may be helpful; however, the results are of limited value and likely to be inconclusive as the study population in TAAL is drawn from several different countries. SEER data come from US populations from selected cities/regions.

5. A definitive study would require a screened population (cancer free) of adequate size, randomly assigned to the study treatments and followed up for adequate time.

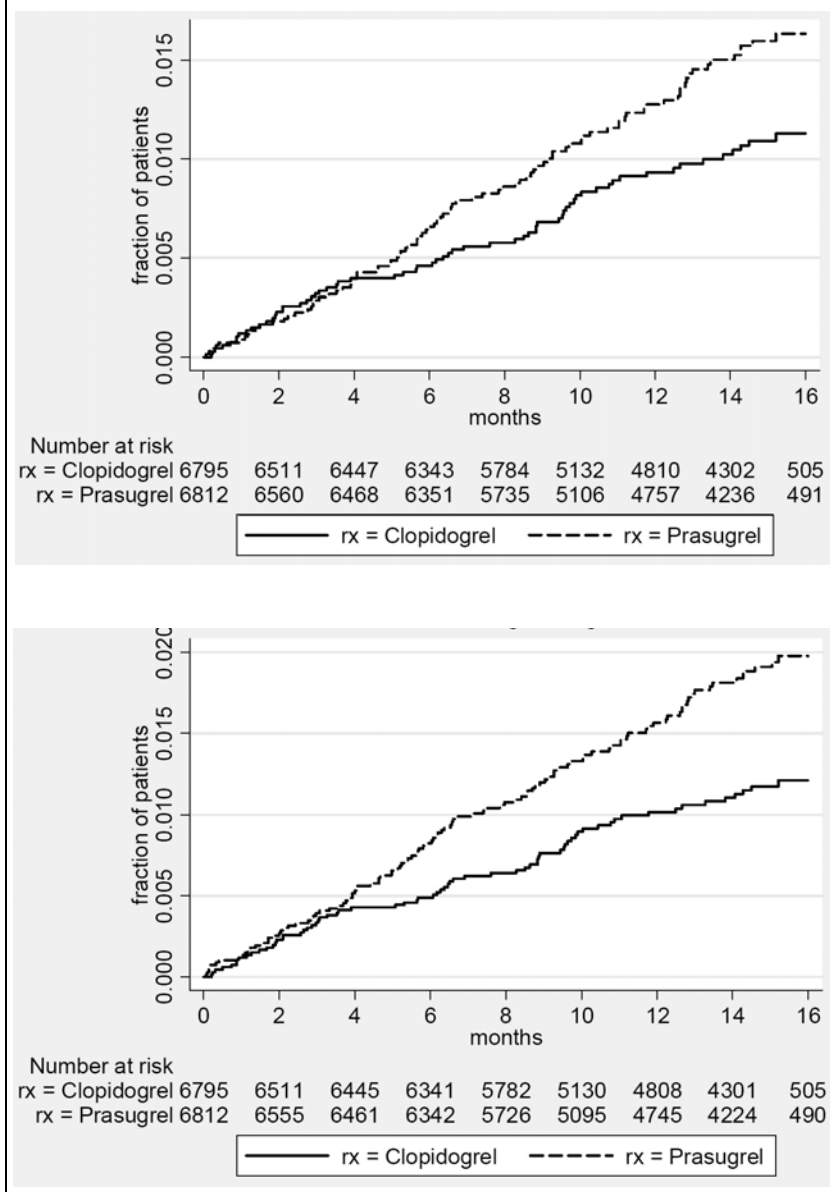
Cancer – Conclusions:
Prasugrel was associated with an excess number of new malignant tumors.

There are two principal interpretations of the neoplasia data: the RR and statistical significance turn on whether or not non-melanomatous skin cancers are included in the analyses. Some in the Division would exclude non-melanomatous skin cancers, because they are cured by excision and their clinical significance

differs greatly from that of other cancer types. Others do not believe that exclusion is justified, because their biology is seemingly similar to other cancers, and because exclusion was performed post-hoc (of course, this is true of most safety analyses). If cases of non-melanomatous skin cancer are excluded from the counts, the RR is 1.3 and almost reaches statistical significance; with Dr. Marciniak's classification, RR is 1.4 and the p-value reaches 0.024. When all tumors, including non-melanomatous skin cancers are considered, the RR is only 1.2 and not statistically significant.

Because safety analyses are observational in nature and conducted without the benefit of pre-specified hypotheses or correction for multiplicity, there is always the possibility of a false positive finding. False positive results are, of course, *expected* under these circumstances.

Figure 21: Solid Cancers, Excluding Non-Melanoma Skin and Brain – Top: New; Bottom: New and Worse



Beyond a mere association between prasugrel and excess cancers, therefore, biological plausibility, exposure-response, and other factors are helpful to support causality.

There is a paucity of non-clinical data suggesting a role for prasugrel in tumor stimulation. One could hypothesize an indirect mechanism, that platelet aggregation and thrombosis provide natural defenses against tumor development and metastasis, and that prasugrel interferes with these processes. Alternatively, one could posit a more direct mechanism, wherein prasugrel is pro-angiogenic, mitogenic, or it acts as a tumor cell growth factor; however, all of this is purely speculative.

Considering the diverse biologies of these tumor types and the relatively brief 15-month time frame of TAAL, it is simply not plausible for carcinogenicity effects to underlie the imbalance in cancer cases (moreover, the results of carcinogenicity studies in the prasugrel development program were not positive). If in fact prasugrel is causally related to the excess cancers, a tumor stimulatory effect is much more likely. Of note, there is no separation of the curves through 5 or 6 months, and the delay would seem consistent with stimulation. The time course of the incidence of new tumors (Figure 20) is consistent with some of the observations with exogenous erythropoietins in patients with cancer.⁵

Given that prasugrel and clopidogrel share similarities in their mechanisms of action, Dr. Marciniak re-visited the large clopidogrel outcome trials, CAPRIE, CREDO, CURE, and CHARISMA, with a combined sample size of over 39,000 subjects. He found no consistent trends suggesting that clopidogrel is a cancer stimulator. This is reassuring, actually. Had clopidogrel been associated with a slight increase in cancer rates verses placebo, it would suggest a class effect, which would make a stronger case for a causal role of prasugrel in cancer.

Although the sponsor maintains that the imbalance was largely due to ascertainment bias, that is, that excess bleeding in the prasugrel group drew attention to excess tumors, the Division does not agree. When cases with antecedent bleeding are completely removed from the analyses, the RR of neoplasia remains principally the same.

Overall, there are reasons to be both reassured and concerned:

Reasons to be reassured: Given the varied tumor types under consideration and apparent time course of effect, a generalized stimulatory effect seems most plausible. As such, the analyses should focus on all tumor types. With the inclusion of non-melanomatous skin cancers, RR is not importantly different from unity. The lack of an identifiable mechanism of action and the multiplicity of potential safety issues analyzed should also assuage apprehension, at least to some extent. An additional reason to be reassured is that even if prasugrel is deemed to be causative, the absolute risk of cancer, based on all of the analyses above, is 0.3 to 0.6% (based on point estimates). To place this risk into perspective with efficacy (Table 6), prasugrel was associated with a 2.1% absolute reduction in the triple efficacy endpoint, primarily due to a reduction in non-fatal myocardial infarction. Thus, for each 1000 patients treated with prasugrel, one might expect to prevent 21 non-fatal myocardial infarctions at a cost of 3-6 cancers (if, in fact the drug is causally related to cancer). This trade seems advantageous, at least for many patients.

⁵ Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. *JCO*. 2005; 23:1-13.

Reasons for concern: The fact that cancer deaths go against prasugrel (27 for prasugrel versus 19 for clopidogrel, RR = 1.42) is reason for consternation. The consideration of death as an endpoint largely removes sources of bias from the analyses. In addition, if there is a 0.3 to 0.6% risk of cancer, the risk is per year. This has to be extrapolated over the length of treatment. The efficacy (prevention of non-fatal MI) is largely front-loaded, but the risk of cancer would presumably continue.

This reviewer suggests a precaution in labeling regarding the excess cancers and cancer deaths. The labeling should suggest that consideration be given to use of alternative agents in patients with known cancer, but I would not go as far as to suggest that patients without a history of cancer switch to other agents after some arbitrary period in time (see below). A postmarketing requirement to study the issue more carefully in a randomized controlled trial may be worth considering. The sponsor is presently conducting a large outcome trial of prasugrel in subjects with ACS managed without PCI, and the data from this trial may suffice. The advice we have received from the Division of Epidemiology, OSE is that because of the limitations of registry data, including missing data, typically low and possibly biased enrollment, and the absence of controls, a registry is not likely to answer the question of cancer etiology.

In addition, the Division requested *in vitro* and *in vivo* tumor progression studies, and the sponsor submitted preliminary results one week ago.

7.4.16. QT Prolongation

The sponsor performed a thorough QT study in normal volunteers (Study TAAP), which was deemed negative and largely adequate by the Division's Interdisciplinary Review Team for QT Studies (S. Balakrishnan, Y. Chen, J. Zhang, N. Mehrotra, and C. Garnett). TAAP was a single-center, randomized, three-period crossover study wherein 60 healthy volunteers received either an 80-mg single dose of prasugrel or placebo. Subjects also received a single 400-mg oral dose of moxifloxacin, administered open label. Delta QTcF for moxifloxacin was 10.7 ms, with 90% C.I. 8.3 ms, 13.0 ms, demonstrating assay sensitivity, i.e., the study was adequately designed and conducted to detect an effect of a QT-prolonging drug on the QT interval. For prasugrel 80 mg, Δ QTcF was 2.1 ms, 90% C.I. -1.3 ms, 5.4 ms. Because the upper limit of the two-sided C.I. for the mean difference between prasugrel and placebo was <10 ms, the threshold for regulatory concern (per ICH E14 Guideline), the study was considered negative in the context of a positive moxifloxacin control.

The review team identified two key study limitations: 1) the 80-mg dose used in the study did not adequately emulate "worst-case" scenarios (based on intrinsic and extrinsic factors) for the 60-mg LD, although it did cover the expected high exposure scenario for the 5-or 10-mg MD; and 2) the ECG sampling schedule did not capture the t_{max} for metabolites, except for R-106583.

Because the lack of a QT effect observation could have been a result of dose and/or timing of ECG sampling, the QT Team compared R-119521 and R-106583 exposures achieved in TAAL to those achieved in TAAP, and concluded that prasugrel is unlikely to prolong QT interval after clinically relevant exposures.

In light of the QT Team's conclusion, and given that QT effects are inherently less important when the benefit of a drug is improvement in a cardiovascular outcome, no additional evaluation is needed for QT.

8. Discussion of Primary Reviewers' Comments and Conclusions

1. The primary clinical reviewer noted, "There appears to be a potential for drug-drug interaction with atorvastatin. One healthy subject in Study TAAV (Subject 115) experienced acute hepatic failure after co-administration of high-dose atorvastatin and prasugrel. Liver function abnormalities resolved after the discontinuation of both medications."

Reviewer's Comments: As noted in section 5.3, it is difficult to know the extent to which prasugrel was contributory, and the interaction occurred in only one subject. Thus, placement of a precaution in labeling seems unnecessary.

2. The primary clinical reviewer suggested that "...prasugrel should probably not be the treatment of choice in patients ≥ 75 years of age," noting that such patients appeared to receive less benefit from prasugrel, compared to clopidogrel.

Reviewer's Comments: In CURE, the study of clopidogrel versus placebo in the setting of ACS, triple endpoint event rates (cardiovascular death, MI, or stroke) for subjects ≥ 75 years of age were 17.8% and 19.2%, respectively. In TAAL, efficacy for subjects ≥ 75 years of age was similar in the prasugrel and clopidogrel groups (16.0% versus 17.0%, respectively). Thus, efficacy is marginal for both products in patients ≥ 75 years old. Importantly, however, the risk of bleeding is much higher in the elderly, and this appears to be particularly true with prasugrel. The frequencies of fatal bleeding in subjects 75 years of age and older were 1.01% for prasugrel and 0.11% for clopidogrel. The respective frequencies of ICH were 0.79% and 0.34%. With increased risks of bleeding in patients ≥ 75 in the face of marginal efficacy, the primary reviewer's recommendation seems reasonable. Some advice to the effect that prasugrel's efficacy is limited and its bleeding risk is increased in patients over the age of 75 would be appropriate for labeling.

Although the sponsor proposes a reduction in the MD from 10 mg to 5 mg daily in the over age 75 population, retention of efficacy is not assured. If prasugrel is approved for all age groups, physicians will need to carefully balance the risks versus benefits when prescribing prasugrel in patients ≥ 75 years of age.

3. With regard to the claim the sponsor is seeking for the prevention of stent thrombosis, the primary clinical reviewer originally opined that the claim should not be allowed. "Furthermore, I recommend that the sponsor participate in a randomized, prospective clinical trial to evaluate the effect of prasugrel on stent thrombosis and to determine the optimal duration of dual antiplatelet therapy. Such a trial should use the standardized ARC definitions and incorporate histopathological confirmation as well as angiographic core laboratory review."

Reviewer's Comments: Following a review of selected cases by an independent, blinded core laboratory, the primary clinical reviewer believes that the sponsor's conclusions are reasonably supported by the data. The reviewer now agrees with the claim, and no longer believes that a new clinical trial is necessary.

4. Given the concern about cancer, as well as increased bleeding risks with prasugrel over time, the clinical reviewer initially recommended "...limiting therapy with prasugrel to short-term use (i.e., one week), so that patients may receive the benefits of this therapy while avoiding some of the possible risks." The secondary reviewer recommended "...approval of prasugrel for the indication of reduction in MI in ACS managed by PCI with a boxed warning regarding cancer and a duration of treatment limited to 30 days."

Reviewer's Comments: Some members of the review team have suggested that the package insert recommend a limited duration of use for prasugrel, because of the risks of cancer and bleeding. In terms discontinuing prasugrel, it is important to recognize that the population for whom this would be approved, i.e., patients with recent PCI, predominantly with stents, should probably not discontinue their thienopyridine, as this may lead to stent thrombosis, which is associated with poor outcomes. Thus, if the label were to encourage a limited duration of use, it would be critical for patients to switch seamlessly to another approved inhibitor of ADP-induced platelet aggregation, which presents practical problems of its own. Because continued therapy is critical, and because the risk management strategy of “switching” has not been tested, this reviewer is not enthusiastic about limiting length of use.

9. Advisory Committee Meeting

In light of what appeared to be robust efficacy findings, the Division, with concurrence of the Office, decided initially that the application should forego a public Advisory Committee meeting. Given that prasugrel appeared to be superior to established treatment for the prevention of non-fatal MI, this approach was planned in the interest of public health, so that regulatory action would not be unnecessarily delayed.

(b) (4)

10. Conclusions and Recommendations

Although the prasugrel development program included only a single adequate and well-controlled trial to support efficacy (TAAL), the study had many of the hallmark features that provide reassurance regarding its evidence of effectiveness. TAAL was a large multicenter study with findings that were statistically persuasive, robust to exploration, and consistent across subgroups. Because TAAL demonstrated prasugrel's superiority, not to a placebo, but to an active drug (clopidogrel), prasugrel's efficacy seems beyond question. There are three key safety concerns: 1) the risk of bleeding, which is well-understood and well-characterized; 2) excess malignancies, and excess deaths in subjects with malignancies, in the prasugrel group; and 3) conversion of the prasugrel salt to free base form and bioinequivalence in the presence of PPIs. These issues generated considerable discussion between the chemistry, pre-clinical pharmacology-toxicology, clinical pharmacology, and clinical review staff within the Division, as well as staff within the Division of Drug Oncology Products, Office of Surveillance and Epidemiology, and Office of Drug Evaluation-I. Ultimately, the Office reached the conclusion that a public presentation of the complex issues to the Cardiovascular and Renal Drugs Advisory Committee would be advisable, and presentation is planned for February 3, 2009.

10.1. Bleeding

Much has already been written in the literature regarding prasugrel's risk of bleeding. Although bleeding can cause serious morbidity and mortality, the most critical consequences of bleeding, i.e., those that cause irreversible morbidity or mortality (exsanguination, MI, and stroke), were included in the primary efficacy endpoint, where prasugrel was superior to clopidogrel.

Prasugrel's benefit and risk are related to greater inhibition of platelet aggregation; although excess fatal and non-fatal bleeding in prasugrel patients is obviously unwelcome, it does not seem to outweigh prasugrel's benefit. The tradeoff between bleeding and efficacy is largely between causation of transient morbidity versus prevention of non-fatal MI. When evaluating the risk-benefit profile for a population, this seems like a reasonable trade. Given that prasugrel would be administered for secondary prevention of acute MI, the problem for the practicing physician is that s/he knows only when the drug has harmed a patient (i.e., when a patient experiences a bleeding event); but does not know when the drug has prevented an MI in a particular patient.

In summary, relative to clopidogrel, prasugrel provides a 25% relative reduction in non-fatal MI without negatively affecting survival or increasing ICH. There is much data to indicate that decreasing the frequency of MIs, even silent ones, has a favorable effect on survival, congestive heart failure, etc., although this is difficult to prove vigorously. This probable benefit, however, is weighed against a small excess of bleeding events that were emergent but did not have long-term consequences.

An additional point to consider is that the risk-benefit profile might be improved in the future, if patients at higher risk of bleeding and its consequences (patients over 75 and those with prior stroke or TIA) are excluded from treatment.

The risk-benefit profile of prasugrel can be conceptualized in starkly quantitative terms:

For each 1000 subjects treated with prasugrel instead of clopidogrel, there were:

24 endpoint events prevented:

- 21 non-fatal myocardial infarctions
- 3 cardiovascular deaths
- 0 strokes.

10 excess TIMI Major or Minor bleeding events:

- 2 fatal bleeding events
- 3 non-fatal TIMI Major bleeding events (ICH, or Hgb decrease >5 g/dL)
- 5 TIMI Minor bleeds (Hgb decrease ≥ 3 to ≤ 5 g/dL)
 - and 19 TIMI Minimal bleeds.

In terms of deaths, therefore, prasugrel treatment (compared to clopidogrel) was associated overall with 3 fewer cardiovascular deaths per 1000 subjects treated, with 2 additional deaths due to fatal hemorrhage. Overall mortality favored prasugrel by 1.4 events/1000 patients treated (p=NS).

The Division believes that this is a worthwhile risk-benefit profile for patients who might receive prasugrel. The risk should be conveyed to prospective patients through a Medication Guide, with appropriate advice on actions to take for bleeding.

10.2. Cancer

The association between prasugrel and cancer is difficult to understand mechanistically and may represent a chance finding. Nevertheless, risk of cancer is always of great interest to

practitioners and patients, and cannot be ignored. A precaution seems appropriate for labeling at this time, although others have argued for a warning or boxed warning. The risk should also be conveyed to prospective patients through a Medication Guide.

10.3. Salt to Base Conversion

The sponsor initiated the development program using the free base of the drug substance, but became aware that the hydrochloride salt form of the drug substance had better bioavailability at higher gastric pH. Gastric acidity is germane to patients in the ACS setting, because a substantial fraction uses PPI or H2 receptor antagonists to raise gastric pH. Thus, with the concurrence of the Division, the sponsor changed the manufacturing process to produce the hydrochloride salt form of the drug substance. Late in development, near the time that TAAL was completed, the sponsor discovered that there was significant in-process form conversion from the salt form to the base form, through an acid-base reaction.

The CMC review team has serious concerns regarding form conversion, in that the manufacturing process fails to ensure consistent product quality, and approval of a product with significant conversion sets a poor precedent. The clinical pharmacology and biometrics review team is concerned as well, because prasugrel product with high salt to base conversion is not bioequivalent to product with low or medium conversion. Conversion affects the pharmacokinetics of the product when it is co-administered with a PPI (and, by extension, possibly a H2 receptor antagonist). The difference in bioavailability between the high-conversion and low/medium-conversion lots is evident in C_{max} , but not AUC, and translates into reduced activity at the 0.5- and 1-hour time points. However, at 2 hours and beyond, the difference is no longer evident. This can be conceptualized as a delay of approximately 20 minutes in achieving maximal inhibition of platelet aggregation. The delay would affect the loading dose, but would have no effect on maintenance doses.

For a number of reasons, however, the consensus within the Division is that it would be shortsighted to delay or deny approval because of the form conversion issue:

1. Prasugrel's inhibition of platelet aggregation greatly exceeds that of clopidogrel at all time points. Thus, even when conditions are most unfavorable for prasugrel (high salt-to-base conversion with high gastric pH), its pharmacodynamic effect is greater than that of the approved dose of clopidogrel.
2. The practical effect of form conversion is only a slight delay in pharmacologic action that would affect only patients on chronic PPI therapy. The delay could only be a factor for the loading dose; it could have no impact whatsoever on response to maintenance doses (consider that the peak effect of each maintenance dose, spaced 24 hours apart, is delayed by 2 hours).
3. Given that all patients receive the same dose of prasugrel, the variability in C_{max} is only moderate when compared to the variability in weight-adjusted dose between patients of higher and lower weight.
4. The variability in C_{max} due to form conversion with concomitant PPI use is small when compared to the effect of a high-fat meal.
5. The clinical benefit demonstrated in TAAL is considerable: prasugrel was found to be superior to an active comparator in preventing non-fatal MI.

6. Prasugrel's efficacy was consistent in all lots tested and across a spectrum of tablet age. Moreover, the use or non-use of PPI had no discernable effect on the efficacy of prasugrel in relation to clopidogrel.

7. In terms of safety, salt-to-base conversion is largely irrelevant. Consider that under the most unfavorable scenario, form conversion has the potential to reduce bioavailability. Thus, there is only the potential for form conversion to lead to *less* bleeding. Because Study TAAL established an acceptable safety profile for prasugrel in patients who were not using PPI or H2 receptor antagonists, and who experienced optimal bioavailability (approximately half of the overall subject population), there is little reason to worry about patients who might experience lower bioavailability.

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

S.

10.4. Recommended Regulatory Action

The Division recommends approval of prasugrel for reduction of myocardial infarction in patients with ACS who are managed with PCI. The claim sought by the sponsor, the reduction of "atherothrombotic events," is ambiguous and implies reductions in all 3 components of the TAAL

primary endpoint. The indication should be restricted to reduction of myocardial infarction, the component where efficacy was actually demonstrated.

It could be argued that the results of TAAL show prasugrel to be non-inferior to clopidogrel in ACS, such that it is appropriate for prasugrel to enjoy the same claims as its comparator. Clopidogrel has the indication “for the reduction of atherothrombotic events as follows: ACS:...to decrease the rate of the combined endpoint of cardiovascular death, MI, or stroke....”.

Although clopidogrel has a claim for “reduction of atherothrombotic events,” the phrase seems inappropriate in retrospect. For cardiovascular death and stroke, the rates with clopidogrel were only marginally better than placebo, and the differences were not statistically significant. The ambiguity in the phrase “atherothrombotic events” mostly serves to encourage loose association and extrapolation.

Some of the reviewers in the Division and some staff in OSE would limit the length of prasugrel’s use to manage the risk of bleeding or to address concerns regarding possible cancer. As noted in this review, there is no clear rationale for selecting a specific length of time. Moreover, mandating or encouraging a limited duration of therapy requires switching to another drug, and this type of risk management strategy has not been tested in the post-PCI setting. By avoiding use of prasugrel in patients at higher risk of bleeding (patients over the age of 75, patients with prior stroke or TIA, and patients who are planned to undergo CABG or other surgery), much of the excess bleeding risk will have been avoided. In terms of cancer risk, lacking definitive data, the strategy of limiting length of use seems ill advised.

10.5. Risk Evaluation and Mitigation Strategy (REMS)

FDA can require a Risk Evaluation and Mitigation Strategy (REMS) for a known or potential serious risk if we find it necessary to ensure that the benefits outweigh the risks of the drug. After extensive internal discussions and consultation with the Office of Surveillance and Epidemiology (OSE), we propose REMS that include:

- A Medication Guide rather than a PPI as stated above
- A Communication Plan to healthcare providers that includes information including:
 - appropriate patient selection, emphasizing that prasugrel should not be used in patients older than 75, or patients with prior history of TIA or stroke
 - the risk of bleeding and instructions on management
 - information on the potential risk of malignancies and need for monitoring

There is ongoing discussion regarding the need to initiate prasugrel in the inpatient setting.

10.6. Postmarketing Requirements

The cancer concern should be addressed through a randomized, controlled clinical trial. Whether or not the ongoing outcome trial would be sufficient to address the issue is under continuing discussion. A registry may be supportive, but could not substitute for a randomized controlled trial. The details of the study(ies) will need to be worked out and agreed upon prior to approval.

10.7. Other Postmarketing Commitments

- The sponsor has initiated Study TABY, a ~13,000 subject study comparing prasugrel to clopidogrel in the UA/NSTEMI patient population, managed without PCI. The study is

evaluating a lower loading dose of 30 mg, and a lower maintenance dose (5 mg) in subjects over age 75 or weighing <60 kg.

- The sponsor has established a registry to follow stent thrombosis.

Executive CAC

Date of Meeting : July 22, 2003

Committee: David Jacobson-Kram, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-901, Member
Abigal Jacobs, Ph.D., HFD-540, Member
C. Joseph Sun, Ph.D., HFD-570, Alternate member
Albert DeFelice, Ph.D., HFD-110
Belay Tesfamariam, Ph.D., HFD-110, Presenting Reviewer

Author of Minutes: Belay Tesfamariam

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review

The committee did not address the sponsor's proposed statistical evaluation for the 2-yr carcinogen bioassays, as this does not affect the sponsor's ability to initiate the bioassays. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following section E of the 'Guidance for Industry, Providing Regulatory Submission in Electronic Format, New Drug Application.'

IND number: 63,449
Drug name: CS-747 (LY 640315)
Sponsor: Eli Lilly & Co., Indianapolis, IN

Background: CS-747 is a member of thienopyridine class of antiplatelet agents. It is an inhibitor of ADP-induced platelet aggregation by direct inhibition of ADP binding to its receptor. CS-747 is a prodrug that is de-esterified to form an active metabolite that irreversibly inhibits P2Y₁₂ ADP receptor and thus prolong bleeding time. Bleeding is a potential risk that may be expected with CS-747 due to the mechanism of action of inhibition of platelet aggregation.

Rat Carcinogenicity Study Protocol and Dose Selection:

The dose selection was based on changes observed in repeated oral administration of CS-747 at doses of 0, 10, 30, 100, or 300 mg/kg/day for 3- and 6-month study in Fisher 344 rat (n=10-15). At 100 mg/kg, body weight gain was decreased by 17 % and 19% in males and females, respectively. Prothrombin times and activated partial thromboplastin times (APTT) were prolonged in rats receiving ≥ 100 mg/kg. Slight anemic tendencies in the group treated with ≥ 100 mg/kg and slight increases of reticulocyte ratio in female rats treated with 300 mg/kg were observed. Prothrombin and activated partial thromboplastin times were prolonged rats treated with ≥ 100 mg/kg, and fibrinogen levels were increased in the 300 mg/kg group. Histopathological examination revealed hypertrophy of the hepatocytes in the ≥ 30 mg/kg group. These changes are consistent with enzyme induction. The maximal tolerated dose (MTD) is estimated to be 100 mg/kg/day. The AUC₀₋₂₄ of the active metabolite (R-138727) at the MTD is about 189-fold higher than that projected in human plasma levels.

The sponsor proposes a 2-year carcinogenicity study with CS-747 HCl in the Fischer 344 rat at oral doses of 0, 10, 30, and 100 mg/kg/day (n=55/sex/group). The vehicle to solubilize CS-747 is 0.5 % w/v tragacanth solution. Animals in the control group will receive the vehicle (0.5% w/v tragacanth solution).

Executive CAC recommendations and Conclusions:

The Committee concurred with the proposed doses of 0, 10, 30, 100 mg/kg/day, based on MTD (decrease in body weight) and a variety of toxicities, including irreversible inhibitor of platelet function and thus prolong bleeding time.

Mouse Carcinogenicity Study Protocol and Dose Selection:

The dose selection was based on changes observed in repeated oral administration of CS-747 at doses of 0, 100, 300, or 1000 mg/kg/day for 3-month study in Crj:B6C3F1 mice (n=10). Doses of 1000 mg/kg/day caused decrease body weight gain by 46 to 62%. In the 300-mg/kg group, the primary effects were suppression of body weight gain by 16 and 28% in males and females, respectively, increased liver weight, and hypertrophy of the centrilobular hepatocytes. Doses of 100 mg/kg/day did not cause overt toxicity, although increased liver weight was observed. Hematology revealed decrease in red blood cell count, hemoglobin, hematocrit and MCHC and increase in reticulocyte ratio and MCV in the 1000 mg/kg group. The MTD is estimated to be 300 mg/kg/day. The AUC₀₋₂₄ of the active metabolite (R-138727) and primary human inactive metabolite (R-106583) at the MTD were > 265-fold higher than that projected in human plasma levels.

The sponsor proposes a 2-year carcinogenicity study with CS-747 HCl in Crj:B6C3F1 mice at oral dose of 0, 30, 100 and 300 mg/kg/day (n=55/sex/group). Organs and tissues of all animals will be fixed with phosphate buffered formalin for histopathology examination. Representative examples of normal and abnormal findings will be photographed when drug-related changes are observed.

Executive CAC recommendations and Conclusions:

The Committee concurred with the proposed doses of 0, 30, 100, 300 mg/kg/day, based on decrease in body weight gain at three months and decrease in RBC count at 300 mg/kg/day. It was also noted that the active metabolite exposure ratio is quite high (about 200:1).

If the sponsor plans histological evaluation of tissues from only control and high dose treatment groups, they will also need to conduct histopathologic examination of other dose groups under any of the following circumstances:

(a) for any macroscopic findings in the low and mid dose groups for a given tissue, they will need to look at that tissue for all of the dose groups

(b) for an increase in the incidence of tumors (rare or common) in the high dose group for a tissue, even if not statistically significant, they will also need to look at the next lower dose group

(c) for an increase in tumors in an organ for a tumor type that should be analyzed across tissue sites as well as by tissue site (e.g., hemangiosarcoma, lymphoma etc.; see McConnell et al, JNCI 76:283, 1986) they should look at all relevant tissues for that dose level and the next lower dose level,

(d) for an excessive decrease in body weight or survival in the examined dose group, they should examine lower dose groups.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\

/Division File, HFD-110
/Team leader, HFD-110
/Reviewer, HFD-110
/CSCO/PM, HFD-110
/ASEifried, HFD-024

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David Jacobson-Kram
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation
CARCINOGENICITY STUDIES

IND/NDA Number: NDA 22-307

Drug Name: CS-747 (Prasugrel)

Indication(s): 104 Week Carcinogenicity in Rats and Mice

Applicant: Sponsor: Eli Lilly & Co., Indianapolis, IN
Test Facility: Gotemba Laboratory, Bozo Research Center Inc.
1284 Kamado, Gotemba-shi, Shizuoka 412-0039, Japan

Documents Reviewed: Electronic submission, Dated: Dec. 26, 2007
Electronic data submitted on Dec. 26, 2007

Review Priority: Priority

Biometrics Division: Division of Biometrics -6

Statistical Reviewer: Mohammad Atiar Rahman, Ph.D.

Concurring Reviewer: Karl Lin, Ph.D.

Medical Division: Division of Cardiovascular and Renal Products

Reviewing Pharmacologist: Belay Tesfamariam, Ph.D.

Project Manager: Meg Pease-Fye

Keywords: Carcinogenicity, Dose response

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1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of CS-747 (Prasugrel) in rats and mice when administered orally by gavage at appropriate drug levels for about 104 weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Tesfamariam.

2. Rat Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and one control group. Two hundred and twenty F344/DuCrj (Fischer) SPF rats of each sex were randomly allocated to treated and control groups in equal size of 55 animals. The dose levels for treated groups were 10, 30, and 100 mg/kg/day. In this review these dose groups would be referred to as the low, medium, and high dose group, respectively. The controls received the vehicle (0.5w/v% tragacanth solution) by gavage.

During the administration period all animals were observed for physical and clinical signs three times everyday on normal week days and twice on weekends and holidays. In addition, palpation was performed once a week to detect superficial masses. A complete histopathological examination was performed on all animals from all groups found dead, killed moribund, or sacrificed during or at the end of the experiment.

2.1. Sponsor's analyses

2.1.1. Survival analysis

Survival function of each treatment group was estimated using the Kaplan-Meier product limit method. The dose response relationship¹ in mortality was tested using similar method as was suggested by Tarone. Pairwise comparisons of control and each treated group were performed using the Log-Rank test. All tests were conducted at one-tailed significance level of 0.05.

Sponsor's findings: Sponsor's analysis showed survival rates of 83.6%, 80.0%, 78.2%, and 89.1% in control, low, medium, and high dose groups, respectively in males and 69.1%, 72.7%, 78.2%, and 81.8%, respectively in females. Sponsor concluded that there was no statistically significant treatment related effect on the survival in either sex.

2.1.2. Tumor data analysis

Analysis for positive dose response relationship for tumor incidences among control, low, medium, and high dose groups and pairwise comparisons of control and treated groups were performed using the methods outlined in the paper of Peto et al. (1980). For incidental tumors, the analysis intervals were: weeks 0 - 52, 53 - 78, 79 - 92, and 93 till termination of the live phase. Exact permutation tests were used for tumors with less than 10 incidences.

Analysis for dose response relationship were conducted at the significance levels of 0.005 (one tailed-level) for common tumors and 0.025 (one tailed-level) for rare tumors. Pairwise comparison were conducted at the significance levels of 0.01 (one tailed-level) for common tumors and 0.05 (one tailed-level) for rare tumors.

¹ In this review, the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor rate as dose increases.

Common tumors were defined as those with a historical incidence in controls of 1% or more and rare tumors as less than 1%.

Reviewer's comment: *The above significance levels for dose response relationship test were suggested by Lin and Rahman (1998) and for pairwise comparisons were suggested by Haseman (1983) to adjust for multiple testing (to keep the false-positive rate at the nominal level of approximately 10%).*

Sponsor's findings: Sponsor's analyses showed no statistically significant positive dose response relationship or pairwise difference between control and any of the treated groups in any of the tested tumor types.

2.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

2.2.1. Survival analysis

The survival distributions of animals in all four treatment groups were estimated by the Kaplan-Meier product limit method. The dose response relationship and homogeneity of survival distributions were tested using the Cox test (Cox, 1972) and the Generalized Wilcoxon test (Gehan, 1965). The intercurrent mortality data are given in Tables 1A and 1B in the appendix for males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for males and females, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for males and females, respectively.

Reviewer's findings: The tests showed no statistically significant dose response relationship or differences between the control and any of the treated groups in survivals across treatment groups in either sex.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationship and pairwise comparisons of control group with each of the treated groups were performed using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for males and females, respectively.

Multiple testing adjustment: Adjustment for the multiple dose response relationship testing was done using the results of Lin and Rahman (1998), which recommends the use of significance level of $\alpha=0.025$ for rare tumors and of $\alpha=0.005$ for common tumors for a submission with two studies, and a significance level of $\alpha=0.05$ for rare tumors and of $\alpha=0.01$ for common tumors for a submission with one study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. Adjustment for multiple pairwise comparisons was done using the results of Haseman (1983), which recommends the use of a significance level of $\alpha=0.05$ for rare tumors and of $\alpha=0.01$ for common tumors, in order to keep the false-positive rate at the nominal level of approximately 10%.

It should be noted that the recommended test levels by Lin and Rahman for the adjustment of multiple testing were originally based on the result of a simulation and an empirical study using the Peto method for dose response relationship analysis. However, some later simulation results by the same authors (unpublished manuscript presented in 2006 BASS meeting in Savanna, Georgia) indicated similar usefulness of their recommendation for Poly-3 analysis also.

Reviewer's findings: Following tumor types showed p-values less than or equal to 0.05 either for dose response relationship and/or pairwise comparisons of control and treated groups.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons

Sex	Organ Name	Tumor Name	Cont N=55	Low N=55	Med N=55	High N=55	P_Val ue Dos Resp	P_Val ue C vs. L	P_Val ue C vs. M	P_Val ue C vs. H
<div> <div>Male</div> <div>Hemolymphoretic</div> <div>LEUKEMIA, LARGE GRANU</div> <div>8</div> <div>8</div> <div>3</div> <div>2</div> <div>0.009</div> <div>0.500</div> <div>0.100</div> <div>0.026</div> </div>										
	Mesothelium	MESOTHELIOMA, MALIGNANT	4	3	1	1	0.047	0.358	0.181	0.100
	Prostate	ADENOMA	11	9	6	4	0.016	0.313	0.144	0.026
<div> <div>Female</div> <div>Adrenal</div> <div>PHEOCHROMOCYTOMA, MALIGNANT</div> <div>2</div> <div>0</div> <div>0</div> <div>0</div> <div>0.031</div> <div>0.248</div> <div>0.121</div> <div>0.121</div> </div>										
	Hemolymphoretic	LEUKEMIA, LARGE GRANU	14	13	6	1	<0.0001	0.500	0.040	<0.0001
	Intestine, ileum	LEIOMYOSARCOMA	2	0	0	0	0.031	0.248	0.121	0.121

Based on the results of Lin and Rahman the incidence of none of the above or any other tested tumor types in either sex was considered to have statistically significant positive dose response relationship. Also based on the results of Haseman, none of the pairwise comparisons of treated groups with the control was considered to be statistically significant in either sex for increased tumor incidence in the treated group. A dose response relationship with negative slope was not considered to be statistically significant.

3. Mouse Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and one control group. Two hundred and twenty Crj:B6C3F₁ SPF mice of each sex were randomly allocated to treated and control groups in equal size of 55 animals. The dose levels for treated groups were 30, 100, and 300 mg/kg/day. In this review these dose groups would be referred to as the low, medium, and high dose group, respectively. The controls received the vehicle (0.5w/v% tragacanth solution) by gavage.

During the administration period all animals were observed for physical and clinical signs three times everyday on normal week days and twice on weekends and holidays. In addition, palpation was performed once a week to detect superficial masses. A complete histopathological examination was performed on all animals from all groups found dead, killed moribund, or sacrificed during or at the end of the experiment.

3.1. Sponsor's analyses

3.1.1. Survival analysis

Survival data from the mouse study were analyzed using the same statistical methodologies as were used to analyze the survival data from the rat study.

Sponsor's findings: Sponsor's analysis showed survival rates of 56.4%, 65.5%, 49.1%, and 49.1%, in control, low, medium, and high dose groups, respectively in males and 63.6%, 60.0%, 58.2%, and 56.4%, respectively in females. Sponsor concluded that there was no statistically significant treatment related effect on the survival in either sex.

3.1.2. Tumor data analysis

Tumor data from the mouse study were also analyzed using the same statistical methodologies as were used to analyze the tumor data from the rat study.

Sponsor's findings: Sponsor's analysis showed a statistically significant positive dose response relationship in the incidence of hepatocellular adenoma in both sexes. Pairwise comparisons showed statistically significant increased incidence of hepatocellular adenoma in high dose group of male and medium and high dose groups of females compared to their respective control.

3.2. Reviewer's analyses

This reviewer independently performed survival and tumor data analyses from the mouse study. For the mouse data analyses this reviewer used similar methodologies as he used to analyze the data from the rat study. Data used in this reviewer's analyses were provided by the sponsor electronically.

3.2.1. Survival analysis

The intercurrent mortality data are given in Tables 4A and 4B in the appendix for males and females, respectively. The Kaplan-Meier curves for death rate are given in Figures 2A and 2B in the appendix for males and females, respectively. Results for test of dose response relationship and homogeneity of survivals among treatment groups are given in Tables 5A and 5B in the appendix for males and females, respectively.

Reviewer's findings: The tests showed no statistically significant dose response relationship or differences between the control and any of the treated groups in survivals across treatment groups in either sex.

3.2.2. Tumor data analysis

The tumor rates and the p-values of the tumor types tested for dose response relationship and pairwise comparisons of control and treated groups are given in Table 6A and 6B in the appendix for males and females, respectively.

Reviewer's findings: Following tumor types showed p-values less than or equal to 0.05 either for dose response relationship or pairwise comparisons of control and treated groups.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons

Sex	Organ Name	Tumor Name	Cont Vehi c N=55	Low 30mg N=55	Med 100mg N=55	Hi gh 300mg N=55	P_Val ue Dos Resp	P_Val ue C vs. L	P_Val ue C vs. M	P_Val ue C vs. H
Male										
Male	Liver	ADENOMA, HEPATOCELLUL	20	11	26	44	<0.0001	0.065	0.051	<0.0001
		ADENOMA+CARCI NOMA	28	22	34	50	<0.0001	0.274	0.032	<0.0001
		HEMANGI OMA	6	3	1	1	0.016	0.244	0.058	0.058
Female	Liver	HEMANGI OMA	4	0	1	0	0.014	0.059	0.183	0.060
		ADENOMA, HEPATOCELLUL	5	5	20	39	<0.0001	0.500	<0.0001	<0.0001
	Pi tui tary	ADENOMA+CARCI NOMA	6	9	22	40	<0.0001	0.288	<0.0001	<0.0001
		ADENOMA, INTERMEDIATE	1	0	3	3	0.049	0.500	0.309	0.181
	Skin	SARCOMA, SPI NDLE CELL	3	0	0	0	0.015	0.121	0.121	0.121

Based on the results of Lin and Rahman, the incidence of hepatocellular adenoma and combined incidences of hepatocellular adenoma and hepatocellular carcinoma in both sexes were considered to have statistically significant positive dose response relationships. Also based on the results of Haseman, the increased incidence of hepatocellular adenoma and combined incidences of hepatocellular adenoma and hepatocellular carcinoma in high dose group in males, and medium and high dose groups in females were considered to be statistically significant compared to their respective control. A dose response relationship with negative slope was not considered to be statistically significant.

4. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of CS-747 (Prasugrel) in rats and mice when administered orally by gavage at appropriate drug levels for about 104 weeks.

In this review, the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor rate as dose increases.

Rat Study: Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and one control group. Two hundred and twenty F344/DuCrj (Fischer) SPF rats of each sex were randomly allocated to treated and control groups in equal size of 55 animals. The dose levels for treated groups were 10, 30, and 100 mg/kg/day. The controls received the vehicle (0.5w/v% tragacanth solution) by gavage. The tests showed no statistically significant dose response relationship or differences in survival across treatment groups in either sex. Tests did not show statistically

significant positive dose response relationship or increased incidence in treated group compared to the control in any of the tested tumor types.

Mouse Study: Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and one control group. Two hundred and 20 Crj:B6C3F₁ SPF mice of each sex were randomly allocated to treated and control groups in equal size of 55 animals. The dose levels for treated groups were 30, 100, and 300 mg/kg/day. The controls received the vehicle (0.5w/v% tragacanth solution) by gavage. The tests showed no statistically significant dose response relationship or differences in survival across treatment groups in either sex. Tests showed statistically significant positive dose response relationship in the incidence of hepatocellular adenoma and combined incidences of hepatocellular adenoma and hepatocellular carcinoma in both sexes. Pairwise comparisons showed statistically significantly increased incidence of hepatocellular adenoma and combined incidences of hepatocellular adenoma and hepatocellular carcinoma in high dose group in males, and medium and high dose groups in females compared to their respective control.

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Ms. Patrician

Table 1A: Intercurrent Mortality Rate
Male Rats

Week	CONTROL		LOW		MEDIUM		High	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
53-78	2	3.6	1	1.8	4	7.3	2	3.6
79-91	2	7.3	3	7.3	3	12.7	.	.
92-104	5	16.4	7	20.0	5	21.8	4	10.9
Term. Sac.	46	83.6	44	80.0	43	78.2	49	89.1

Female Rats

Week	CONTROL		LOW		MEDI UM		Hi gh	
	No. of		No. of		No. of		No. of	
	Death	Cum. %	Death	Cum. %	Death	Cum. %	Death	Cum. %
0-52	.	.	1	1.8
53-78	.	.	1	3.6	1	1.8	1	1.8
79-91	6	10.9	3	9.1	4	9.1	4	9.1
92-104	11	30.9	10	27.3	7	21.8	5	18.2
Term. Sac.	38	69.1	40	72.7	43	78.2	45	81.8

Male Rats

Test	P-Value Cox	P-Value Kruskal-Wallis
Dose Response	0.2388	0.2358
Homogeneity	0.4330	0.4150

Female Rats

Test	P-Value Cox	P-Value Kruskal-Wallis
Dose Response	0.1422	0.1564
Homogeneity	0.4371	0.4642

**Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Rats**

Organ Name	Tumor Name	Count	Low	Med	High	P_Value	P_Value	P_Value	P_Value
		N=55	N=55	N=55	N=55	Dos Resp	C vs. L	C vs. M	C vs. H
=====									
Adrenal	CARCINOMA, CORTICAL	1	0	0	0	0.125	0.500	0.500	0.245
	PHEOCHROMOCYTOMA	3	2	3	0	0.088	0.500	0.500	0.059
	PHEOCHROMOCYTOMA, MALIGNANT	2	2	2	2	0.478	0.500	0.500	0.500
Bone, Cranial	OSTEOSARCOMA	0	1	0	0	0.381	0.500	.	.
Cerebrum	ASTROCYTOMA, MALIGNANT	0	1	2	0	0.500	0.500	0.119	.
	OLIGODENDROGLIOMA, MALIGNANT	0	0	1	0	0.500	.	0.248	.
	RETICULOSARCOMA, MALIGNANT	0	0	0	1	0.255	.	.	0.500
Harderian gland	LEIOMYOSARCOMA	0	1	0	0	0.380	0.500	.	.
Heart	SCHWANNOMA	0	0	2	0	0.374	.	0.119	.
Hemolymphoretic	LEUKEMIA, LARGE GRANULOCYTIC	8	8	3	2	0.009	0.500	0.100	0.026
	SARCOMA, HISTIOCYTIC	1	0	0	0	0.127	0.500	0.500	0.248
Intestine, ileum	ADENOMA	0	1	0	0	0.380	0.500	.	.
	LEIOMYOSARCOMA	0	0	1	0	0.500	.	0.245	.
Kidney	LIPOMA	0	0	0	1	0.255	.	.	0.500
	PAPILLOMA, TRANSITION	0	0	0	1	0.255	.	.	0.500
Liver	ADENOMA, HEPATOCELLULAR	2	4	0	1	0.121	0.339	0.248	0.307
Lung(bronchus)	ADENOMA, BRONCHIOLOALVEOLAR	2	3	1	1	0.202	0.500	0.500	0.307
	CARCINOMA	0	1	1	1	0.307	0.500	0.245	0.500
Mammary gland	ADENOCARCINOMA	0	1	0	0	0.380	0.500	.	.
	FIBROADENOMA	1	0	1	0	0.250	0.500	0.500	0.245
Mesothelium	MESOTHELIOMA, MALIGNANT	4	3	1	1	0.047	0.358	0.181	0.100
Pancreas	ADENOMA, ACINAR-ISLET	0	2	0	0	0.281	0.248	.	.
	ADENOMA, ISLET CELL	8	8	8	9	0.423	0.500	0.500	0.500
	CARCINOMA, ISLET CELL	0	0	1	0	0.500	.	0.245	.
Parathyroid	ADENOMA	0	0	1	0	0.500	.	0.245	.
Pituitary	ADENOMA, ANTERIOR	11	13	18	7	0.284	0.408	0.065	0.156
Preputial gland	ADENOMA	1	0	0	0	0.125	0.500	0.500	0.245
	CARCINOMA	1	1	2	2	0.285	0.500	0.307	0.500
Prostate	ADENOMA	11	9	6	4	0.016	0.313	0.144	0.026
Skin	FIBROMA	4	2	4	5	0.315	0.339	0.500	0.500
	KERATOACANTHOMA	1	2	0	2	0.450	0.500	0.500	0.500
	SCHWANNOMA, MALIGNANT	0	2	0	0	0.281	0.248	.	.
Spinal cord, cervical	OLIGODENDROGLIOMA, MALIGNANT	0	0	1	0	0.500	.	0.245	.
Stomach	CARCINOID	0	1	0	0	0.380	0.500	.	.
Testis	LEYDIG CELL TUMOR	48	50	45	47	0.296	0.358	0.500	0.500

**Table 3A (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Rats**

Organ Name	Tumor Name	Cont N=55	Low N=55	Med N=55	High N=55	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Thymus	THYMOMA	1	0	0	0	0.125	0.500	0.500	0.245
Thyroid	ADENOMA, C CELL	13	9	11	10	0.282	0.236	0.408	0.243
	CARCINOMA, C CELL	2	1	5	0	0.319	0.500	0.135	0.119
	CARCINOMA, FOLLICULAR	1	1	0	1	0.407	0.500	0.500	0.500
Urinary bladder	PAPILLOMA	1	0	1	0	0.250	0.500	0.500	0.245
Zymbal gland	CARCINOMA	0	0	1	0	0.500	.	0.248	.

**Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Rats**

		Cont	Low	Med	Hi gh	P_Val ue	P_Val ue	P_Val ue	P_Val ue
Organ Name	Tumor Name	N=55	N=55	N=55	N=55	Dos Resp	C vs. L	C vs. M	C vs. H
%%%									
Adrenal	CARCINOMA, CORTICAL	1	0	0	1	0.500	0.500	0.248	0.500
	PHEOCHROMOCYTOMA	3	0	2	3	0.384	0.121	0.339	0.500
	PHEOCHROMOCYTOMA, MALIGNANT	2	0	0	0	0.031	0.248	0.121	0.121
Cerebrum	ASTROCYTOMA, MALIGNANT	0	0	1	0	0.500	.	0.500	.
	OLIGODENDROGLIOMA, MALIGNANT	0	0	1	0	0.500	.	0.500	.
Heart	SCHWANNOMA	1	1	0	0	0.123	0.500	0.248	0.248
Hemolymphoretic	LEUKEMIA, LARGE GRANULAR	14	13	6	1	<0.0001	0.500	0.040	<0.0001
	SARCOMA, HISTIOCYTIC	1	1	1	0	0.209	0.500	0.500	0.248
Intestine, ileum	LEIOMYOSARCOMA	2	0	0	0	0.031	0.248	0.121	0.121
Kidney	LIPOMA	0	0	1	0	0.500	.	0.500	.
Lung(bronchus)	ADENOMA, BRONCHIOL-ALVEOLAR	1	0	3	3	0.076	0.500	0.309	0.309
Mammary gland	ADENOCARCINOMA	1	2	2	1	0.460	0.309	0.500	0.500
	FIBROADENOMA	2	4	6	3	0.316	0.218	0.135	0.500
Pancreas	ADENOMA, ISLET CELL	1	2	2	2	0.354	0.309	0.500	0.500
Parathyroid	ADENOMA	0	0	0	1	0.251	.	.	0.500
Pituitary	ADENOMA, ANTERIOR	17	15	17	17	0.486	0.416	0.500	0.500
Skin	FIBROMA	1	0	1	2	0.219	0.500	0.500	0.500
Thymus	THYMOMA	0	0	0	1	0.251	.	.	0.500
Thyroid	ADENOMA, COLLOIDAL	7	7	4	9	0.398	0.500	0.179	0.393
	CARCINOMA, COLLOIDAL	4	3	3	4	0.491	0.500	0.358	0.500
Urinary bladder	PAPILLOMA	0	1	0	0	0.373	0.248	.	.

Table 4A: Intercurrent Mortality Rate in Male Mice

Week	CONTROL		LOW		MEDI UM		Hi gh	
	No. of	Cum. %	No. of	Cum. %	No. of	Cum. %	No. of	Cum. %
0-52	.	.	1	1.8	1	1.8	1	1.8
53-78	2	3.6	5	10.9	7	14.5	7	14.5
79-91	7	16.4	7	23.6	6	25.5	5	23.6
92-104	15	43.6	6	34.5	13	49.1	15	50.9
Term. Sac.	31	56.4	36	65.5	28	50.9	27	49.1

**Table 4B: Intercurrent Mortality Rate
Female Mice**

Week	CONTROL		LOW		MEDIUM		High	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0-52	2	3.6	1	1.8	.	.	2	3.6
53-78	2	7.3	5	10.9	5	9.1	6	14.5
79-91	7	20.0	4	18.2	7	21.8	4	21.8
92-104	9	36.4	11	38.2	11	41.8	12	43.6
Term. Sac.	35	63.6	34	61.8	32	58.2	31	56.4

Table 5A: Intercurrent Mortality Comparison
Male Mice

Test	P-Value Cox	P-Value Kruskal-Wallis
Dose	0.1571	0.1360
Homogeneity	0.3548	0.3741

Table 5B: Intercurrent Mortality Comparison
Female Mice

Test	P-Value Cox	P-Value Kruskal-Wallis
Dose	0.3995	0.3859
Homogeneity	0.8454	0.8430

**Table 6A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Mice**

		Cont	Low	Med	Hi gh	P_Val ue	P_Val ue	P_Val ue	P_Val ue
Organ Name	Tumor Name	N=55	N=55	N=55	N=55	Dos Resp	C vs. L	C vs. M	C vs. H
%%%									
Adrenal	PHEOCHROMOCYTOMA	1	0	0	1	0.500	0.500	0.500	0.500
Bone+Bone marro	HEMANGI OMA	1	0	1	0	0.343	0.500	0.500	0.500
	HEMANGI OSARCOMA	0	1	0	0	0.500	0.245	.	.
Ear	NEURAL CREST TUMOR	1	0	0	0	0.253	0.500	0.500	0.500
Epi di dymi s	HEMANGI OMA	0	0	0	1	0.121	.	.	0.239
Harderian gland	ADENOMA, ACINAR CELL	5	8	2	2	0.070	0.191	0.220	0.220
Heart	HEMANGI OSARCOMA	1	0	0	0	0.254	0.500	0.500	0.500
Hemolymphoreti c	LYMPHOMA, MALIGNANT	4	9	3	5	0.454	0.071	0.500	0.366
	SARCOMA, HISTIOCYTIC	1	3	1	1	0.419	0.181	0.500	0.500
Intestine, duode	ADENOCARCINOMA	1	0	0	0	0.253	0.500	0.500	0.500
Intestine, ileum	ADENOCARCINOMA	0	0	0	1	0.121	.	.	0.239
Intestine, rectu	ADENOCARCINOMA	0	0	0	1	0.121	.	.	0.239
Liver	ADENOMA, HEPATOCELLULAR	20	11	26	44	<0.0001	0.065	0.051	<0.0001
	ADENOMA+CARCINOMA	28	22	34	50	<0.0001	0.274	0.032	<0.0001
	CARCINOMA, HEPATOCELLULAR	11	12	13	16	0.095	0.407	0.319	0.130
	HEMANGI OMA	6	3	1	1	0.016	0.244	0.058	0.058
	HEMANGI OSARCOMA	0	3	1	0	0.414	0.059	0.239	.
	HEPATOBLASTOMA	0	0	0	1	0.121	.	.	0.239
Lung(bronchus)	ADENOMA, BRONCHIOL-ALVEOLAR	5	5	5	6	0.329	0.500	0.500	0.376
	CARCINOMA, BRONCHIOL-ALVEOLAR	3	3	8	4	0.143	0.500	0.055	0.352
	HEMANGI OSARCOMA	1	0	0	0	0.254	0.500	0.500	0.500
Lymph node, nos	HEMANGI OSARCOMA	0	0	1	0	0.374	.	0.239	.
Mesothelium	MESOTHELIAL, MALIGNANT	1	0	0	0	0.254	0.500	0.500	0.500
Pancreas	HEMANGI OMA	0	0	0	1	0.121	.	.	0.239
Pituitary	ADENOMA, INTERMEDIAL	1	0	0	0	0.253	0.500	0.500	0.500
Skin	HEMANGI OMA	1	0	0	0	0.253	0.500	0.500	0.500
	HEMANGI OSARCOMA	0	0	1	0	0.374	.	0.239	.
	LIPOMA	1	0	0	0	0.253	0.500	0.500	0.500
	PAPILLOMA, SQUAMOUS CELL	0	0	0	1	0.121	.	.	0.239
Spleen	HEMANGI OMA	4	0	1	0	0.014	0.059	0.183	0.060
	HEMANGI OSARCOMA	0	0	1	0	0.374	.	0.239	.
Stomach	PAPILLOMA, SQUAMOUS CELL	0	1	1	0	0.436	0.245	0.239	.
Testis	LEYDIG CELL TUMOR	0	0	0	1	0.121	.	.	0.239

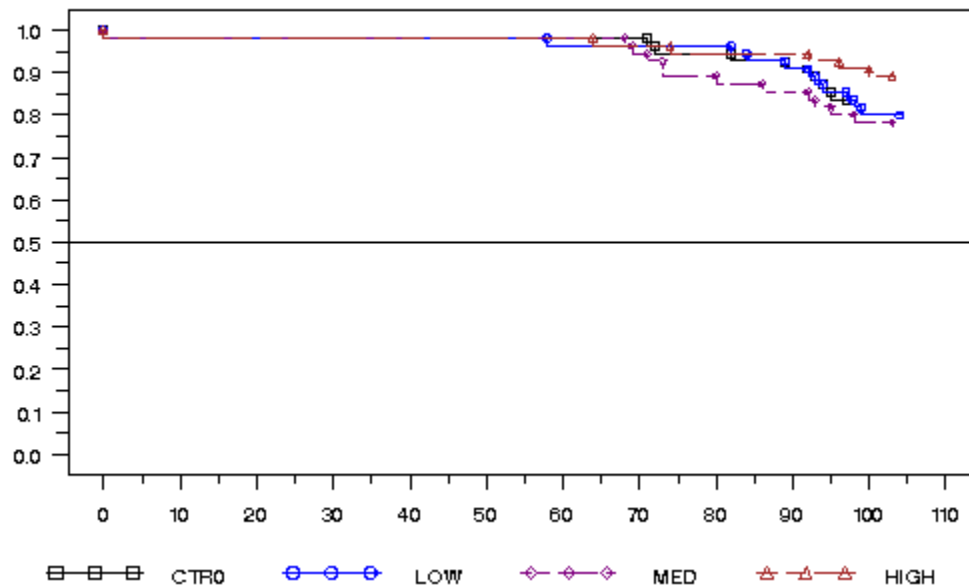
**Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Mice**

		Cont N=55	Low N=55	Med N=55	High N=55	P_Val ue Dos Resp	P_Val ue C vs. L	P_Val ue C vs. M	P_Val ue C vs. H
Organ Name	Tumor Name	N=55	N=55	N=55	N=55	Dos Resp	C vs. L	C vs. M	C vs. H
%%%									
Abdominal cavity	HEMANGIOSARCOMA	1	0	0	0	0.249	0.500	0.500	0.500
	LIPOMA	0	0	1	0	0.374	.	0.500	.
Adrenal	ADENOMA, SUBCAPSULAR	1	0	0	0	0.249	0.500	0.500	0.500
	PHEOCHROMOCYTOMA, MAL	0	0	0	1	0.122	.	.	0.245
Bone+Bone marrow	HEMANGIOMA	0	2	0	0	0.374	0.247	.	.
	HEMANGIOSARCOMA	1	1	0	0	0.187	0.500	0.500	0.500
Harderian gland	ADENOMA, ACINAR CELL	5	3	6	6	0.277	0.357	0.500	0.500
	CARCINOMA, ACINAR CELL	0	0	0	1	0.122	.	.	0.245
	MASTOCYTOMA	0	0	1	0	0.373	.	0.247	.
Hemolymphoretic	LYMPHOMA, MALIGNANT	14	22	13	12	0.203	0.071	0.500	0.410
	SARCOMA, HISTIOCYTIC	5	2	7	4	0.389	0.218	0.379	0.500
Hindlimb	FIBROSARCOMA	0	1	0	0	0.500	0.500	.	.
Intestine, cecum	LEIOMYOSARCOMA	0	1	0	0	0.500	0.500	.	.
Intestine, duode	ADENOCARCINOMA	0	0	1	0	0.373	.	0.247	.
Intestine, jejun	ADENOCARCINOMA	0	1	1	1	0.208	0.500	0.247	0.245
	ADENOMA	0	0	0	1	0.122	.	.	0.245
Kidney	ADENOCARCINOMA	0	0	0	1	0.122	.	.	0.245
Liver	ADENOMA, HEPATOCELLUL	5	5	20	39	<0.0001	0.500	<0.0001	<0.0001
	ADENOMA+CARCINOMA	6	9	22	40	<0.0001	0.288	<0.0001	<0.0001
	CARCINOMA, HEPATOCELL	1	4	2	5	0.089	0.181	0.500	0.055
	HEMANGIOMA	1	2	0	0	0.154	0.500	0.500	0.500
	HEMANGIOSARCOMA	1	2	0	0	0.154	0.500	0.500	0.500
	HEPATOBLASTOMA	0	0	1	0	0.374	.	0.500	.
Lung(bronchus)	ADENOMA, BRONCHIOLO-A	1	2	4	3	0.107	0.500	0.102	0.178
	CARCINOMA, BRONCHIOLO	2	2	1	2	0.464	0.500	0.500	0.500
	OSTEOSARCOMA	1	0	0	0	0.249	0.500	0.500	0.500
Lymph node, mese	HEMANGIOMA	1	0	0	0	0.249	0.500	0.500	0.500
Mammary gland	ADENOCARCINOMA	1	0	0	0	0.249	0.500	0.500	0.500
Mesothelium	MESOTHELIOMA, MALIGNA	0	1	0	0	0.500	0.500	.	.
Ovary	ADENOMA, TUBULOSTROMA	0	0	0	1	0.122	.	.	0.245
	CHORIOCARCINOMA	0	0	0	1	0.124	.	.	0.247
	CYSTADENOMA	1	0	0	0	0.249	0.500	0.500	0.500
	HEMANGIOMA	0	1	0	0	0.500	0.500	.	.
	LUTEOMA	0	0	0	1	0.122	.	.	0.245
Pituitary	ADENOMA, ANTERIOR	1	3	1	0	0.213	0.308	0.500	0.500
	ADENOMA, INTERMEDIATE	1	0	3	3	0.049	0.500	0.309	0.187

Table 6B (Continued): Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Mice

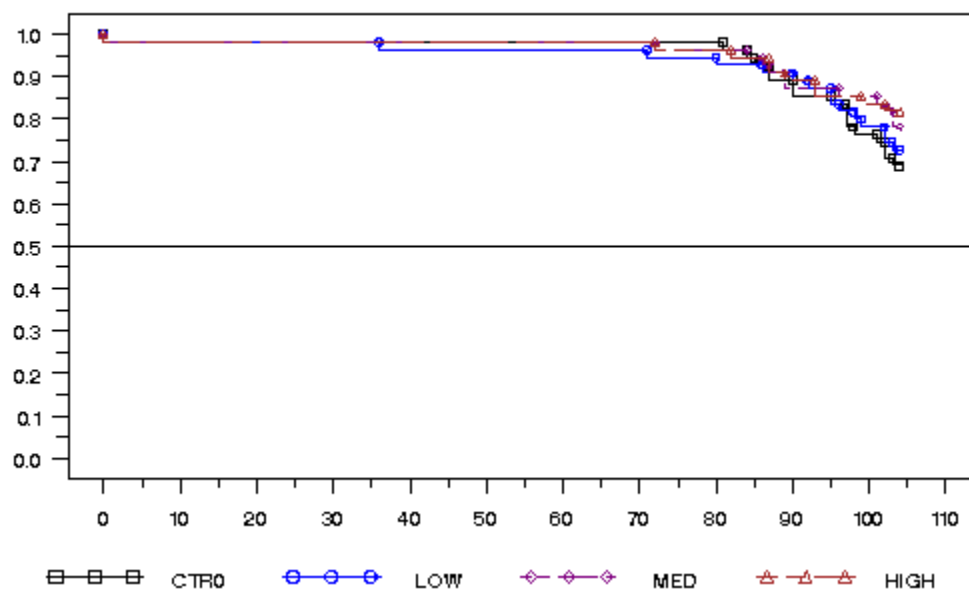
		Cont	Low	Med	Hi gh	P_Val ue	P_Val ue	P_Val ue	P_Val ue
Organ Name	Tumor Name	N=55	N=55	N=55	N=55	Dos Resp	C vs. L	C vs. M	C vs. H
%%%									
Ski n	FIBROSARCOMA	1	0	1	2	0.194	0.500	0.500	0.308
	HEMANGIOMA	2	0	0	1	0.254	0.247	0.247	0.500
	HEMANGIOSARCOMA	0	1	0	0	0.500	0.500	.	.
	LIPOSARCOMA	0	0	1	0	0.374	.	0.500	.
	SARCOMA, SPINDLE CELL	3	0	0	0	0.015	0.121	0.121	0.121
Skull	OSTEOSARCOMA	0	1	0	0	0.500	0.500	.	.
Spinal cord, lum	GLIOMATOMA	0	0	0	1	0.122	.	.	0.245
Spleen	HEMANGIOMA	2	3	0	1	0.163	0.500	0.247	0.500
	HEMANGIOSARCOMA	1	3	0	1	0.324	0.308	0.500	0.500
Stomach	PAPILLOMA, SQUAMOUS C	0	0	1	0	0.373	.	0.247	.
	POLYP, ADENOMATOUS	0	1	0	0	0.500	0.500	.	.
Thyroid	ADENOMA, FOLLICULAR C	1	2	0	1	0.381	0.500	0.500	0.500
Tongue	PAPILLOMA, SQUAMOUS C	1	0	0	0	0.249	0.500	0.500	0.500
Uterus	ADENOCARCINOMA	0	1	0	0	0.500	0.500	.	.
	HEMANGIOMA	1	1	0	0	0.187	0.500	0.500	0.500
	POLYP, ENDOMETRIAL ST	1	2	3	2	0.237	0.500	0.308	0.306

Figure 1A: Kaplan-Meier Survival Functions for Male Rats
Male Rats



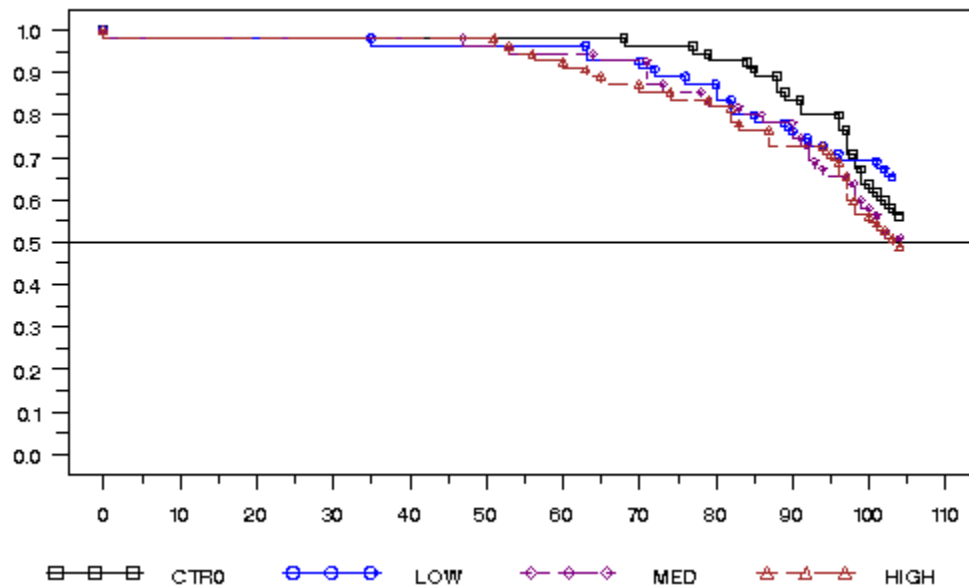
X-Axis: Weeks, Y-Axis: Survival rates

Figure 1B: Kaplan-Meier Survival Functions for Female Rats
Female Rats



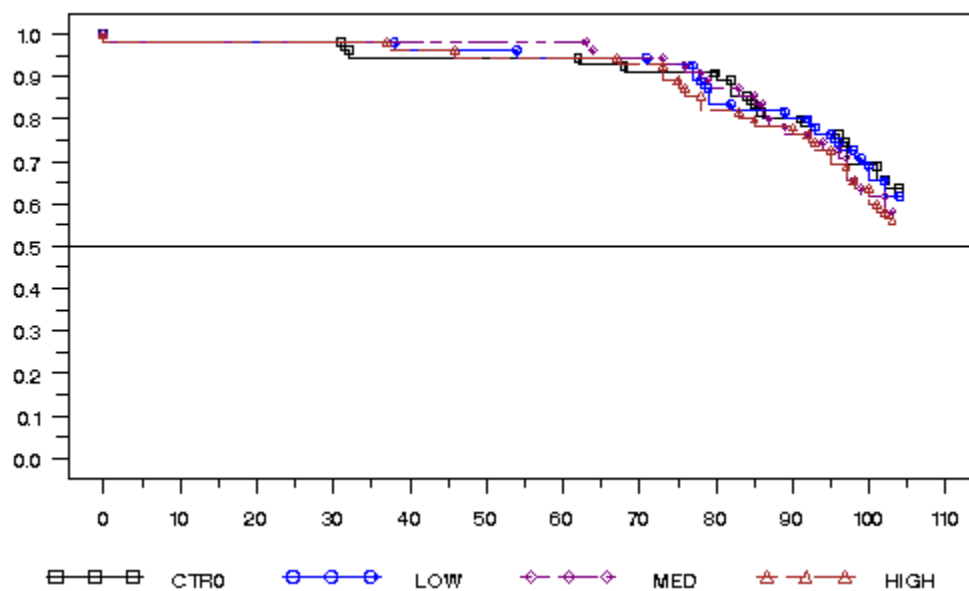
X-Axis: Weeks, Y-Axis: Survival rates

Figure 2A: Kaplan-Meier Survival Functions for Male Mice
Male Mice



X-Axis: Weeks, Y-Axis: Survival rates

Figure 2B: Kaplan-Meier Survival Functions for Female Mice
Female Mice



X-Axis: Weeks, Y-Axis: Survival rates

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CLINICAL REVIEW

Application Type	NDA 22,307
Submission Number	000
Submission Code	N

Letter Date	December 26, 2007
Stamp Date	December 26, 2007
PDUFA Goal Date	June 26, 2008

Reviewer Name	Karen A. Hicks, M.D.
Review Completion Date	April 28, 2008

Established Name	Prasugrel
(Proposed) Trade Name	Effient
Therapeutic Class	P2Y ₁₂ ADP receptor inhibitor
Applicant	Eli Lilly and Company

Priority Designation	P
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Formulation	Oral
Dosing Regimen	60 mg loading dose then 10 mg/d
Indication	Reduction of atherothrombotic events and stent thrombosis
Intended Population	Acute coronary syndrome

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Abbreviations

ABT=All But TAAL studies
ACS=acute coronary syndromes
ACT=activated clotting time
ADP=adenosine diphosphate
AE=adverse event
Afib=atrial fibrillation
Afl=atrial flutter
ALT=alanine aminotransaminase
ARB=angiotensin receptor blockers
ARC=Academic Research Consortium
ASA=aspirin
AST=aspartate aminotransaminase
AUC=area under the curve
BMS=bare metal stent
BP=blood pressure
BUN=blood urea nitrogen
CABG=coronary artery bypass graft surgery
CAD=coronary artery disease
CBC=complete blood count
CEC=Clinical Endpoints Committee
CHF=congestive heart failure
CI=confidence interval
CIB=Clinical Investigator's Brochure
CIE=cardiac ischemic events
CK=creatinine kinase
CK-MB=creatinine kinase-myocardial bands
Completion of the PCI procedure=defined as 60 minutes after the subject leaves the cardiac catheterization laboratory
COX2=cyclooxygenase-2
CRF=case report form
CRO=contract research organization
CS-747=prasugrel
CT=computed tomography
CURE=The Clopidogrel in Unstable angina to prevent Recurrent Events Study
CV=cardiovascular
CVA=cerebrovascular accident
DBP=diastolic blood pressure
DES=drug eluting stent
DM=diabetes mellitus
DMC=Data Monitoring Committee
ECG=electrocardiogram
End of Study (Trial)=End of study (trial) is the date of the last visit shown in the study schedule of the last subject active in the study
GP=glycoprotein
H2=histamine 2 receptor
Hct=hematocrit
HDL=high density lipoprotein
Hgb=hemoglobin
HMG Co-A=3 hydroxy-3-methylglutaryl coenzyme A
HTN=hypertension

HR=heart rate
ICH=intracranial hemorrhage
INR=International Normalized Ratio
Index procedure=PCI during the initial hospitalization
IPA=inhibition of platelet aggregation
IRB/ERB=Institutional review board/ethical review board
ITT=intent-to-treat
IVRS=Interactive Voice Response System
JUMBO=The Joint Utilization of Medications to Block Platelets Optimally study
LBBB=left bundle branch block
LD=loading dose
MACE=major adverse cardiovascular events
MD=maintenance dose
MI=myocardial infarction
MPA=maximum platelet aggregation
MRI=magnetic resonance imaging
N/A=not applicable
NE=not evaluated
NQWMI=non-Q-wave myocardial infarction
NSAIDS=nonsteroidal anti-inflammatory drugs
NSTEMI=non-ST-segment elevation myocardial infarction
NYHA CHF=New York Heart Association Congestive Heart Failure
PCI=percutaneous coronary intervention
PPI=proton pump inhibitors
QD=once daily
QwMI=Q-wave myocardial infarction
RBC=red blood cells
SAE=serious adverse event
SAP=Statistical Analysis Plan
SBP=systolic blood pressure
SGOT=serum glutamic oxaloacetic transaminases
SGPT=serum glutamic pyruvic transaminases
SOC=system organ class
STEMI=ST-segment elevation myocardial infarction
TAAL=Study H7T-MC-TAAL. A Comparison of CS-747 and Clopidogrel in Acute Coronary Syndrome Subjects Who Are To Undergo Percutaneous Coronary Intervention/TIMI-38=TRITON
TEAE=Treatment-emergent adverse event. Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and which does not necessarily have to have a causal relationship with this treatment.
TESAE=treatment emergent serious adverse event
TIA=transient ischemic attack
TIMI=The TIMI Study Group. Named for a series of national clinical studies know as the TIMI (Thrombolysis in Myocardial Infarction) studies launched in 1984 by Brigham and Women's Hospital
TRITON=TAAL
TVR=target vessel revascularization
UA=unstable angina
UA/NSTEMI=unstable angina and non-ST-segment elevation myocardial infarction
ULN=upper limit of normal
US=United States of America
UTVR=urgent target vessel revascularization
Vfib=ventricular fibrillation
WBC=white blood cells

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend approval of prasugrel for the reduction of atherothrombotic events in patients with 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.

In TAAL, prasugrel significantly reduced the rate of the combined primary endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in the UA/NSTEMI, All ACS, and STEMI populations at a median follow-up of 12 months, compared to clopidogrel. Subjects appeared to receive most of the treatment benefit from prasugrel within the first thirty days of therapy.

In the prasugrel treatment group, however, there was a 36% increased risk of overall bleeding and a 46% increased risk of serious bleeding, compared to clopidogrel. Although the rates of intracranial hemorrhage were similar between the two treatment groups, the fatality rate associated with this event was two-fold higher with prasugrel. In both treatment groups, many of the bleeding events occurred within the first 3 to 5 days of the index procedure; however, the cumulative risk of bleeding with prasugrel appeared to increase over time.

Furthermore, preliminary analyses from TAAL suggest there may be an increased rate of new malignancies in the prasugrel treatment group, compared to clopidogrel ($p=0.006$), with a divergence in the incidence of these malignancies at 4 months.

Based on these preliminary analyses as well as increased bleeding risks with prasugrel over time, I recommend limiting therapy with prasugrel to short-term use (i.e., one week), so that patients may receive the benefits of this therapy while avoiding some of the possible risks.

I do not recommend approval of prasugrel for the reduction of stent thrombosis because the sponsor has not met the scientific rigor required for such a claim and has selectively used the standardized definitions for stent thrombosis developed in 2007 by the Academic Research Consortium (ARC) and our CDRH colleagues. For such a claim to be considered, angiographic confirmation of stent thrombosis would be necessary, generally determined by an angiographic core laboratory, or pathological confirmation with evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy. In TAAL, there was no review of angiograms by an angiographic core laboratory, and there was limited pathological confirmation. The CEC made the determination of stent thrombosis by clinical adjudication and review of cardiac catheterization and percutaneous coronary intervention reports. The CEC did not review angiograms and did not review all suspected events of stent thrombosis. In some cases, there was evidence of poor adjudication by the CEC. Furthermore, there was no prospective attempt in TAAL to gather pathological evidence of stent thrombosis. Although two autopsies were subsequently obtained and demonstrated stent thrombosis, this limited amount of pathological confirmation for a trial of this size is not adequate. Since the results of clinical adjudication can be different from outside angiographic and pathologic review, which is currently required by our CDRH colleagues, I consider the results from TAAL to be promising but exploratory. Therefore, I recommend the sponsor participate in a randomized, prospective, clinical trial to further evaluate these preliminary findings.

1.2 Recommendation on Postmarketing Actions

The sponsor plans to perform TABY, a study comparing prasugrel to clopidogrel in UA/NSTEMI patients (n > 13,000) who are medically managed. In this study, the sponsor proposes lowering the loading dose to 30 mg for patients needing a loading dose and lowering the maintenance dose from 10 mg to 5 mg in patients ≥ 75 years of age or weighing < 60 kg.

Based on our preliminary analysis which suggests there may be an increased rate of malignancy in the prasugrel treatment group, the sponsor will need to carefully collect all information related to neoplasia and bleeding. Perhaps cancer screening can be incorporated into the trial following the index hospitalization. Additionally, the sponsor will need to clearly distinguish neoplasia as past medical history from a new diagnosis in the clinical trial. Patients with worsening of their underlying malignancy should also be followed closely.

1.2.1 Risk Management Activity

The sponsor has proposed a risk management plan for prasugrel. Important identified risks include intracranial hemorrhage, gastrointestinal hemorrhage, intraocular hemorrhage, epistaxis, percutaneous coronary intervention-related hemorrhage, CABG-related hemorrhage, other procedure-related hemorrhage, and anemia. The sponsor has also identified important potential risks to include phototoxicity (skin or ocular), drug-induced hepatic injury, allergic reactions, thrombocytopenia, thrombotic thrombocytopenic purpura, and neutropenia. To date, neoplasia has not been identified as an important risk but needs to be incorporated into the sponsor's risk management plan.

Elements of the risk management plan include routine pharmacovigilance of adverse events with prasugrel, targeted surveillance activities with specific follow-up forms for the important identified risks and potential risks, and active surveillance in the ongoing clinical trials with prasugrel.

1.2.2 Required Phase 4 Commitments

[REDACTED]

[REDACTED]

[REDACTED]

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The prasugrel clinical development program consisted of 52 pharmacokinetic, pharmacodynamic, and clinical studies including TAAL (n=13,608), TABL (n=201), and TAAH (n=904). TAAL was a Phase 3, multicenter, randomized, parallel-group, double-blind, double-dummy, active-controlled study in subjects with acute coronary syndrome and was the predominant study submitted for consideration of the efficacy claim. In TAAL, subjects were randomized to prasugrel (60 mg loading dose, 10 mg maintenance dose) or clopidogrel (300 mg loading dose, 75 mg

maintenance dose). The primary endpoint was the composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke at a median follow-up of 12 months. TABL was a multicenter, randomized, parallel, double-blind, double-dummy, cross-over, active comparator-controlled study in subjects undergoing elective cardiac catheterization with planned PCI. In TABL, subjects were randomized to prasugrel (60 mg loading dose; 10 mg maintenance dose x 14 ± 2 days) or clopidogrel (600 mg loading dose; 150 mg maintenance dose x 14 ± 2 days) and subsequently crossed over to the alternative regimen for an additional 14 days. The primary endpoints included the inhibition of platelet aggregation 6 hours (± 30 minutes) after the loading dose or after 14 ± 2 days of maintenance dosing. Lastly, TAAH was a multicenter, randomized, parallel, double-blind, double-dummy, active comparator-controlled trial in subjects undergoing elective or urgent PCI with coronary stenting. In TAAH, subjects were randomized to clopidogrel (300 mg loading dose, 75 mg maintenance dose x 30-35 days) or three different regimens of prasugrel (40 mg loading dose/7.5 mg maintenance dose; 60 mg loading dose/10 mg maintenance dose; or 60 mg loading dose/15 mg maintenance dose). 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.

1.3.2 Efficacy

In TAAL, prasugrel significantly reduced the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke using the original and expanded definitions of peri-procedural myocardial infarction, as displayed in Table 1 and Table 2, respectively. The original definition of peri-procedural myocardial infarction required an elevation of creatine kinase-myocardial band (CK-MB) to > 3x upper limit of normal (ULN) on a minimum of two samples within 48 hours of PCI. The modified definition, specified in Protocol Amendment (a) dated January 10, 2006, maintained the original definition but extended periprocedural myocardial infarctions to a CK-MB > 5x ULN on one sample if it was the last available sample and was drawn ≥ 12 hours after PCI.

Table 1. Sponsor's Analysis: Number and Percentage of Subjects Reaching the Composite Endpoint of CV Death, Nonfatal MI or Nonfatal Stroke Using the Definition of Peri-Procedural Myocardial Infarction Prior to Protocol Amendment (CEC Adjudicated) (All Randomized Subjects) (TAAL)

Subject Population	Prasugrel			Clopidogrel			Total			HR	(95% CI) ^b	p-value ^c
	N	n	(%) ^a	N	n	(%) ^a	N	n	(%) ^a			
UA/NSTEMI	5044	443	(8.78)	5030	536	(10.66)	10074	979	(9.72)	0.817	(0.720, 0.926)	0.002
STEMI	1769	162	(9.16)	1765	201	(11.39)	3534	363	(10.27)	0.793	(0.645, 0.976)	0.024
All ACS	6813	605	(8.88)	6795	737	(10.85)	13608	1342	(9.86)	0.810	(0.727, 0.902)	<0.001

CI=confidence interval, CV=cardiovascular, HR=hazard ratio, N=number treated, n=number of subjects reaching primary endpoint.
^a% is percentage of randomized subjects reaching the primary endpoint.
^bHR and two-sided 95% CI derived using Cox proportional hazards model.
^cTwo-sided p-values are based on Gehan-Wilcoxon test comparing event free survival distributions of Prasugrel and Clopidogrel.
Clinical presentation, UA/NSTEMI vs. STEMI, was used as a stratification factor in analysis involving All ACS subjects.
(Reproduced from Sponsor, Table TAAL.14.20, page 1407 of 27,024)
Analysis verified by Ququan Liu, M.D., M.S., Biometrics, FDA.

Table 2. Sponsor's Analysis: Number and Percentage of Subjects Reaching the Composite Endpoint of CV Death, Nonfatal MI, or Nonfatal Stroke Using the Expanded Definition (CEC Adjudicated) (All Randomized Subjects) (TAAL)

Subject Population	Prasugrel			Clopidogrel			Total			HR	(95% CI) ^b	p-value ^c
	N	n	(%) ^a	N	n	(%) ^a	N	n	(%) ^a			
UA/NSTEMI	5044	469	(9.30)	5030	565	(11.23)	10074	1034	(10.26)	0.820	(0.726, 0.927)	0.002
STEMI	1769	174	(9.84)	1765	216	(12.24)	3534	390	(11.04)	0.793	(0.649, 0.968)	0.019
All ACS	6813	643	(9.44)	6795	781	(11.49)	13608	1424	(10.46)	0.812	(0.732, 0.902)	<0.001

CI=confidence interval, HR=hazard ratio, N=number treated, n=number of subjects reaching primary endpoint.
^a% is percentage of randomized subjects reaching the primary endpoint.
^bHR and two-sided 95% CI used as an estimate of overall relative risk, Prasugrel versus Clopidogrel, over the course of the study.
^cTwo-sided p-values are based on Gehan-Wilcoxon test comparing event free survival distributions of Prasugrel and Clopidogrel.
Clinical presentation, UA/NSTEMI vs. STEMI, was used as a stratification factor in analysis involving All ACS subjects.
(Reproduced from Sponsor, Table TAAL.11.5, page 202 of 27,024).
Analysis verified by Ququan Liu, M.D., M.S., Biometrics, FDA.

1.3.3 Safety

In the UA/NSTEMI and all ACS populations, prasugrel significantly increased non-CABG related TIMI major, TIMI life-threatening, TIMI fatal, and TIMI minor bleeding compared to clopidogrel, as shown in Table 3.

Table 3. Sponsor's Analysis: CEC Adjudicated Non-CABG-Related Bleeding (TAAL)

Subject Population	Prasugrel			Clopidogrel			Total			HR	(95% CI) ^b	p-value ^c
	N	n	(%)	N	n	(%)	N	n	(%)			
TIMI Major ^a												
UA/NSTEMI	5001	108	(2.16)	4980	77	(1.55)	9981	185	(1.85)	1.404	(1.048, 1.881)	0.022
STEMI	1740	38	(2.18)	1736	34	(1.96)	3476	72	(2.07)	1.115	(0.702, 1.770)	0.645
All ACS	6741	146	(2.17)	6716	111	(1.65)	13457	257	(1.91)	1.315	(1.028, 1.683)	0.029
TIMI Life-Threatening ^a												
UA/NSTEMI	5001	65	(1.30)	4980	38	(0.76)	9981	103	(1.03)	1.711	(1.146, 2.553)	0.008
STEMI	1740	20	(1.15)	1736	18	(1.04)	3476	38	(1.09)	1.109	(0.587, 2.096)	0.750
All ACS	6741	85	(1.26)	6716	56	(0.83)	13457	141	(1.05)	1.517	(1.083, 2.126)	0.015
TIMI Fatal												
UA/NSTEMI	5001	14	(0.28)	4980	3	(0.06)	9981	17	(0.17)	4.664	(1.341, 16.230)	0.008
STEMI	1740	7	(0.40)	1736	2	(0.12)	3476	9	(0.26)	3.480	(0.723, 16.753)	0.097
All ACS	6741	21	(0.31)	6716	5	(0.07)	13457	26	(0.19)	4.191	(1.580, 11.113)	0.002
TIMI Minor ^a												
UA/NSTEMI	5001	117	(2.34)	4980	80	(1.61)	9981	197	(1.97)	1.466	(1.103, 1.948)	0.008
STEMI	1740	47	(2.70)	1736	45	(2.59)	3476	92	(2.65)	1.041	(0.691, 1.566)	0.848
All ACS	6741	164	(2.43)	6716	125	(1.86)	13457	289	(2.15)	1.313	(1.040, 1.656)	0.022
CI=confidence interval; HR=hazard ratio; N=number of subjects; n=number of subjects with event.												
^a Subjects experiencing multiple bleeding events may be included in more than one category.												
^b HR and two-sided 95% CI derived using Cox proportional hazards model.												
^c Two-sided log-rank p-value based on time to first event analysis compares the event free survival distributions for Prasugrel and Clopidogrel. Clinical presentation, UA/NSTEMI vs. STEMI, was used as a stratification factor in analyses of All ACS subjects.												
Reproduced from Sponsor, Table TAAL.12.3, page 511 and Table 12.4, pages 517-520.												
Analysis verified by Karen A. Hicks, M.D. and Ququan Liu, M.D., M.S., Biometrics, FDA.												

In the UA/NSTEMI, STEMI, and All ACS populations, prasugrel also significantly increased CABG-related TIMI major bleeding, as shown in Table 4. Bleeding analyses from TAAL suggest that prasugrel should be discontinued at least 7 days prior to CABG, if possible.

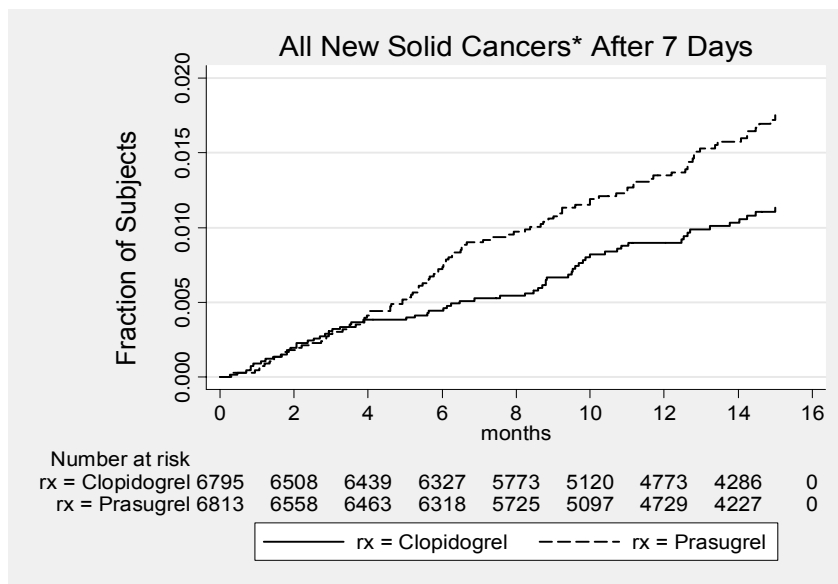
Table 4. Sponsor's Analysis: CEC-Adjudicated CABG-Related Bleeding Events Through Study End (Overall) (TAAL)

Subject Population	Prasugrel			Clopidogrel			Total			OR	(95% CI) ^b	p-value ^c
	N	n	(%) ^a	N	n	(%) ^a	N	n	(%) ^a			
TIMI Major												
UA/NSTEMI	138	12	(8.70)	141	4	(2.84)	279	16	(5.73)	3.262	(1.025, 10.38)	0.035
STEMI	75	12	(16.00)	83	4	(4.82)	158	16	(10.13)	3.762	(1.157, 12.23)	0.020
All ACS	213	24	(11.27)	224	8	(3.57)	437	32	(7.32)	3.496	(1.531, 7.986)	0.002
TIMI Fatal												
UA/NSTEMI	138	0		141	0		279	0				NE
STEMI	75	2	(2.67)	83	0		158	2	(1.27)			NE
All ACS	213	2	(0.94)	224	0		437	2	(0.46)			NE
CI=confidence interval; OR=odds ratio; N=number of treated subjects undergoing CABG; n=number of treated subjects undergoing CABG with CABG-related bleeding events; NE=not evaluated due to insufficient data.												
^a % is percentage of N.												
^b Odds ratio (OR) is based on the frequency procedure.												
^c Two-sided p-values based on Pearson chi-square in UA/NSTEMI and STEMI, CMH general association test with clinical presentation as a blocking factor in All ACS.												
Reproduced from Sponsor, Table TAAL.12.42, pages 763-770.												
Analysis verified by Karen A. Hicks, M.D. and Ququan Liu, M.D., M.S., Biometrics, FDA.												

In TAAL, an unexpected safety finding in the prasugrel treatment group was the increased rate of all cancers, particularly the solid tumors (e.g., breast, colorectal, esophageal, lung) (p = 0.006). Since tumor findings were sometimes noted at screening but not further evaluated until after enrollment, initial FDA analyses excluded cancers diagnosed during Days 0 to 7. While these results are preliminary, the Kaplan-Meier incidence plot by treatment for

all new first cancers (excluding skin and brain tumors) demonstrates a divergence in incidence between the prasugrel and clopidogrel treatment groups at 4 months with continuing divergence through the duration of the study, as shown in Figure 1.

Figure 1. Kaplan-Meier (K-M) Incidence Plot for All New Solid Cancers Diagnosed After 7 Days in TRITON (TAAL)



*excluding non-melanoma skin cancers and brain tumors; p = 0.006 by log rank

(Analysis by Thomas A. Marciniak, M.D., Division of Cardiovascular and Renal Products)

Consultants from the Division of Oncology Products agreed that when the incidences of “all cancers” between the two Triton study arms were compared, a p-value of < 0.05 was obtained; however, they were not certain of the statistical or clinical significance of this finding. The consult states, “given the absence of a well-defined cancer screening at Triton study entry and short drug exposure to the study drugs (6 to 15 months), the cancers diagnosed in this study are more likely to be incidental.” Recommendations included consultation with the Office of Surveillance and Epidemiology, incorporation of these neoplasia findings in labeling, and establishment of a registry by the sponsor to track the incidence of cancer on prasugrel, all of which we are doing.

We requested additional data from the sponsor on neoplasms from TAAL which are pending at the time of this review. Final recommendations on the approvability of prasugrel will depend on a thorough analysis of these data.

1.3.4 Dosing Regimen and Administration

The sponsor recommends oral dosing to include a single 60-mg loading dose followed by 10-mg once daily maintenance dosing.

For patients weighing < 60 kg (132 pounds), the sponsor recommends a single 60-mg loading dose followed by a 5-mg once daily maintenance dose.

For patients ≥ 75 years of age, the sponsor recommends a single 60-mg loading dose with consideration given to a 5-mg once daily maintenance dose as an alternative to a 10-mg once daily maintenance dose.

1.3.5 Drug-Drug Interactions

In Study TACS, high (70%), intermediate (58%), and low conversion tablets (5%) of prasugrel were found to be bio-inequivalent in healthy subjects pre-treated with lansoprazole (30 mg). The difference in plasma levels translated into differences in platelet aggregation which could be clinically relevant.¹

Inhibitors of CYP3A decreased the C_{max} of the active metabolite, R-138727, by 46% but had no effect on the AUC and T_{max} . Rifampicin (600 mg daily), a potent inducer of CYP3A and CYP2B6 and an inducer of CYP2C9, CYP2C19, and CYP2C8, did not significantly affect the pharmacokinetics of prasugrel.

There appears to be a potential for drug-drug interaction with atorvastatin. One healthy subject in Study TAAV (Subject 11) experienced acute hepatic failure after coadministration of high-dose atorvastatin and prasugrel. Liver function abnormalities resolved after the discontinuation of both medications.

1.3.6 Special Populations

1.3.6.1 Age ≥ 75 years

Subjects ≥ 75 years of age appeared to receive less benefit from prasugrel, compared to clopidogrel, as shown in Table 5.

Table 5. FDA Subgroup Analysis: Composite of Cardiovascular Death, Nonfatal Myocardial Infarction, or Nonfatal Stroke at a Median of 12 Months of Follow-Up by Age (TAAL)

	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
< 75 years									
N	4328	4344	0.78	1584	1543	0.80	5912	5887	0.78
n	356	454	0.68, 0.90	143	173	0.64, 0.99	499	627	0.70, 0.88
%	8.23	10.45	0.0006	9.02	11.21	0.0370	8.44	10.65	<0.0001
≥ 75 years									
N	716	686	0.97	185	222	0.85	901	908	0.94
n	113	111	0.75, 1.26	31	43	0.54, 1.35	144	154	0.75, 1.18
%	15.78	16.18	0.8539	16.76	19.37	0.4478	15.98	16.96	0.5329
Analysis by Ququan Liu, M.D., M.S., Division of Biometrics, FDA.									

In both treatment groups, subjects ≥ 75 years of age had a higher incidence of Non-CABG-related TIMI Major or Minor bleeding events (8.98% prasugrel, 6.94% clopidogrel for subjects ≥ 75 years; 3.81% prasugrel, 2.90% clopidogrel for subjects < 75 years).² Additionally, subjects ≥ 75 years of age had a higher risk of Non-CABG-related TIMI Major Life-Threatening bleeding events, including fatal bleeds and symptomatic intracranial hemorrhage for both treatment groups (fatal bleeding: 1.01% prasugrel, 0.11% clopidogrel; symptomatic intracranial hemorrhage: 0.79% prasugrel, 0.34% clopidogrel).³

Based on these data, prasugrel should probably not be the treatment of choice in patients ≥ 75 years of age. Even with a maintenance dose reduction from 10 mg to 5 mg daily in this population, efficacy is unclear and the risk of bleeding is higher. If prasugrel is approved for all age groups, physicians will need to carefully balance the risks versus benefits when prescribing prasugrel in patients ≥ 75 years of age.

¹Analysis by Patrick Marroum, Ph.D., Biopharmaceutics Review, Division of Clinical Pharmacology, FDA.

²Sponsor, Risk Management Plan, page 21 of 97.

³Sponsor, Risk Management Plan, page 21 of 97 and TAAL Clinical Study Report, Table TAAL.12.15, page 601.

1.3.6.2 Patients with a Prior History of Transient Ischemic Attack (TIA)/Cerebrovascular Accident (CVA)

Prasugrel appeared to have less benefit in patients with a prior history of TIA/CVA, as shown in Table 6.

Table 6. FDA Subgroup Analysis: Composite of Cardiovascular Death, Nonfatal Myocardial Infarction, or Nonfatal Stroke at a Median of 12 Months of Follow-up in Patients With and Without a Prior History of Transient Ischemic Attack/Cerebrovascular Accident (TAAL)

	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Prior History of TIA/CVA									
N	213	192	1.53	49	64	0.98	262	256	1.38
n	39	24	0.92, 2.55	8	11	0.39, 2.42	47	35	0.89, 2.13
%	18.31	12.50	0.0677	16.33	17.19	0.9127	17.94	13.67	0.1382
No Prior History of TIA/CVA									
N	5831	4838	0.79	1720	1701	0.79	6551	6539	0.79
n	430	541	0.69, 0.89	166	205	0.64, 0.97	596	746	0.71, 0.88
%	8.90	11.18	0.0003	9.65	12.05	0.020	9.10	11.41	<0.0001
ACS=acute coronary syndrome; CVA=cerebrovascular accident; NSTEMI=non-ST-segment elevation myocardial infarction; STEMI=ST-elevation myocardial infarction; TIA=transient ischemic attack; UA=unstable angina Analysis by Ququan Liu, M.D., M.S., Division of Biometrics, FDA.									

Additionally, in patients with a prior history of TIA/CVA, the incidence of stroke was 6.5% (2.3% intracranial hemorrhage (ICH)) in the prasugrel treatment group, compared to 1.2% (0% ICH) in the clopidogrel treatment group (p-value < 0.001 for interaction).⁴ In patients without a prior history of TIA/CVA, the incidence of stroke was 0.9% (0.2% ICH) in the prasugrel treatment group and 1.0% (0.3%) in the clopidogrel treatment group.

In subjects ≥ 75 years of age, there was a significantly higher incidence of stroke in the prasugrel treatment group compared to clopidogrel (2.89% versus 1.43%, p=.024) and a similar incidence between treatment groups in subjects < 75 years of age (0.83% versus 0.99%, not significant).⁵

Based on these data, I recommend prasugrel is contraindicated in patients with a prior history of TIA/CVA.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

CS-747 (prasugrel) is a new molecular entity that inhibits platelet activation and aggregation. Prasugrel is a prodrug that undergoes deacetylation by esterases to form a thiolactone (inactive), which is converted to the active moiety, R-138727, via the cytochrome P450 system. Similar to clopidogrel, the active metabolite of prasugrel irreversibly inhibits the P2Y₁₂ ADP receptor for the entire lifespan of the platelet.

2.2 Currently Available Treatment for Indications

Ticlopidine hydrochloride and clopidogrel bisulfate are FDA-approved adenosine diphosphate (ADP) receptor antagonists of the thienopyridine class that inhibit platelet activation and aggregation.

⁴TAAL Clinical Study Report, Table TAAL.11.36, Number and Percentage of Subjects Reaching Primary, Secondary, and Other Efficacy Endpoints (CEC Adjudicated) (Subgroup Analysis by Prior TIA or Stroke), page 448.

⁵Sponsor, Risk Management Plan, page 22 of 97.

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)

[REDACTED]

[REDACTED]

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.

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

⁷Analysis 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 49 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 Summaries 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 Liberté 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.
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 [REDACTED]. 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.
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 [REDACTED], she experienced gastrointestinal bleeding adjudicated as a TIMI minor bleed. On [REDACTED], 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 [REDACTED]. 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.

4. Subject 01000613703 (81 yo male) (STEMI) (clopidogrel): This subject underwent PCI with placement of a 2.75 x 24 mm Taxus stent in the proximal left anterior descending artery on [REDACTED]. He was rehospitalized for a NSTEMI on [REDACTED] and underwent non urgent target vessel revascularization on [REDACTED]. Repeat coronary angiography on [REDACTED] demonstrated a 95% stenosis in the left anterior descending artery just proximal to the stent with 40-50% in-stent restenosis in the distal aspect of the stent. The patient also had a 50-70% stenosis in the mid right coronary artery. Although the PCI report mentioned there was a “haziness” in the 40% in-stent restenotic lesion in the distal aspect of the stent and that a “minimal thrombus burden [could not] be totally excluded,” the description did not seem to meet criteria described by the Academic Research Consortium for definite stent thrombosis. The CEC adjudicated this case as a definite stent thrombosis. Since stent thrombosis is not a subtle event and usually requires emergency coronary angiography/revascularization, I am not convinced that stent thrombosis occurred in this subject who underwent cardiac catheterization three days after initial hospitalization.

4.5 Compliance with Good Clinical Practices

A sponsor representative signed a debarment certification stating that Lilly did not use the services of any person debarred under Section 306 of the Federal FD&C Act in connection with NDA 22,307.

The pivotal phase 3 studies were conducted in accordance with the ICH consolidated guidelines for Good Clinical Practice (GCP) and the Code of Federal Regulations which originates from the ethical principles laid down in the Declaration of Helsinki. Ethical Review Boards reviewed the protocols, protocol amendments, and informed consent documents (ICDs) and provided written approval of the study protocol and ICDs. Written informed consent was to be obtained in all study subjects.

4.6 Financial Disclosures

The sponsor provided financial disclosure information for “covered clinical studies” that included the Phase 3 study, two Phase 2 studies, and three Phase 1 studies (e.g., H7T-MC-TAAL, H7T-MC-TAAH, H7T-MC-TABL, H7T-MC-TABR, H7T-EW-TACS, and H7T-EW-TAAW).

A sponsor representative signed FDA Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) for each of the “covered clinical studies.” Box (1) was checked. For TAAL, a sponsor representative also signed FDA Form 3454 for three investigators with significant financial interests and included a statement as to why the disclosure did not have any potential impact on study results. These three investigators, Dr. Bruce Norman Brent (Investigator Number 10333, United States), Dr. Martin Höher (Investigator Number 490620, Germany), and Dr. Ronnie G. Smalling (Investigator Number 10295, United States) enrolled a total of 32 patients in TAAL. Based on the size of the clinical trial (N=13,608), I agree that these investigators did not significantly impact the results of TAAL.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

In this section, some key highlights with respect to prasugrel pharmacokinetics and clinical pharmacology are bulleted.

- Prasugrel.HCl has higher solubility and is absorbed more quickly than prasugrel base at higher pH.
- [REDACTED]
- In healthy humans receiving a proton pump inhibitor (lansoprazole 30 mg daily), the prasugrel.HCl low (5%), intermediate (58%), and high (70%) extent of conversion tablets following a single 60 mg dose were bioequivalent. The difference in plasma levels translated into differences in maximum platelet aggregation.

- In the setting of lansoprazole, the C_{max} 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 T_{max} of prasugrel ranges from 0.25 hours to 2.25 hours and for the metabolites ranges from 0.5 – 1 hour. The terminal t_{1/2} 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 C_{max} 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 C_{max} by 49%, but did not affect the AUC of R-138727. In a fed state, the T_{max} 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 ¹⁴C 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 [¹⁴C] 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 C_{max} 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

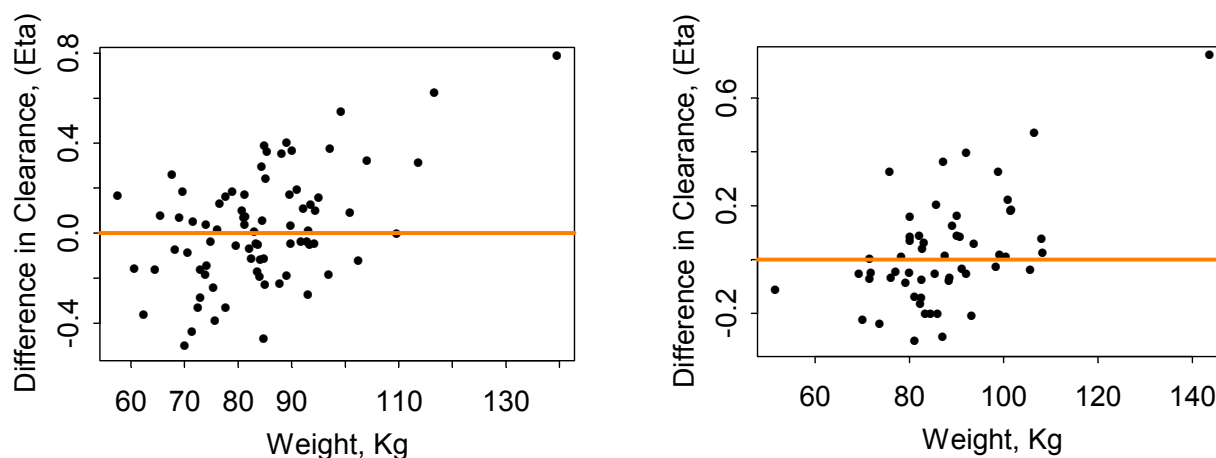
In Study TACS, the objective was to determine the effect of salt conversion to base during storage of prasugrel tablets on the pharmacokinetics of prasugrel's active metabolite in healthy subjects taking a proton pump inhibitor (lansoprazole 30 mg once daily). Prasugrel was administered orally as a single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

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 C_{max} 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.

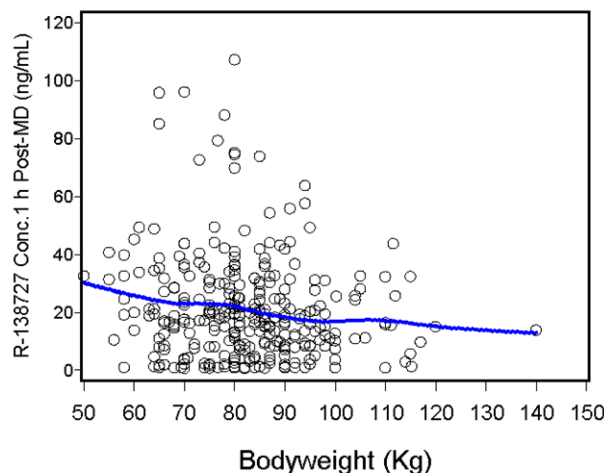
Figure 2. Clearance of R-138727 Increases with Increase in Body Weight (Left: Study TAAD. Right: Study TABR.)



(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.

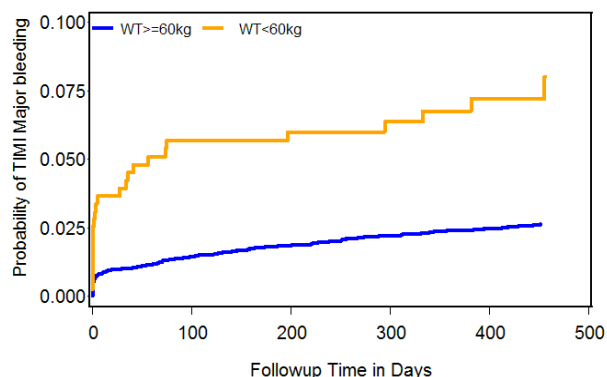
Figure 3. Increased Exposures of R-138727 with Decreased Body Weight (TAAL)



(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.

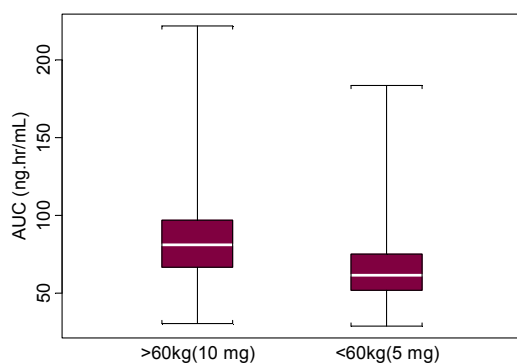
Figure 4. Risk for TIMI Major Bleeding is Higher in Patients with Body Weight < 60 kg



(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. However, the efficacy of the 5 mg maintenance dose in subjects weighing < 60 kg has not been studied. 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 = $123 \times (WT/85)^{0.798}$; 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 definition⁸) 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).

⁸Cutlip 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.

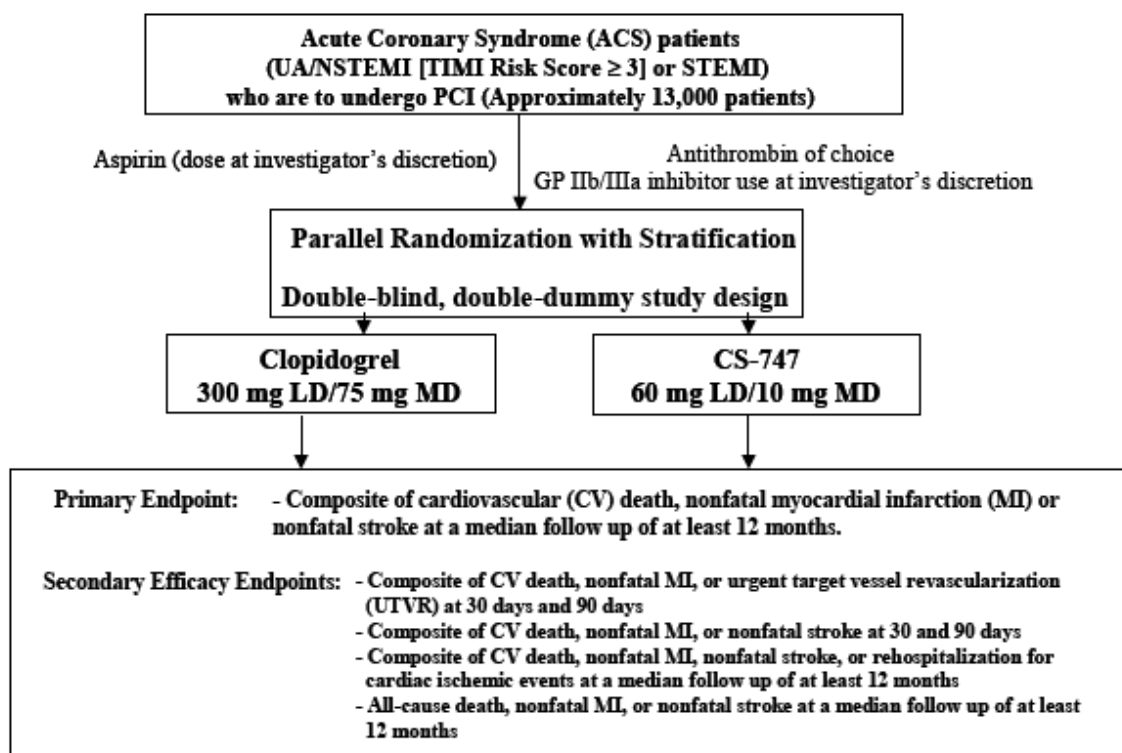
Following screening and informed consent, subjects underwent parallel randomization with stratification as follows:

- 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).

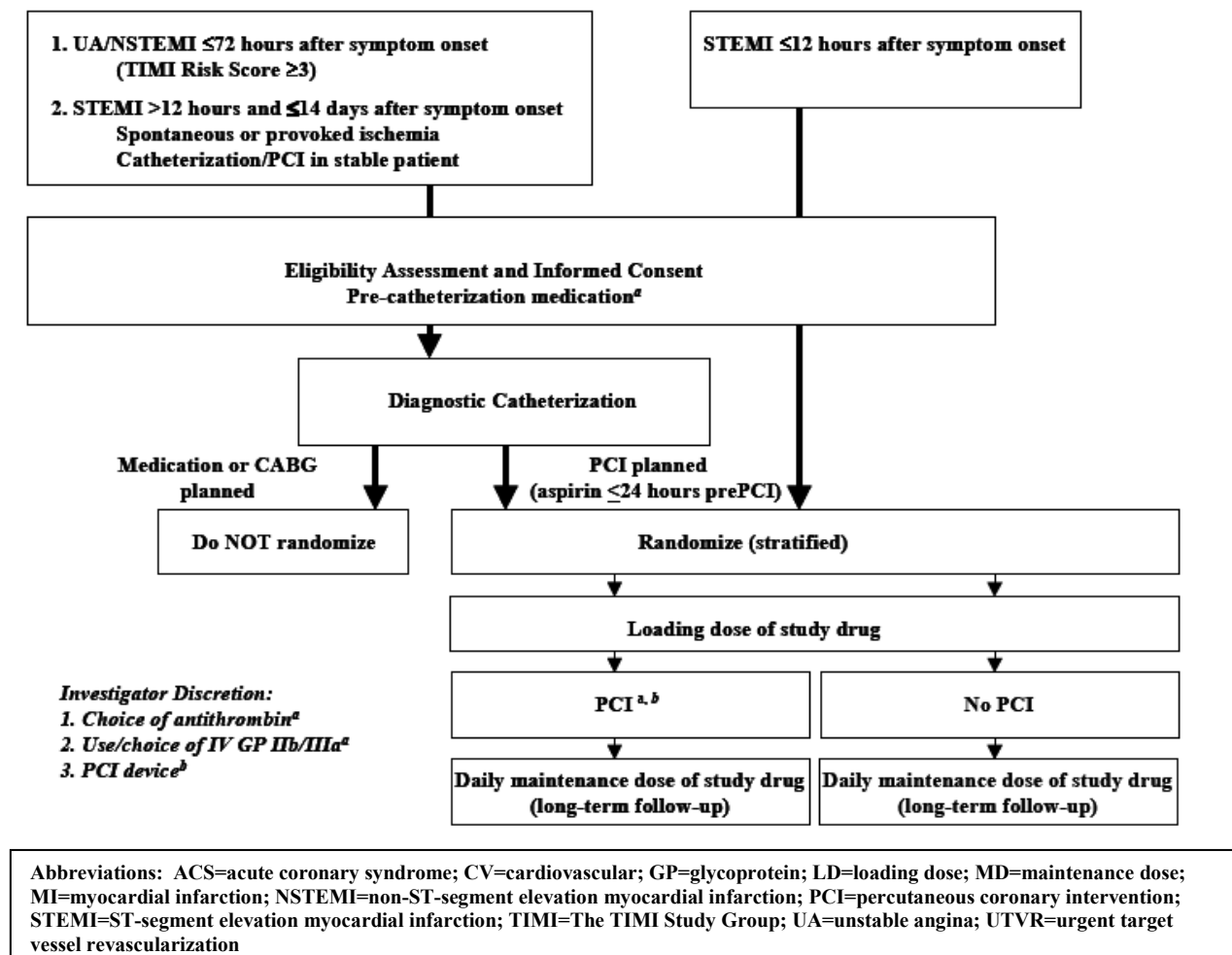
Figure 6. Study H7T-MC-TAAL Study Design



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



(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 without 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

investigator's discretion. Although daily doses of ASA ranging from 75 to 162 mg were recommended after discharge, the aspirin dose was left to the investigator's discretion.

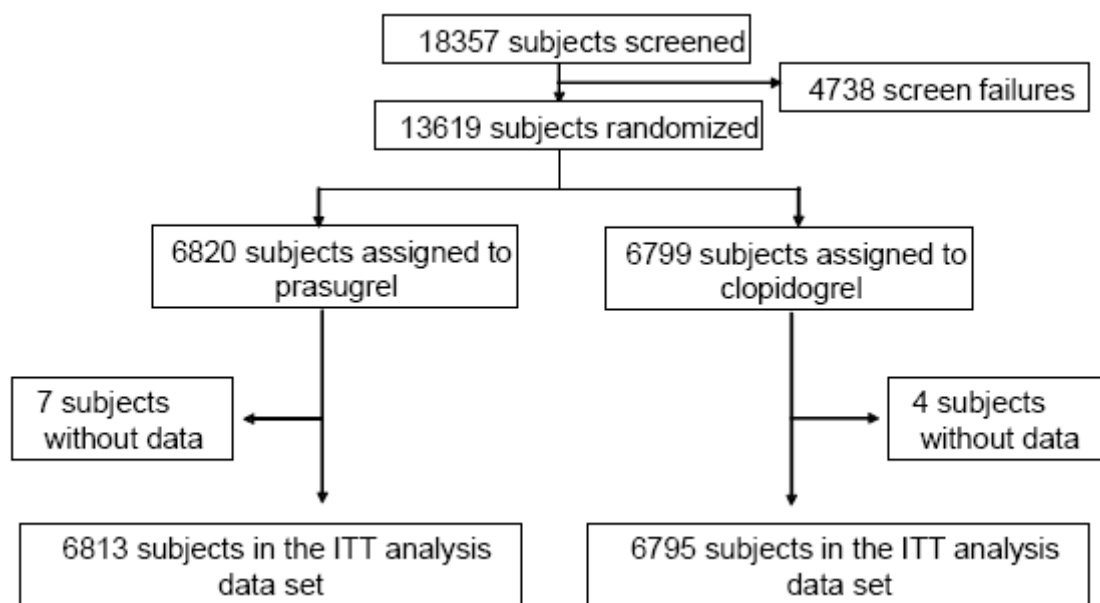
Subjects were to be followed for a maximum of 15 months. They were to return on Days 30, 90, and 180 for clinic visits and if enrolled in the study over 180 days were also to return on Days 270, 360, and 450.

6.1.3.1.1 Disposition of Subjects

A total of 13,619 subjects with ACS were randomized, including 6,799 subjects to clopidogrel (300 mg loading dose followed by once-daily 75 mg maintenance dose) and 6,820 subjects to prasugrel (60 mg loading dose followed by once-daily 10 mg maintenance dose). Subjects were treated until the subject's termination or 464 days from randomization, whichever was earlier. The maximum follow-up was 15 months.

Seven subjects randomly assigned to prasugrel and four subjects randomly assigned to clopidogrel were not included in the final analysis dataset due to an incomplete informed consent document. The remaining 13,608 subjects, including 6813 subjects in the prasugrel treatment group and 6795 subjects in the clopidogrel treatment group, comprised the intent-to-treat (ITT) analysis data set and were referred to as "All Randomized Subjects." Enrollment is summarized in Figure 26.

Figure 8. Enrollment of Subjects (TAAL)



(Reproduced from Sponsor, Figure TAAL. 10.1, page 138 of 27024)

Out of the 13,608 randomized patients, 13,457 subjects were treated, including 6741 in the prasugrel treatment group and 6716 subjects in the clopidogrel treatment group.

At the time of the index hospitalization, 6715 (98.56%) subjects underwent PCI in the prasugrel treatment group, including 5004 (99.21%) in the UA/NSTEMI population and 1711 (96.72%) in the STEMI population. In the clopidogrel treatment group, 6698 (98.57%) underwent PCI, including 4984 (99.09%) in the UA/NSTEMI population and 1714 (97.11%) in the STEMI population.

During the index hospitalization, 25 (0.37%) subjects in the prasugrel treatment group underwent CABG, including 16 (0.32%) in the UA/NSTEMI population and 9 (0.51%) in the STEMI population. In the clopidogrel treatment

group, 23 (0.34%) subjects underwent CABG, including 12 (0.24%) in the UA/NSTEMI population and 11 (0.62%) in the STEMI population.

A total of 73 (1.07%) subjects in the prasugrel treatment group and 74 (1.09%) subjects in the clopidogrel treatment group were medically managed during the index hospitalization. In the UA/NSTEMI population, 24 (0.48%) and 34 (0.68%) subjects in the prasugrel and clopidogrel treatment groups, respectively, did not undergo revascularization. In the STEMI population, 49 (2.77%) and 40 (2.27%) in the prasugrel and clopidogrel treatment groups, respectively, did not undergo revascularization.

From index hospitalization to study end, 213 subjects in the prasugrel treatment group underwent CABG, including 180 elective and 33 urgent surgeries. In the clopidogrel treatment group, 224 subjects underwent CABG, including 186 elective and 38 urgent surgeries.

6.1.4 Efficacy Findings

6.1.4.1 Primary Efficacy Endpoint

In TAAL, prasugrel significantly reduced the composite endpoint of cardiovascular (CV) death, nonfatal myocardial infarction, or nonfatal stroke at a median of twelve months of follow-up using the original and expanded definitions of peri-procedural myocardial infarction, as displayed in Table 8 and Table 9, respectively. The original definition of peri-procedural myocardial infarction required an elevation of creatine kinase-myocardial band (CK-MB) to > 3x upper limit of normal (ULN) on a minimum of two samples within 48 hours of PCI. The modified definition, specified in Protocol Amendment (a) dated January 10, 2006, maintained the original definition but extended periprocedural myocardial infarctions to a CK-MB > 5x ULN on one sample if it was the last available sample and was drawn ≥ 12 hours after PCI. Since there was no difference in cardiovascular death and nonfatal stroke between treatment groups, the difference in the primary endpoint was driven by the difference in nonfatal myocardial infarctions.

Table 8. Sponsor's Analysis: Number and Percentage of Subjects Reaching the Composite Endpoint of CV Death, Nonfatal MI or Nonfatal Stroke Using the Definition of Peri-Procedural Myocardial Infarction Prior to Protocol Amendment (CEC Adjudicated) (All Randomized Subjects) (TAAL)

Subject Population	Prasugrel			Clopidogrel			Total			HR	(95% CI) ^b	p-value ^c
	N	n	(%) ^a	N	n	(%) ^a	N	n	(%) ^a			
UA/NSTEMI	5044	443	(8.78)	5030	536	(10.66)	10074	979	(9.72)	0.817	(0.720, 0.926)	0.002
STEMI	1769	162	(9.16)	1765	201	(11.39)	3534	363	(10.27)	0.793	(0.645, 0.976)	0.024
All ACS	6813	605	(8.88)	6795	737	(10.85)	13608	1342	(9.86)	0.810	(0.727, 0.902)	<0.001

CI=confidence interval, CV=cardiovascular, HR=hazard ratio, N=number treated, n=number of subjects reaching primary endpoint.
^a% is percentage of randomized subjects reaching the primary endpoint.
^bHR and two-sided 95% CI derived using Cox proportional hazards model.
^cTwo-sided p-values are based on Gehan-Wilcoxon test comparing event free survival distributions of Prasugrel and Clopidogrel.
Clinical presentation, UA/NSTEMI vs. STEMI, was used as a stratification factor in analysis involving All ACS subjects.
(Reproduced from Sponsor, Table TAAL.14.20, page 1407 of 27,024)
Analysis verified by Ququan Liu, M.D., M.S., Biometrics, FDA.

Table 9. Sponsor's Analysis: Number and Percentage of Subjects Reaching the Composite Endpoint of CV Death, Nonfatal MI, or Nonfatal Stroke Using the Expanded Definition of Peri-Procedural Myocardial Infarction After Protocol Amendment (CEC Adjudicated) (All Randomized Subjects) (TAAL)

Subject Population	Prasugrel			Clopidogrel			Total			HR	(95% CI) ^b	p-value ^c
	N	n	(%) ^a	N	n	(%) ^a	N	n	(%) ^a			
UA/NSTEMI	5044	469	(9.30)	5030	565	(11.23)	10074	1034	(10.26)	0.820	(0.726, 0.927)	0.002
STEMI	1769	174	(9.84)	1765	216	(12.24)	3534	390	(11.04)	0.793	(0.649, 0.968)	0.019
All ACS	6813	643	(9.44)	6795	781	(11.49)	13608	1424	(10.46)	0.812	(0.732, 0.902)	<0.001

CI=confidence interval, CV=cardiovascular, HR=hazard ratio, N=number treated, n=number of subjects reaching primary endpoint.
^a% is percentage of randomized subjects reaching the primary endpoint.
^bHR and two-sided 95% CI used as an estimate of overall relative risk, Prasugrel versus Clopidogrel, over the course of the study.
^cTwo-sided p-values are based on Gehan-Wilcoxon test comparing event free survival distributions of Prasugrel and Clopidogrel.
Clinical presentation, UA/NSTEMI vs. STEMI, was used as a stratification factor in analysis involving All ACS subjects.
(Reproduced from Sponsor, Table TAAL.11.5, page 202 of 27,024).
Analysis verified by Ququan Liu, M.D., M.S., Biometrics, FDA.

Using the original definition, there were 437 nonfatal myocardial infarctions in the prasugrel treatment group and 576 nonfatal myocardial infarctions in the clopidogrel treatment group for a total of 1013 nonfatal myocardial infarctions. Using the expanded definition, there were 475 nonfatal myocardial infarctions in the prasugrel treatment group and 620 nonfatal myocardial infarctions in the clopidogrel treatment group for a total of 1095 nonfatal myocardial infarctions. These results are displayed by treatment group and by population in Table 10.

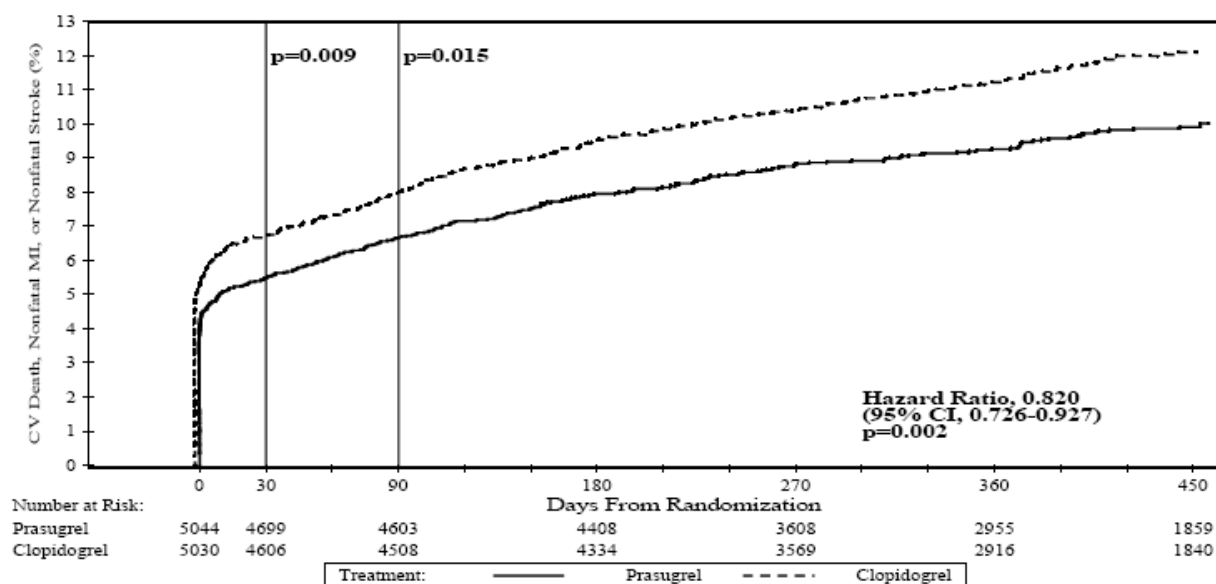
Table 10. Sponsor's Analysis: Nonfatal MI (TAAL)

Myocardial Infarction		Prasugrel N, n, (%)	Clopidogrel N, n, (%)	p-value
Original Definition	UA/NSTEMI	5044, 331, (6.56)	5030, 435, (8.65)	< 0.001
	STEMI	1769, 106, (5.99)	1765, 141, (7.99)	0.020
	All ACS	6813, 437 , (6.41)	6795, 576 , (8.48)	<0.001
Expanded Definition	UA/NSTEMI	5044, 357, (7.08)	5030, 464, (9.22)	<0.001
	STEMI	1769, 118, (6.67)	1765, 156, (8.84)	0.016
	All ACS	6813, 475 , (6.97)	6795, 620 , (9.12)	<0.001

N=number of subjects; n=number of subjects experiencing a nonfatal MI.

In all three study populations, most of the treatment effect with prasugrel was realized early, within 30 days of study drug administration. The Kaplan-Meier estimate of the incidence of the CEC-adjudicated composite endpoint of CV death, nonfatal MI, or nonfatal stroke in the UA/NSTEMI population at a median of 12 months of follow-up is shown in Figure 9.

Figure 9. Kaplan-Meier Estimate of the Incidence of the Composite Endpoint of Cardiovascular Death, Nonfatal MI, or Nonfatal Stroke (CEC Adjudicated) (All Randomized UA/NSTEMI Subjects) (TAAL)



(Reproduced from Sponsor, Clinical Study Report, Figure TAAL.11.6a, page 218)

A total of 961 nonfatal myocardial infarctions occurred outside the setting of stent thrombosis, including 529 in the clopidogrel treatment group and 432 in the prasugrel treatment group. In both treatment groups, most of these nonfatal MIs occurred either within 24 hours of PCI or from > 30 days to 1 year.

In the setting of stent thrombosis, there were 91 nonfatal myocardial infarctions in the clopidogrel treatment group and 43 nonfatal myocardial infarctions in the prasugrel treatment group. The timing of the nonfatal MIs is displayed in Table 11. Outside the setting of stent thrombosis, most nonfatal MIs in both treatment groups occurred periprocedurally (≤ 24 hours) or > 30 days to 1 year. However, in the setting of stent thrombosis, most nonfatal MIs in the clopidogrel treatment group occurred > 24 hours to 30 days post index PCI while most nonfatal MIs in the prasugrel treatment group occurred > 30 days to 1 year.

Table 11. Sponsor's Analysis: Summary of Nonfatal Myocardial Infarction

Time Interval	Nonfatal MI Not Associated with Stent Thrombosis		Nonfatal MI Associated with Stent Thrombosis	
	Clopidogrel N ^a (%) ^b	Prasugrel N ^a (%) ^b	Clopidogrel N ^a (%) ^b	Prasugrel N ^a (%) ^b
≤ 24 hours	308 (58.2%)	266 (61.6%)	19 (20.9%)	13 (28.6%)
> 24 hours – 30 days	48 (9.1%)	34 (7.9%)	47 (51.6%)	5 (11.9%)
> 30 days to 1 year	154 (29.1%)	119 (27.5%)	19 (20.9%)	22 (52.4%)
> 1 year	16 (3.0%)	10 (2.3%)	6 (6.6%)	3 (7.1%)
Unknown	3 (0.6%)	3 (0.7%)	0	0
Total	529	432	91	43

^aN=Number of subjects experiencing the indicated event.
^b%=N divided by the column total.

6.1.4.2 Subgroup Analyses of the Primary Endpoint

6.1.4.2.1 Age

In the UA/NSTEMI, STEMI, and All ACS populations, patients ≥ 75 years of age appeared to receive less benefit with prasugrel, compared to patients < 75 years of age, as shown in Table 12.

Table 12. FDA Subgroup Analysis of Primary Endpoint by Age (Composite of CV Death, Nonfatal MI, or Nonfatal Stroke) (TAAL)

	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Age (yr)									
<75 N	4328	4344	0.78	1584	1543	0.80	5912	5887	0.78
n	356	454	0.68, 0.90	143	173	0.64, 0.99	499	627	0.70, 0.88
%	8.23	10.45	0.0006	9.02	11.21	0.0370	8.44	10.65	$<.0001$
≥ 75 N	716	686	0.97	185	222	0.85	901	908	0.94
n	113	111	0.75, 1.26	31	43	0.54, 1.35	144	154	0.75, 1.18
%	15.78	16.18	0.8539	16.76	19.37	0.4478	15.98	16.96	0.5329
≥ 75 Female N	292	309	0.98	79	96	0.71	371	405	0.91
n	43	46	0.65, 1.49	12	20	0.35, 1.46	55	66	0.63, 1.29
%	14.73	14.89	0.9723	15.19	20.83	0.3637	14.82	16.30	0.5891
≥ 75 Male N	424	377	0.96	106	126	0.97	530	503	0.96
n	70	65	0.68, 1.34	19	23	0.53, 1.79	89	88	0.72, 1.29
%	16.51	17.24	0.7598	17.92	18.25	0.8197	16.79	17.50	0.6908
ACS=acute coronary syndrome; CI=confidence interval; CV=cardiovascular; HR=hazard ratio; NSTEMI=non-ST-elevation myocardial infarction; STEMI=ST-elevation myocardial infarction; UA=unstable angina. N=number of subjects in subgroup; n=number of subjects experiencing the primary endpoint. Analysis by Ququan Liu, M.D., M.S., Biometrics, FDA.									

6.1.4.2.2 Sex

Approximately 27% of the patients randomized in TAAL were women. Women appeared to receive less benefit from prasugrel compared to men, as displayed in Table 13.

Table 13. FDA Subgroup Analysis of Primary Endpoint by Sex (Composite of CV Death, Nonfatal MI, or Nonfatal Stroke) (TAAL)

	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Sex									
Female N	1325	1399	0.91	380	419	0.79	1705	1818	0.88
n	137	159	0.72, 1.14	41	56	0.53, 1.19	178	215	0.73, 1.07
%	10.34	11.37	0.5150	10.79	13.37	0.2107	10.44	11.83	0.1962
Male N	3719	3631	0.79	1389	1346	0.80	5108	4977	0.79
n	332	406	0.68, 0.91	133	160	0.63, 1.00	465	566	0.7, 0.9
%	8.93	11.18	0.0014	9.58	11.89	0.0503	9.10	11.37	0.0002
ACS=acute coronary syndrome; CI=confidence interval; CV=cardiovascular; HR=hazard ratio; NSTEMI=non-ST-elevation myocardial infarction; STEMI=ST-elevation myocardial infarction; UA=unstable angina. N=number of subjects in subgroup; n=number of subjects experiencing the primary endpoint. Analysis by Ququan Liu, M.D., M.S., Biometrics, FDA.									

6.1.4.2.3 Ethnicity

Ninety-two percent of patients enrolled in TAAL were Caucasian. Other ethnicities were poorly represented, limiting any conclusions from this subgroup analysis. Prasugrel significantly decreased the primary endpoint in Caucasians.

Table 14. FDA Subgroup Analysis of Primary Endpoint by Ethnicity (Composite of CV Death, Nonfatal MI, or Nonfatal Stroke) (TAAL)

	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Ethnicity									
Caucasian									
N	4575	4569	0.80	1688	1705	0.80	6263	6274	0.80
n	414	511	0.70, 0.91	167	209	0.65, 0.98	581	720	0.72, 0.89
%	9.05	11.18	0.0011	9.89	12.26	0.0242	9.28	11.48	<.0001
African									
N	177	168	1.03	28	19	0.66	205	187	0.98
n	22	20	0.56, 1.89	3	3	0.13, 3.25	25	23	0.55, 1.72
%	12.43	11.91	0.8896	10.71	15.79	0.5967	12.20	12.30	0.9647
Hispanic									
N	242	237	1.08	27	19	0.70	269	256	1.04
n	33	30	0.66, 1.77	3	3	0.14, 3.46	36	33	0.65, 1.67
%	13.64	12.66	0.7287	11.11	15.79	0.6436	13.38	12.89	0.8737
Asian									
N	37	42	NE	23	22	NE	60	64	NE
n	0	3		1	1		1	4	
%	-	7.14		4.35	4.55		1.67	6.25	
Other									
N	13	14	NE	3	0	NE	16	14	NE
n	0	1		0	0		0	1	
%	-	7.14					-	7.14	
ACS=acute coronary syndrome; CI=confidence interval; CV=cardiovascular; HR=hazard ratio; NE=not evaluated due to insufficient data; NSTEMI=non-ST-elevation myocardial infarction; STEMI=ST-elevation myocardial infarction; UA=unstable angina. N=number of subjects in subgroup; n=number of subjects experiencing the primary endpoint.									
Analysis by Ququan Liu, M.D., M.S., Biometrics, FDA.									

6.1.4.2.4 Prior History of Transient Ischemic Attack/Stroke

In All ACS subjects with a prior history of transient ischemic attack or stroke, there was a 38% increased risk of experiencing death, nonfatal myocardial infarction, or nonfatal stroke at a median of 12 months of follow-up on prasugrel, compared to clopidogrel (p = 0.1382).

Table 15. FDA Subgroup Analysis of Primary Endpoint by Prior History of Transient Ischemic Attack or Stroke (Composite of CV Death, Nonfatal MI, or Nonfatal Stroke) (TAAL)

	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Prior History of Transient Ischemic Attack/Stroke									
Yes									
N	213	192	1.53	49	64	0.98	262	256	1.38
n	39	24	0.92, 2.55	8	11	0.39, 2.42	47	35	0.89, 2.13
%	18.31	12.50	0.0677	16.33	17.19	0.9127	17.94	13.67	0.1382
No									
N	4831	4838	0.79	1720	1701	0.79	6551	6539	0.79
n	430	541	0.69, 0.89	166	205	0.64, 0.97	596	746	0.71, 0.88
%	8.90	11.18	0.0003	9.65	12.05	0.020	9.10	11.41	<.0001
ACS=acute coronary syndrome; CI=confidence interval; CV=cardiovascular; HR=hazard ratio; NE=not evaluated; NSTEMI=non-ST-elevation myocardial infarction; STEMI=ST-elevation myocardial infarction; UA=unstable angina. N=number of subjects in subgroup; n=number of subjects experiencing the primary endpoint.									
Analysis by Ququan Liu, M.D., M.S., Biometrics, FDA.									

6.1.4.2.5 Timing of Loading Dose

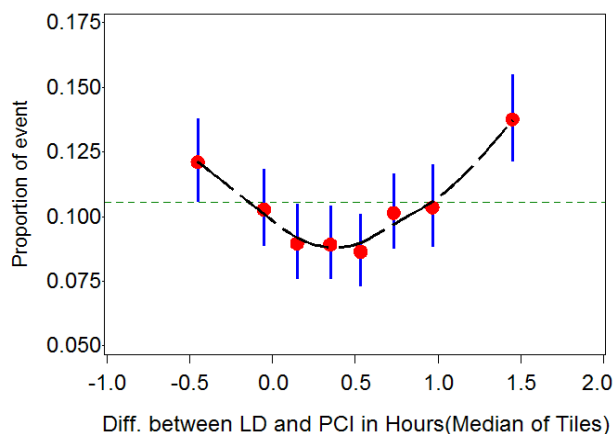
In TAAL, 73% of the loading doses were given during PCI and 26% of the loading doses were given 0-2 hours prior to PCI. Only 1% of subjects received the loading dose post PCI. However, the timing of the loading dose appears to be important and suggests that prasugrel should be given during PCI. Unfortunately, the number of patients in the post PCI treatment group is too small to draw a definitive conclusion about the post PCI timing of the loading dose. With regard to timing of loading dose and efficacy, our FDA analysis is presented in Table 16 and is consistent with the findings of the sponsor.

Table 16. FDA Subgroup Analysis of Primary Endpoint by Timing of Loading Dose (Composite of CV Death, Nonfatal MI, or Nonfatal Stroke) (TAAL)

Timing of Loading Dose	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
0-2 hrs prior to PCI	N=1078 n=103	N=1045 n=117	0.85 0.65, 1.11 0.3212	N=432 n=52	N=440 n=59	0.90 0.62, 1.30 0.5843	N=1510 n=155	N=1485 n=176	0.86 0.70, 1.08 0.2340
2-6 hrs prior to PCI	N=61 n=4	N=67 n=5	0.9191	N=9 n=1	N=7 n=1	NE	N=70 n=5	N=74 n=6	0.90 0.28, 2.95 0.8927
6-12 hrs prior to PCI	N=16 n=3	N=9 n=2	0.84 0.14, 5.08 0.8530	N=4 n=0	N=1 n=1	NE	N=20 n=3	N=10 n=3	0.46 0.09, 2.30 0.3263
≥12 hrs prior to PCI	N=102 n=15	84 12	1.01 0.47, 2.16 0.9651	N=10 n=1	N=5 n=1	NE-	N=112 n=16	N=89 n=13	1.01 0.47, 2.16 0.8358
During PCI	N=3660 n=329	3671 400	0.82 0.71, 0.95 0.0081	N=1221 n=110	N=1213 n=143	0.75 0.59, 0.97 0.0209	N=4881 n=439	N=4884 n=543	0.80 0.71, 0.91 0.0005
Post PCI	N=1078 n=103	1045 117	0.85 0.65, 1.11 0.3212	N=15 n=2	N=21 n=2	NE	N=63 n=7	N=68 n=16	0.43 0.18, 1.04 0.0391
ACS=acute coronary syndrome; CI=confidence interval, CV=cardiovascular, HR=hazard ratio; NE=not evaluated; NSTEMI=non-ST-elevation myocardial infarction; STEMI=ST-elevation myocardial infarction; UA=unstable angina. N=number of subjects in subgroup; n=number of subjects experiencing the primary endpoint. Analysis by Ququan Liu, M.D., M.S., Biometrics, FDA.									

Dividing the timing of the loading dose into octiles, maximum effectiveness with prasugrel and the lowest incidence of cardiovascular death, nonfatal MI, or nonfatal stroke was achieved when the loading dose was administered at the start or within 30 minutes of the start of PCI, as shown in Figure 10.

Figure 10. Incidence of Cardiovascular Death, Nonfatal MI, or Nonfatal Stroke (TAAL) Based on Timing of Loading Dose

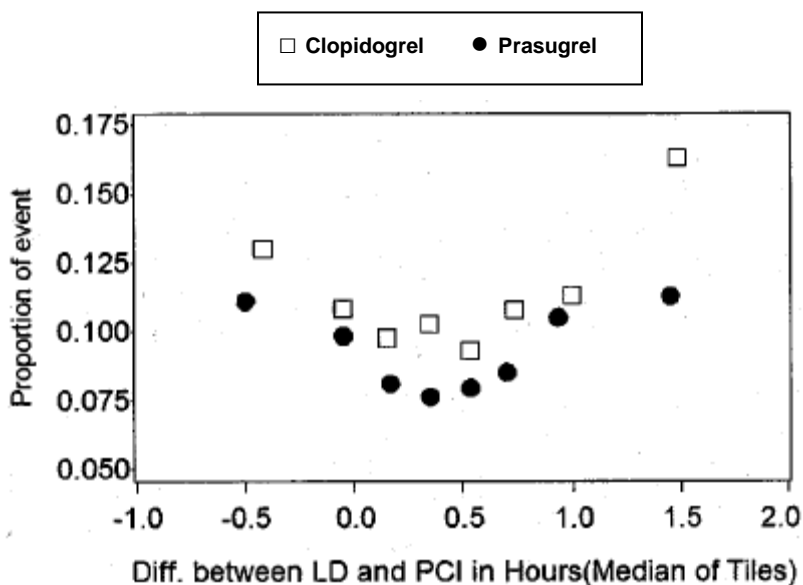


(Dots: represent proportion of events corresponding to the midpoints of the octiles; Bars: 95% Confidence interval; Black line: smooth trend line; Dotted line: lowest confidence limit of the extremes)

(Analysis by Rajanikanth Madabushi, Ph.D., Pharmacometrics, FDA)

The timing of loading dose was important for both prasugrel and clopidogrel. When the loading dose was given during PCI or within 30 minutes of the start of PCI, both treatments resulted in a decreased incidence of the primary endpoint over the course of the study, as shown in Figure 11. Figure 11 breaks down Figure 10 by treatment group.

Figure 11. Timing of Loading Dose and Effect on Primary Endpoint (TAAL)



(Analysis by Rajanikanth Madabushi, Ph.D., Pharmacometrics, FDA)

6.1.4.2.6 Proton Pump Inhibitors

Approximately 50% of the All ACS population received proton pump inhibitors in TAAL. The use of proton pump inhibitors did not appear to affect the efficacy of prasugrel for the primary endpoint.

Table 17. FDA Subgroup Analysis of Primary Endpoint by Use of Proton Pump Inhibitors (Composite of CV Death, Nonfatal MI, or Nonfatal Stroke) (TAAL)

	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Use of Proton Pump Inhibitors									
Yes									
N	2474	2463	0.83	916	882	0.80	3390	3345	0.82
n	262	310	0.70, 0.98	103	122	0.62, 1.05	365	432	0.72, 0.95
%	10.59	12.59	0.0319	11.24	13.83	0.0857	10.77	12.91	0.0056
No									
N	2570	2567	0.81	853	883	0.77	3423	3450	0.80
n	207	255	0.67, 0.97	71	94	0.57, 1.05	278	349	0.68, 0.93
%	8.05	9.93	0.0248	8.32	10.65	0.0986	8.12	10.12	0.0046
ACS=acute coronary syndrome; CI=confidence interval; HR=hazard ratio; NSTEMI=non-ST-elevation myocardial infarction; STEMI=ST-elevation myocardial infarction; UA=unstable angina N=number of subjects in subgroup; n=number of subjects experiencing the primary endpoint Analysis by Ququan Liu, M.D., M.S., Biometrics, FDA.									

6.1.4.2.7 Weight

Except for the weight category < 50 kg which demonstrated a 5% increased risk (p=0.83) of the primary endpoint, prasugrel significantly reduced the risk of the composite endpoint of death, nonfatal MI, and nonfatal stroke at a median follow-up of 12 months in all other weight categories, compared to clopidogrel.

Table 18. FDA Subgroup Analysis of Primary Endpoint by Weight (Composite of CV Death, Nonfatal MI, or Nonfatal Stroke) (TAAL)

	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Weight (kg)									
< 50									
N	92	86	1.14	45	39	0.90	137	125	1.05
n	17	15	0.57, 2.29	9	9	0.36, 2.28	26	24	0.60, 1.82
%	18.48	17.44	0.7713	20.00	23.08	0.9671	18.98	19.2	0.8318
< 60									
N	5044	5030	0.82	1769	1765	0.79	6813	6795	0.81
n	469	565	0.73, 0.93	174	216	0.65, 0.97	643	781	0.73, 0.90
%	9.30	11.23	0.0021	9.84	12.24	0.0192	9.44	11.49	<0.0001
≥ 50 < 70									
N	844	910	0.86	298	333	0.66	1142	1243	0.79
n	83	103	0.64, 1.14	34	56	0.43, 1.00	117	159	0.62, 1.00
%	9.83	11.32	0.3270	11.41	16.82	0.0388	10.25	12.79	0.0436
≥ 70									
N	2451	2433	0.84	942	895	0.78	3393	3328	0.83
n	234	275	0.70, 1.00	85	100	0.60, 1.06	319	375	0.71, 0.96
%	9.55	11.30	0.0549	9.02	11.17	0.1138	9.40	11.27	0.0119
≥ 70 < 90									
N	1657	1601	0.75	484	498	0.93	2141	2099	0.79
n	135	172	0.60, 0.94	46	51	0.62, 1.38	181	223	0.65, 0.96
%	8.15	10.74	0.0112	9.50	10.24	0.6796	8.45	10.62	0.0138
ACS=acute coronary syndrome; CI=confidence interval; HR=hazard ratio; NE=not evaluated; NSTEMI=non-ST-elevation myocardial infarction; STEMI=ST-elevation myocardial infarction; UA=unstable angina. N=number of subjects in subgroup; n=number of subjects experiencing the primary endpoint. Analysis by Ququan Liu, M.D., M.S., Biometrics, FDA.									

6.1.4.2.8 Additional Subgroup Analyses of the Primary Endpoint

Please see the Appendix under Study TAAL for further subgroup analyses of the primary endpoint.

6.1.4.3 Secondary Composite Endpoints

Compared to clopidogrel, prasugrel significantly reduced the following CEC adjudicated secondary composite endpoints in all study populations:

- CV death, nonfatal MI or nonfatal stroke through 90 days, compared to clopidogrel
- CV death, nonfatal MI or nonfatal stroke through 30 days, compared to clopidogrel
- CV death, nonfatal MI, or urgent target vessel revascularization through 90 days
- CV death, nonfatal MI, or urgent target vessel revascularization through 30 days
- All cause death, nonfatal MI, or nonfatal stroke through study end
- CV death, nonfatal MI, nonfatal stroke or rehospitalization for cardiac ischemic events through study end

These results are summarized in Table 19.

6.1.4.3.1 Secondary and Other Efficacy Endpoints

Prasugrel, compared to clopidogrel, did not significantly decrease CV death, all cause death, nonfatal stroke, all stroke, or rehospitalization due to an ischemic event. However, compared to clopidogrel, prasugrel reduced the incidence of the following endpoints:

- CV death or nonfatal MI
- Nonfatal MI
- All MI
- Urgent target vessel revascularization (in the UA/NSTEMI and All ACS populations)

The results of these secondary and other efficacy endpoints are presented in Table 20.

Table 19. Sponsor's Analysis: Number and Percentage of Subjects Reaching the Secondary Composite Endpoints--CEC Adjudicated (All Randomized Subjects) (TAAL)

Analyzed Endpoint	Subject Population	Prasugrel			Clopidogrel			Total			HR	(95% CI)	p-value
		N	n	(%) ^a	N	n	(%) ^a	N	n	(%) ^a			
CV Death, Nonfatal MI, or Nonfatal Stroke Through 90 Days													
	UA/NSTEMI	5044	333	(6.60)	5030	395	(7.85)	10074	728	(7.23)	0.835	(0.721, 0.966)	0.015
	STEMI	1769	129	(7.29)	1765	178	(10.08)	3534	307	(8.69)	0.715	(0.570, 0.897)	0.004
	All ACS	6813	462	(6.78)	6795	573	(8.43)	13608	1035	(7.61)	0.797	(0.705, 0.901)	<0.001
CV Death, Nonfatal MI, or Nonfatal Stroke Through 30 Days													
	UA/NSTEMI	5044	274	(5.43)	5030	336	(6.68)	10074	610	(6.06)	0.808	(0.689, 0.948)	0.009
	STEMI	1769	115	(6.50)	1765	166	(9.41)	3534	281	(7.95)	0.684	(0.540, 0.868)	0.002
	All ACS	6813	389	(5.71)	6795	502	(7.39)	13608	891	(6.55)	0.767	(0.672, 0.876)	<0.001
CV Death, Nonfatal MI, or UTVR Through 90 Days													
	UA/NSTEMI	5044	345	(6.84)	5030	420	(8.35)	10074	765	(7.59)	0.812	(0.704, 0.937)	0.004
	STEMI	1769	127	(7.18)	1765	168	(9.52)	3534	295	(8.35)	0.748	(0.594, 0.942)	0.013
	All ACS	6813	472	(6.93)	6795	588	(8.65)	13608	1060	(7.79)	0.794	(0.703, 0.896)	<0.001
CV Death, Nonfatal MI or UTVR Through 30 Days													
	UA/NSTEMI	5044	281	(5.57)	5030	349	(6.94)	10074	630	(6.25)	0.798	(0.682, 0.933)	0.005
	STEMI	1769	118	(6.67)	1765	155	(8.78)	3534	273	(7.72)	0.754	(0.594, 0.958)	0.020
	All ACS	6813	399	(5.86)	6795	504	(7.42)	13608	903	(6.64)	0.784	(0.688, 0.894)	<0.001
All Cause Death, Nonfatal MI, or Nonfatal Stroke Through Study End													
	UA/NSTEMI	5044	504	(9.99)	5030	590	(11.73)	10074	1094	(10.86)	0.844	(0.749, 0.950)	0.005
	STEMI	1769	188	(10.63)	1765	232	(13.14)	3534	420	(11.88)	0.797	(0.657, 0.966)	0.020
	All ACS	6813	692	(10.16)	6795	822	(12.10)	13608	1514	(11.13)	0.831	(0.751, 0.919)	<0.001
CV Death, Nonfatal MI, Nonfatal Stroke, or Rehospitalization for CIE Through Study End													
	UA/NSTEMI	5044	598	(11.86)	5030	688	(13.68)	10074	1286	(12.77)	0.858	(0.769, 0.958)	0.006
	STEMI	1769	199	(11.25)	1765	250	(14.16)	3534	449	(12.71)	0.781	(0.648, 0.941)	0.009
	All ACS	6813	797	(11.70)	6795	938	(13.80)	13608	1735	(12.75)	0.838	(0.762, 0.921)	<0.001
Definite or Probable Stent Thrombosis through Study End ^{d†}													
	UA/NSTEMI	4798	39	(0.81)	4789	78	(1.63)	9587	117	(1.22)	0.48	(0.33, 0.70)	<0.0001
	STEMI	1624	19	(1.17)	1633	38	(2.33)	3257	57	(1.75)	0.49	(0.28, 0.84)	0.0074
	All ACS	6422	58	(0.90)	6422	116	(1.81)	12844	174	(1.35)	0.48	(0.35, 0.66)	<0.0001
CI=confidence interval; CV=cardiovascular; HR=hazard ratio; MI=myocardial infarction; N=number treated; n=number of subjects reaching the endpoint; NE=not evaluated due to insufficient data.													
^a % is percentage of randomized subjects reaching the endpoint.													
^b HR and two-sided 95% CI derived using Cox proportional hazards model. Clinical presentation, UA/NSTEMI vs. STEMI, was used as a stratification													

factor in analysis involving All ACS subjects.

^cTwo-sided p-values are based on a log-rank test comparing event free survival distributions of prasugrel and clopidogrel within the subgroup. Clinical presentation, UA/NSTEMI vs. STEMI, was used as a stratification factor in analysis involving all ACS subjects.

^dDenominator consists of subjects who had a stent placed during their index procedure.

[†]FDA Analysis. Initial analysis by sponsor included 4 additional patients in the clopidogrel treatment arm (n=120), but these four events of stent thrombosis occurred outside of the efficacy window. In the clopidogrel treatment group, the number of events of stent thrombosis within the efficacy window should be 116. This analysis does not include 4 clopidogrel and 2 prasugrel patients who were thought to have stent thrombosis but whose cases were not referred to the CEC for adjudication (Subjects TAAL-010050-13384, 010355-13961, 390691-14674, 970989-13056, 490607-14838, and 550855-22276).

Reproduced from Sponsor, Clinical Study Report, Table TAAL.11.7, pages 233-234.

Analyses verified by Ququan Liu, M.D., M.S., Biometrics, FDA.

Table 20. Sponsor's Analysis: Number and Percentage of Subjects Reaching Secondary and Other Efficacy Endpoints--CEC Adjudicated (All Randomized Subjects) (TAAL)

Analyzed Endpoint	Subject Population	Prasugrel			Clopidogrel			Total			HR	(95% CI)	p-value
		N	n	(%) ^a	N	n	(%) ^a	N	n	(%) ^a			
CV Death or Nonfatal MI													
	UA/NSTEMI	5044	436	(8.64)	5030	527	(10.48)	10074	963	(9.56)	0.818	(0.720, 0.929)	0.002
	STEMI	1769	153	(8.65)	1765	201	(11.39)	3534	354	(10.02)	0.750	(0.608, 0.926)	0.007
	All ACS	6813	589	(8.65)	6795	728	(10.71)	13608	1317	(9.68)	0.799	(0.717, 0.890)	<0.001
CV Death													
	UA/NSTEMI	5044	90	(1.78)	5030	92	(1.83)	10074	182	(1.81)	0.979	(0.732, 1.309)	0.885
	STEMI	1769	43	(2.43)	1765	58	(3.29)	3534	101	(2.86)	0.738	(0.497, 1.094)	0.129
	All ACS	6813	133	(1.95)	6795	150	(2.21)	13608	283	(2.08)	0.886	(0.701, 1.118)	0.307
All Cause Death													
	UA/NSTEMI	5044	130	(2.58)	5030	121	(2.41)	10074	251	(2.49)	1.076	(0.840, 1.378)	0.563
	STEMI	1769	58	(3.28)	1765	76	(4.31)	3534	134	(3.79)	0.759	(0.539, 1.068)	0.113
	All ACS	6813	188	(2.76)	6795	197	(2.90)	13608	385	(2.83)	0.953	(0.781, 1.164)	0.639
Nonfatal MI													
	UA/NSTEMI	5044	357	(7.08)	5030	464	(9.22)	10074	821	(8.15)	0.761	(0.663, 0.873)	<0.001
	STEMI	1769	118	(6.67)	1765	156	(8.84)	3534	274	(7.75)	0.746	(0.588, 0.948)	0.016
	All ACS	6813	475	(6.97)	6795	620	(9.12)	13608	1095	(8.05)	0.757	(0.672, 0.853)	<0.001
All MI													
	UA/NSTEMI	5044	366	(7.26)	5030	476	(9.46)	10074	842	(8.36)	0.760	(0.663, 0.871)	<0.001
	STEMI	1769	119	(6.73)	1765	157	(8.90)	3534	276	(7.81)	0.748	(0.589, 0.949)	0.016
	All ACS	6813	485	(7.12)	6795	633	(9.32)	13608	1118	(8.22)	0.757	(0.673, 0.852)	<0.001
Nonfatal Stroke													
	UA/NSTEMI	5044	40	(0.79)	5030	41	(0.82)	10074	81	(0.80)	0.979	(0.633, 1.513)	0.922
	STEMI	1769	21	(1.19)	1765	19	(1.08)	3534	40	(1.13)	1.097	((0.590, 2.040)	0.770
	All ACS	6813	61	(0.90)	6795	60	(0.88)	13608	121	(0.89)	1.016	(0.712, 1.451)	0.930
All Stroke													
	UA/NSTEMI	5044	49	(0.97)	5030	46	(0.91)	10074	95	(0.94)	1.068	(0.714, 1.597)	0.748
	STEMI	1769	26	(1.47)	1765	25	(1.42)	3534	51	(1.44)	1.032	(0.596, 1.787)	0.911
	All ACS	6813	75	(1.10)	6795	71	(1.04)	13608	146	(1.07)	1.055	(0.763, 1.460)	0.745
Rehospitalization Due to Ischemic Event													
	UA/NSTEMI	5044	153	(3.03)	5030	161	(3.20)	10074	314	(3.12)	0.950	(0.761, 1.185)	0.648
	STEMI	1769	31	(1.75)	1765	42	(2.38)	3534	73	(2.07)	0.731	(0.460, 1.163)	0.184
	All ACS	6813	184	(2.70)	6795	203	(2.99)	13608	387	(2.84)	0.904	(0.741, 1.104)	0.323

Analyzed Endpoint	Subject Population	Prasugrel			Clopidogrel			Total			HR	(95% CI)	p-value
		N	n	(%) ^a	N	n	(%) ^a	N	n	(%) ^a			
Urgent Target Vessel Revascularization													
	UA/NSTEMI	5044	118	(2.34)	5030	179	(3.56)	10074	297	(2.95)	0.654	(0.518, 0.825)	<0.001
	STEMI	1769	38	(2.15)	1765	54	(3.06)	3534	92	(2.60)	0.697	(0.460, 1.056)	0.087
	All ACS	6813	156	(2.29)	6795	233	(3.43)	13608	389	(2.86)	0.664	(0.542, 0.813)	<0.001
CI=confidence interval; CV=cardiovascular; HR=hazard ratio; MI=myocardial infarction; N=number treated; n=number of subjects reaching the specified endpoint; NE=not evaluated due to insufficient data.													
^a % is percentage of randomized subjects reaching the specified endpoint.													
^b HR and two-sided 95% CI derived using Cox proportional hazards model.													
^c Two-sided p-values are based on a log-rank test comparing event free survival distributions of prasugrel and clopidogrel. Clinical presentation, UA/NSTEMI vs. STEMI, was used as a stratification factor in analysis involving all ACS subjects.													
^d Denominator consists of subjects who had a stent placed during their index procedure.													
Reproduced from Sponsor, Clinical Study Report, Table TAAL.11.7, pages 235-236.													
Analyses verified by Ouquan Liu, M.D., M.S., Biometrics, FDA.													

6.1.5 Clinical Microbiology N/A

6.1.6 Efficacy Conclusions (Study TAAL)

In patients with acute coronary syndrome, prasugrel significantly reduced the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke at a median of 12 months of follow-up in the UA/NSTEMI, All ACS, and STEMI populations, compared to clopidogrel.

With regard to the major secondary endpoints in the UA/NSTEMI, STEMI, and all ACS populations, prasugrel, compared to clopidogrel,

- significantly reduced CV death, nonfatal MI or nonfatal stroke through 90 days
- significantly reduced CV death, nonfatal MI or nonfatal stroke through 30 days
- significantly reduced CV death, nonfatal MI, or urgent target vessel revascularization through 90 days
- significantly reduced CV death, nonfatal MI, or urgent target vessel revascularization through 30 days
- significantly reduced all cause death, nonfatal MI, or nonfatal stroke through study end
- significantly reduced CV death, nonfatal MI, nonfatal stroke or rehospitalization for cardiac ischemic events through study end

Finally, although prasugrel appeared to reduce ARC definite or probable stent thrombosis through study end in all three of these populations, in my opinion, the sponsor did not adhere to the scientific rigor required for such a claim. The determination of stent thrombosis was made by clinical adjudication, without the use of an angiographic core laboratory and without pathological confirmation. The CEC did not review any angiograms and did not review all cases of presumed stent thrombosis. In some cases, there was evidence of suboptimal adjudication by the CEC. Furthermore, there was no prospective attempt in TAAL to gather pathological evidence of stent thrombosis. Although two autopsies were subsequently obtained and demonstrated stent thrombosis, this limited amount of pathological confirmation for a trial of this size is not adequate. Since the results of clinical adjudication can be different from outside angiographic and pathologic review, which is currently required by our CDRH colleagues, I consider the results from TAAL to be promising but exploratory. Therefore, I recommend the sponsor participate in a randomized, prospective clinical trial to further evaluate these preliminary findings.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The prasugrel safety database included primary, secondary, and tertiary safety databases, in addition to 5 individually reported studies.

Study TAAL served as the primary safety database and included 13,457 subjects (6741 prasugrel, 6716 clopidogrel) with ACS who were to be managed by PCI. Within TAAL, there were 707 prasugrel subjects and 769 clopidogrel subjects with abnormal renal function, defined as a creatinine clearance ≤ 60 mL/min as estimated by the Cockcroft-Gault equation. Additionally, there were 32 prasugrel subjects and 37 clopidogrel subjects with hepatic impairment based on pre-existing conditions, including ALT $> 3 \times$ upper limit of normal and total bilirubin $> 1.5 \times$ ULN. Severe hepatic dysfunction was an exclusion criterion for TAAL.

The secondary safety database included all subjects enrolled in TAAD, TAAH, TABL, and TABR with either ACS or other different clinical manifestations of atherosclerosis that may not have required PCI (940 prasugrel, 484 clopidogrel).

The tertiary safety database included integrated clinical pharmacology study data of 839 healthy subjects, 22 subjects with hepatic impairment, and 37 subjects with renal impairment (898 subjects total). The 5 completed clinical pharmacology studies in healthy subjects conducted in Japan (non-investigational new drug studies with a different formulation of prasugrel) were not integrated with the clinical pharmacology studies, as these studies were considered supportive studies.

7.1.1 Deaths

In TAAL, there was no significant difference in all cause death or cardiovascular death between treatment groups.

By CEC adjudication in TAAL, there were a total of 188 (2.76%) all cause deaths in the prasugrel treatment group and 197 (2.90%) all cause deaths in the clopidogrel treatment group in the All ACS population. In the UA/NSTEMI population, there were 130 (2.58%) deaths in the prasugrel treatment group and 121 (2.41%) deaths in the clopidogrel treatment group. In the STEMI population, there were 58 (3.28%) deaths in the prasugrel treatment group and 76 (4.31%) deaths in the clopidogrel treatment group.

With respect to cardiovascular deaths in the All ACS population, there were 133 events in the prasugrel treatment group and 150 events in the clopidogrel treatment group. In both treatment groups, most of the cardiovascular deaths were sudden or unwitnessed. The fatality rate for intracranial hemorrhages was twice as high in the prasugrel treatment group compared to the clopidogrel treatment group. A summary of CEC adjudicated deaths is displayed in Table 21.

In the All But TAAL (ABT) studies included in the secondary safety database, there were 3 deaths. These three subjects from Study TAAH were treated with prasugrel and died due to non-hemorrhagic cardiovascular adverse events including sudden death, circulatory collapse, and decreased cardiac output. There were no deaths in Studies TAAD, TABR, and TABL.

In the tertiary safety database, there were no deaths.

Table 21. Sponsor's Analysis: Summary of CEC-Adjudicated Deaths (All Randomized Subjects) (TAAL)

	UA/NSTEMI					STEMI					All ACS				
	Prasugrel (N=5044)		Clopidogrel (N=5030)		p- value ^b	Prasugrel (N=1769)		Clopidogrel (N=1765)		p- value ^b	Prasugrel (N=6813)		Clopidogrel (N=6795)		p- value ^b
Variable	n	(%) ^a	n	(%) ^a		n	(%) ^a	n	(%) ^a		n	(%) ^a	n	(%) ^a	
All Cause Death	130	(2.58)	121	(2.41)	0.563	58	(3.28)	76	(4.31)	0.113	188	(2.76)	197	(2.90)	0.639
Cardiovascular	90	(1.78)	92	(1.83)	0.885	43	(2.43)	58	(3.29)	0.129	133	(1.95)	150	(2.21)	0.307
Atherosclerotic Vascular Disease (Excluding Coronary)	0		3	(0.06)		0		0			0		3	(0.04)	
Congestive Heart Failure/Cardiogenic Shock	17	(0.34)	15	(0.30)		14	(0.79)	15	(0.85)		31	(0.46)	30	(0.44)	
Directly Related to Revascularization (CABG or PCI)	12	(0.24)	11	(0.22)		3	(0.17)	5	(0.28)		15	(0.22)	16	(0.24)	
Dysrhythmia	2	(0.04)	5	(0.10)		2	(0.11)	2	(0.11)		4	(0.06)	7	(0.10)	
Pulmonary Embolism	3	(0.06)	0			0		0			3	(0.04)	0		
Myocardial Infarction	14	(0.28)	21	(0.42)		10	(0.57)	15	(0.85)		24	(0.35)	36	(0.53)	
Sudden or Unwitnessed	30	(0.59)	29	(0.58)		6	(0.34)	13	(0.74)		36	(0.53)	42	(0.62)	
Intracranial Hemorrhage	6	(0.12)	3	(0.06)		3	(0.17)	2	(0.11)		9	(0.13)	5	(0.07)	
Non-Hemorrhagic Stroke	3	(0.06)	2	(0.04)		2	(0.11)	4	(0.23)		5	(0.07)	6	(0.09)	
Other Cardiovascular	3	(0.06)	3	(0.06)		3	(0.17)	2	(0.11)		6	(0.09)	5	(0.07)	
Non-Cardiovascular	40	(0.79)	29	(0.58)	0.181	15	(0.85)	18	(1.02)	0.589	55	(0.81)	47	(0.69)	0.428
Accidental/Trauma	3	(0.06)	3	(0.06)		1	(0.06)	1	(0.06)	0.589	4	(0.06)	4	(0.06)	
Hemorrhage, nonintracranial	6	(0.12)	0			3	(0.17)	1	(0.06)		9	(0.13)	1	(0.01)	
Infection	9	(0.18)	7	(0.14)		2	(0.11)	3	(0.17)		11	(0.16)	10	(0.15)	
Malignancy	16	(0.32)	11	(0.22)		5	(0.28)	6	(0.34)		21	(0.31)	17	(0.25)	
Suicide	2	(0.04)	1	(0.02)		1	(0.06)	1	(0.06)		3	(0.04)	2	(0.03)	
Other Non-Cardiovascular	4	(0.08)	7	(0.14)		3	(0.17)	6	(0.34)		7	(0.10)	13	(0.19)	

N=randomized subjects, n=number of deaths, NE=not evaluated due to insufficient data.

^a% is percentage of randomized subjects.

^bTwo-sided p-values are based on a log-rank test comparing event free survival distributions of Prasugrel and Clopidogrel. Clinical presentation, UA/NSTEMI vs. STEMI, used as a stratification factor in analysis involving all ACS subjects.

Reproduced from Sponsor, ISS, Table APP.2.7.4.71, pages 267-268.

7.1.2 Other Serious Adverse Events

7.1.2.1 Bleeding

Safety endpoints for Study TAAL included:

- Non-CABG-related TIMI major bleeding
- Non-CABG-related TIMI life-threatening bleeding
- Non-CABG-related TIMI minor bleeding
- Non-CABG-related fatal bleeding
- CABG related bleeding

7.1.2.1.1 Non-CABG-Related Bleeding

In the UA/NSTEMI and all ACS populations, prasugrel significantly increased non-CABG related TIMI major, TIMI life-threatening, TIMI fatal, and TIMI minor bleeding, compared to clopidogrel, as shown in Table 22.

Table 22. Sponsor's Analysis: CEC Adjudicated Non-CABG-Related Bleeding (TAAL)

Subject Population	Prasugrel			Clopidogrel			Total			HR	(95% CI) ^b	p-value ^c
	N	n	(%)	N	n	(%)	N	n	(%)			
TIMI Major ^a												
UA/NSTEMI	5001	108	(2.16)	4980	77	(1.55)	9981	185	(1.85)	1.404	(1.048, 1.881)	0.022
STEMI	1740	38	(2.18)	1736	34	(1.96)	3476	72	(2.07)	1.115	(0.702, 1.770)	0.645
All ACS	6741	146	(2.17)	6716	111	(1.65)	13457	257	(1.91)	1.315	(1.028, 1.683)	0.029
TIMI Life-Threatening ^a												
UA/NSTEMI	5001	65	(1.30)	4980	38	(0.76)	9981	103	(1.03)	1.711	(1.146, 2.553)	0.008
STEMI	1740	20	(1.15)	1736	18	(1.04)	3476	38	(1.09)	1.109	(0.587, 2.096)	0.750
All ACS	6741	85	(1.26)	6716	56	(0.83)	13457	141	(1.05)	1.517	(1.083, 2.126)	0.015
TIMI Fatal												
UA/NSTEMI	5001	14	(0.28)	4980	3	(0.06)	9981	17	(0.17)	4.664	(1.341, 16.230)	0.008
STEMI	1740	7	(0.40)	1736	2	(0.12)	3476	9	(0.26)	3.480	(0.723, 16.753)	0.097
All ACS	6741	21	(0.31)	6716	5	(0.07)	13457	26	(0.19)	4.191	(1.580, 11.113)	0.002
TIMI Minor ^a												
UA/NSTEMI	5001	117	(2.34)	4980	80	(1.61)	9981	197	(1.97)	1.466	(1.103, 1.948)	0.008
STEMI	1740	47	(2.70)	1736	45	(2.59)	3476	92	(2.65)	1.041	(0.691, 1.566)	0.848
All ACS	6741	164	(2.43)	6716	125	(1.86)	13457	289	(2.15)	1.313	(1.040, 1.656)	0.022

CI=confidence interval; HR=hazard ratio; N=number of subjects; n=number of subjects with event.

^aSubjects experiencing multiple bleeding events may be included in more than one category.

^bHR and two-sided 95% CI derived using Cox proportional hazards model.

^cTwo-sided log-rank p-value based on time to first event analysis compares the event free survival distributions for Prasugrel and Clopidogrel. Clinical presentation, UA/NSTEMI vs. STEMI, was used as a stratification factor in analyses of All ACS subjects. Reproduced from Sponsor, Table TAAL.12.3, page 511 and Table 12.4, pages 517-520.

Analysis verified by Karen A. Hicks, M.D. and Ququan Liu, M.D., M.S., Biometrics, FDA.

7.1.2.1.2 CABG-Related Bleeding

In the UA/NSTEMI, STEMI, and All ACS populations, CABG-related TIMI major bleeding was 3.2 to 3.7-fold higher with prasugrel compared to clopidogrel, as shown in Table 23.

Table 23. Sponsor's Analysis: CEC-Adjudicated CABG-Related Bleeding Events Through Study End (Overall) (TAAL)

Subject Population	Prasugrel			Clopidogrel			Total			OR	(95% CI) ^b	p-value ^c
	N	n	(%) ^a	N	n	(%) ^a	N	n	(%) ^a			
TIMI Major												
UA/NSTEMI	138	12	(8.70)	141	4	(2.84)	279	16	(5.73)	3.262	(1.025, 10.38)	0.035
STEMI	75	12	(16.00)	83	4	(4.82)	158	16	(10.13)	3.762	(1.157, 12.23)	0.020
All ACS	213	24	(11.27)	224	8	(3.57)	437	32	(7.32)	3.496	(1.531, 7.986)	0.002
TIMI Fatal												
UA/NSTEMI	138	0		141	0		279	0				NE
STEMI	75	2	(2.67)	83	0		158	2	(1.27)			NE
All ACS	213	2	(0.94)	224	0		437	2	(0.46)			NE

CI=confidence interval; OR=odds ratio; N=number of treated subjects undergoing CABG; n=number of treated subjects undergoing CABG with CABG-related bleeding events; NE=not evaluated due to insufficient data.

^a% is percentage of N.

^bOdds ratio (OR) is based on the frequency procedure.

^cTwo-sided p-values based on Pearson chi-square in UA/NSTEMI and STEMI, CMH general association test with clinical presentation as a blocking factor in All ACS.

Reproduced from Sponsor, Table TAAL.12.42, pages 763-770.

Analysis verified by Karen A. Hicks, M.D. and Ququan Liu, M.D., M.S., Biometrics, FDA.

If a subject required CABG, the percentage of subjects having CABG-related TIMI major bleeding events was always higher on prasugrel, compared to clopidogrel. The highest percentage of bleeding was seen in STEMI subjects whose last dose of prasugrel was 0-2 days prior to CABG (prasugrel: 4/19 (21.05%) versus clopidogrel: 1/17 (5.88%)). The percentage of subjects on prasugrel experiencing CABG-related TIMI major bleeding events was lowest when the prasugrel was discontinued > 7 days prior to surgery, as seen in Table 24. These data suggest prasugrel should be discontinued at least 7 days prior to undergoing CABG, if possible.

Table 24. Sponsor's Analysis: Number and Percentage of Subjects with CABG-Related TIMI Major Bleeding Events Through Study End (CEC-Adjudicated) (All Treated Subjects)

	Prasugrel			Clopidogrel			Total			OR	(95% CI) ^c	p-value
	N	n	(%) ^b	N	n	(%) ^b	N	n	(%) ^b			
Days from Most Recent Dose to CABG												
UA/NSTEMI												
0-2 Days	39	3	(7.69)	48	2	(4.17)	87	5	(5.75)			NE
3-5 Days	16	2	(12.50)	24	2	(8.33)	40	4	(10.00)			NE
> 5 Days	83	7	(8.43)	69	0		152	7	(4.61)			NE
> 7 Days	53	4	(7.55)	43	0		96	4	(4.17)			NE
STEMI												
0-2 Days	19	4	(21.05)	17	1	(5.88)	36	5	(13.89)			NE
3-5 Days	14	2	(14.29)	17	1	(5.88)	31	3	(9.68)			NE
> 5 Days	42	6	(14.29)	49	2	(4.08)	91	8	(8.79)			NE
> 7 Days	26	3	(11.54)	26	2	(7.69)	52	5	(9.62)			NE
All ACS												
0-2 Days	58	7	(12.07)	65	3	(4.62)	123	10	(8.13)	2.704	(0.758, 11.11)	0.161
3-5 Days	30	4	(13.33)	41	3	(7.32)	71	7	(9.86)			NE
> 5 Days	125	13	(10.40)	118	2	(1.69)	243	15	(6.17)	7.933	(1.646, 38.22)	0.003
> 7 Days	79	7	(8.86)	69	2	(2.90)	148	9	(6.08)			NE

N=number of treated subjects undergoing CABG; n=number of treated subjects undergoing CABG with CABG-related bleeding events;
OR=Odds Ratio; NE=not evaluated due to insufficient data.
^aSubject undergoing multiple CABG may be included in more than 1 category.
^b% is percentage of N.
^cOdds ratio (OR) is based on the frequency procedure.
^dTwo-sided p-values based on Pearson chi-square in UA/NSTEMI and STEMI, CMH general association test with clinical presentation as a blocking factor in All ACS.

Reproduced from Sponsor, Table TAAL.12.42, page 769. Analysis verified by Karen A. Hicks, M.D.

7.1.2.1.3 Intracranial Hemorrhage

In Study TAAL, there were 20 (0.29%) and 16 (0.24%) CEC-adjudicated intracranial hemorrhages (ICH) in the prasugrel and clopidogrel treatment groups, respectively.

However, in several of the sponsor's analyses, the number of intracranial hemorrhages reported is slightly different (19-prasugrel; 17-clopidogrel), given the fact that there was separate CEC adjudication of efficacy (stroke) and bleeding (ICH) endpoints. A summary of CEC-adjudicated intracranial hemorrhages occurring 'while at risk' is displayed in Table 25. "While at risk" included safety events occurring from the first dose of study drug up to the date of the close-out visit, within 7 days after the permanent study drug discontinuation, or 464 days from randomization, whichever was earlier. In both treatment groups, most of the intracranial hemorrhages occurred between 30 and 180 days, inclusive. Intracranial hemorrhages in the prasugrel treatment group were more severe and recovery from these events was lower than in the clopidogrel treatment group. Compared to clopidogrel, almost twice as many subjects treated with prasugrel died from intracranial hemorrhages.

Table 25. Summary of Intracranial Hemorrhages While at Risk (CEC Adjudicated) (All Treated All ACS Subjects) (TAAL)

	Prasugrel n/N (%)	Clopidogrel n/N (%)	Total n/N (%)
Number of Treated Subjects	6741	6716	13457
Total ICH Cases	19/6741 (0.28)	17 (6716) (0.25)	36/13457 (0.27)
Time to Bleeding Event			
≤ 3 days	1	1	2
> 3 days, ≤ 30 days	2	2	4
> 30 days, ≤ 180 days	9	9	18
> 180 days, ≤ 365 days	3	4	7
> 365 days, ≤ 464 days	4	1	5
Age			
≥ 75 years old	7/891 (0.79)	3/894 (0.34)	10/1785 (0.56)
< 75 years old	12/5850 (0.21)	14/5822 (0.24)	26/11672 (0.22)
Sex			
Female	5/1684 (0.30)	7/1798 (0.39)	12/3482 (0.34)
Male	14/5057 (0.28)	10/4918 (0.20)	24/9975 (0.24)
Body Weight			
< 50 kg	0/45 (0.00)	1/45 (2.22)	1/90 (1.11)
50 - < 70 kg	3/1133 (0.26)	6/1232 (0.49)	9/2365 (0.38)
70- < 90 kg	14/3378 (0.41)	9/3297 (0.27)	23/6675 (0.34)
≥ 90 kg	2/2125 (0.09)	1/2081 (0.05)	3/4206 (0.07)
History of Prior TIA or Stroke			
Yes	6/257 (2.33)	0/252 (0.00)	6/509 (1.18)
No	13/6484 (0.20)	17/6464 (0.26)	30/12948 (0.23)
Prior History of Hypertension			
Yes	14/4321 (0.32)	16/4324 (0.37)	30/8645 (0.35)
No	5/2420 (0.21)	1/2392 (0.04)	6/4812 (0.12)
Maximum Severity			
Mild	0	1/17 (5.88)	-
Moderate	2/19 (10.53)	5/17 (29.41)	-
Severe	17/19 (89.47)	11/17 (64.71)	-
Outcome			
Recovered	4/19 (21.05)	8/17 (47.06)	-
Recovering/Resolving	3/19 (15.79)	2/17 (11.76)	-
Not Recovered	1/19 (5.26)	0	-
Recovered with Sequelae	1/19 (5.26)	1/17 (5.88)	-
Died	9/19 (47.37)	5/17 (29.41)	-
Missing Data	1/19 (5.26)	1/17 (5.88)	-
ICH=intracranial hemorrhage; TIA=transient ischemic attack			
Reproduced from Sponsor, TAAL Clinical Study Report, TAAL.12.15, page 601, and from Risk Management Plan, Table 1.9, page 23..			

Approximately 1/3 of patients in the prasugrel treatment group who experienced intracranial hemorrhage had a prior history of TIA/CVA. In the prasugrel treatment group, three out of the nine subjects who died as a result of

intracranial hemorrhage had a history of atrial fibrillation and were not taking warfarin. All three subjects were > 75 years of age, and one subject had a history of prior TIA/CVA.

7.1.2.1.4 FDA Bleeding Analysis (TAAL)

In TAAL, we analyzed all bleeding events in treated subjects (n = 13,457), including 6741 subjects in the prasugrel treatment group and 6716 subjects in the clopidogrel treatment group. We determined the number and percentage of subjects in each treatment group who experienced particular bleeding events. Additionally, we analyzed the following variables and calculated the relative risk of bleeding on prasugrel compared to clopidogrel:

- Age
- Sex
- Ethnicity
- Weight
- Glomerular Filtration Rate
- History of a Prior TIA/CVA
- Stent Type (BMS vs. DES)
- Killip Class
- TIMI Risk Score
- TIMI Risk Index
- Maximum activated clotting time (ACT) during PCI
- Timing of Loading Dose
- Varying Aspirin Doses at Different time points in the study
- Use of unfractionated heparin, glycoprotein IIb/IIIa inhibitors, low molecular weight heparin, bivalirudin, or fondaparinux during PCI
- Use of multiple antithrombotic agents during PCI
- Glycoprotein IIb/IIIa inhibitor use up to 3 days
- Bivalirudin use to hospital discharge
- Warfarin and other coumarin use after randomization
- Argatroban use from symptom onset \leq 3 days
- Proton pump inhibitors
- Hormone replacement therapy
- Statin use
- Sheath size
- Sheath site
- Use of closure device
- Type of closure device used

Pertinent findings are presented below.

7.1.2.1.4.1 Number and Percentage of Bleeding Events (TAAL)

The number and percentage of subjects developing particular types of bleeding events in TAAL is summarized by treatment group in Table 26 and Table 27. With the exception of pulmonary bleeding, a greater percentage of subjects in the prasugrel treatment group experienced bleeding events compared to clopidogrel.

Table 26. FDA Analysis: Number and Percentage of Subjects with Bleeding Events (TAAL)

All (N=13,457)	N	Any Bleed?	Moderate/Severe Bleed?	Severe Bleed?	Serious Bleed?
Prasugrel	6741	1926 (28.6%)	732 (10.9%)	196 (2.9%)	370 (5.5%)
Clopidogrel	6716	1412 (21.0%)	535 (8.0%)	144 (2.1%)	252 (3.8%)
Analysis by Karen Hicks, M.D. and Ellis Unger, M.D.					

Table 27. Number and Percentage of Subjects with Bleeding by Organ System (TAAL)

All (n=13,457)	N	Gastrointestinal Bleed	Hematuria	Uterine/Vaginal/Male Reproductive Bleed	Intracranial Hemorrhage	Pulmonary Bleed	Retroperitoneal Bleed
Prasugrel	6741	261 (3.9%)	99 (1.5%)	29 (0.4%)	20 (0.3%)	34 (0.5%)	23 (0.3%)
Clopidogrel	6716	197 (2.9%)	85 (1.3%)	22 (0.3%)	16 (0.2%)	31 (0.5%)	14 (0.2%)

Analysis by Karen Hicks, M.D. and Ellis Unger, M.D.

7.1.2.1.4.2 Relative Risk of Bleeding on Prasugrel Compared to Clopidogrel

The relative risk of bleeding on prasugrel compared to clopidogrel is displayed in Table 28 and Table 29. Overall, there was a 36% increased risk of experiencing any bleed and a 46% increased risk of experiencing a serious bleed on prasugrel, compared to clopidogrel. In general, the risk of bleeding on prasugrel was higher in subjects ≥ 75 years of age, subjects with a prior history of a transient ischemic attack or cerebrovascular accident, and subjects who were not on a proton pump inhibitor.

Since the risk of bleeding on prasugrel was reduced in all organ systems on proton pump inhibitors (PPI), we were concerned that subjects were receiving less drug product due to varying degrees of absorption from the salt to base conversion. At higher pH, prasugrel HCl has higher solubility and is absorbed more quickly than prasugrel base. However, subsequent analyses demonstrated that the disparity in relative risk between subjects who did and did not receive a proton pump inhibitor was due to a lower frequency of bleeding seen in clopidogrel subjects who did not receive a PPI, compared to those who did.

With respect to the timing of the loading dose, subjects on prasugrel had a greater risk of bleeding at all time points, compared to clopidogrel. While previous analyses have shown that if the prasugrel loading dose was given during PCI or within 30 minutes of the start of PCI, there was a reduction in the primary endpoint, the comparative bleeding risk on prasugrel did not seem to be higher when given during that time frame, except for severe bleeding events. In the setting of a retroperitoneal bleed when the loading dose was given prior to PCI, there was a two-fold increase in the risk of bleeding on prasugrel compared to clopidogrel.

Table 28. FDA Analysis: Relative Risk (95% CI) of Bleeding on Prasugrel Compared to Clopidogrel (TAAL)

	Any Bleed?	Moderate/Severe Bleed?	Severe Bleed?	Serious Bleed?
All Subjects	1.36 (1.28, 1.44)	1.36 (1.23, 1.52)	1.36 (1.1, 1.68)	1.46 (1.25, 1.71)
Age (years)				
< 65	1.35 (1.24, 1.46)	1.35 (1.16, 1.57)	1.3 (0.95, 1.79)	1.58 (1.24, 2.01)
65 - < 75	1.34 (1.19, 1.5)	1.31 (1.07, 1.59)	1.28 (0.86, 1.91)	1.51 (1.13, 2.02)
≥ 75	1.44 (1.27, 1.65)	1.48 (1.19, 1.84)	1.56 (1.04, 2.35)	1.27 (0.95, 1.7)
Weight				
< 60 kg	1.43 (1.16, 1.78)	1.67 (1.17, 2.38)	1.36 (0.73, 2.55)	1.46 (0.93, 2.3)
≥ 60 kg	1.36 (1.28, 1.45)	1.35 (1.21, 1.51)	1.35 (1.08, 1.69)	1.47 (1.24, 1.74)
Prior TIA/CVA				
Yes	1.36 (1.28, 1.45)	1.35 (1.21, 1.51)	1.34 (1.08, 1.67)	1.46 (1.24, 1.71)
No	1.34 (1.02, 1.77)	1.7 (1, 2.91)	1.68 (0.67, 4.2)	1.51 (0.77, 2.97)
Proton Pump Inhibitors				
Yes	1.28 (1.19, 1.39)	1.19 (1.04, 1.36)	1.26 (0.97, 1.62)	1.36 (1.12, 1.63)
No	1.45 (1.33, 1.59)	1.68 (1.41, 2)	1.58 (1.08, 2.32)	1.71 (1.29, 2.27)
Timing of Loading Dose				
Pre-PCI	1.36 (1.2, 1.55)	1.38 (1.09, 1.76)	1.04 (0.68, 1.6)	1.64 (1.2, 2.25)
During PCI	1.36 (1.27, 1.46)	1.37 (1.22, 1.55)	1.49 (1.16, 1.91)	1.43 (1.19, 1.72)
Post-PCI	1.27 (0.82, 1.96)	1.00 (0.49, 2.02)	1.08 (0.23, 5.15)	1.44 (0.34, 6.18)

CI=confidence interval; CVA=cerebrovascular accident; TIA=transient ischemic attack

Analysis by Karen Hicks, M.D. and Ellis Unger, M.D.

Table 29. Relative Risk (95% CI) of Bleeding on Prasugrel Compared to Clopidogrel (TAAL)

	Gastrointestinal Bleed	Hematuria	Uterine/Vaginal/ Male Reproductive Bleed	Intracranial Hemorrhage	Pulmonary Bleed	Retroperitoneal Bleed
All Subjects	1.32 (1.1, 1.58)	1.16 (0.87, 1.55)	1.31 (0.76, 2.28)	1.14 (0.56, 2.33)	1.09 (0.67, 1.78)	1.64 (0.84, 3.18)
Age (years)						
< 65	1.33 (1.03, 1.74)	0.80 (0.49, 1.29)	1.28 (0.68, 2.40)	1.97 (0.49, 7.89)	0.85 (0.39, 1.83)	1.38 (0.61, 3.11)
65 - < 75	1.51 (1.04, 2.19)	1.25 (0.75, 2.09)	0.61 (0.15, 2.54)	0.58 (0.17, 1.98)	1.42 (0.63, 3.19)	2.54 (0.49, 13.06)
≥ 75	1.16 (0.83, 1.63)	1.66 (1.00, 2.76)	-	1.51 (0.43, 5.32)	1.15 (0.42, 3.15)	2.01 (0.37, 10.93)
Weight						
< 60 kg	1.03 (0.53, 1.98)	1.16 (0.16, 8.16)	1.16 (0.23, 5.69)	-	2.31 (0.58, 9.17)	4.62 (0.52, 41.15)
≥ 60 kg	1.37 (1.13, 1.66)	1.17 (0.87, 1.57)	1.35 (0.75, 2.44)	1.22 (0.59, 2.53)	0.99 (0.59, 1.67)	1.48 (0.71, 3.08)
Prior TIA/CVA						
Yes	0.91 (0.42, 1.95)	1.47 (0.25, 8.73)	-	-	0.98 (0.06, 15.59)	-
No	1.35 (1.12, 1.63)	1.15 (0.86, 1.54)	1.22 (0.7, 2.15)	0.78 (0.36, 1.72)	1.1 (0.67, 1.8)	1.57 (0.8, 3.06)
Proton Pump Inhibitors						
Yes	1.21 (0.98, 1.49)	1.17 (0.8, 1.71)	1.15 (0.53, 2.48)	1.11 (0.43, 2.87)	0.94 (0.53, 1.69)	1.69 (0.67, 4.29)
No	1.68 (1.16, 2.42)	1.14 (0.74, 1.77)	1.51 (0.68, 3.36)	1.17 (0.40, 3.49)	1.51 (0.62, 3.69)	1.58 (0.61, 4.08)
Timing of Loading Dose						
Pre-PCI	1.43 (0.94, 2.17)	1.49 (0.74, 2.99)	0.65 (0.18, 2.28)	-	0.87 (0.36, 2.14)	2.26 (0.59, 8.72)
During PCI	1.30 (1.06, 1.59)	1.14 (0.82, 1.57)	1.44 (0.76, 2.72)	0.86 (0.40, 1.85)	1.26 (0.69, 2.3)	1.36 (0.63, 2.97)
Post-PCI	1.62 (0.28, 9.37)	1.62 (0.28, 9.37)	-	-	-	-
CI=confidence interval; CVA=cerebrovascular accident; TIA=transient ischemic attack; - = not evaluated due to insufficient data						
Analysis by Karen Hicks, M.D. and Ellis Unger, M.D.						

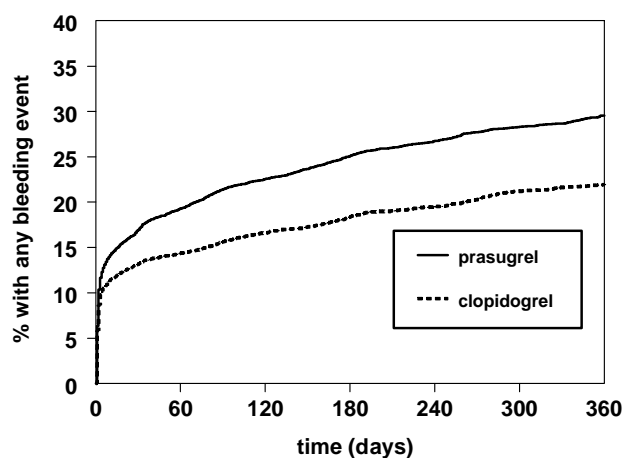
Kaplan-Meier Plots for Bleeding

Kaplan-Meier time-to-event analyses for bleeding events are presented in the figures below. These analyses were performed by Karen Hicks, M.D. and Ellis Unger, M.D..

Time to Any Bleed

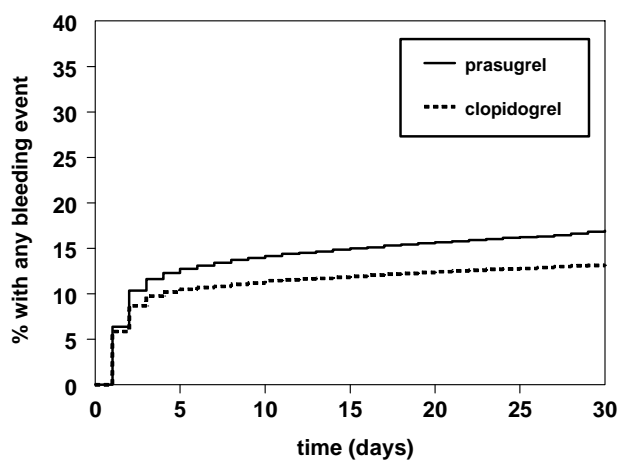
The percentage of subjects in each treatment group experiencing any bleeding event over time is displayed in Figure 12. Approximately 29% of subjects on prasugrel and 21% of subjects on clopidogrel experienced a bleeding event in TAAL. In both treatment groups, many of the bleeding events occurred within the first 3 to 5 days of the index procedure, as seen in Figure 13. However, the percentage of subjects experiencing any bleeding event on prasugrel or clopidogrel increased over time, with the greatest divergence between days 45 and 60.

Figure 12. FDA Analysis: Kaplan-Meier Plot for Any Bleeding Event (Day 0 to 360) (TAAL)



($p < 0.0001$ by log rank)

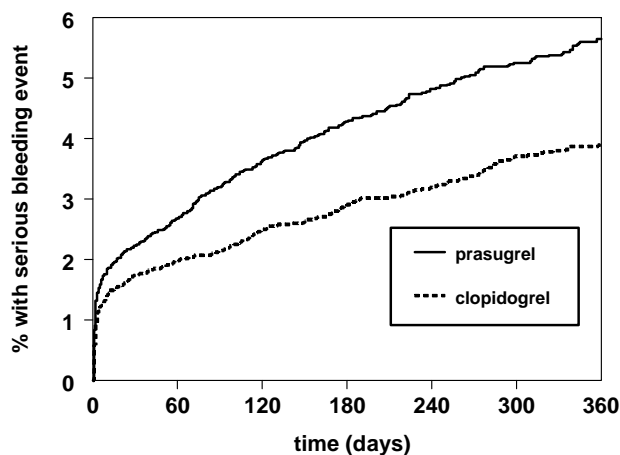
Figure 13. FDA Analysis: Kaplan-Meier Plot for Any Bleeding Event (Day 0 to 30) (TAAL)



Time to Serious Bleeding

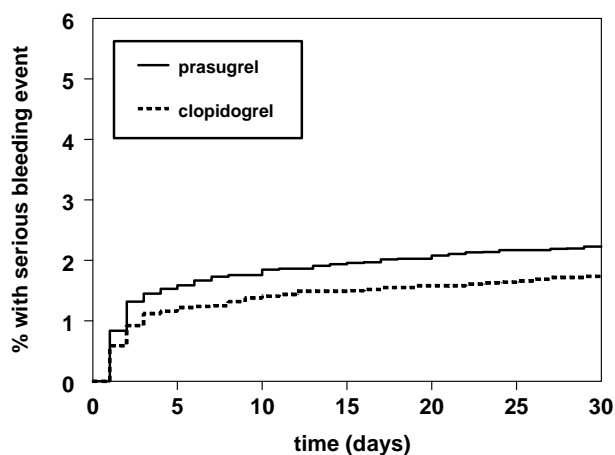
The percentage of subjects in each treatment group experiencing a serious bleeding event over time is displayed in Figure 14. Approximately 5.5% of subjects in the prasugrel treatment group experienced serious bleeding events, compared to 3.8% of subjects in the clopidogrel treatment group. Many of the serious bleeding events also occurred within the first 3 to 5 days of the index procedure, as displayed in Figure 15. However, the percentage of subjects experiencing a serious bleeding event in both treatment groups increased over time, with diverging curves at the 45 to 60 day time point.

Figure 14. FDA Analysis: Kaplan-Meier Plot for Serious Bleeding Events (Day 0 to 360) (TAAL)



($p < 0.0001$ by log rank)

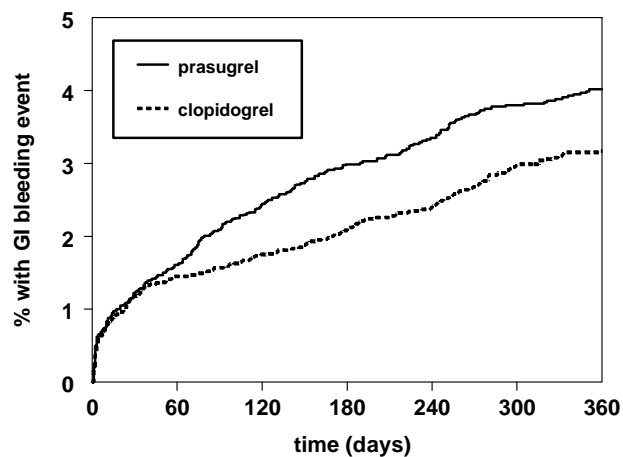
Figure 15. Kaplan-Meier Plot for Serious Bleeding Events (Day 0 to 30) (TAAL)



Time to Gastrointestinal Bleeding

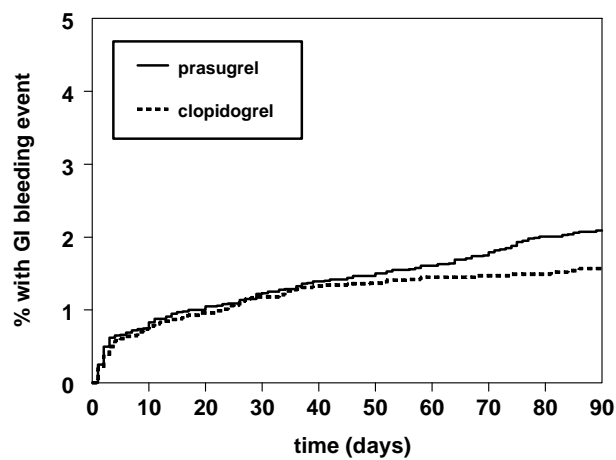
The percentage of subjects in each treatment group experiencing a gastrointestinal bleeding event over time is displayed in Figure 16. Approximately 3.9% of subjects in the prasugrel treatment group experienced gastrointestinal bleeding events, compared to 2.9% of subjects in the clopidogrel treatment group. The bleeding curves diverged at 40-60 days, as shown in Figure 17.

Figure 16. Kaplan-Meier Plot for Gastrointestinal Bleeding Events (Day 0 to 360) (TAAL)



(p = 0.0030 by log rank)

Figure 17. Kaplan-Meier Plot for Gastrointestinal Bleeding (Day 0 to 90) (TAAL)



7.1.2.2 Neoplasms

In TAAL, there was an increased rate of all neoplasms, particularly the solid tumors, in the prasugrel treatment group compared to clopidogrel ($p = 0.006$). In the prasugrel treatment group, there were 104 nonskin, nonbrain cancers, compared to 69 in the clopidogrel group. The neoplasms are summarized in Table 30.

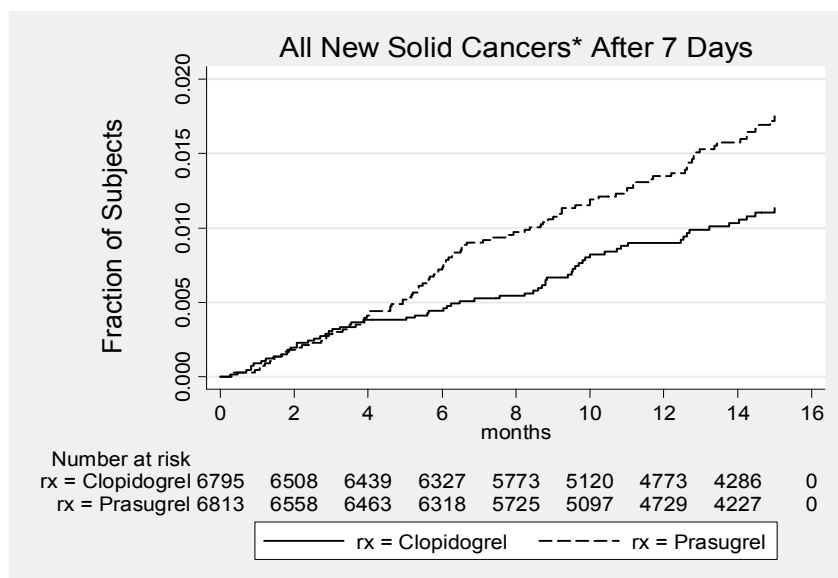
Table 30. Number of New First Cancers by Site and Treatment (TAAL)

	clopidogrel	prasugrel
patients	6,696	6,682
bladder	8	7
breast	1	5
cervix	0	1
colorectal	8	19
esophagus	2	5
gall bladder	0	2
gastrointestinal	1	0
head & neck	2	2
kidney	4	4
leukemia	2	1
liver	1	0
lung	13	21
lymphoma	2	2
melanoma	3	3
mesothelioma	0	1
myelodysplastic	1	2
ovary	0	1
pancreas	3	2
prostate	8	10
sarcoma	0	2
stomach	7	6
thyroid	0	1
unknown/other	2	7
uterus	1	0
all nonskin/ nonbrain	69	104
brain	0	2 (pituitary)
skin	14	10
squamous	4	5

(Analysis by Thomas A. Marciniak, M.D., Division of Cardiovascular and Renal Products)

Since tumor findings were sometimes noted at screening but not further evaluated until after enrollment, initial FDA analyses excluded cancers diagnosed during Days 0 to 7. The Kaplan-Meier incidence plot for all new solid cancers demonstrates a divergence in incidence between the prasugrel and clopidogrel treatment groups at 4 months, with continuing divergence through the duration of the study, as shown in Figure 18.

Figure 18. Kaplan-Meier (K-M) Incidence Plot for All New Solid Cancers Diagnosed After 7 Days in TRITON (TAAL)

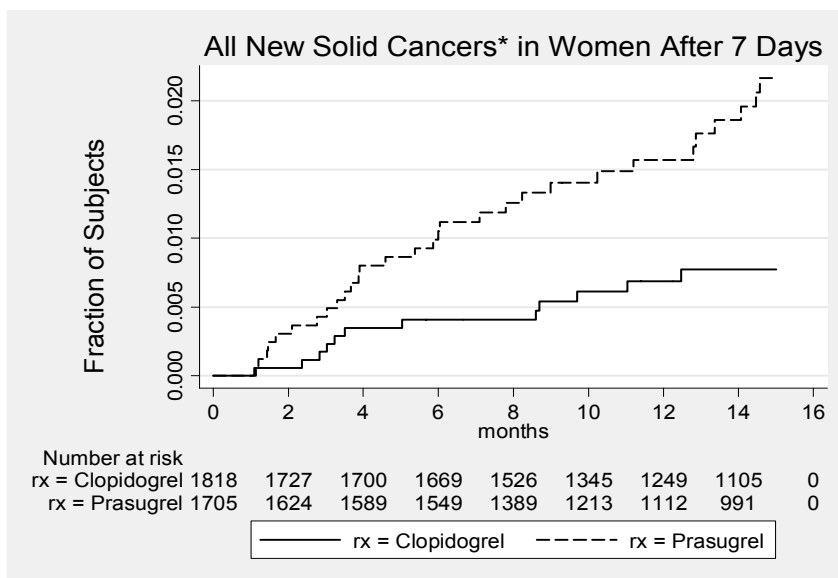


*excluding non-melanoma skin cancers and brain tumors; $p = 0.006$ by log rank

(Analysis by Thomas A. Marciniak, M.D., Division of Cardiovascular and Renal Products)

If the neoplasms are analyzed by sex, there are 18 excess neoplasms in women and 17 excess neoplasms in men in the prasugrel treatment group, compared to clopidogrel. The incidence of new solid cancers in women after 7 days is significant between treatment groups ($p = 0.0024$) while the incidence in men is not ($p = 0.16$). The Kaplan-Meier Incidence plots for these analyses are displayed in Figure 19 and Figure 20.

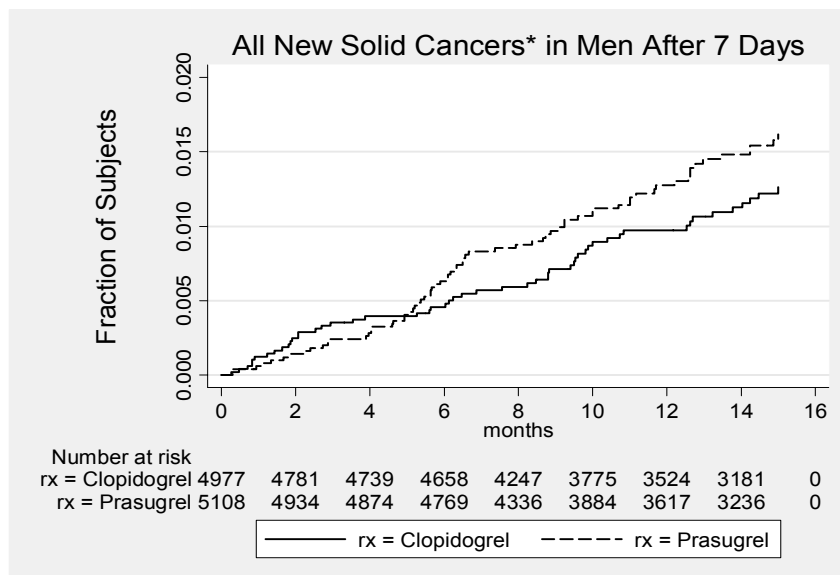
Figure 19. Kaplan-Meier Incidence Plot for All New Solid Cancers in Women After 7 Days (TRITON)



*excluding non-melanoma skin cancers and brain tumors; $p = 0.0024$ by log rank

(Analysis by Thomas A. Marciniak, M.D., Division of Cardiovascular and Renal Products)

Figure 20. Kaplan-Meier Incidence Plot for All New Solid Cancers in Men After 7 Days (TRITON) (TAAL)

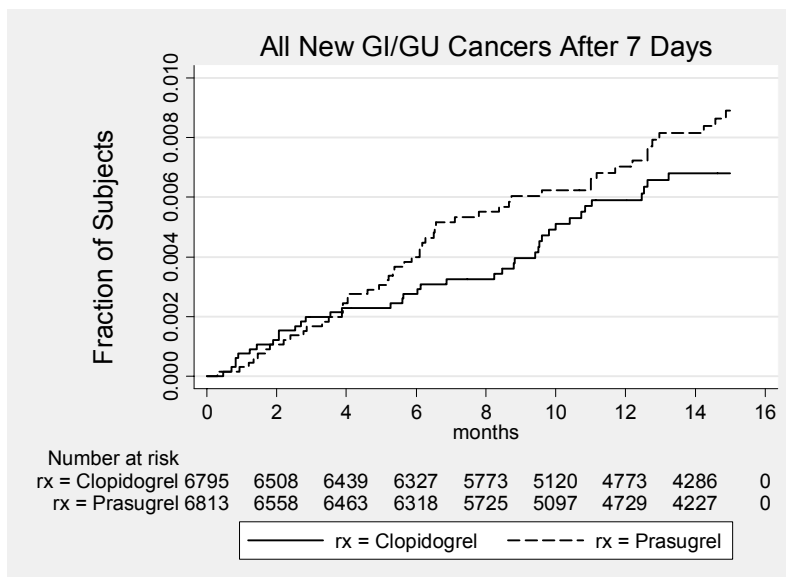


*excluding non-melanoma skin cancers and brain tumors; $p = 0.16$ by log rank

(Analysis by Thomas A. Marciniak, M.D., Division of Cardiovascular and Renal Products)

The incidence of new gastrointestinal/genitourinary cancers diagnosed after 7 days was not significantly different between treatment groups ($p = 0.2$ by log-rank), as seen in Figure 21.

Figure 21. Kaplan-Meier Incidence Plot for New Gastrointestinal/Genitourinary Cancers Diagnosed After 7 Days in TRITON (TAAL)

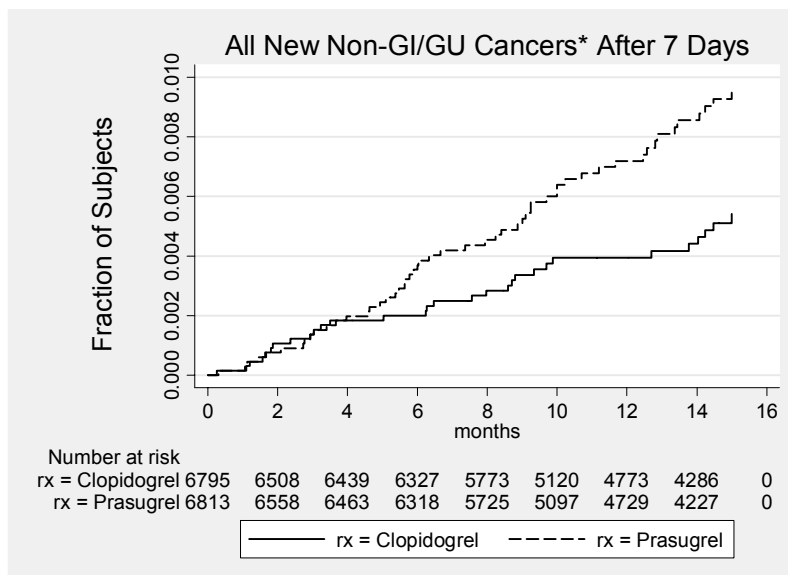


*excluding non-melanoma skin cancers and brain tumors; $p = 0.2$ by log rank

(Analysis by Thomas A. Marciniak, M.D., Division of Cardiovascular and Renal Products)

Examined separately, new gastrointestinal or genitourinary cancers were also not significantly different between treatment groups. However, new non-gastrointestinal or non-genitourinary cancers were significantly different between the prasugrel and clopidogrel treatment groups ($p = 0.01$), as displayed in Figure 22.

Figure 22. Kaplan-Meier Incidence Plot for New Non-Gastrointestinal/Genitourinary Cancers Diagnosed After 7 Days in TRITON (TAAL)



* excluding non-melanoma skin cancers and brain tumors; $p = 0.01$ by log rank

(Analysis by Thomas A. Marciniak, M.D., Division of Cardiovascular and Renal Products)

In summary, in TAAL there was a significantly increased rate of new cancers in the prasugrel treatment group, compared to clopidogrel ($p=0.006$ by log rank). The sponsor argued that the cancer rate was higher in the prasugrel-treated subjects because more cancers were being identified through bleeding adverse events. However, when we performed an analysis eliminating all the subjects in both treatment groups who had bleeding in the particular organ system that subsequently developed cancer, there was still a significant difference in the incidence of cancer between treatment groups ($p = 0.0218$).

7.1.2.3 Additional Serious Adverse Events

In TAAL, the incidence of the following serious adverse events was significantly higher in subjects treated with prasugrel compared to clopidogrel:

- Atrial flutter (All ACS: 0.18% prasugrel versus 0.06% clopidogrel; $p = 0.046$)
- Respiratory failure (All ACS: 0.22% prasugrel versus 0.09% clopidogrel; $p = 0.050$)
- Hypotension (All ACS: 0.21% prasugrel versus 0.06% clopidogrel; $p = 0.019$)

Several of the events of respiratory failure occurred in the setting of TIMI bleeding.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

In both the prasugrel and clopidogrel treatment groups, a greater percentage of subjects with the following characteristics discontinued study drug:

- Increased age (≥ 65 , ≥ 70 , ≥ 75 y)
- Female sex
- Low body weight (< 70 kg STEMI and All ACS; < 50 kg UA/NSTEMI)
- Increased Thrombolysis In Myocardial Infarction (TIMI) risk score
- Diabetes mellitus
- Hepatic impairment based on pre-existing conditions (UA/NSTEMI and All ACS)
- Prior transient ischemic attack (TIA) or stroke
- Atrial fibrillation
- Congestive heart failure
- Peripheral arterial disease

A lower percentage of subjects discontinued study drug in eastern Europe, compared to other geographic regions.

In the UA/NSTEMI, STEMI, and All ACS populations, the overall incidence of study drug discontinuation due to adverse events was higher in subjects treated with prasugrel, compared to clopidogrel. In the All ACS population, discontinuations were primarily due to hemorrhagic events in the prasugrel treatment group.

7.1.3.2 Adverse events associated with dropouts

There were significantly more adverse events leading to discontinuation in the prasugrel treatment group, compared to clopidogrel. The most common hemorrhagic treatment emergent adverse events (TEAEs) leading to discontinuation of study drug included gastrointestinal hemorrhage, epistaxis, contusion, and hematuria.

The most common nonhemorrhagic TEAEs leading to study drug discontinuation were atrial fibrillation, intracardiac thrombus, atrial flutter, rash, coronary artery bypass, and deep vein thrombosis.

A summary of the primary reason for premature study drug discontinuation in the All ACS population is displayed in Table 31. The prasugrel treatment group had significantly more discontinuations related to serious and non-serious hemorrhagic adverse events, compared to clopidogrel.

Table 31. Primary Reason for Premature Study Drug Discontinuation (All ACS) (TAAL)

	Prasugrel		Clopidogrel		Total		OR	(95% CI) ^b	p-value ^b
	n	(%) ^a	n	(%) ^a	n	(%) ^a			
Treated	6741		6716		13457				
Total	1207	(17.91)	1163	(17.32)	2370	(17.61)	1.042	(0.953, 1.138)	0.369
Entry Criteria Violation	25	(0.37)	27	(0.40)	52	(0.39)	0.922	(0.535, 1.591)	0.771
Adverse Event	485	(7.19)	424	(6.31)	909	(6.75)	1.150	(1.005, 1.317)	0.042
Hemorrhagic	169	(2.51)	91	(1.35)	260	(1.93)	1.872	(1.448, 2.421)	<0.001
Serious	106	(1.57)	61	(0.91)	167	(1.24)	1.743	(1.270, 2.393)	<0.001
Non-Serious	64	(0.95)	31	(0.46)	95	(0.71)	2.067	(1.344, 3.179)	<0.001
Non-Hemorrhagic	316	(4.69)	333	(4.96)	649	(4.82)	0.943	(0.805, 1.104)	0.464
Serious	125	(1.85)	111	(1.65)	236	(1.75)	1.124	1.124 (0.869, 1.455)	0.373
Non-Serious	196	(2.91)	232	(3.45)	428	(3.18)	0.837	(0.690, 1.015)	0.071
Other	0		2	(0.03)	2	(0.01)			NE

	Prasugrel		Clopidogrel		Total		OR	(95% CI) ^b	p-value ^b
	n	(%) ^a	n	(%) ^a	n	(%) ^a			
Investigator Decision	99	(1.47)	95	(1.41)	194	(1.44)	1.039	(0.782, 1.380)	0.791
Subject Decision	598	(8.87)	613	(9.13)	1211	(9.00)	0.969	(0.861, 1.091)	0.604
Study Drug Unblinded	0		2	(0.03)	2	(0.01)			NE

CI=confidence interval; n=number of subjects, OR=odds ratio, NE=not evaluated due to insufficient data.
^a% is percent of treated subjects.
^bTwo-sided p-value based on Pearson chi-square test. The two-sided p-value and odds ratio for All ACS were adjusted for clinical presentation as a stratification factor using Cochran-Mantel-Haenszel method.
Reproduced from Sponsor, Clinical Study Report, Table TAAL.12.2, page 490.

7.1.3.3 Other significant adverse events

The number of treatment emergent adverse events, serious adverse events, and clinically significant treatment emergent adverse events (CSTEAEs) between treatment groups were similar in the UA/NSTEMI, STEMI, and All ACS populations. In the All ACS population, however, prasugrel subjects had significantly more CSTEAEs than clopidogrel subjects, as seen in Table 32.

Clinically significant TEAEs included bleeding events adjudicated as TIMI Major or TIMI Minor, thrombotic thrombocytopenic purpura, and the following reported as a serious adverse event or abnormal laboratory value: hematologic adverse events (thrombocytopenia, pancytopenia, agranulocytosis, neutropenia), abnormal hepatic function, allergic reactions, torsade de pointes, and any TEAE leading to permanent discontinuation of study drug.

Table 32. Overview of Treatment-Emergent Adverse Events Through Study End (All ACS Population) (TAAL)

Adverse Event Type ^a	Prasugrel			Clopidogrel			Total			OR ^b	p-value ^b
	N	n	(%)	N	n	(%)	N	n	(%)		
TEAE	6741	5441	(80.72)	6716	5403	(80.45)	13457	10844	(80.58)	1.017	0.696
SAE	6741	1665	(24.70)	6716	1629	(24.26)	13457	3294	(24.48)	1.024	0.549
Clinically Significant TEAE	6741	925	(13.72)	6716	842	(12.54)	13457	1767	(13.13)	1.110	0.042

SAE=serious adverse event; TEAE=treatment emergent adverse event.
^aSubjects may be counted in more than one category.
^bThe p-value is obtained from a 2-sided Chi-Square test. Odds ratio (OR) is based on the frequency procedure.
Reproduced from Sponsor, Table TAAL.14.89, page 1850.

7.1.4 Common Adverse Events

7.1.4.1 Incidence of common adverse events

TAAL

Common adverse events in the prasugrel treatment group were primarily hemorrhagic. Please see Section 7.1.2 for further details.

Rash was reported in 2.8% of prasugrel and 2.4% of clopidogrel subjects.

Anemia was reported in 2.2% of prasugrel and 2.0% of clopidogrel subjects.

Pyrexia and increased tendency to bruise were reported in at least 1% of prasugrel subjects and the incidence of these adverse events was significantly higher than that in the clopidogrel treatment group.

ABT

In the Clinical Pharmacology dataset, post-procedural hemorrhage, headache, contusion, dizziness, nausea, and epistaxis were reported by at least 5% of prasugrel-treated subjects.

7.1.5 Less Common Adverse Events

TAAL

There were 4 reported cases (0.06%) of neutropenia in the prasugrel treatment group, compared to 21 cases (0.31%) in the clopidogrel treatment group.

Severe neutropenia was defined as an absolute neutrophil count $< 0.5 \times 10^9/L$. Two subjects (0.03%) in the prasugrel treatment group and 4 subjects (0.06%) in the clopidogrel treatment group experienced clinically significant treatment-emergent severe neutropenia.

There were no reported events of thrombotic thrombocytopenia purpura (TTP) in prasugrel subjects, compared to one event in a clopidogrel subject (0.01%).

Severe thrombocytopenia was defined as a platelet count $< 50 \times 10^9/L$. Four subjects (0.06%) in the prasugrel treatment group and three subjects (0.04%) in the clopidogrel treatment group experienced clinically significant severe thrombocytopenia. Seventeen subjects (0.25%) in the prasugrel treatment group and eighteen subjects (0.27%) in the clopidogrel treatment group experienced thrombocytopenia as a severe adverse event. In most of the cases of thrombocytopenia, subjects were also receiving a glycoprotein IIb/IIIa inhibitor.

Leukopenia, defined as a white blood cell count $< 4 \times 10^9/L$, occurred in 187 (2.77%) prasugrel subjects and 236 (3.51%) clopidogrel subjects.

No events of pancytopenia were reported in subjects receiving either prasugrel or clopidogrel.

In the prasugrel treatment group, fifteen (0.22%) subjects developed abnormal hepatic function, 8 (0.12%) subjects had abnormal hepatic function reported as a serious adverse event, and 8 (0.12%) subjects developed ALT $> 3 \times$ ULN and total bilirubin $> 1.5 \times$ ULN, compared to 18 (0.27%), 15 (0.22%), and 4 (0.06%) subjects, respectively, in the clopidogrel treatment group.

Twenty-four prasugrel (0.36%) and clopidogrel (0.36%) subjects had allergic reactions reported as serious adverse events.

Four (0.06%) prasugrel subjects and 3 (0.04%) clopidogrel subjects had angioedema reported as a serious adverse event. One of the prasugrel subjects was also receiving an angiotensin converting enzyme inhibitor (ACE-I).

ABT

- 1 subject developed angioedema 5 days after starting prasugrel. The subject had also started an ACE-I and herbal preparation 10 days earlier.
- Subject TAAV-115 was a 58 year old healthy male who developed acute liver failure after receiving prasugrel and atorvastatin. The subject participated in 2 treatment periods. In Treatment Period 1, he received prasugrel 60 mg LD on 1/10/2006 and 10 mg MD from 1/11/2006 to 1/20/2006. In Treatment Period 2, he received 80 mg atorvastatin daily from 2/8/2006 (Day -6) until 2/16/2006 (Day 3) with concomitant prasugrel (60 mg LD on 2/14/2006 (Day 1) and 10 mg MD on 2/15 and 2/16/2006 (Days 2 and 3)). He received his final dose of atorvastatin and prasugrel on 2/16/2006 (Day 3). Liver enzymes were mildly elevated on Day -1, compared to Day -7. His liver enzymes continued to increase, and the subject was withdrawn from the study. Or [REDACTED] Subject 115 was admitted to the hospital with acute liver failure with AST $15 \times$ ULN, ALT $18 \times$ ULN, lactic dehydrogenase $2 \times$ ULN, alkaline phosphatase $3 \times$ ULN, direct bilirubin $7 \times$ ULN, and normal creatinine kinase.

He was discharged from the hospital on [REDACTED] and as of [REDACTED], his liver function enzymes were decreasing.

7.1.6 Laboratory Findings

Please see Section 7.1.6.

7.1.7 Vital Signs

7.1.7.1 Overview of vital signs testing in the development program

In the primary safety database, blood pressure and heart rate were measured at baseline and at visits corresponding to 24 hours post-PCI or hospital discharge (whichever came first) and at the 30-, 90-, 180-, 270-, 360-, and 450-day visits. These vital sign measurements were not standardized and were meant for subject management only. There were no clinically important differences between the prasugrel and clopidogrel treatment groups.

In ABT studies, postbaseline arterial blood pressure and heart rate were systematically measured in Study TAAD and demonstrated no clinically significant differences.

Lastly, there were no clinically significant changes in vital signs noted in the tertiary safety database.

7.1.8 Electrocardiograms (ECGs)

The QT Interdisciplinary Review Team (QTIRT) reviewed the thorough QT(TQT) study entitled, Study H7T-EW-TAAP. Please refer to the QTIRT review for full details.

Study TAAP was a single-centre, randomized, three-period crossover study in 60 healthy male and female subjects who received placebo or an 80-mg single dose of prasugrel. Subjects also received a single oral dose of moxifloxacin 400 mg administered open label. Twelve-lead ECGs were sampled at 1, 2, and 6 hours on Day -1 and at 1, 2, 6, and 24 hours post-dose on Day 1. Each of the three treatment periods was separated by a washout of at least 10 days.

With regard to TQT design, Study TAAP had several limitations:

- The 80-mg single dose was not sufficient to cover worst case scenarios after a 60-mg loading dose. However, this dose does cover the expected high exposure scenario for the 5- or 10-mg maintenance dose.
- The ECG sampling times were not adequate to capture T_{max} for three of the metabolites
- The time-matched baseline (1, 2, and 6 hours only) was captured prior to period 1 only and was used for all periods in double-delta analysis. Therefore, the present double-delta analysis (change from placebo adjusted for baseline) was equivalent to a single-delta analysis (change from placebo)

Despite the limitations, Study TAAP was performed adequately and was considered to be a negative QT study. The results are displayed in Table 33. The largest upper limit of the two-sided 90% CI for the mean difference between prasugrel and placebo was below 10 ms, the threshold for regulatory concern as described in ICH E14 guideline.

Table 33. QTIRT Analysis: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Prasugrel 80 mg and the Largest Lower Bounds for Moxifloxacin (H7T-EW-TAAP)

Treatment	Time (h)	$\Delta QTcF$ (ms)	90% CI
Prasugrel 80 mg	24	2.1	(-1.3, 5.40)
Moxifloxacin 400 mg	1	10.7	(8.3, 13.0)*

*After Bonferroni correction.

The lack of positive signal from the concentration-QT modeling together with comparable levels of at least two metabolites in TAAP and TAAL suggest that prasugrel may not prolong QT at clinically relevant exposures.

7.1.9 Immunogenicity N/A

7.1.10 Human Carcinogenicity (Please see Section 7.1.2.2 for further details)

7.1.11 Special Safety Studies N/A

7.1.12 Withdrawal Phenomena and/or Abuse Potential N/A

7.1.13 Human Reproduction and Pregnancy Data

Prasugrel has not been studied in pregnant or lactating women. There are no pregnancies reported in the prasugrel clinical program.

7.1.14 Assessment of Effect on Growth N/A

7.1.15 Overdose Experience

To date, there are no reports of subjects who experienced a prasugrel overdose.

7.1.16 Postmarketing Experience

Prasugrel has not been approved for marketing in any country.

7.2 Adequacy of Patient Exposure and Safety Assessments

In Study TAAL, 4088 subjects were exposed to prasugrel for at least 1 year, and 2,656 subjects were exposed for at least 15 months. A summary of exposure for the primary and secondary safety databases is presented in Table 34.

Table 34. Exposure to Prasugrel (by Days) in Subjects with Atherosclerosis in the Primary and Secondary Safety Databases

Primary Safety Database: All ACS subjects treated with prasugrel in Study TAAL (N=6741)		
Days of Exposure	Subjects	Subject-Years ^a
LD (60 mg)	6718	NA
MD (10 mg)	6672	6464.60
1 – 3	77	0.38
>3 – 30	216	8.29
>30 – 90	232	34.88
>90 – 180	365	146.37
>180 – 270	876	518.11
>270 – 360	753	651.87
>360 – 450	1497	1725.31
>450	2656	3379.40
Secondary Safety Database: All subjects treated with prasugrel in ABT studies (N=940)		
Days of Exposure	Subjects	Subject-Years ^a
Any LD ^b	885	NA
Any MD ^c	880	71.28
1 – 3	6	0.04
>3-30	287	17.05
>30	587	54.19

Abbreviations: ABT = All but TAAL (Studies TAAD, TAAH, TABL, and TABR); ACS = acute coronary syndrome; LD = loading dose; MD = maintenance dose; NA = not applicable.

Subject exposure = Last dose date – First maintenance dose date + 1.

^a Subject-years = Mean exposure in days times number of treated subjects/365.25.

^b Either 40 or 60 mg prasugrel.

^c Either 5, 7.5, 10, or 15 mg prasugrel.

Exposure by days for the 2 populations (UA/NSTEMI and STEMI) in the primary safety database is located in [Table APP.2.7.4.36](#) and [Table APP.2.7.4.37](#), respectively.

Source: Q3055, Q3060.

(Reproduced from Sponsor, Integrated Summary of Safety (ISS), Table 2.7.4.5., page 33)

Prasugrel exposure in hepatically and renally impaired subjects was limited, as shown in Table 35.

Table 35. Prasugrel Exposure in Clinical Pharmacology Studies

Tertiary Database: Prasugrel Subjects in Clinical Pharmacology Studies (N=898)			
Subjects	# of Subject Doses		# of Subject Doses (Multiple Dose Studies)
	# of Subjects	(Single Dose or Loading Dose)	
Healthy ^a	839	1194	5885
Hepatically-impaired ^b	22	29	85
Renally-impaired ^c	37	37	0
Total	898	1260	5970

^a Studies in healthy subjects included single loading dose studies with multiple phases for dosing and appropriate wash-out periods (2.5-, 5-, 10-, 15-, 20-, 25-, 30-, 40-, 60-, 75-, and 80-mg prasugrel) and multiple dose (maintenance dose) studies (2.5-, 5-, 7.5-, 10-, 15-, and 20-mg prasugrel).

^b Studies in hepatically-impaired subjects included single loading dose studies with multiple phases for dosing and appropriate wash-out periods (60-mg prasugrel) and multiple-dose (maintenance dose) studies (10-mg prasugrel).

^c Studies in renally-impaired subjects included single loading-dose studies with multiple phases for dosing and appropriate wash-out periods (5-, 10-, 30-, and 60-mg prasugrel) and no multiple-dose studies.

Studies include: S001, S002, S003, S004, TAAA, TAAB, TAAC, TAAE, TAAF, TAAI, TAAJ, TAAK, TAAN, TAAO, TAAP, TAAQ, TAAR, TAAS, TAAT, TAAU, TAAV, TAAW, TAAX, TAAZ, TABF, TABS, TABV, TABW, TABZ, TACF, TACG, TACJ, TACK.

Source: Section 2.7.4.7; Table APP.2.7.4.1; Table APP.2.7.4.2; Table APP.2.7.4.3.

(Reproduced from Sponsor, Risk Management Plan, Table 1.5, page 15 of 97)

7.2.1 Demographics

Demographics and baseline characteristics for TAAL are presented in Table 36. For a complete summary of these characteristics, please see Section 9.1. Baseline characteristics appeared to be balanced between treatment groups. Women, the elderly, and subjects with renal impairment were underrepresented.

Table 36. Demographics and Baseline Characteristics (All Randomized All ACS Subjects) (TAAL)

	Prasugrel	Clopidogrel
Clinical Presentation n (%)^a		
UA/NSTEMI	N=5042	N=5027
UA	1271 (25.21)	1257 (25.00)
NSTEMI	3771 (74.79)	3770 (75.00)
STEMI	N=1767	N=1765
STEMI ≤ 12 hours	1203 (68.08%)	1235 (69.97)
STEMI > 12 hours	564 (31.92%)	530 (30.03)
Age (years)	N=6813	N=6795
Mean/SD	60.9/11.2	60.9/11.4
≥ 75 years	901 (13.22)	908 (13.36)
Sex n (%)^a	N=6813	N=6795
Male	5108 (74.97)	4977 (73.25)
Ethnicity	N=6813	N=6795
Caucasian	6263 (91.93)	6274 (92.33)
Geographic Region	N=6813	N=6795
Europe	3436 (50.43)	3439 (50.61)
Eastern Europe	1657 (24.32)	1665 (24.50)
Western Europe	1779 (26.11)	1774 (26.11)
North America	2164 (31.76)	2146 (31.58)
United States	2039 (29.93)	2020 (29.73)

	Prasugrel	Clopidogrel
South America	270 (3.96)	264 (3.89)
Rest of World	943 (13.84)	946 (13.92)
Tobacco Use n (%)^a	N=6813	N=6795
Any Tobacco Use	4462 (65.49)	4490 (66.08)
Creatinine Clearance (mL/min)	N=6699	N=6681
< 60 mL/min n (%)^a	717 (10.70)	774 (11.59)
Medical History n (%)^a	N=6813	N=6795
Diabetes ^a	1576 (23.13)	1570 (23.11)
Hypertension ^a	4370 (64.14)	4371 (64.33)
Hypercholesterolemia ^a	3790 (55.63)	3790 (55.78)
Prior MI ^a	1226 (18.00)	1208 (17.78)
Prior PCI ^a	904 (13.27)	926 (13.63)
Prior CABG ^a	541 (7.94)	497 (7.31)
Atrial Fibrillation ^a	211 (3.10)	212 (3.12)
History of Heart Failure ^a	265 (3.89)	247 (3.64)
Prior TIA or Stroke ^a	257 (3.77)	252 (3.71)
Peptic Ulcer Disease ^a	400 (5.87)	415 (6.11)
Peripheral Artery Disease ^a	349 (5.12)	363 (5.34)
ACS=acute coronary syndromes; CABG=coronary artery bypass graft; MI=myocardial infarction; N=number of randomized subjects; n=number of subjects in subcategory; NSTEMI=non-ST segment elevation myocardial infarction; PCI=percutaneous coronary intervention; SD=standard deviation; STEMI=ST-segment elevation myocardial infarction; TIA=transient ischemic attack; UA=unstable angina. ^a% is percent of number of subjects with non-missing values for category. (Reproduced from Sponsor, Integrated Summary of Safety, Table 2.7.4.7, pages 35-37)		

7.2.1.1 Postmarketing experience N/A

7.2.1.2 Literature N/A

7.2.2 Adequacy of Overall Clinical Experience

The overall clinical experience is adequate.

7.2.3 Adequacy of Special Animal and/or In Vitro Testing

The special animal and/or in vitro testing appear to be adequate. Please see the Pharmacology/Toxicology review for full details.

7.2.4 Adequacy of Routine Clinical Testing

Routine clinical testing appears adequate.

7.2.5 Adequacy of Metabolic, Clearance, and Interaction Workup

While the metabolic, clearance, and interaction workup appear to be adequate, one should refer to the Clinical Pharmacology/Biopharmaceutics review for further details.

7.2.6 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Please see Section 1.2 for recommendations on postmarketing requirements.

7.2.7 Assessment of Quality and Completeness of Data

Please refer to section 4.4 of this review for additional details on quality and completeness of data.

7.2.8 Additional Submissions, Including Safety Update

I reviewed the 4-month safety update, and there are no new safety issues.

8 ADDITIONAL CLINICAL ISSUES

8.1 Conclusions

Prasugrel significantly reduced the composite of cardiovascular death, nonfatal MI, or nonfatal stroke at the expense of more bleeding. Subjects ≥ 75 years of age, subjects with a history of transient ischemic attack/cerebrovascular accident, and subjects with weight category < 60 kg have an increased risk of bleeding on prasugrel, compared to clopidogrel.

Preliminary analyses from TAAL suggest there is an increased incidence of new cancers in prasugrel subjects, compared to clopidogrel subjects.

9 APPENDICES (REVIEW OF INDIVIDUAL STUDY REPORTS)

9.1 Study H7T-MC-TAAL (Primary) (Clinical Study Report: “A Comparison of CS-747 and Clopidogrel in Acute Coronary Syndrome Subjects Who are to Undergo Percutaneous Coronary Intervention/TIMI 38”) (Study Dates: November 5, 2004 – July 22, 2007) (Date of Report: November 28, 2007)

9.1.1 Protocol, Amendment, and Post Hoc Changes

The study description was based on the original protocol dated August 10, 2004, Protocol Amendment 1(a) dated January 10, 2006, 11 addenda sponsored by Lilly, and 2 addenda initiated by independent investigators.

Amendment or Addendum	Date	Brief Description	Outsourced Responsibilities
H7T-MC-TAAL(A)	1/10/2006	Protocol amendment to modify the definition of non-fatal myocardial infarction (MI). Specifically, the modification adds to the definition of peri-procedural MI if the CK-MB is > 5X ULN on one sample if it is the last available sample and was drawn ≥ 12 hours after PCI.	Additionally, subjects who could not return to the study site could have visits conducted by other means, such as via telephone. Although this was planned to be used for those subjects who had discontinued study drug only, telephone follow-up was also used for some subjects who remained on study drug (page 89 of CSR).
H7T-MC-TAAL(2)		Biological sample banking at selected sites in North America	
H7T-MC-TAAL (3.1)	11/10/2004	Evaluation of the influence of prasugrel versus clopidogrel on changes in health related quality of life	Economic and quality of –life data analysis (Saint Lukes Mid-America Heart Institute, Kansas City, Missouri USA)
H7T-MC-TAAL (4)		Biological sample banking at selected sites outside of North America	
H7T-MC-TAAL (5)		Assessment of effect of prasugrel as compared with clopidogrel on improvement in ST-segment resolution (STRES) following primary PCI.	Angiogram and ECG analysis, and substudy report completion (Thrombolysis in Myocardial Infarction [TIMI] Study Group, Boston, Massachusetts USA)
H7T-MC-TAAL(6)		Comparison of the effectiveness of prasugrel versus clopidogrel for providing inhibition of P2Y ₁₂ as measured by vasodilator-associated phosphoprotein (VASP) phosphorylation, leukocyte platelet aggregation, and light transmission aggregometry (LTA).	Platelet function analysis and report completion (University of Massachusetts Medical School, Center for Platelet Function Studies, Worcester, Massachusetts USA)
H7T-MC-TAAL (7)		Assessment of the population pharmacokinetics of 2 inactive prasugrel metabolites after the loading dose and during chronic maintenance dosing.	PK sample analysis (Advion Biosciences, Inc, Ithaca, new York USA)

Amendment or Addendum	Date	Brief Description	Outsourced Responsibilities
H7T-MC-TAAL (8)	2/11/2005	Assessment of the effect of high dose atorvastatin or pravastatin on the platelet-inhibitory activity of prasugrel and clopidogrel	Platelet function analysis (Center for Molecular and Vascular Biology, Onderwijs & Navorsing, Leuven, Belgium)
H7T-MC-TAAL (9)		Comparison of the effectiveness of prasugrel versus clopidogrel for providing inhibition of P2Y ₁₂ as measured by VASP and leukocyte platelet aggregation.	Platelet function analysis and report completion (University of Massachusetts Medical School, Center for Platelet Function Studies, Worcester, Massachusetts USA)
H7T-MC-TAAL (10)		Evaluation of the population pharmacokinetics of the prasugrel active metabolite and 2 inactive prasugrel metabolites	PK sample analysis (Advion Biosciences, Inc, Ithaca, New York USA)
H7T-MC-TAAL (11)		Assessment of the safety and efficacy of prasugrel in subjects treated with GPIIb/IIIa antagonists	
H7T-MC-TAAL (12)		Assessment of the population pharmacokinetics of 2 inactive prasugrel metabolites during chronic maintenance dosing	
Independent substudy initiated by Professor Jose Carlos Nicolau, MD		Evaluation of HDL Function in the Early and Late Phases of Acute Coronary Syndromes	
Independent substudy initiated by Dominick J. Angiolillo, MD		Comparison of the effectiveness of prasugrel versus clopidogrel for providing inhibition of P2Y ₁₂ using the VerifyNow™ (Ultegra) and the TEG Thromboelastograph Hemostasis systems.	
^aResults for this addendum are incorporated into the subgroup analyses in Section 12.2.1.7.4 of the TAAL Clinical Study Report. Brief synopses of the addenda sponsored by Eli Lilly and Company follow this study report in Module 5 of the original marketing application for prasugrel. These synopses include the ICD and any addendum specific CRFs. (Reproduced from Sponsor, pages 2658-2659)			

9.1.2 Study Design

This was a Phase 3, multicenter, randomized, parallel-group, double-blind, double-dummy, active-controlled study.

9.1.3 Study Population

The study population included subjects with acute coronary syndrome (ACS; 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).

9.1.4 Objectives

Primary Objective:

To determine if CS-747 (prasugrel) plus aspirin was superior to clopidogrel plus aspirin in the treatment of subjects with acute coronary syndrome (ACS) who were to undergo percutaneous coronary intervention (PCI), as measured by a reduction in the composite endpoint of cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal stroke at a median follow-up of at least 12 months.

Key Secondary Objectives:

Efficacy Objectives:

To compare CS-747 with clopidogrel with respect to:

- the risk of CV death, nonfatal MI, or nonfatal stroke at 90 days
- the risk of CV death, nonfatal MI, or nonfatal stroke at 30 days
- the risk of CV death, nonfatal MI, or urgent target vessel revascularization (UTVR) at 90 days
- the risk of CV death, nonfatal MI, or UTVR at 30 days
- the risk of all-cause death, nonfatal MI, or nonfatal stroke at a median of at least 12 months
- the risk of CV death, nonfatal MI, nonfatal stroke, or rehospitalization for cardiac ischemic events at a median of at least 12 months

In the Clinical Study Report dated November 28, 2007, the sponsor added the following objective:

- the risk of definite or probable stent thrombosis per Academic Research Consortium (ARC) definition at study end

ARC Definitions of Definite, Probable, and Possible Stent Thrombosis⁹

• Definite Stent Thrombosis

Definite stent thrombosis is considered to have occurred by *either* angiographic or pathologic confirmation:

- a. Angiographic confirmation of stent thrombosis†
 - i. The presence of a thrombus‡ that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:
 1. Acute onset of ischemic symptoms at rest
 2. New ischemic ECG changes that suggest acute ischemia
 3. Typical rise and fall in cardiac biomarkers
 4. Nonocclusive thrombus
 - a. Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream
 5. Occlusive thrombus
 - a. TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch)
- b. Pathological confirmation of stent thrombosis
 - i. Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy

⁹Cutlip 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.

- **Probable Stent Thrombosis**

Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

- a. Any unexplained death within the first 30 days§
- b. Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

- **Possible Stent Thrombosis**

Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.

†The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion)

‡Intracoronary thrombus

§For studies with ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis

Safety Objectives:

- to evaluate the incidence of non-coronary artery bypass graft (CABG) surgery-related TIMI Study Group (TIMI) major bleeding in subjects receiving prasugrel or clopidogrel
- to evaluate the incidence of life-threatening bleeding (a subset of non-CABG-related TIMI major bleeding) in subjects receiving prasugrel or clopidogrel
- to evaluate the incidence of non-CABG-related TIMI minor bleeding in subjects receiving prasugrel or clopidogrel
- To evaluate the overall safety and tolerability of CS-747 administration based on clinical findings, laboratory values, and the occurrence of treatment-emergent adverse events (TEAEs)

Health Economics Objectives:

- Total 1-year medical care costs for ACS subjects undergoing PCI treated with CS-747 or clopidogrel
- Initial hospitalization costs between the two treatment groups
- Total 30-day costs between the two treatment groups

Other Objectives:

- To repeat all analyses, including the triple composite endpoint of CV death, nonfatal MI, or nonfatal stroke at a median follow-up of at least 12 months, in the STEMI population
- To evaluate the time course of the relative benefit of therapy as measured by hazard ratios
- To evaluate the incidence of TIMI major bleeding reported in subjects who undergo coronary artery bypass graft surgery

TIMI major, minor, and minimal bleeding are described in Table 37.

Table 37. TIMI Hemorrhage Criteria^a

	ICH	Clinically Overt (including imaging)	Hgb Drop ^{b,c} (g/dL)
Major Bleeding	X	X	≥ 5
Minor Bleeding	-	X	3 to < 5
Minimal Bleeding	-	X	<3
Hgb=hemoglobin; ICH=intracranial hemorrhage; TIMI=The TIMI Study Group. ^a Accounting for the effect of transfusions on change in hemoglobin (Hgb) as described in footnote b. ^b One unit packed red blood cells = 1 g Hgb = 3% hematocrit (Hct). ^c Hgb drop must be associated with clinically overt bleeding. Reproduced from Sponsor, Protocol dated August 10, 2004, page 63.			

9.1.5 Inclusion/Exclusion Criteria

Inclusion Criteria (Must be present) (Reproduced from Sponsor)

1. Presented with acute coronary syndrome (ACS) based on the disease diagnostic criteria and were to undergo percutaneous coronary intervention (PCI)
2. Were of a legal age (and at least 18 years of age) and competent mental condition to provide written informed consent before entering the study. Informed consent must have been signed by the study participant or authorized representative, according to local rules and regulations
3. For women of child-bearing potential only (that is, women who were not surgically or chemically sterilized and who were between menarche and 1 year postmenopause), test negative for pregnancy between ACS presentation and enrollment (based on a urine or serum pregnancy test) and agreed to use a reliable method of birth control during the study

Disease Diagnostic Criteria

For TAAL, ACS included 1) moderate to high risk unstable angina and non-ST-segment elevation myocardial infarction (UA/NSTEMI) and 2) ST-segment elevation myocardial infarction [STEMI] as follows:

- Moderate to high risk unstable angina (UA) was defined as a history of chest discomfort or ischemic symptoms of ≥ 10 minutes duration at rest ≤ 72 hours prior to randomization, with persistent or transient ST-segment deviation ≥ 1 mm in one or more electrocardiographic leads without elevation of creatine kinase-myocardial bands (CK-MB) or troponin T or I but with a TIMI Study Group (TIMI) risk score ≥ 3.
- Moderate to high-risk non-ST-segment elevation myocardial infarction (NSTEMI) was defined as a history of chest discomfort or ischemic symptoms of ≥ 10 minutes duration at rest ≤ 72 hours prior to randomization with no evidence of persistent ST-segment elevation. Subjects must also have CK-MB or troponin T or I greater than the upper limit of normal (ULN) and a TIMI risk score ≥ 3. If CK-MB or troponin are not available, total CK greater than 2 times ULN is acceptable.
- ST-segment elevation myocardial infarction (STEMI) was defined as a history of chest discomfort or ischemic symptoms of > 20 minutes duration at rest ≤ 14 days prior to randomization with one of the following present on at least one ECG prior to randomization:
 - a. ST-segment elevation ≥ 1 mm in two or more contiguous ECG leads
 - b. New or presumably new left bundle branch block (LBBB)
 - c. ST-segment depression ≥ 1 mm in two anterior precordial leads (V1 through V4) with clinical history and evidence suggestive of true posterior infarction
- Subjects receiving fibrin-specific fibrinolytic therapy (for example, alteplase, reteplase, tenecteplase) could be randomized ≥ 24 hours after completion of infusion of the fibrinolytic for the index STEMI event. Subjects receiving nonfibrin-specific fibrinolytic therapy (for example, streptokinase) could be randomized ≥ 48 hours after completion of infusion of the fibrinolytic for the index STEMI.

TIMI Risk score for unstable angina and non-ST-segment elevation myocardial infarction is described in Table 38.

Table 38. TIMI Risk Score for UA/NSTEMI

				Risk of Cardiac Events (%) by 14 Days in TIMI 11B*	
Parameters	Points		Risk Score	Death or MI	Death, MI, or Urgent Revascularization
Historical					
Age ≥ 65	1		0/1	3	5
≥ 3 CAD risk factors (Family History, HTN, HLP, DM, active smoker)	1		2	3	8
Known CAD (stenosis $\geq 50\%$)	1		3	5	13
ASA use in past 7 days	1		4	7	20
Presentation			5	12	26
Recent (≤ 24 h) severe angina	1		6/7	19	41
Increased cardiac markers	1				
ST deviation ≥ 0.5 mm	1				
RISK SCORE = Total Points	(0-7)				
*Entry criteria: unstable angina or NSTEMI defined as ischemic pain at rest within past 24 hours, with evidence of coronary artery disease (ST segment deviation or +marker)					
Reproduced from Sponsor, Protocol dated August 10, 2004, page 70.					

Exclusion Criteria (Cannot be present) (Reproduced from Sponsor)

Cardiovascular Exclusion Criteria

1. Have cardiogenic shock at the time of randomization (systolic blood pressure < 90 mm Hg associated with clinical evidence of end-organ hypoperfusion, or subjects requiring vasopressors to maintain systolic blood pressure over 90 mm Hg and associated with clinical evidence of end-organ hypoperfusion)
2. Have refractory ventricular arrhythmias
3. Have New York Heart Association (NYHA) Class IV congestive heart failure

NYHA classifications for congestive heart failure are displayed in Table 39.

Table 39. New York Heart Association Congestive Heart Failure (NYHA CHF) Classifications

Class I	Patients with no limitation of activities; they suffer no symptoms from ordinary activities
Class II	Patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion
Class III	Patients with marked limitation of activity; they are comfortable only at rest
Class IV	Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest
New York Heart Association, 1994.	

Bleeding Risk Exclusion Criteria

4. Have received fibrin-specific fibrinolytic therapy < 24 hours prior to randomization
5. Have received nonfibrin-specific fibrinolytic therapy < 48 hours prior to randomization
6. Have active internal bleeding or history of bleeding diathesis
7. Have clinical findings, in the judgment of the investigator, associated with an increased risk of bleeding.
8. Have any of the following
 - a. Prior history of hemorrhagic stroke
 - b. Intracranial neoplasm, arteriovenous malformation, or aneurysm
 - c. Ischemic stroke \leq 3 months prior to screening
9. Have an International Normalized Ratio (INR) known to be > 1.5 at the time of evaluation
10. Have a platelet count of $\leq 100,000/\text{mm}^3$ at the time of screening
11. Have anemia (hemoglobin [Hgb] < 10 gm/dl) at the time of screening

Prior/Concomitant Therapy Exclusion Criteria

12. Have received one or more doses of a thienopyridine (ticlopidine or clopidogrel) ≤ 5 days prior to PCI
13. Are receiving or will receive oral anticoagulation or other antiplatelet therapy that cannot be safely discontinued for the duration of the study
14. Are receiving daily treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX2) inhibitors that cannot be discontinued or are anticipated to require > 2 weeks of daily treatment with NSAID or COX2 inhibitors during the study

General Exclusion Criteria

15. 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
16. Are employed by Eli Lilly & Company, Ube Industries Limited, Sankyo Company Limited, The TIMI Study Group, or the contract research organization (CRO) (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 studies 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
17. Have received treatment within the last 30 days with a drug that has not received regulatory approval for any indication at the time of study entry or are presently enrolled in another drug or device study
18. Have previously completed or withdrawn from this study or any other study investigating CS-747
19. Are women who are known to be pregnant, who have given birth within the past 90 days, or who are breastfeeding
20. Have a concomitant medical illness (for example, terminal malignancy) that in the opinion of the investigator is associated with reduced survival over the expected treatment period (maximum of 15 months)
21. Have known severe hepatic dysfunction (that is, with cirrhosis or portal hypertension)
22. Have a condition associated with poor treatment compliance, including alcoholism, mental illness, or drug dependence
23. Have a history of intolerance or allergy to aspirin or approved thienopyridines (ticlopidine or clopidogrel)
24. May be unable to cooperate with protocol requirements and follow-up procedures

9.1.6 Study Plan

The TAAL study design is displayed in Figure 23.

Following screening and informed consent, subjects were randomized 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

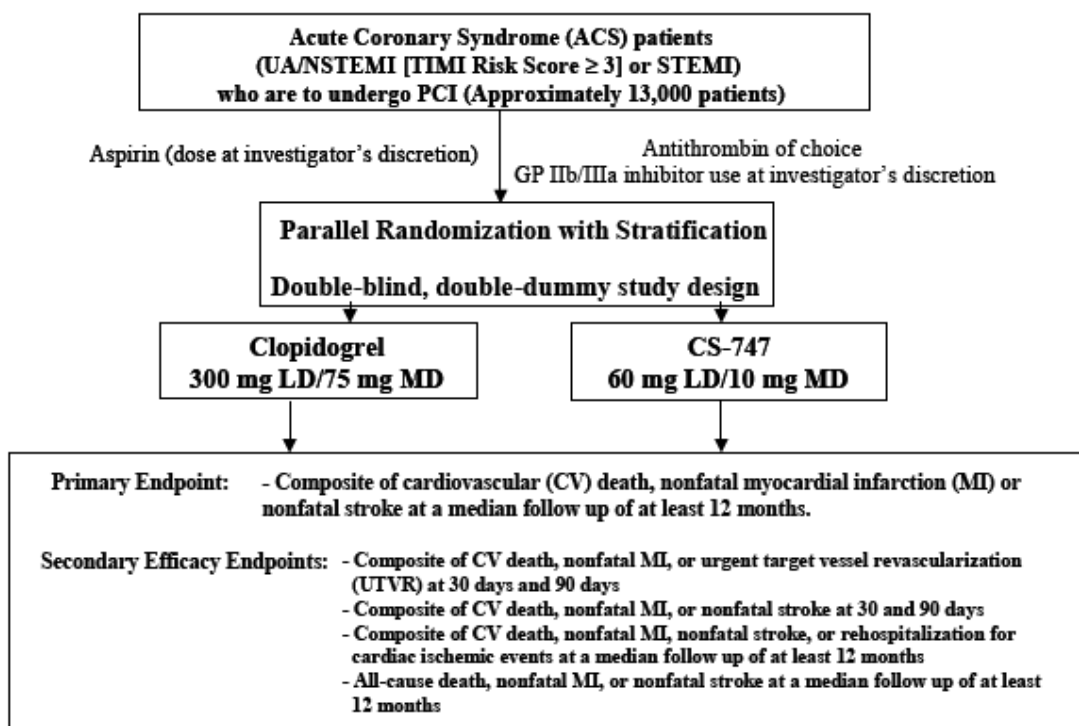
Subjects were randomized via an interactive voice response system (IVRS) in a 1:1 fashion to receive either CS-747 (prasugrel: 60 mg oral loading dose followed by 10 mg daily oral maintenance dose) or clopidogrel (300 mg oral loading dose followed by 75 mg daily oral maintenance dose) using a double-dummy design. Subjects received active formulation of one drug and placebo formulation of the other drug for the loading and maintenance doses, as shown in Figure 24.

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).

The study was to continue until all of the following conditions were met:

1. Median treatment period of at least 12 months
2. Completion of at least 6 months of follow-up
3. Achievement of the primary endpoint in at least 875 UA/NSTEMI subjects

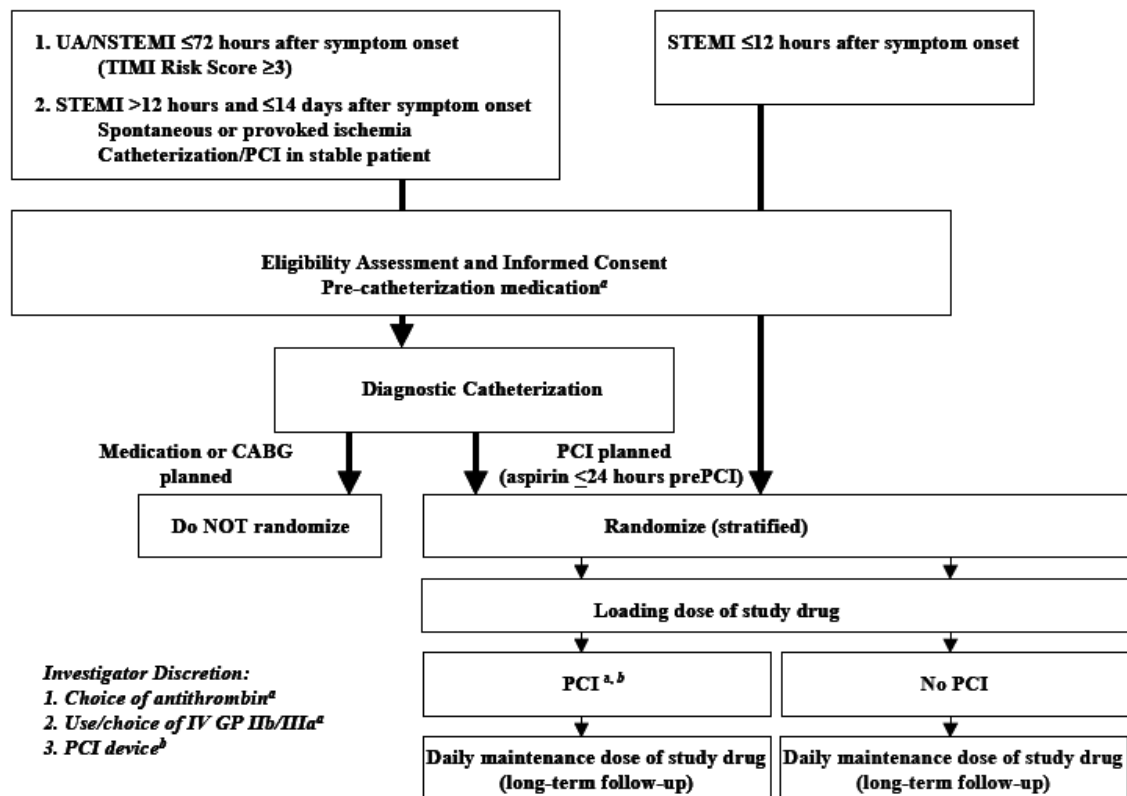
Figure 23. Study H7T-MC-TAAL Study Design



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, Protocol dated August 10, 2004, page 19)

Figure 24. Study H7T-MC-TAAL Treatment Plan



Abbreviations: CABG = coronary artery bypass graft surgery;
GP = glycoprotein; IV = intravenous; 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.

(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 without GP IIb/IIIa inhibition, the recommended maximal ACT was 350 seconds.

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.

If subjects were randomized, but PCI was not performed, they were to continue on study drug, remain in the study, and be evaluated for clinical and adverse events.

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 investigator's discretion. Although daily doses of ASA ranging from 75 to 162 mg were recommended after discharge, the aspirin dose was left to the investigator's discretion.

Within the first 24 hours after PCI, three blood samples were to be obtained for CK-MB. The first sample was to be obtained 6 hours (\pm 2 hours) after PCI. The second and third samples were to be obtained 6 hours (6-8 hours recommended) after the first and second samples, respectively.

In STEMI patients who remained hospitalized longer than 24 hours, three additional samples for CK-MB were to be obtained at least 6 hours apart (6-8 hours recommended).

Post PCI CK-MB samples were to be sent to a central laboratory.

If a subject needed to undergo emergency or urgent CABG or other surgical procedure within 5 days of the loading dose, the study drug was to be temporarily discontinued and restarted when thought to be safe.

Subjects were to be followed for a maximum of 15 months. If necessary, the study drug could be temporarily discontinued. For discontinuations > 14 days, consultation with the CRO Helpline was required.

Subjects were to return on Days 30, 90, and 180 for clinic visits and if enrolled in the study over 180 days were also to return on Days 270, 360, and 450. If subjects experienced cardiac symptoms following discharge, CK-MBs were to be checked locally and treatment was left to the investigator's discretion.

Permitted medications included but were not limited to histamine 2 receptor (H2) blockers and proton pump inhibitors (PPIs); oral, sublingual, or intravenous nitrates; calcium channel blockers; beta blockers; Angiotensin converting enzyme inhibitors (ACEIs); Angiotensin receptor blockers (ARBs); 3-hydroxy-3-methylglutaryl coenzyme A (HMG Co-A) reductase inhibitors (statins); anti-arrhythmic drugs; vasodilators; and intravenous vasopressors agents.

9.1.7 Schedule of Evaluations and Procedures

The schedule of evaluations and procedures is displayed in Table 40.

Table 40. Study Schedule for Study H7T-MC-TAAL

Procedure	PrePCI	PCI	24 ±4 hrs post-PCI or at hospital discharge, whichever comes first	Day 30 ^b	Day 90 ^b	Day 180 ^b	Day 270 ^{b,c}	Day 360 ^{b,c}	Day 450 or last visit ^{b,c}
Screening	X								
Informed consent (before study procedures)	X								
Randomization through IVRS ^a	X ^a								
Medical history/preexisting conditions	X								
Concomitant medications recorded (including aspirin) ^d	X		X	X	X	X	X	X	X
Physical exam	X		X	X	X	X	X	X	X
Vital signs	X		X	X	X	X	X	X	X
ECG ⁿ	X		X	X	X	X	X	X	X
Local laboratory measures									
Urine or serum pregnancy	X ^f								
Hgb/Hct/plt count	X		X						
Central laboratory measures^{e, g}									
CBC w/ diff and plt count	X			X	X	X			X
Clinical chemistry	X		X (fasting when possible)	X	X	X			X
CK-MB	X ⁱ	X ⁱ	X ^j	as needed (local laboratory) ^h					
Adverse events recorded	X	X	X	X	X	X	X	X	X
Study drug dispensed	X(LD) ^l		X(MD) ^m	X(MD)	X(MD)	X(MD)	X(MD)	X(MD)	
Study drug collected				X	X	X	X	X	X

Abbreviations: CBC w/ diff=complete blood count with differential; CK-MB=creatine kinase-myocardial bands; CRF=case report form;

ECG=electrocardiogram; Hgb=hemoglobin; Hct=hematocrit; hrs=hours; IVRS=interactive voice response system; LD=loading dose; MD = maintenance dose; PCI=percutaneous coronary intervention; plt count=platelet count.

- ^a Occurs prePCI after informed consent is signed. UA/NSTEMI, STEMI >12 hours from symptom onset subjects are to be randomized after diagnostic cath. STEMI ≤12 hours from symptom onset subjects may be randomized before diagnostic cath.

- b Follow-up may be performed within Day 28 to Day 35 of the Day 30 day timepoint, and within ± 2 week of the other timepoints. Window does not apply to dosing.
- c Patients will be observed for a minimum follow-up period of 6 months. Maximum follow-up is anticipated to be 15 months. The end of study activities should be completed at the subject's last visit, even if this occurs prior to Day 450.
- d Patients will supply their own daily aspirin therapy with the dose determined at the investigator's discretion. The recommended dose after discharge from the index hospitalization is 75 mg to 162 mg.
- e See Attachment TAAL.3 for details on all central laboratory measures.
- f A urine or serum pregnancy test will be performed locally for women of child bearing potential, and a negative result must be obtained prior to randomization.
- g Samples will be sent to a central laboratory for analysis unless otherwise stated.
- h CK-MB (and/or troponin) obtained for cardiac ischemic symptoms after discharge from the index hospitalization will be performed locally.
- i If informed consent and PCI are more than 1 hour apart, two samples are recommended, one at the time of enrollment and one during the PCI procedure, prior to balloon inflation.
- j In all patients, it is required that three blood samples be drawn for CK-MB within the first 24 hours after PCI. The first sample should be 6 hours (± 2 hours) after PCI. The second sample should be drawn at least 6 hours later (6 to 8 hours recommended), and the third sample should be drawn at least 6 hours after the second sample (6 to 8 hours recommended). In patients with STEMI who remain hospitalized longer than 24 hours, three additional blood samples should be drawn for CK-MB at least 6 hours apart (6 to 8 hours recommended).
- l The loading dose is to occur prior to the completion of the PCI procedure.
- m The first maintenance dose should be administered 20 to 28 hours after administration of the loading dose.
- n Data acceptable if obtained after the onset of qualifying symptoms and prior to randomization.

Abbreviations: CBC w/ diff=complete blood count with differential; CK-MB=creatine kinase-myocardial bands; CRF=case report form; ECG=electrocardiogram; Hgb=hemoglobin; Hct=hematocrit; hrs=hours; IVRS=interactive voice response system; LD=loading dose; MD = maintenance dose; PCI=percutaneous coronary intervention; plt count=platelet count.

- a Occurs prePCI after informed consent is signed.

(Reproduced from Sponsor, Study Schedule for Study H7T-MC-TAAL, Protocol dated January 10, 2006, pages 2720-2721)

Please note that superscript ^m in the initial protocol stated "the once-daily maintenance dose [was] to start after the PCI procedure."

9.1.8 Endpoints

9.1.8.1 Primary Efficacy Endpoint

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.

Definitions Per Sponsor:

- **Cardiovascular Death (CV Death):** death due to documented cardiovascular cause. Additionally, death not clearly attributable to noncardiovascular causes was considered to be CV death.
- **Nonfatal Myocardial Infarction (MI):** The definition of MI was adapted from the standard American College of Cardiology (ACC) definition and was dependent on the clinical timing of the event in relation to presenting syndrome and cardiovascular procedures.

A peri-procedural event must have been distinct from the index event.¹⁰ If an ischemic biomarker was elevated at the onset of the suspected event, there must have been demonstration of a falling biomarker level prior to the onset of the suspected event, and that the subsequent peak was greater than 1.5 times the value prior to the onset of the event (these criteria did not need to be met if the ischemic biomarker was not elevated at the time of the suspected event). The biomarker levels required for the diagnosis of MI were dependent on relationship to cardiac procedures.

- If the suspected event was within 48 hours of a percutaneous coronary intervention (PCI), the creatine kinase-myocardial bands (CK-MB) value (on at least two samples) must have been > 3x the upper limit of normal (ULN); no symptoms were required. **The Amendment dated January 10, 2006 extended the definition of peri-procedural MI to include a CK-MB > 5x ULN on one sample if it was the last available sample and was drawn ≥ 12 hours after PCI.**
- If the suspected event was within 48 hours of a CABG, the CK-MB value (on a single measure) must have been >10x the upper limit of normal; no symptoms were required.
- If the suspected event was not within 48 hours of a PCI or CABG, the diagnostic criteria were met if the subject had CK-MB or cardiac troponin > ULN and the presence of either chest pain ≥ 20 minutes in duration or ST-segment deviation ≥ 1mm on the electrocardiogram (ECG).

In any clinical circumstance, the appearance of new Q-waves on the electrocardiogram distinct from a prior event (including the presenting event) or pathologic evidence (such as autopsy) showing a new myocardial infarction felt to be distinct from a prior event would be considered appropriate evidence for MI, as would ST-segment elevation (meeting enrollment criteria) lasting for at least 20 minutes and accompanied by ischemic chest pain or hemodynamic decompensation.

¹⁰A clarification of peri-procedural and index events was added in Amendment 1 dated January 10, 2006.

There were five major sets of criteria used for the diagnosis of nonfatal MI:

1. ST elevation or re-elevation of ST segment, AND one of the following: ischemic chest pain ≥ 20 minutes in duration or hemodynamic decompensation.
2. Spontaneous CK-MB or troponin $> \text{ULN}$, AND one of the following:
 - Ischemic chest pain (or anginal equivalent) ≥ 20 minutes in duration or
 - ST segment deviation ≥ 1 mm in one or more leads
3. CK-MB $> 3\text{x ULN}$ on at least two samples following PCI
4. CK-MB $> 10\text{x ULN}$ on one sample following CABG
5. New Q waves ≥ 0.04 seconds, or pathology distinct from prior MI

ECGs or other supporting clinical tests or evaluations such as imaging used to identify clinical endpoints would be adjudicated with documents submitted to the Clinical Endpoints Committee (CEC) for evaluation.

- **Nonfatal Stroke:** the rapid onset of new-persistent neurologic deficit lasting more than 24 hours. In the case of clinical diagnosis of nonfatal stroke, computed tomography (CT) or magnetic resonance imaging (MRI) scan imaging was strongly recommended. CT or MRI scans would be considered by the CEC to support the clinical impression. Supplemental information from head CT or MRI scans would determine if there was a demonstrable lesion compatible with an acute nonfatal stroke. Furthermore, nonfatal stroke would be classified as either ischemic or hemorrhagic based on imaging data, if available, or uncertain cause if imaging data was not available.

Prespecified subgroup analyses for the primary endpoint included but were not limited to

- Clinical presentation
- Demographics and Baseline Characteristics
- Medical History
- Index PCI Procedure—culprit lesion and all intervened lesions
- Anti-thrombotics used in support of the index PCI procedure
- Selected concomitant medications
- Aspirin use
- Timing of the Loading Dose Relative to the index PCI

9.1.8.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints included

1. CV death, nonfatal MI, or nonfatal stroke at 90 days post randomization (Group 1)
2. CV death, nonfatal MI, or nonfatal stroke at 30 days post randomization (Group 1)
3. CV death, nonfatal MI, or UTVR at 90 days post randomization
4. CV death, nonfatal MI, or UTVR at 30 days post randomization
5. All-cause death, nonfatal MI, or nonfatal stroke at study end (after a median follow-up of at least 1 year post randomization)
6. CV death, nonfatal MI, nonfatal stroke, or rehospitalization for CIE at study end

In the Statistical Analysis Plan Amended (b) dated September 18, 2007 and in the Clinical Study Report dated November 28, 2007, the sponsor added the following objective:

7. the risk of definite or probable stent thrombosis per Academic Research Consortium (ARC) definition at study end

Definitions:

1. **Rehospitalization for cardiac ischemic events (CIE):** Rehospitalization for symptoms of myocardial ischemia at rest with at least one of the following:
 - New ST-segment deviation ≥ 1 mm or
 - Performance of a coronary revascularization procedure (PCI or CABG) during the same hospital stay. Revascularization could include the vessel(s) dilated at the initial procedure and/or additional vessels.

Planned rehospitalization for performance of staged PCI identified at the time of index hospitalization was not included under the definition of Rehospitalization for cardiac ischemic events.
2. **Urgent target vessel revascularization (UTVR):** PCI or CABG for recurrent ischemia that, in the investigator's opinion, could not be delayed for more than 24 hours and was defined by the investigator as a nonelective procedure. Revascularization, either with CABG or PCI, must have included the vessel(s) dilated at the initial procedure.
3. **All-cause death:** death due to cardiac or noncardiac cause.
4. **Definition of Definite, Probable, and Possible Stent Thrombosis (Clinical Study Report, page 110)**

Definite or confirmed angiographic stent thrombosis:

- TIMI flow grade 0 with occlusion originating in the stent or in the segment 5 mm proximal or distal to the stented region in the presence of a thrombus.*
or
- TIMI flow grade 1, 2, or 3 and the presence of thrombus* originating in the stent or in the segment 5 mm proximal or distal to the stented region
and
- At least one of the following criteria (within 48 hours):
 - New onset of ischemic symptoms at rest (typical pain > 20 min)
 - New ischemic ECG changes suggestive of acute ischemia
 - Typical rise and fall in cardiac biomarkers

*The incidental angiographic documentation of silent stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis.

Please note that the sponsor's definition of definite stent thrombosis does not include the ARC pathological confirmation of stent thrombosis which is defined as the evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

Probable stent thrombosis

- Any unexplained death within the first 30 days, irrespective of the time after the index procedure; any myocardial infarction, which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.

Possible stent thrombosis

- Any unexplained death from 30 days following intracoronary stenting until end of study follow-up

9.1.8.3 Other Efficacy Endpoints

Other efficacy endpoints included but were not limited to

- Any target vessel revascularization (TVR)
- Any coronary vessel revascularization
- Transient ischemic attack (TIA)

9.1.8.4 Economic Endpoints

- Total 1-year medical care costs
- Initial hospitalization costs
- Total 30-day costs
- Incremental cost-effectiveness in terms of cost per death, nonfatal MI, or nonfatal stroke averted, cost per life year gained, and cost per quality adjusted life year

9.1.8.5 Safety Endpoints

- **Non-CABG related TIMI major bleeding:** any intracranial hemorrhage (ICH) OR any clinically overt bleeding (including bleeding evident on imaging studies) associated with a fall in hemoglobin (Hgb) of ≥ 5 gm/dL from baseline (accounting for the effect of transfusions on change in Hgb, defined as one unit packed red blood cells = 1 gm/dL Hgb = 3% hematocrit [Hct]).
- **Non-CABG-related TIMI life-threatening bleeding:** any non-CABG-related TIMI major bleeding that is fatal, leads to hypotension that requires treatment with intravenous inotropic agents, **OR** requires surgical intervention for ongoing bleeding, **OR** necessitates the transfusion of 4 or more units of blood (whole blood or packed red blood cells [RBC]) over a 48-hour period, **OR** any symptomatic ICH.
- **Non-CABG-related fatal bleeding:** death due to Non-CABG-related bleeding.
- **Non-CABG-related TIMI minor bleeding:** any clinically overt bleeding (including bleeding evident on imaging studies) associated with a fall in Hgb of ≥ 3 gm/dL but < 5 gm/dL from baseline (accounting for the effect of transfusions on change in Hgb, defined as one unit packed red blood cells = 1 gm/dL Hgb = 3% Hct).
- **CABG-related bleeding:** bleeding related to CABG.

9.1.9 Clinical Events Committee (CEC)

The CEC adjudicated deaths as CV or non-CV related, and deaths of unknown cause were considered CV related. Cardiac ischemic events (CIEs) were adjudicated as MIs separate from the index event, rehospitalization for CIE, or other. Cerebrovascular events were adjudicated as stroke or transient ischemic attack. Additionally, the CEC adjudicated bleeding endpoints according to TIMI classification: Major, Life-Threatening, Minor, Minimal, or no bleed and adjudicated whether or not bleeding was CABG-related. The CEC clinically adjudicated stent thrombosis.

9.1.10 Statistical Considerations

9.1.10.1 Power and Sample Size

For UA/NSTEMI subjects, the study was to provide 90% power to establish superiority relative to the triple endpoint based on the following assumptions:

- 10.5% of subjects in the clopidogrel group reaching the triple endpoint within 1 year of the PCI procedure based on event rates of the Unstable angina to prevent Recurrent Events study (CURE) for subset of subjects with a TIMI Study Group (TIMI) risk score ≥ 3 .
- Average hazard ratio of 0.80 for CS-747 versus clopidogrel relative to the primary endpoint, and
- The time-to-first event analysis based on a two-sided log-rank test used a two-sided significance level (alpha) of 0.05 to assess superiority relative to the triple endpoint.

Treatment by subgroup interaction p-values were considered statistically significant at the 0.10 level.

Except for stent thrombosis, for each of the prespecified secondary endpoints in UA/NSTEMI subjects, the proposed sample size was to provide $\geq 80\%$ power at a two-sided 0.05 significance level to establish superiority of prasugrel under the assumption of at least a 20% reduction in hazard in UA/NSTEMI subjects and an event rate of at least 7.75% in the clopidogrel group.

The proposed sample size was 13,000 subjects, assuming that $\leq 5\%$ of the subjects would not be evaluable for the primary endpoint and that STEMI subjects would comprise 20 to 30% of the total enrollment (with a cap of 3500 subjects).

The study was to continue until 875 unstable angina and non-ST-segment elevation myocardial infarction (UA/NSTEMI) subjects reached one of the events in the triple composite endpoint (CV death, nonfatal MI, or nonfatal stroke) and a median duration of therapy of 12 months and a minimum follow-up of 6 months.

The blinded event rate was to be evaluated when 650 UA/NSTEMI subjects had reached the primary endpoint. However, the Study Operations Committee conducted a blinded review of the aggregated event rate when 589 subjects with UA/NSTEMI reached the primary endpoint and determined there was a slightly lower than anticipated aggregated event rate. Therefore, the size of the UA/NSTEMI population was increased to 10,100 subjects to meet the target of 875 events.

9.1.10.2 Plan for Evaluating the Primary Endpoint

The Statistical Analysis Plan was finalized on September 18, 2007.

The primary outcome was the composite of cardiovascular (CV) death, nonfatal MI, or nonfatal stroke. Due to a potentially varying hazard ratio, the primary analysis was based on the time from randomization to the onset of the first primary outcome using the Gehan-Wilcoxon test. Primary analyses were carried out in a hierarchical manner. At the first step, time-to-primary outcome was carried out at a one-sided significance level of 0.025 (equivalent to a two-sided test at 0.05) in the UA/NSTEMI subject population. If superiority of prasugrel treatment in the UA/NSTEMI subject population was successfully established, then time-to-first primary outcome was carried out at a one-sided significance level of 0.025 in the All ACS subject population. In this analysis, ACS classification (UA/NSTEMI or STEMI) was used as a stratification factor.

Corresponding two-sided 95% confidence intervals for the hazard ratios under the proportional hazards assumption were provided.

9.1.10.3 Plan for Evaluating Secondary Endpoints

After establishing the superiority of prasugrel over clopidogrel relative to the primary endpoint, analyses for secondary efficacy endpoints were performed using the log-rank test.

The secondary endpoints were comprised of two groups: the first group (Group 1) were those endpoints that did not need to be adjusted for multiplicity, and the second group (Group 2) were those that needed to be predefined in a hierarchical manner.

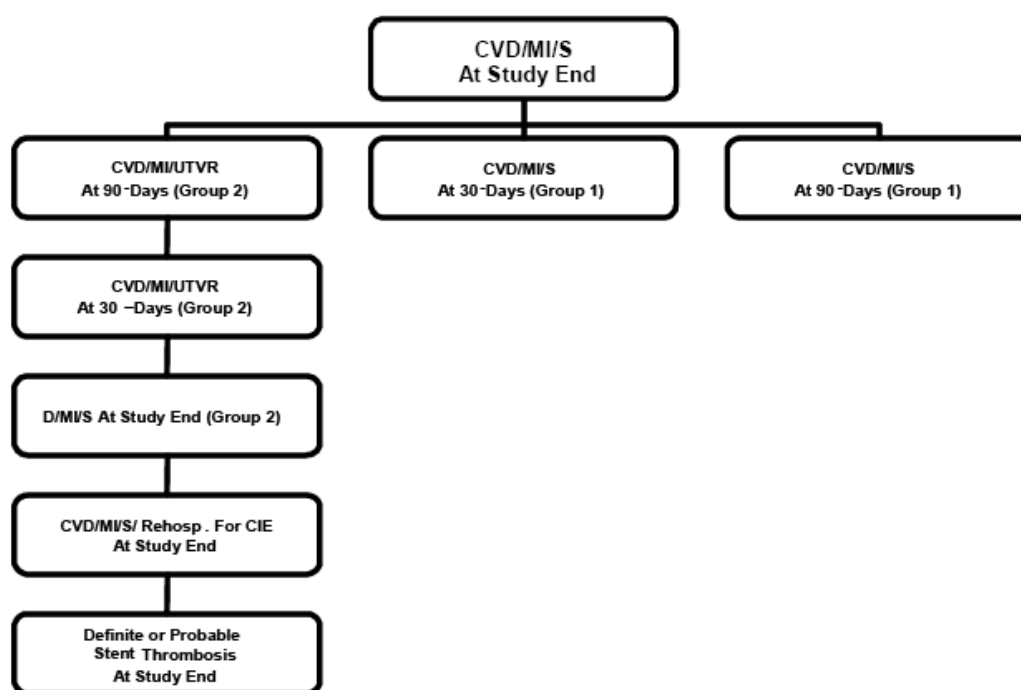
Group I was evaluated without adjusting for multiplicity, each at a one-sided 0.025 alpha level (equivalent to a two-sided 0.05 level):

- CV death, nonfatal MI, or nonfatal stroke at 90 days post randomization
- CV death, nonfatal MI, or nonfatal stroke at 30 days post randomization

The evaluations of subsequent endpoints relied on the superiority of prasugrel relative to the primary endpoint in the UA/NSTEMI subject population. To protect the overall type I error rate at a level of 0.05, the four remaining secondary endpoints included in Group 2 were evaluated hierarchically each at a one-sided 0.025 alpha level, as shown in Table 28.

- CV death, nonfatal MI, or UTVR at 90 days post randomization
- CV death, nonfatal MI, or UTVR at 30 days post randomization
- All-cause mortality, 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 event (CIE) at study end
- Definite or probable stent thrombosis per Academic Research Consortium definition

Figure 25. Evaluate the Superiority of Prasugrel Compared to Clopidogrel at a One-Sided Alpha Level of 0.025 in UA/NSTEMI Cohort Relative to



CIE: cardiac ischemic events; CVD: cardiovascular death; MI: myocardial infarction; Rehosp: Rehospitalization for CIE; S: stroke; UTVR: urgent target vessel revascularization

(Reproduced from Sponsor, Statistical Analysis Plan Amendment (b) dated September 18, 2007, page 9169)

9.1.10.4 Evaluation of Secondary Endpoints in the All ACS Subject Population

Each of the six secondary endpoints (Groups 1 and 2) were evaluated using the log-rank test in the All ACS subject population, each at a one-sided 0.025 significance level, provided that superiority of prasugrel was established relative to the primary endpoint in the All ACS (UA/NSTEMI/STEMI) subject population (and in the UA/NSTEMI subject population). UA/NSTEMI versus STEMI was used as the stratification factor in these analyses.

9.1.10.5 Evaluation of Endpoints in the STEMI Population

All primary and secondary study endpoints were evaluated in the STEMI population in an exploratory fashion.

9.1.10.6 Other Statistical Considerations

Since some subjects experienced particular adverse events more than once, the sponsor used a Poisson Regression model with the subject's duration of follow-up as an offset variable.

Safety endpoint analyses used the treated population consisting of subjects who received at least one dose of study drug (including the loading dose).

Three unblinded interim analyses were planned when 250, 450, and 650 UA/NSTEMI subjects reached the primary endpoint. However, the Data Monitoring Committee performed the three interim analyses when 161, 433, and 589 UA/NSTEMI subjects reached the primary endpoint, as shown in Table 41.

Table 41. Interim Analyses by the Data Monitoring Committee

Interim Analysis	Data Cut-off Date	Date of Report	Number of Subjects Enrolled as of Data Cut-off Date		Number of UA/NSTEMI subjects confirmed to have reached the primary endpoint
			UA/NSTEMI	STEMI	
1	12 April 2006	9 May 2006	5919	3527	161
2	02 August 2006	22 August 2006	7757	3539	433
3	11 October 2006	01 November 2006	8776	3532	589

Abbreviations: NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.

(Reproduced from Sponsor, Clinical Study Report, page 132)

9.1.10.7 Subgroup Analyses

There were numerous prespecified subgroup analyses for efficacy and safety. Definitions for some of the subgroups are described as follows:

- History of vascular disease was defined as meeting any of the following criteria:
 - Peripheral arterial disease (PAD)
 - Carotid/vertebral arterial disease
 - Prior > 50% stenosis of coronary artery
 - History of chronic stable angina
 - History of unstable angina (UA)
 - Prior MI
 - Prior stroke
 - Prior transient ischemic attack (TIA)
- Metabolic syndrome was defined as meeting any 3 of the following 5 criteria:
 - Waist circumference > 102 cm in men or > 88 cm in women
 - Fasting triglyceride \geq 150 mg/dL
 - High-density lipoprotein cholesterol (HDL-C) < 40 mg/dL in men, < 50 mg/dL in women
 - Blood pressure \geq 130/85 mm Hg
 - Fasting glucose \geq 110 mg/dL
- The TIMI risk score for subjects with UA/NSTEMI (Antman et al. 2000) or STEMI (within 12 hours of symptom onset; Morrow et al. 2001) was calculated as the sum of points corresponding to the risk factors at baseline

Table 42. Calculation of TIMI RISK SCORE for Subjects with UA/NSTEMI or STEMI

Characteristics	Point
UA/NSTEMI	
Age ≥ 65	1
≥ 3 of following 5 CAD risk factors	1
Family history of CAD	
Hypertension	
Hypercholesterolemia	
Diabetes Mellitus	
Current tobacco use	
Prior Coronary Angiography that shows $\geq 50\%$ Stenosis	1
ASA within 7 days prior to the onset of symptoms	1
Recent (≤ 24 hour) severe angina	1
Any pre-PCI biomarker $> \text{ULN}^a$	1
ST segment deviation $\geq 0.5\text{mm}$	1
Maximum number of points	7
STEMI ≤ 12 hours	
Age ≥ 75	3
65 – 74	2
Any of the following risk factors:	1
Diabetes Mellitus	
Hypertension	
History of angina	
Baseline SBP < 100 mm Hg	3
Baseline Heart rate > 100 bpm	2
Killip class II - IV	2
Weight < 67 kg	1
Maximum number of points	14

Abbreviations: ASA = aspirin; CAD = coronary artery disease; HDL = high-density lipoprotein; LBBB = left bundle branch block; SBP = systolic blood pressure; ULN = upper limit of normal.

^a biomarkers include: troponin and creatine kinase-myocardial bands.

Source: Antman et al. 2000; Morrow et al. 2006.

(Reproduced from Sponsor, Clinical Study Report, Table TAAL.9.4, page 130 of 27024)

- TIMI Risk Index = Heart Rate X $[(\text{age}/10)^2/\text{Systolic BP}]$

- Hepatic impairment at baseline
 - Concurrent elevations of alanine transaminases (ALT) results > 3 x ULN and total bilirubin results > 1.5 x ULN
 - Identified through a database search of pre-existing conditions
- Renal Impairment at baseline
 - Creatinine Clearance ≥ 2 mg/dL/min
 - Creatinine Clearance < 60 mL/min (Cockcroft-Gault Formula, 1976)

9.1.11 Results

9.1.11.1 Sites, Investigators, and Study Dates

The study was conducted from November 5, 2004 through July 22, 2007, with enrollment from November 5, 2004 to January 14, 2007. There were 725 study centers in 30 countries; however, 99 of these sites did not screen or enroll subjects. There were a total of 717 principal investigators, and 8 investigators had 2 study sites.

9.1.11.2 Good Practice, Monitoring, and Protocol Deviations

The study was conducted in accordance with Good Clinical Practices and the current Declaration of Helsinki. In 2005, blinded data suggested the rate of subacute stent thrombosis (SAT) in South African sites was higher than in other countries. On June 19, 2005, per Dr. Anthony Dalby, the South African Lead Investigator, study enrollment was stopped so that the clinical study material could be tested. It was subsequently determined that the higher incidence of SAT was related to the enrollment of high-risk subjects, statistical play of chance, and/or PCI technique with underdeployment of stents or use of a “crush” technique for bifurcation lesions. The randomization system for TRITON-TIMI 38 in South Africa was reactivated on July 11, 2005.

The protocol deviations that had the potential to influence efficacy or safety results are described in Table 43. These deviations occurred at similar rates between treatment groups, and were not thought to affect study outcome.

Table 43. Sponsor's Analysis: Summary of Protocol Violations Identified from the Clinical Database (TAAL)

Violation	UA/NSTEMI		STEMI		All ACS	
	Prasugrel n	Clopidogrel n	Prasugrel n	Clopidogrel n	Prasugrel n	Clopidogrel n
Inclusion/Exclusion Criteria (Fibrinolytic Therapy Outside of Specified Time Window Prior to Randomization (STEMI only)) ^a	0	0	7	15	7	15
Study Drug (Late Administration of Loading Dose) ^b	21	30	10	17	31	47
Excluded Medications (Concomitant Use of Open-Label Thienopyridine and Study Drug) ^c	213	222	74	77	287	299
Study Conduct (Randomization Based on Incorrect Strata (i.e. Subject presenting with UA/NSTEMI randomized in IVRS as STEMI or vice versa))	45	51	59	70	104	121
Study Conduct (Non-compliance for CK-MB Blood Samples) ^c	64	59	34	36	98	95
^a Refers to subjects randomized within 24 hours after receiving fibrin-specific fibrinolytic therapy or randomized within 48 hours after receiving non-fibrin-specific fibrinolytic therapy. ^b Defined as the administration of the loading dose > 1 hour after leaving the catheterization laboratory. ^c Refers to subjects without at least one evaluable creatine kinase-myocardial band (CK-MB) measurement from the central laboratory prior to the end of percutaneous coronary intervention (one hour after leaving the catheterization laboratory) or not having at least 2 evaluable CK-MB measurements from the central laboratory taken after the end of PCI. Reproduced from Sponsor, Clinical Study Report, Table TAAL.10.2, page 148 of 27024.						

Site monitors performed 100% source data verification on at least the 1st, 3rd, and 5th subject and every 5th subject thereafter. As a result, at least 3785 subjects had source data verified. The significant protocol violations identified through this process are described in Table 44. None of these protocol violations were thought to significantly influence study outcome.

Table 44. Sponsor's Analysis: Number of Protocol Violations Identified by Site Monitoring (TAAL)

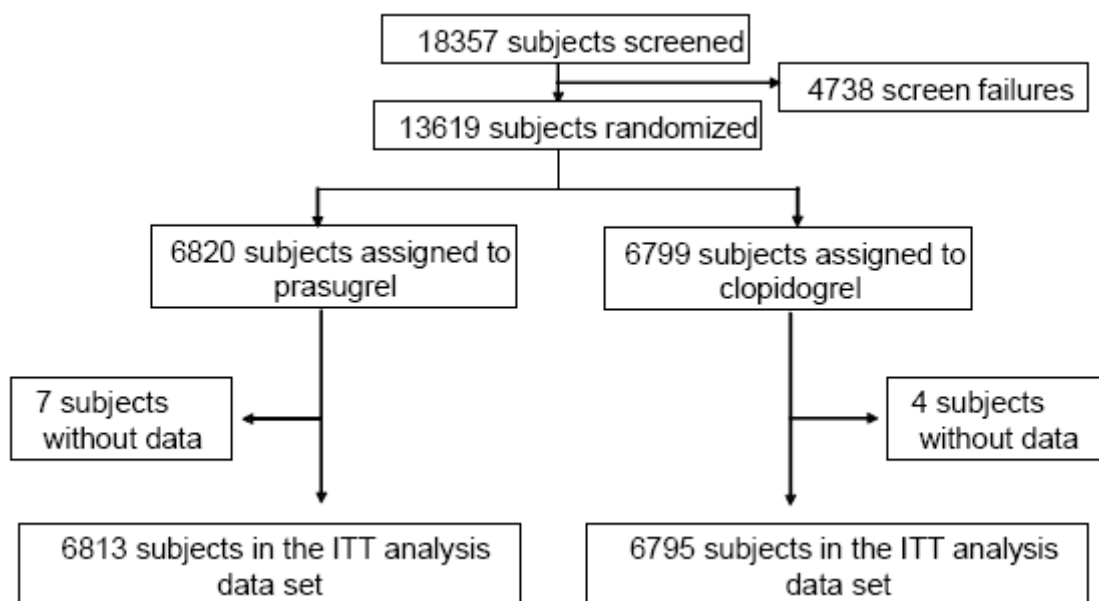
Violation	UA/NSTEMI		STEMI		All ACS	
	Prasugrel n	Clopidogrel n	Prasugrel n	Clopidogrel n	Prasugrel n	Clopidogrel n
Inclusion/Exclusion Criteria (High Risk of Bleeding, Hgb < 10 gm/dl)	1	7	0	3	1	10
Inclusion/Exclusion Criteria (Platelet Count < 100,000/mm ³)	0	2	1	1	1	3
Inclusion/Exclusion Criteria (Thienopyridine Use ≤ 5 Days Prior to Randomization)	6	16	6	5	12	21
Inclusion/Exclusion Criteria (International Normalized Ratio (INR) Known to be > 1.5 at the Time of Evaluation)	1	3	3	0	4	3
Study Drug (Administration of Wrong Kit)	11	15	8	4	19	19
Study Drug (Administration of Wrong Drug)	2	5	3	0	5	5
Study Drug (Administration of Expired Drug)	1	0	1	1	2	1
n=number of subjects with specified protocol violation. Reproduced from Sponsor, Clinical Study Report, Table TAAL.10.3, page 150 of 27024.						

9.1.11.3 Disposition of Subjects

A total of 13,619 subjects with ACS were randomized, including 6,799 subjects to clopidogrel (300 mg loading dose followed by once-daily 75 mg maintenance dose) and 6,820 subjects to prasugrel (60 mg loading dose followed by once-daily 10 mg maintenance dose). Subjects were treated until the subject's termination or 464 days from randomization, whichever was earlier. The maximum follow-up was 15 months.

Seven subjects randomly assigned to prasugrel and four subjects randomly assigned to clopidogrel were not included in the final analysis dataset due to an incomplete informed consent document. The remaining 13,608 subjects, including 6813 subjects in the prasugrel treatment group and 6795 subjects in the clopidogrel treatment group, comprised the intent-to-treat (ITT) analysis data set and were referred to as "All Randomized Subjects." Enrollment is summarized in Figure 26.

Figure 26. Enrollment of Subjects (TAAL)



(Reproduced from Sponsor, Figure TAAL. 10.1, page 138 of 27024)

Disposition of All Randomized Subjects is displayed in Table 45. In all populations, there were no significant differences between treatment groups.

Out of the 13,608 randomized patients, 13,457 subjects were treated, including 6741 in the prasugrel treatment group and 6716 subjects in the clopidogrel treatment group.

At the time of the index hospitalization, 6715 (98.56%) subjects underwent PCI in the prasugrel treatment group, including 5004 (99.21%) in the UA/NSTEMI population and 1711 (96.72%) in the STEMI population. In the clopidogrel treatment group, 6698 (98.57%) underwent PCI, including 4984 (99.09%) in the UA/NSTEMI population and 1714 (97.11%) in the STEMI population.

During the index hospitalization, 25 (0.37%) subjects in the prasugrel treatment group underwent CABG, including 16 (0.32%) in the UA/NSTEMI population and 9 (0.51%) in the STEMI population. In the clopidogrel treatment group, 23 (0.34%) subjects underwent CABG, including 12 (0.24%) in the UA/NSTEMI population and 11 (0.62%) in the STEMI population.

A total of 73 (1.07%) subjects in the prasugrel treatment group and 74 (1.09%) subjects in the clopidogrel treatment group were medically managed during the index hospitalization. In the UA/NSTEMI population, 24 (0.48%) and 34 (0.68%) subjects in the prasugrel and clopidogrel treatment groups, respectively, did not undergo revascularization. In the STEMI population, 49 (2.77%) and 40 (2.27%) in the prasugrel and clopidogrel treatment groups did not undergo revascularization.

From index hospitalization to study end, 213 subjects in the prasugrel treatment group underwent CABG, including 180 elective and 33 urgent surgeries. In the clopidogrel treatment group, 224 subjects underwent CABG, including 186 elective and 38 urgent surgeries.

Table 45. Sponsor's Analysis: Subject Disposition (All Randomized Subjects) (TAAL)

Subject Population	Disposition	Prasugrel n (%) ^a	Clopidogrel n (%) ^a	Total n (%) ^a	OR (95% CI) ^b	p-value ^b
UA/NSTEMI	Randomized	5044	5030	10074		
	Protocol Completed	4766 (94.49)	4760 (94.63)	9526 (94.56)	0.972 (0.819, 1.155)	0.750
	Protocol Completed Alive	4635 (91.89)	4639 (92.23)	9274 (92.06)	0.955 (0.827, 1.104)	0.534
	Died	131 (2.60)	121 (2.41)	252 (2.50)	1.082 (0.842, 1.389)	0.538
	Not Completed	278 (5.51)	270 (5.37)	548 (5.44)	1.028 (0.866, 1.222)	0.750
	Withdrawal of Consent	228 (4.52)	217 (4.31)	445 (4.42)	1.050 (0.868, 1.270)	0.615
	Less than Minimum Expected Follow-Up	7 (0.14)	6 (0.12)	13 (0.13)	1.164 (0.391, 3.465)	0.785
	Alive but Unable to Attend Study Termination Visit	37 (0.73)	35 (0.70)	72 (0.71)	1.055 (0.663, 1.677)	0.822
	Lost to Follow-Up	6 (0.12)	9 (0.18)	15 (0.15)	0.664 (0.236, 1.868)	0.435
	Other	0	3 (0.06)	3 (0.03)		NE
STEMI	Randomized	1769	1765	3534		
	Protocol Completed	1637 (92.54)	1641 (92.97)	3278 (92.76)	0.937 (0.727, 1.209)	0.617
	Protocol Completed Alive	1579 (89.26)	1565 (88.67)	3144 (88.96)	1.062 (0.860, 1.311)	0.575
	Died	58 (3.28)	76 (4.31)	134 (3.79)	0.753 (0.532, 1.067)	0.110
	Not Completed	132 (7.46)	124 (7.03)	256 (7.24)	1.067 (0.827, 1.376)	0.617
	Withdrawal of Consent	114 (6.44)	106 (6.01)	220 (6.23)	1.078 (0.820, 1.417)	0.589
	Less than minimum Expected Follow-Up (< 166 days)	2 (0.11)	1 (0.06)	3 (0.08)		NE
	Alive but Unable to Attend Study Termination Visit	16 (0.90)	16 (0.91)	32 (0.91)	0.998 (0.497, 2.001)	0.995
	Lost to Follow-Up	0	1 (0.06)	1 (0.03)		NE
	Other	0	0	0		NE
All ACS	Randomized	6813	6795	13,608		
	Protocol Completed	6403 (93.98)	6401 (94.20)	12804 (94.09)	0.961 (0.833, 1.109)	0.587
	Protocol Completed Alive	6214 (91.21)	6204 (91.30)	12418 (91.26)	0.988 (0.877, 1.113)	0.845
	Died	189 (2.77)	197 (2.90)	386 (2.84)	0.956 (0.780, 1.170)	0.660
	Not Completed	410 (6.02)	394 (5.80)	804 (5.91)	1.040 (0.902, 1.200)	0.587
	Withdrawal of Consent	342 (5.02)	323 (4.75)	665 (4.89)	1.059 (0.906, 1.238)	0.471
	Less than minimum Expected Follow-Up (< 166 days)	9 (0.13)	7 (0.10)	16 (0.12)	1.283 (0.477, 3.446)	0.621
	Alive but Unable to Attend Study Termination Visit	53 (0.78)	51 (0.75)	104 (0.76)	1.037 (0.705, 1.525)	0.854
	Lost to Follow-Up	6 (0.09)	10 (0.15)	16 (0.12)	0.598 (0.217, 1.646)	0.314
	Other	0	3 (0.04)	3 (0.02)		NE
CI=confidence interval, n=number of subjects, OR=odds ratio, NE=not evaluated due to insufficient data. ^a % is percent of randomized subjects. ^b Two-sided p-value based on Pearson chi-square test. The two-sided p-value and odds ratio for All ACS were adjusted for clinical presentation as a stratification factor using Cochran-Mantel-Haenszel method. Reproduced from Sponsor, Clinical Study Report, Table TAAL 10.1, pages 141-143 of 27024.						

Two subjects who were considered lost-to-follow-up in the analysis data set were located after the database lock on September 20, 2007. One subject, randomly assigned to prasugrel, had experienced an adjudicated MI prior to being considered lost-to-follow-up. The other subject had been randomly assigned to clopidogrel. Therefore, final clinical status was obtained for 13594 subjects (99.9%) and not 13592 subjects (99.9%).

Although there was an increased incidence of subjects who withdrew consent or were considered lost-to-follow up with the following baseline characteristics: older age (≥ 65 , ≥ 70 , ≥ 75), female, weight < 70 kg (STEMI), creatinine clearance < 60 mL/min, and peripheral arterial disease, the incidence was similar between treatment groups at 15 months. Table 46 displays the Kaplan-Meier estimates for this analysis.

Table 46. Sponsor's Analysis: Kaplan-Meier Estimates for the Incidence of Withdrawal of Consent or Lost-to-Follow-Up (TAAL)

Subjects	Hazard Ratio (Prasugrel vs. Clopidogrel)	95% Confidence Interval	p-value
UA/NSTEMI	1.035	(0.862, 1.242)	0.716
STEMI	1.073	(0.824, 1.397)	0.601
All ACS	1.047	(0.901, 1.217)	0.550
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9.1.11.4 Demographics and Baseline Characteristics

Demographics and baseline characteristics are displayed in Table 47. The baseline characteristic of prior TIA or stroke was statistically significantly higher in subjects randomized to prasugrel compared to clopidogrel, and there was a statistically significant by-treatment interaction for this subgroup in the All ACS population. Additionally, there were statistically significant differences in age and diabetic treatment in the STEMI population, sex in the All ACS population, and the use of angiotensin-converting enzymes inhibitors (ACEI) in the UA/NSTEMI and the All ACS populations.

Characteristics of the index procedure are displayed in Table 48.

Table 47. Demographics and Baseline Characteristics (TAAL)

	UA/NSTEMI			STEMI			All ACS		
Randomized Subjects	Prasugrel (N=5044)	Clopidogrel (N=5030)	p-value ^a	Prasugrel (N=1769)	Clopidogrel (N=1765)	p-value ^a	Prasugrel (N=6813)	Clopidogrel (N=6795)	p-value ^a
Clinical Presentation n (%^b):									
Num Subjects	5042	5027	0.814 ¹						
UA	1271 (25.21)	1257 (25.00)							
NSTEMI	3771 (74.79)	3770 (75.00)							
Num Subjects				1767	1765	0.224 ¹			
STEMI ≤ 12 hours				1203 (68.08)	1235 (69.97)				
STEMI > 12 hours				564 (31.92)	530 (30.03)				
Baseline Demographics									
Sex (n, %^b)									
Num Subjects	5044	5030	0.081 ¹	1769	1765	0.109 ¹	6813	6795	0.021 ²
Female	1325 (26.27)	1399 (27.81)		380 (21.48)	419 (23.74)		1705 (25.03)	1818 (26.75)	
Male	3719 (73.73)	3631 (72.19)		1389 (78.52)	1346 (76.26)		5108 (74.97)	4977 (73.25)	
Age in Years									
Num Subjects	5044	5030	0.438 ⁴	1769	1765	0.038 ⁴	6813	6795	0.686 ⁵
Mean	61.5	61.3		59.0	59.8		60.9	60.9	
SD	11.2	11.4		11.2	11.6		11.2	11.4	
Minimum	27	27		28	30		27	27	
Lower Quartile	53	53		51	52		53	53	
Median	61	61		58	59		61	61	
Upper Quartile	70	70		67	69		69	70	
Maximum	96	94		92	90		96	94	
Age ≥ 65 years (n, %^b)									
Num Subjects	5044	5030	0.665 ¹	1769	1765	0.022 ¹	6813	6795	0.448 ²
Age ≥ 65 years	2057 (40.78%)	2030 (40.36%)		568 (32.11)	631 (35.75)		2625 (38.53)	2661 (39.16)	
Age ≥ 70 years (n, %^b)									
Num Subjects	5044	5030	0.779 ¹	1769	1765	0.049 ¹	6813	6795	0.480 ²
Age ≥ 70 years	1316 (26.09)	1300 (25.84)		352 (19.90)	399 (22.61)		1668 (24.48)	1699 (25.00)	

	UA/NSTEMI			STEMI			All ACS		
Randomized Subjects	Prasugrel (N=5044)	Clopidogrel (N=5030)	p-value ^a	Prasugrel (N=1769)	Clopidogrel (N=1765)	p-value ^a	Prasugrel (N=6813)	Clopidogrel (N=6795)	p-value ^a
Age ≥ 75 years (n, %^b)									
Num Subjects	5044	5030	0.419 ¹	1769	1765	0.048 ¹	6813	6795	0.812 ²
Age ≥ 75 years	716 (14.20)	686 (13.64)		185 (10.46)	222 (12.58)		901 (13.22)	908 (13.36)	
Ethnicity (n, %^b)									
Num Subjects	5044	5030	0.960 ¹	1769	1765	NE	6813	6795	0.843 ²
Caucasian	4575 (90.70)	4569 (90.83)		1688 (95.42)	1705 (96.60)		6263 (91.93)	6274 (92.33)	
African	177 (3.51)	168 (3.34)		28 (1.58)	19 (1.08)		205 (3.01)	187 (2.75)	
Hispanic	242 (4.80)	237 (4.71)		27 (1.53)	19 (1.08)		269 (3.95)	256 (3.77)	
Asian	37 (0.73)	42 (0.83)		23 (1.30)	22 (1.25)		60 (0.88)	64 (0.94)	
Other	13 (0.26)	14 (0.28)		3 (0.17)	0		16 (0.23)	14 (0.21)	
Geographic Region (n, %^b)									
Num Subjects	5044	5030	0.994 ¹	1769	1765	0.936 ¹	6813	6795	0.997 ²
North America	1774 (35.17)	1764 (35.07)		390 (22.05)	382 (21.64)		2164 (31.76)	2146 (31.58)	
United States	1694 (33.58)	1688 (33.56)		345 (19.50)	332 (18.81)		2039 (29.93)	2020 (29.73)	
South America	270 (5.35)	264 (5.25)		0	0		270 (3.96)	264 (3.89)	
Western Europe	1262 (25.02)	1265 (25.15)		517 (29.23)	509 (28.84)		1779 (26.11)	1774 (26.11)	
Eastern Europe	1145 (22.70)	1155 (22.96)		512 (28.94)	510 (28.90)		1657 (24.32)	1665 (24.50)	
Rest of World	593 (11.76)	582 (11.57)		350 (19.79)	364 (20.62)		943 (13.84)	946 (13.92)	
Mid-East	366 (7.26)	354 (7.04)		240 (13.57)	259 (14.67)		606 (8.89)	613 (9.02)	
Africa	143 (2.84)	144 (2.86)		61 (3.45)	56 (3.17)		204 (2.99)	200 (2.94)	
Asia Pacific	84 (1.67)	84 (1.67)		49 (2.77)	49 (2.78)		133 (1.95)	133 (1.96)	
Weight (kg) (n, %^b)									
Num Subjects	4983	4978	0.083 ³	1739	1737	0.753 ³	6722	6715	0.078 ³
< 50	31 (0.62)	34 (0.68)		15 (0.86)	11 (0.63)		46 (0.68)	45 (0.67)	
50 - < 70	844 (16.94)	910 (18.28)		298 (17.14)	333 (19.17)		1142 (16.99)	1243 (18.51)	
70 - < 90	2451 (49.19)	2433 (48.88)		942 (54.17)	895 (51.53)		3393 (50.48)	3328 (49.56)	
≥ 90	1657 (33.25)	1601 (32.16)		484 (27.83)	498 (28.67)		2141 (31.85)	2099 (31.26)	
Weight (kg):									
Num Subjects	4983	4978	0.065 ⁴	1739	1737	0.837 ⁴	6722	6715	0.129 ⁵
Mean	84.190	83.556		82.009	82.120		83.626	83.185	
SD	17.068	17.229		15.934	15.729		16.808	16.864	
Minimum	32.00	34.00		43.00	37.64		32.00	34.00	
Lower Quartile	73.00	72.00		72.00	71.00		72.57	72.00	

Randomized Subjects	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	p-value ^a	Prasugrel (N=1769)	Clopidogrel (N=1765)	p-value ^a	Prasugrel (N=6813)	Clopidogrel (N=6795)	p-value ^a
Median	82.00	82.00		80.00	80.00		82.00	81.00	
Upper Quartile	93.43	93.00		90.00	91.00		93.00	92.07	
Maximum	165.00	180.00		249.44	159.00		249.44	180.00	
Body Mass Index (BMI) (kg/m²) (n, %^b)									
Num Subjects	4971	4964	0.567 ³	1737	1729	0.347 ³	6708	6693	0.711 ³
< 18.5	17 (0.34)	32 (0.64)		8 (0.46)	9 (0.52)		25 (0.37)	41 (0.61)	
18.5 - < 25	1092 (21.97)	1121 (22.58)		459 (26.42)	456 (26.37)		1551 (23.12)	1577 (23.56)	
25 - < 30	2175 (43.75)	2123 (42.77)		815 (46.92)	770 (44.53)		2990 (44.57)	2893 (43.22)	
≥ 30	1687 (33.94)	1688 (34.00)		455 (26.19)	494 (28.57)		2142 (31.93)	2182 (32.60)	
BMI (kg/m²)									
Num Subjects	4971	4964	0.354 ⁴	1737	1729	0.125 ⁴	6708	6693	0.940 ⁵
Mean	28.795	28.699		27.809	28.059		28.540	28.534	
SD	5.131	5.183		4.696	4.881		5.040	5.114	
Minimum	12.11	12.41		15.12	11.62		12.11	11.62	
Lower Quartile	25.31	25.25		24.77	24.82		25.15	25.10	
Median	28.07	27.89		27.12	27.37		27.76	27.76	
Upper Quartile	31.35	31.26		30.12	30.48		31.07	31.14	
Maximum	62.88	72.61		74.58	60.60		74.58	72.61	
TIMI Risk Score UA/NSTEMI (n, %^b)									
Num Subjects	4962	4931	NE						
0	3 (0.06)	3 (0.06)							
1	73 (1.47)	75 (1.52)							
2	537 (10.82)	527 (10.69)							
3	1507 (30.37)	1521 (30.85)							
4	1538 (31.00)	1523 (30.89)							
5	840 (16.93)	854 (17.32)							
6	394 (7.94)	366 (7.42)							
7	70 (1.41)	62 (1.26)							
TIMI Risk Score UA/NSTEMI (n, %^b)									
Num Subjects	4962	4931	0.855 ³						
0-2	613 (12.35)	605 (12.27)							

Randomized Subjects	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	p-value ^a	Prasugrel (N=1769)	Clopidogrel (N=1765)	p-value ^a	Prasugrel (N=6813)	Clopidogrel (N=6795)	p-value ^a
3-4	3045 (61.37)	3044 (61.73)							
5-7	1304 (26.28)	1282 (26.00)							
TIMI Risk Score UA/NSTEMI:									
Num Subjects	4962	4931	0.544 ⁴						
Mean	3.8	3.8							
SD	1.2	1.2							
Minimum	0	0							
Lower Quartile	3	3							
Median	4	4							
Upper Quartile	5	5							
Maximum	7	7							
TIMI Risk Score for STEMI ≤ 12 hours (n, %^b)									
Num Subjects				1124	1157	NE			
0				97 (8.63)	103 (8.90)				
1				245 (21.80)	257 (22.21)				
2				250 (22.24)	241 (20.83)				
3				185 (16.46)	190 (16.42)				
4				154 (13.70)	136 (11.75)				
5				96 (8.54)	124 (10.72)				
6				58 (5.16)	53 (4.58)				
7				26 (2.31)	27 (2.33)				
8				6 (0.53)	15 (1.30)				
9				5 (0.44)	9 (0.78)				
10				2 (0.18)	1 (0.09)				
11				0	1 (0.09)				
12				0	0				
13				0	0				
14				0	0				

Randomized Subjects	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	p-value ^a	Prasugrel (N=1769)	Clopidogrel (N=1765)	p-value ^a	Prasugrel (N=6813)	Clopidogrel (N=6795)	p-value ^a
TIMI Risk Score for STEMI ≤ 12 hours (n, %^b)									
Num Subjects				1124	1157	0.392 ³			
0-2				592 (52.67)	601 (51.94)				
3-4				339 (30.16)	326 (28.18)				
5-14				193 (17.17)	230 (19.88)				
TIMI Risk Score for STEMI ≤ 12 hours									
Num Subjects				1124	1157	0.427 ⁴			
Mean				2.7	2.8				
SD				1.9	2.0				
Minimum				0	0				
Lower Quartile				1	1				
Median				2	2				
Upper Quartile				4	4				
Maximum				10	11				
TIMI Risk Index for UA/NSTEMI (n, %^b)									
Num Subjects	5037	5024	0.206 ³						
Q1: 3.90 – 13.60	1015 (20.15)	1039 (20.68)							
Q2: > 13.60 – 17.50	1005 (19.95)	998 (19.86)							
Q3: > 17.50 – 21.70	972 (19.30)	1031 (20.52)							
Q4: > 21.70 – 27.40	1016 (20.17)	977 (19.45)							
Q5: > 27.40 – 94.00	1029 (20.43)	979 (19.49)							
TIMI Risk Index UA/NSTEMI									
Num Subjects	5037	5024	0.142 ⁴						
Mean	21.119	20.860							
SD	8.956	8.710							
Minimum	4.10	3.90							
Lower Quartile	14.70	14.50							
Median	19.50	19.40							
Upper Quartile	25.90	25.60							

Randomized Subjects	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	p- value ^a	Prasugrel (N=1769)	Clopidogrel (N=1765)	p- value ^a	Prasugrel (N=6813)	Clopidogrel (N=6795)	p- value ^a
Maximum	94.00	79.90							
TIMI Risk Index for STEMI (n, %^b)									
Num Subjects				1761	1762	0.498 ³			
Q1: 3.50 – 13.00				362 (20.56)	354 (20.09)				
Q2: > 13.00 – 17.00				347 (19.70)	354 (20.09)				
Q3: > 17.00 – 21.30				364 (20.67)	338 (19.18)				
Q4: > 21.30 – 27.80				347 (19.70)	355 (20.15)				
Q5: > 27.80 – 75.20				341 (19.36)	361 (20.49)				
TIMI Risk Index for STEMI									
Num Subjects				1761	1762	0.263 ⁴			
Mean				20.631	20.984				
SD				9.105	9.597				
Minimum				3.90	3.50				
Lower Quartile				14.10	14.00				
Median				19.00	19.50				
Upper Quartile				25.80	25.90				
Maximum				71.20	75.20				
TIMI Risk Index for All ACS (n, %^b)									
Num Subjects							6798	6786	0.258 ³
Q1: 3.50 – 13.40							1356 (19.95)	1387 (20.44)	
Q2: > 13.40 – 17.40							1400 (20.59)	1365 (20.11)	
Q3: > 17.40 – 21.60							1310 (19.27)	1369 (20.17)	
Q4: > 21.60 – 27.50							1359 (19.99)	1327 (19.55)	
Q5: > 27.50 – 94.00							1373 (20.20)	1338 (19.72)	

Randomized Subjects	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	p-value ^a	Prasugrel (N=1769)	Clopidogrel (N=1765)	p-value ^a	Prasugrel (N=6813)	Clopidogrel (N=6795)	p-value ^a
TIMI Risk Index for All ACS									
Num Subjects							6798	6786	0.515 ⁵
Mean							20.992	20.892	
SD							8.997	8.948	
Minimum							3.90	3.50	
Lower Quartile							14.50	14.40	
Median							19.40	19.40	
Upper Quartile							25.90	25.70	
Maximum							94.00	79.90	
Cardiac Marker > ULN (n, %)^{b,d}									
Num Subjects	5044	5030	0.654 ¹	1769	1765	0.497 ¹	6813	6795	>0.999 ²
None	1040 (20.62)	1019 (20.26)		483 (27.30)	500 (28.33)		1523 (22.35)	1519 (22.35)	
Any	4004 (79.38)	4011 (79.74)		1286 (72.70)	1265 (71.67)		5290 (77.65)	5276 (77.65)	
Troponin	3538 (70.14)	3561 (70.80)		864 (48.84)	879 (49.80)		4402 (64.61)	4440 (65.34)	
CK-MB	2935 (58.19)	2887 (57.40)		1102 (62.30)	1084 (61.42)		4037 (59.25)	3971 (58.44)	
ECG Abnormality (n, %)^{b,d}									
Num Subjects	5044	5030	0.653 ¹	1769	1765	0.761 ¹	6813	6795	0.690 ²
None	1400 (27.76)	1376 (27.36)		22 (1.24)	24 (1.36)		1422 (20.87)	1400 (20.60)	
Any	3644 (72.24)	3654 (72.64)		1747 (98.76)	1741 (98.64)		5391 (79.13)	5395 (79.40)	
ST Elevation	307 (6.09)	305 (6.06)		1528 (86.38)	1484 (84.08)		1835 (26.93)	1789 (26.33)	
≥ 1 mm	470 (9.32)	463 (9.20)		221 (12.49)	216 (12.24)		691 (10.14)	679 (9.99)	
≥ 0.5 - < 1	1143 (22.66)	1104 (21.95)		187 (10.57)	184 (10.42)		1330 (19.52)	1288 (18.96)	
ST Depression									
≥ 1	1429 (28.33)	1369 (27.22)		524 (29.62)	560 (31.73)		1953 (28.67)	1929 (28.39)	
≥ 0.5 - < 1	1143 (22.66)	1104 (21.95)		187 (10.57)	184 (10.42)		1330 (19.52)	1288 (18.96)	
T-Wave Inversion									
≥ 3 mm	1194 (23.67)	1240 (24.65)		230 (13.00)	240 (13.60)		1424 (20.90)	1480 (21.78)	
New Left Bundle Branch Block	50 (0.99)	66 (1.31)		18 (1.02)	32 (1.81)		68 (1.00)	98 (1.44)	
Q-Wave Associated With Index Event	366 (7.26)	453 (9.01)		573 (32.39)	542 (30.71)		939 (13.78)	995 (14.64)	

Randomized Subjects	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	p-value ^a	Prasugrel (N=1769)	Clopidogrel (N=1765)	p-value ^a	Prasugrel (N=6813)	Clopidogrel (N=6795)	p-value ^a
History of Diabetes (n, %^b)									
Num Subjects	5044	5030	0.701 ¹	1769	1765	0.527 ¹	6813	6795	0.971 ²
Diabetes	1246 (24.70)	1226 (24.37)		330 (18.65)	344 (19.49)		1576 (23.13)	1570 (23.11)	
If Diabetic, treated with (n, %^b)									
Insulin	295 (23.68)	331 (27.00)	0.192 ¹	84 (25.45)	66 (19.19)	0.024 ¹	379 (24.05)	397 (25.29)	0.858 ²
Oral Agents	705 (56.58)	668 (54.49)		172 (52.12)	195 (56.69)		877 (55.65)	863 (54.97)	
Dietary Control	147 (11.80)	147 (11.99)		52 (15.76)	43 (12.50)		199 (12.63)	190 (12.10)	
Not Treated	98 (7.87)	80 (6.53)		22 (6.67)	40 (11.63)		120 (7.61)	120 (7.64)	
Prior MI (n, %^b)									
Num Subjects	5044	5030	0.552 ¹	1769	1765	0.600 ¹	6813	6795	0.740 ²
Prior MI	1051 (20.84)	1024 (20.36)		175 (9.89)	184 (10.42)		1226 (18.00)	1208 (17.78)	
Prior Stroke (n, %^b)									
Num Subjects	5044	5030	0.069 ¹	1769	1765	0.270 ¹	6813	6795	0.260 ²
Prior Stroke	151 (2.99)	121 (2.41)		30 (1.70)	39 (2.21)		181 (2.66)	160 (2.35)	
Prior TIA (n, %^b)									
Num Subjects	5044	5030	0.260 ¹	1769	1765	0.193 ¹	6813	6795	0.106 ²
Prior TIA	74 (1.47)	88 (1.75)		20 (1.13)	29 (1.64)		94 (1.38)	117 (1.72)	
Creatinine Clearance Using Cockcroft-Gault Formula (ml/min) (n, %^b)									
Num Subjects	4971	4954	0.358 ³	1728	1727	0.098 ³	6699	6681	0.220 ³
< 30	38 (0.76)	50 (1.01)		13 (0.75)	4 (0.23)		51 (0.76)	54 (0.81)	
30-60	511 (10.28)	525 (10.60)		155 (8.97)	195 (11.29)		666 (9.94)	720 (10.78)	
> 60	4422 (88.96)	4379 (88.39)		1560 (90.28)	1528 (88.48)		5982 (89.30)	5907 (88.41)	
Hypertension (n, %^b)									
Num Subjects	5044	5030	0.919 ¹	1769	1765	0.788 ¹	6813	6795	0.817 ²
Hypertension	3495 (69.29)	3490 (69.38)		875 (49.46)	881 (49.92)		4370 (64.14)	4371 (64.33)	
Hypercholesterolemia (n, %^b)									
Num Subjects	5044	5030	0.814 ¹	1769	1765	0.963 ¹	6813	6795	0.859 ²
Hypercholesterolemia	3065 (60.77)	3068 (60.99)		725 (40.98)	722 (40.91)		3790 (55.63)	3790 (55.78)	

	UA/NSTEMI			STEMI			All ACS		
Randomized Subjects	Prasugrel (N=5044)	Clopidogrel (N=5030)	p-value ^a	Prasugrel (N=1769)	Clopidogrel (N=1765)	p-value ^a	Prasugrel (N=6813)	Clopidogrel (N=6795)	p-value ^a
History of Heart Failure (n, %^b)									
Num Subjects	5044	5030	0.789 ¹	1769	1765	0.189 ¹	6813	6795	0.435 ²
Heart Failure	217 (4.30)	211 (4.19)		48 (2.71)	36 (2.04)		265 (3.89)	247 (3.64)	
Atrial Fibrillation (n, %^b)									
Num Subjects	5044	5030	0.892 ¹	1769	1765	0.919 ¹	6813	6795	0.938 ²
Heart Failure	170 (3.37)	172 (3.42)		41 (2.32)	40 (2.27)		211 (3.10)	212 (3.12)	
History of Peripheral Artery Disease (PAD) (n, %^b)									
Num Subjects	5044	5030	0.612 ¹	1769	1765	0.783 ¹	6813	6795	0.565 ²
PAD	282 (5.59)	293 (5.83)		67 (3.79)	70 (3.97)		349 (5.12)	363 (5.34)	
History of Carotid/Vertebral Artery Disease (CVD) (n, %^b)									
Num Subjects	5044	5030	0.636 ¹	1769	1765	0.805 ¹	6813	6795	0.738 ²
CVD	161 (3.19)	169 (3.36)		32 (1.81)	30 (1.70)		193 (2.83)	199 (2.93)	
Metabolic Syndrome (n, %^b)									
Num Subjects	5044	5030	0.948 ¹	1769	1765	0.420 ¹	6813	6795	0.727 ²
Metabolic Syndrome	2257 (44.75)	2254 (44.81)		709 (40.08)	684 (38.75)		2966 (43.53)	2938 (43.24)	
Prior PCI (n, %^b)									
Num Subjects	5044	5030	0.600 ¹	1769	1765	0.721 ¹	6813	6795	0.536 ²
Prior PCI	790 (15.66)	807 (16.04)		114 (6.44)	119 (6.74)		904 (13.27)	926 (13.63)	
Prior CABG (n, %^b)									
Num Subjects	5044	5030	0.157 ¹	1769	1765	0.919 ¹	6813	6795	0.166 ²
Prior CABG	500 (9.91)	457 (9.09)		41 (2.32)	40 (2.27)		541 (7.94)	497 (7.31)	
Prior Coronary Angiography with ≥ 50% Stenosis of Major Epicardial Vessel (n, %^b)									
Num Subjects	5044	5030	0.426 ¹	1769	1765	0.879 ¹	6813	6795	0.427 ²
Stenosis ≥ 50%	1191 (23.61)	1154 (22.94)		165 (9.33)	162 (9.18)		1356 (19.90)	1316 (19.37)	

Randomized Subjects	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	p-value ^a	Prasugrel (N=1769)	Clopidogrel (N=1765)	p-value ^a	Prasugrel (N=6813)	Clopidogrel (N=6795)	p-value ^a
Hepatic Impairment Based on Hy's Rule at Baseline (n, %^b)									
Num Subjects	5044	5030	NE	1769	1765	NE	6813	6795	NE
Yes	2 (0.04)	0		0	0		2 (0.03)	0	
Hepatic Impairment Based on Pre-Existing Conditions (n, %^b)									
Num Subjects	5044	5030	0.330 ¹	1769	1765	0.996 ¹	6813	6795	0.3292 ²
Yes	23 (0.46)	30 (0.60)		8 (0.45)	8 (0.45)		31 (0.46)	38 (0.56)	
Peptic Ulcer Disease (n, %^b)									
Num Subjects	5044	5030	0.296 ¹	1769	1765	0.538 ¹	6813	6795	0.561 ²
Yes	288 (5.71)	312 (6.20)		112 (6.33)	103 (5.84)		400 (5.87)	415 (6.11)	
Tobacco Use (n, %^b)									
Num Subjects	5044	5030	0.598 ¹	1769	1765	0.052 ¹	6813	6795	0.481 ²
Any Use	3255 (64.53)	3292 (65.45)		1207 (68.23)	1198 (67.88)		4462 (65.49)	4490 (66.08)	
Current Use	1778 (35.25)	1811 (36.00)		834 (47.15)	772 (43.74)		2612 (38.34)	2583 (38.01)	
Prior Use	1477 (29.28)	1481 (29.44)		373 (21.09)	426 (24.14)		1850 (27.15)	1907 (28.06)	
Never Used	1789 (35.47)	1738 (34.55)		562 (31.77)	567 (32.12)		2351 (34.51)	2305 (33.92)	
Time from Onset of Qualifying symptoms to Randomization (hours) (n, %^b)									
Num Subjects	4956	4922	0.404 ¹	1733	1729	0.704 ¹	6689	6651	0.579 ²
≤ 24 hours	1978 (39.91)	1924 (39.09)		1259 (72.65)	1266 (73.22)		3237 (48.39)	3190 (47.96)	
> 24 hours	2978 (60.09)	2998 (60.91)		474 (27.35)	463 (26.78)		3452 (51.61)	3461 (52.04)	

Randomized Subjects	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	p-value ^a	Prasugrel (N=1769)	Clopidogrel (N=1765)	p-value ^a	Prasugrel (N=6813)	Clopidogrel (N=6795)	p-value ^a
Time from Onset of Qualifying Symptoms to Randomization (h)									
Num Subjects	4956	4922	0.484 ⁴	1733	1729	0.546 ⁴	6689	6651	0.404 ⁵
Mean	38.236	36.853		26.379	25.426		35.164	33.882	
SD	132.989	40.349		45.940	47.005		116.942	42.474	
Minimum	0.00	0.35		0.02	0.00		0.00	0.00	
Lower Quartile	16.63	16.68		2.93	2.83		10.08	9.30	
Median	28.92	29.04		6.42	5.62		24.85	25.20	
Upper Quartile	48.62	49.02		27.82	26.90		46.48	46.68	
Maximum	8830.25 [†]	841.03		332.13	334.83		8830.25	841.03	
GPIIb/IIIa Use Through 3 Days After Randomization (n, %^b)									
Num Subjects	5044	5030	0.317 ¹	1769	1765	0.433 ¹	6813	6795	0.208 ²
Yes	2570 (50.95)	2613 (51.95)		1100 (62.18)	1120 (63.46)		3670 (53.87)	3733 (54.94)	
Statin Use (n, %^b)									
Num Subjects	5044	5030	0.945 ¹	1769	1765		6813	6795	0.932 ²
Any Statin	4029 (79.88)	4008 (79.68)		1343 (75.92)	1332 (75.47)		5372 (78.85)	5340 (78.59)	
Atorvastatin									
Any Dose	2024 (40.13)	2003 (39.82)		683 (38.61)	690 (39.09)	0.845 ¹	2707 (39.73)	2693 (39.63)	0.932 ²
≥ 80	426 (8.45)	428 (8.51)		170 (9.61)	176 (9.97)		596 (8.75)	604 (8.89)	
< 80	1252 (24.82)	1248 (24.81)		398 (22.50)	400 (22.66)		1650 (24.22)	1648 (24.25)	
Other Statin	2005 (39.75)	2005 (39.86)		660 (37.31)	642 (36.37)		2665 (39.12)	2647 (38.96)	
No Statin	1015 (20.12)	1022 (20.32)		426 (24.08)	433 (24.53)		1441 (21.15)	1455 (21.41)	
ACE Inhibitor (n, %^b)									
Num Subjects	5044	5030	0.002 ¹	1769	1765	0.518 ¹	6813	6795	0.003 ²
Yes	2714 (53.81)	2550 (50.70)		827 (46.75)	806 (45.67)		3541 (51.97)	3356 (49.39)	
Beta Blocker (n, %^b)									
Num Subjects	5044	5030	0.616 ¹	1769	1765	0.581 ¹	6813	6795	0.912 ²
Yes	3892 (77.16)	3860 (76.74)		1150 (65.01)	1163 (65.89)		5042 (74.01)	5023 (73.92)	

	UA/NSTEMI			STEMI			All ACS		
Randomized Subjects	Prasugrel (N=5044)	Clopidogrel (N=5030)	p-value ^a	Prasugrel (N=1769)	Clopidogrel (N=1765)	p-value ^a	Prasugrel (N=6813)	Clopidogrel (N=6795)	p-value ^a
Calcium Channel Blocker (n, %^b)									
Num Subjects	5044	5030	0.184 ¹	1769	1765	0.451 ¹	6813	6795	0.361 ²
Yes	866 (17.17)	814 (16.18)		140 (7.91)	152 (8.61)		1006 (14.77)	966 (14.22)	
Received Aspirin within 7 Days Prior to Symptom Onset (n, %^b)									
Num Subjects	5044	5030	0.899 ¹	1769	1765	0.363 ¹	6813	6795	0.804 ²
Yes	2060 (40.84)	2048 (40.72)		266 (15.04)	285 (16.15)		2326 (34.14)	2333 (34.33)	
<p>Num Subjects=number of subjects with non-missing values for category, n=number of subjects in sub-category, NE=not evaluated due to insufficient data.</p> <p>†Sponsor was queried about this time from onset of qualifying symptoms to randomization. The sponsor believes the investigator incorrectly entered the date for symptom onset. A Data Clarification form had been sent to the study site.</p> <p>^aTwo-sided p-values: ¹Pearson chi-square, ²CMH general association, ³CMH row mean with rank scores, ⁴t-test, ⁵ANOVA with clinical presentation as a blocking factor.</p> <p>^b% is percent of Num Subjects.</p> <p>^cp-value is based on North America, South America, Western Europe, Eastern Europe, Rest of World.</p> <p>^dp-value is based on None vs. Any.</p> <p>^ep-value is based on Yes vs. No.</p> <p>^fp-value is based on Current, Prior, and Never.</p> <p>^gp-value is based on Atorvastatin, Other Statins, and No Statins.</p> <p>Reproduced from Sponsor, Clinical Study Report, Table TAAL.11.1, pages 153- 180 of 27024.</p>									

Table 48. Index Procedure (All Randomized Subjects) (TAAL)

	UA/NSTEMI			STEMI			All ACS		
Randomized Subjects	Prasugrel (N=5044)	Clopidogrel (N=5030)	p-value ^a	Prasugrel (N=1769)	Clopidogrel (N=1765)	p-value ^a	Prasugrel (N=6813)	Clopidogrel (N=6795)	p-value ^a
Index Procedure n (%^b)^c									
Num Subjects	5044	5030	0.508 ¹	1769	1765	0.503 ¹	6813	6795	0.956 ²
PCI	5004 (99.21)	4984 (99.09)		1711 (96.72)	1714 (97.11)		6715 (98.56)	6698 (98.57)	
No PCI	40(0.79)	46 (0.91)		58 (3.28)	51 (2.89)		98 (1.44)	97 (1.43)	
CABG	16(0.32)	12 (0.24)		9 (0.51)	11 (0.62)		25 (0.37)	23 (0.34)	
Medically Treated	24(0.48)	34 (0.68)		49 (2.77)	40 (2.77)		73 (1.07)	74 (1.09)	
Culprit Lesion(s)									
Number of Intervened Culprit Lesions per Subject n (% ^b):									
Num Subjects	4897	4854	0.886 ¹	1677	1670	0.320 ¹	6574	6524	0.735 ²
1 Culprit Lesion	4679 (95.55)	4635 (95.49)		1611 (96.06)	1615 (96.71)		6290 (95.68)	6250 (95.80)	
≥ 2 Culprit Lesions	218 (4.45)	219 (4.51)		66 (3.94)	55 (3.29)		284 (4.32)	274 (4.20)	
Subjects with Single Culprit Lesion									
Type of intervention in Culprit Lesion n (% ^b) ^d									
Num Subjects	4679	4635	0.356 ¹	1611	1615	0.551 ¹	6290	6250	0.272 ²
Any Stent	4487 (95.90)	4462 (96.27)		1531 (95.03)	1542 (95.48)		6018 (95.68)	6004 (96.06)	
Drug Eluting	2345 (50.12)	2345 (50.59)		515 (31.97)	527 (32.63)		2860 (45.47)	2872 (45.95)	
Cypher	1027 (21.95)	1013 (21.86)		228 (14.15)	256 (15.85)		1255 (19.95)	1269 (20.30)	
Taxus	1160 (24.79)	1156 (24.94)		262 (16.26)	251 (15.54)		1422 (22.61)	1407 (22.51)	
Other	164 (3.51)	181 (3.91)		28 (1.74)	26 (1.61)		192 (3.05)	207 (3.31)	
Bare Metal	2163 (46.23)	2159 (46.58)		1027 (63.75)	1026 (63.53)		3190 (50.72)	3185 (50.96)	
No Stent	192 (4.10)	173 (3.73)		80 (4.97)	73 (4.52)		272 (4.32)	246 (3.94)	
PTCA Only	182 (3.89)	165 (3.56)		78 (4.84)	70 (4.33)		260 (4.13)	235 (3.76)	
Other PCI Procedure	10 (0.21)	8 (0.17)		2 (0.12)	3 (0.19)		12 (0.19)	11 (0.18)	

	UA/NSTEMI			STEMI			All ACS		
Randomized Subjects	Prasugrel (N=5044)	Clopidogrel (N=5030)	p-value ^a	Prasugrel (N=1769)	Clopidogrel (N=1765)	p-value ^a	Prasugrel (N=6813)	Clopidogrel (N=6795)	p-value ^a
Total Stent Length (mm) in Culprit Lesion n (%^b)									
Num Subjects	4487	4462	0.628 ³	1531	1542	0.830 ³	6018	6004	0.666 ³
≤ 20	2844 (63.38)	2824 (63.29)		903 (58.98)	918 (59.53)		3747 (62.26)	3742 (62.33)	
21-30	1080 (24.07)	1035 (23.20)		397 (25.93)	398 (25.81)		1477 (24.54)	1433 (23.87)	
31-40	397 (8.85)	400 (8.96)		150 (9.80)	121 (7.85)		547 (9.09)	521 (8.68)	
>40	166 (3.70)	203 (4.55)		81 (5.29)	105 (6.81)		247 (4.10)	308 (5.13)	
Number of Stents in Culprit Lesion n (%^b)									
Num Subjects	4487	4462	0.396 ³	1531	1542	NE	6018	6004	0.340 ³
1	4188 (93.34)	4145 (92.90)		1405 (91.77)	1406 (91.18)		5593 (92.94)	5551 (92.46)	
2	265 (5.91)	273 (6.12)		105 (6.86)	115 (7.46)		370 (6.15)	388 (6.46)	
3	29 (0.65)	29 (0.65)		21 (1.27)	17 (1.10)		60 (0.83)	46 (0.77)	
4	5 (0.11)	15 (0.34)		0	4 (0.26)		5 (0.08)	19 (0.32)	
Vessel of the Culprit Lesion n (%^b)									
Num Subjects	4679	4635	0.209 ¹	1611	1614	NE	6290	6249	0.215 ²
Native Coronary Artery	4485 (95.85)	4433 (95.64)		1594 (98.94)	1594 (98.76)		6079 (96.65)	6027 (96.45)	
LM	44 (0.94)	40 (0.86)		2 (0.12)	7 (0.43)		46 (0.73)	47 (0.75)	
LAD	1680 (35.91)	1690 (36.46)		632 (39.23)	640 (39.65)		2312 (36.76)	2330 (37.29)	
RCA	1305 (27.89)	1368 (29.51)		703 (43.64)	699 (43.31)		2008 (31.92)	2067 (33.08)	
LCX	1371 (29.30)	1270 (27.40)		242 (15.02)	237 (14.68)		1613 (25.64)	1507 (24.12)	
RI	85 (1.82)	65 (1.40)		15 (0.93)	11 (0.68)		100 (1.59)	76 (1.22)	
Graft	194 (4.15)	202 (4.36)		17 (1.06)	20 (1.24)		211 (3.35)	222 (3.55)	
Venous	177 (3.78)	187 (4.03)		13 (0.81)	17 (1.05)		190 (3.02)	204 (3.26)	
Arterial	17 (0.36)	15 (0.32)		4 (0.25)	3 (0.19)		21 (0.33)	18 (0.29)	
Bifurcation Lesion in Culprit n (%^b)									
Num Subjects	4679	4635	0.451 ¹	1611	1615	0.788 ¹	6290	6250	0.594 ²
Yes	242 (5.17)	256 (5.52)		75 (4.66)	72 (4.46)		317 (5.04)	328 (5.25)	
No	4437 (94.83)	4379 (94.48)		1536 (95.34)	1543 (95.54)		5973 (94.96)	5922 (94.75)	

Randomized Subjects	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	p-value ^a	Prasugrel (N=1769)	Clopidogrel (N=1765)	p-value ^a	Prasugrel (N=6813)	Clopidogrel (N=6795)	p-value ^a
Study Drug									
Timing of Loading Dose Relative to Index PCI (n, (%)^h)									
Num Subjects	4965	4923	0.623 ¹	1691	1687	0.599 ¹	6656	6610	0.637 ²
Pre-PCI	1257 (25.32)	1205 (24.48)		455 (26.91)	453 (26.85)		1712 (25.72)	1658 (25.08)	
≥ 6 Prior	118 (2.38)	93 (1.89)		14 (0.83)	6 (0.36)		132 (1.98)	99 (1.50)	
< 6 Prior	1139 (22.94)	1112 (22.59)		441 (26.08)	447 (26.50)		1580 (23.74)	1559 (23.59)	
During PCI	3660 (73.72)	3671 (74.57)		1221 (72.21)	1213 (71.90)		4881 (73.33)	4884 (73.89)	
First Wire in to Last Wire Out	958 (19.30)	932 (18.93)		254 (15.02)	236 (13.99)		1212 (18.21)	1168 (17.67)	
Last Wire Out to Leaving Cath Lab	1473 (29.67)	1435 (29.15)		459 (27.14)	466 (27.62)		1932 (29.03)	1901 (28.76)	
Leaving Cath Lab to 1h later	1229 (24.75)	1304 (26.49)		508 (30.04)	511 (30.29)		1737 (26.10)	1815 (27.46)	
Post PCI	48 (0.97)	47 (0.95)		15 (0.89)	21 (1.24)		63 (0.95)	68 (1.03)	
Num Subjects = number of subjects with nonmissing values for category, n = number of subjects in sub-category, NE = not evaluated due to insufficient data. ^a Two-sided p-values: ¹ Pearson chi-square, ² CMH general association, ³ CMH row mean with rank scores. ^b % is percent of Num Subjects. ^c p-value is based on PCI vs. No PCI. ^d p-value is based on Any Stent vs. No stent. ^e p-value is based on single vessel categories: LM, LAD, RCA, LCX, RI, Venous Graft and Arterial Graft. ^f p-value is based on Single Vessel vs. Multiple Vessels. ^g p-value is based on Monotherapy vs. Multiple Therapies. ^h p-value is based on Pre-PCI, During PCI, and Post-PCI. Reproduced from Sponsor, Clinical Study Report, Table TAAL.11.2, pages 182-194.									

9.1.11.5 Duration of Follow-Up (All Randomized Subjects)

The mean duration of follow-up was similar in the UA/NSTEMI population by treatment group. Patients in the STEMI population had a longer mean follow-up because enrollment was capped and completed earlier than the UA/NSTEMI population. The duration of follow-up is displayed in Table 49.

Table 49. Duration of Follow-Up (All Randomized Subjects) (TAAL)

	UA/NSTEMI			STEMI			All ACS		
	Prasugrel	Clopidogrel	p-value ^a	Prasugrel	Clopidogrel	p-value ^a	Prasugrel	Clopidogrel	p-value ^a
Randomized	5044	5030	0.335 ¹	1769	1765	0.680 ¹	6813	6795	0.520 ²
Mean (days)	363.7	366.0		423.1	421.5		379.1	380.4	
SD	120.0	120.4		111.0	113.7		120.5	121.2	
Minimum	1	1		1	1		1	1	
Lower Quartile	274	275		450	450		322	337	
Median	438	441		458	458		450	450	
Upper Quartile	458	459		464	464		462	462	
Maximum	464	464		464	464		464	464	

^aTwo-sided p-values: ¹t test, ²ANOVA with clinical presentation as a blocking factor.
Reproduced from Sponsor, Clinical Study Report, Table TAAL.11.4, page 200.

9.1.11.6 Primary Efficacy Endpoint

In all treatment groups, prasugrel significantly reduced the CEC Adjudicated composite endpoint of CV death, nonfatal MI, and nonfatal stroke, as displayed in Table 50.

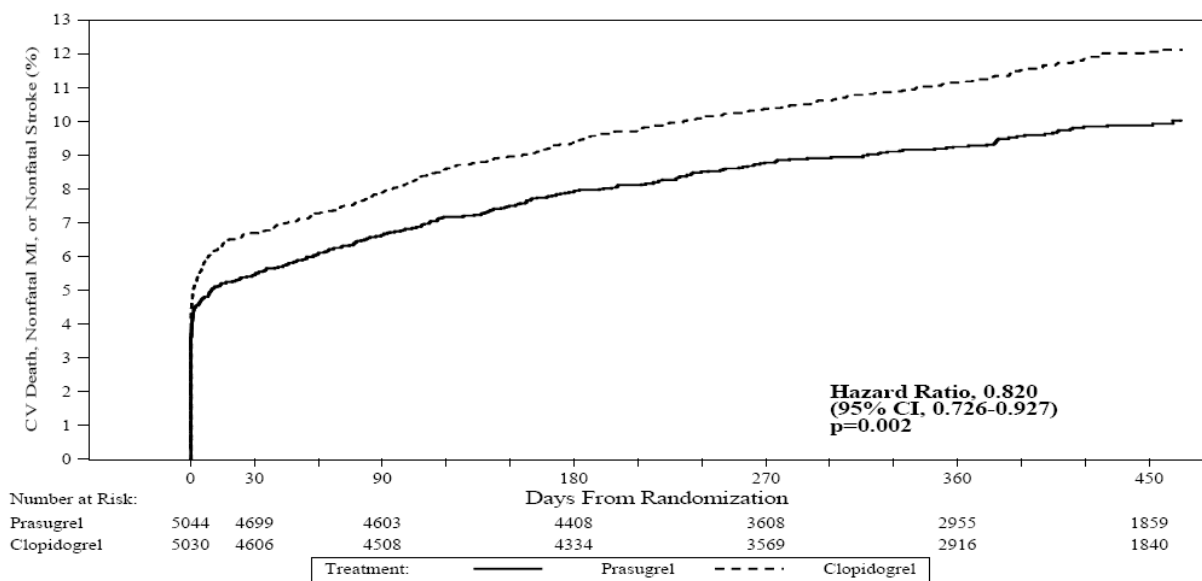
Table 50. Number and Percentage of Subjects Reaching the Composite Endpoint of CV Death, Nonfatal MI, or Nonfatal Stroke Using the Expanded Definition--CEC Adjudicated (All Randomized Subjects) (TAAL)

Subject Population	Prasugrel			Clopidogrel			Total			Cox Proportional HR (95% CI) ^b	Gehan-Wilcoxon p-value ^c
	N	n	(% ^a)	N	n	(% ^a)	N	n	(% ^a)		
UA/NSTEMI	5044	469	(9.30)	5030	565	(11.23)	10074	1034	(10.26)	0.820 (0.726, 0.927)	0.002
STEMI	1769	174	(9.84)	1765	216	(12.24)	3534	390	(11.04)	0.793 (0.649, 0.968)	0.019
All ACS	6813	643	(9.44)	6795	781	(11.49)	13608	1424	(10.46)	0.812 (0.732, 0.902)	< 0.001

CI: confidence interval; HR: hazard ratio; N=number randomized; n=number of subjects reaching the endpoint; NE=not evaluated due to insufficient data.
^a% is percentage of randomized subjects reaching the primary endpoint.
^bHazard ratio and a 95% confidence interval used as an estimate of overall relative risk, Prasugrel versus Clopidogrel, over the course of the study.
^cTwo-sided p-values are based on Gehan-Wilcoxon test comparing event free survival distributions of Prasugrel and Clopidogrel. Clinical presentation, UA/NSTEMI vs. STEMI, was used as a stratification factor in analysis involving all ACS subjects.
Reproduced from Sponsor, Clinical Study Report, Table TAAL.11.5, page 202 of 27024)
Analysis verified by Ququan Liu, M.D., M.S., Biometrics, FDA.

The Kaplan-Meier estimates of the incidence of the primary composite endpoint in the UA/NSTEMI population is displayed in Figure 27. It appears that most of the treatment effect was realized within the first 30 days of study drug administration.

Figure 27. Hazard Ratio and 95% Confidence Interval for the Composite Endpoint of CV Death, Nonfatal MI, or Nonfatal Stroke--CEC Adjudicated (All Randomized UA/NSTEMI Subjects) (TAAL)



(Reproduced from Sponsor, Clinical Study Report, Figure TAAL.11.2a, page 204 of 27024)

Please see the Integrated Summary of Efficacy and the Integrated Summary of Safety for all other results.

9.1.11.7 Results of FDA Subgroup Analyses

Numerous subgroup analyses are displayed in Table 51.

Table 51. FDA Subgroup Analyses of Primary Endpoint (TAAL)

Subgroup Analysis of Primary endpoint									
	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Age (yr)									
<65 N	2987	3000	0.75	1201	1134	0.76	4188	4134	0.75
n	224	299	0.63, 0.89	98	121	0.58, 0.99	322	420	0.65, 0.87
%	7.50	9.97	0.0008	6.16	10.67	0.0364	7.69	10.16	<.0001
≥65 N	2057	2030	0.90	568	631	0.88	2625	2661	0.90
n	245	266	0.76, 1.07	76	95	0.65, 1.18	321	361	0.77, 1.04
%	11.91	13.10	0.3075	13.38	15.06	0.3445	12.23	13.57	0.1513
≥65 Female N	727	740	0.92	191	219	0.79	918	959	0.89
n	85	93	0.68, 1.23	26	37	0.48, 1.31	111	130	0.69, 1.14
%	11.69	12.57	0.6354	13.61	16.89	0.3562	12.09	13.56	0.3295
≥65 Male N	1330	1290	0.89	377	412	0.93	1707	1702	0.90
n	160	173	0.72, 1.11	50	58	0.64, 1.35	210	231	0.75, 1.09
%	12.03	13.41	0.3571	13.2	14.08	0.6349	12.30	13.57	0.2880
<70 N	3728	3730	0.75	1417	1366	0.79	5145	5096	0.76
n	287	378	0.65, 0.88	121	146	0.62, 1.00	408	524	0.67, 0.87
%	7.70	10.13	0.0002	8.54	10.69	0.0467	7.93	10.29	<.0001
≥70 N	1316	1300	0.96	352	399	0.85	1668	1699	0.93
n	182	187	0.78, 1.17	53	70	0.59, 1.21	235	257	0.78, 1.11
%	13.83	14.38	0.8126	15.06	17.54	0.3365	14.09	15.13	0.444
≥70 Female N	514	17	1.03	135	151	0.75	649	668	0.95
n	67	65	0.73, 1.45	19	28	0.42, 1.34	86	93	0.71, 1.27
%	13.04	12.57	0.6933	14.07	18.54	0.3498	13.25	13.92	0.8253
≥70 Male N	802	783	0.92	217	248	0.91	1019	1031	0.92
n	115	122	0.71, 1.18	34	42	0.58, 1.43	149	164	0.73, 1.14
%	14.34	15.58	0.5602	15.67	16.94	0.6138	14.62	9.70	0.4305

Subgroup Analysis of Primary endpoint									
	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
<75 N	4328	4344	0.78	1584	1543	0.80	5912	5887	0.78
n	356	454	0.68, 0.90	143	173	0.64, 0.99	499	627	0.70, 0.88
%	8.23	10.45	0.0006	9.02	11.21	0.0370	8.44	10.65	<.0001
≥75 N	716	686	0.97	185	222	0.85	901	908	0.94
n	113	111	0.75, 1.26	31	43	0.54, 1.35	144	154	0.75, 1.18
%	15.78	16.18	0.8539	16.76	19.37	0.4478	15.98	16.96	0.5329
≥75 Female N	292	309	0.98	79	96	0.71	371	405	0.91
n	43	46	0.65, 1.49	12	20	0.35, 1.46	55	66	0.63, 1.29
%	14.73	14.89	0.9723	15.19	20.83	0.3637	14.82	16.30	0.5891
≥75 Male N	424	77	0.96	106	126	0.97	530	503	0.96
n	70	65	0.68, 1.34	19	23	0.53, 1.79	89	88	0.72, 1.29
%	16.51	17.24	0.7598	17.92	18.25	0.8197	16.79	17.50	0.6908
Sex									
Female N	1325	1399	0.91	380	419	0.79	1705	1818	0.88
n	137	159	0.72, 1.14	41	56	0.53, 1.19	178	215	0.73, 1.07
%	10.34	11.37	0.5150	10.79	13.37	0.2107	10.44	11.83	0.1962
Male N	3719	3631	0.79	1389	1346	0.80	5108	4977	0.79
n	332	406	0.68, 0.91	133	160	0.63, 1.00	465	566	0.7, 0.9
%	8.93	11.18	0.0014	9.58	11.89	0.0503	9.10	11.37	0.0002

Subgroup Analysis of Primary endpoint									
	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Ethnicity									
Caucasian									
N	4575	4569	0.80	1688	1705	0.80	6263	6274	0.80
n	414	511	0.70, 0.91	167	209	0.65, 0.98	581	720	0.72, 0.89
%	9.05	11.18	0.0011	9.89	12.26	0.0242	9.28	11.48	<.0001
African									
N	177	168	1.03	28	19	0.66	205	187	0.98
n	22	20	0.56, 1.89	3	3	0.13, 3.25	25	23	0.55, 1.72
%	12.43	11.91	0.8896	10.71	15.79	0.5967	12.20	12.30	0.9647
Hispanic									
N	242	237	1.08	27	19	0.70	269	256	1.04
n	33	30	0.66, 1.77	3	3	0.14, 3.46	36	33	0.65, 1.67
%	13.64	12.66	0.7287	11.11	15.79	0.6436	13.38	12.89	0.8737
Asian									
N	37	42	-	23	22	-	60	64	-
n	0	3	-	1	1	-	1	4	-
%	-	7.14	-	4.35	4.55	-	1.67	6.25	-
Other									
N	13	14	-	3	0	-	16	14	-
n	0	1	-	0	0	-	0	1	-
%	-	7.14	-	-	-	-	-	7.14	-
Prior TIA/stroke									
yes									
N	213	192	1.53	49	64	0.98	262	256	1.38
n	39	24	0.92, 2.55	8	11	0.39, 2.42	47	35	0.89, 2.13
%	18.31	12.50	0.0677	16.33	17.19	0.9127	17.94	13.67	0.1382
no									
N	4831	4838	0.79	1720	1701	0.79	6551	6539	0.79
n	430	541	0.69, 0.89	166	205	0.64, 0.97	596	746	0.71, 0.88
%	8.90	11.18	0.0003	9.65	12.05	0.020	9.10	11.41	<.0001

Subgroup Analysis of Primary endpoint									
	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Weight (kg)									
<50 N	92	86	1.14	45	39	0.90	137	125	1.05
n	17	15	0.57, 2.29	9	9	0.36, 2.28	26	24	0.60, 1.82
%	18.48	17.44	0.7713			0.9671	18.98	19.2	0.8318
≥50<70 N	844	910	0.86	298	333	0.66	1142	1243	0.79
n	83	103	0.64, 1.14	34	56	0.43, 1.00	117	159	0.62, 1.00
%	9.83	11.32	0.3270			0.0388	10.25	12.79	0.0436
≥70 N	2451	2433	0.84	942	895	0.78	3393	3328	0.83
n	234	275	0.70, 1.00	85	100	0.60, 1.06	319	375	0.71, 0.96
%	9.55	11.30	0.0549			0.1138	9.40	11.27	0.0119
≥70<90 N	1657	1601	0.75	484	498	0.93	2141	2099	0.79
n	135	172	0.60, 0.94	46	51	0.62, 1.38	181	223	0.65, 0.96
%	8.15	10.74	0.0112			0.6796	8.45	10.62	0.0138
<60 N	5044	5030	0.82	1769	1765	0.79	6813	6795	0.81
n	469	565	0.73, 0.93	174	216	0.65, 0.97	643	781	0.73, 0.90
%	9.30	11.23	0.0021	9.84	12.24	0.0192	9.44	11.49	<0.0001
Creatinine Clearance									
<30 N	38	50	0.55	13	4	0.17	51	54	0.47
n	9	19	0.25, 1.21	2	2	0.02, 1.24	11	21	0.22, 1.01
%	23.68	38.00	0.3355	15.39	50.00	0.0211	21.57	38.89	0.1272
30-60 N	511	525	1.04	155	195	0.66	666	720	0.93
n	74	73	0.75, 1.43	18	33	0.37, 1.17	92	106	0.70, 1.23
%	14.48	13.90	0.9282	11.61	16.92	0.1664	13.81	14.72	0.5443
>60 N	4422	4379	0.80	1560	1528	0.80	5982	5907	0.80
n	372	457	0.70, 0.92	143	173	0.64, 1.00	515	630	0.71, 0.90
%	8.41	10.44	0.0016	9.17	11.32	0.0388	8.61	10.07	0.0001

Subgroup Analysis of Primary endpoint										
		UA/NSTEMI			STEMI			All ACS		
		Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Use of GPIIb/IIIa inhibitors prior to and during PCI										
Yes	N	1764	1768	0.82	924	953	0.73	2688	2721	0.79
	n	172	208	0.67, 1.01	91	125	0.56, 0.96	263	333	0.67, 0.93
	%	9.75	11.77	0.0939	9.85	13.12	0.018	9.78	12.24	0.0047
No	N	3280	3262	0.82	845	812	0.87	4125	4074	0.83
	n	297	357	0.70, 0.96	83	91	0.65, 1.18	380	448	0.72, 0.95
	%	9.06	10.94	0.0089	9.82	11.21	0.3987	9.21	11.00	0.0058
Female										
Yes	N	433	486	0.88	198	205	0.68	631	691	0.80
	n	41	52	0.58, 1.32	22	32	0.39, 1.17	63	84	0.58, 1.12
	%	9.47	10.70		11.11	15.61		9.98	12.16	0.2178
No	N	892	913	0.92	182	214	0.94	1074	1127	0.92
	n	96	107	0.70, 1.21	19	24	0.52, 1.72	115	131	0.72, 1.18
	%	10.76	11.72		10.44	11.21		10.71	11.62	0.4771
Male										
Yes	N	1331	1282	0.80	726	748	0.75	2057	2030	0.78
	n	131	156	0.64, 1.01	69	93	0.55, 1.03	200	249	0.65, 0.94
	%	9.84	12.17		9.50	12.43		9.72	12.27	0.0108
No	N	2388	2349	0.78	663	598	0.86	3051	2947	0.80
	n	201	250	0.65, 0.94	64	67	0.61, 1.21	265	317	0.68, 0.94
	%	8.42	10.64		9.65	11.20		8.69	10.76	0.0054
Use of GPIIb/IIIa inhibitors up to cath lab										
Yes	N	366	353	0.85	171	199	0.69	537	552	0.80
	n	37	42	0.54, 1.31	14	23	0.36, 0.34	51	65	0.55, 1.15
	%	10.11	11.90	0.5441	8.19	11.56	0.2663	9.50	11.78	0.2769
No	N	4678	4677	0.82	1598	1566	0.80	6276	6243	0.81
	n	435	523	0.72, 0.93	160	193	0.65, 0.99	592	716	0.73, 0.91
	%	9.23	11.18	0.0023	10.01	12.32	0.0348	9.43	11.47	0.0002

Subgroup Analysis of Primary endpoint										
		UA/NSTEMI			STEMI			All ACS		
		Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Female										
Yes	N	84	92	0.13	33	48	0.33	117	140	0.80
	n	10	10	0.47, 2.70	2	8	0.07, 1.57	12	18	0.38, 1.65
	%	11.90	10.87	0.5974	6.06	16.67	0.1476	10.26	12.86	0.6710
No	N	1241	1307	0.89	347	371	0.86	1588	1678	0.88
	n	127	149	0.70, 1.13	39	48	0.56, 1.31	166	197	0.72, 1.09
	%	10.23	11.40	0.4138	11.24	12.94	0.4076	10.45	11.74	0.2214
Male										
Yes	N	282	261	0.77	138	151	0.86	420	412	0.80
	n	27	32	0.46, 1.28	12	15	0.41, 1.85	39	47	0.53, 1.23
	%	9.57	12.26	0.3268	8.70	9.93	0.6897	9.29	11.41	0.3241
No	N	3437	3370	0.79	1251	1195	0.79	4688	4565	0.79
	n	305	374	0.68, 0.92	121	145	0.62, 1.0	426	519	0.70, 0.90
	%	8.87	11.10	0.0022	9.67	12.13	0.0533	9.09	11.37	0.0003
Use of GPIIb/IIIa inhibitors up to cath lab and cath only (no PCI)										
Yes	N							3	9	
	n							0	1	
	%							-	11.11	
No	N							87	83	
	n							7	5	
	%							8.05	6.02	

Subgroup Analysis of Primary endpoint										
	UA/NSTEMI			STEMI			All ACS			
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value	
Timing of Loading Dose										
0-2 hrs prior to PCI	1078 103	1045 117	0.85 0.65, 1.11 0.3212	432 52	440 59	0.90 0.62, 1.30 0.5843	1510 155	1485 176	0.86 0.70, 1.08 0.2340	
2-6 hrs prior to PCI	61 4	67 5	0.9191	9 1	7 1	-	70 5	74 6	0.90 0.28, 2.95 0.8927	
6-12 hrs prior to PCI	16 3	9 2	0.84 0.14, 5.08 0.8530	4 0	1 1	-	20 3	10 3	0.46 0.09, 2.30 0.3263	
≥12 hrs prior to PCI	102 15	84 12	1.01 0.47, 2.16 0.9651	10 1	5 1	-	112 16	89 13	1.01 0.47, 2.16 0.8358	
During PCI	3660 329	3671 400	0.82 0.71, 0.95 0.0081	1221 110	1213 143	0.75 0.59, 0.97 0.0209	4881 439	4884 543	0.80 0.71, 0.91 0.0005	
Post PCI	48 5	47 14	0.30 0.11, 0.84 0.0145	15 2	21 2	-	63 7	68 16	0.43 0.18, 1.04 0.0391	
Use of any statin										
Yes	N n %	4859 446 9.18	4878 543 11.13	0.82 0.72, 0.93 0.002	1717 164 9.55	1698 194 11.43	0.83 0.67, 1.02 0.0653	6576 610 9.28	6576 737 11.21	0.82 0.74, 0.91 0.0002
No	N n %	185 23 12.43	152 22 14.47	0.88 0.49, 1.57 0.7254	52 10 19.23	67 22 32.84	0.54 0.26, 1.14 0.0787	237 33 13.92	219 44 20.09	0.69 0.44, 1.08 0.1124

Subgroup Analysis of Primary endpoint										
		UA/NSTEMI			STEMI			All ACS		
		Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Use of proton pump inhibitor										
Yes	N	2474	2463	0.83	916	882	0.80	3390	3345	0.82
	n	262	310	0.70, 0.98	103	122	0.62, 1.05	365	432	0.72, 0.95
	%	10.59	12.59	0.0319	11.24	13.83	0.0857	10.77	12.91	0.0056
No	N	2570	2567	0.81	853	883	0.77	3423	3450	0.80
	n	207	255	0.67, 0.97	71	94	0.57, 1.05	278	349	0.68, 0.93
	%	8.05	9.93	0.0248	8.32	10.65	0.0986	8.12	10.12	0.0046
Diabetes										
Yes	N	1246	1226	0.70	330	344	0.71	1576	1570	0.70
	n	135	184	0.56, 0.88	45	64	0.49, 1.04	180	248	0.58, 0.85
	%	10.84	15.01	0.0018	13.64	18.61	0.0610	11.42	15.80	0.0002
No	N	3798	3804	0.87	1439	1421	0.83	5237	5225	0.86
	n	334	381	0.76, 1.01	129	152	0.66, 1.05	463	533	0.76, 0.98
	%	8.79	10.02	0.0856	8.96	10.70	0.1174	8.84	10.20	0.0193
Analysis by Ququan Liu, M.D., M.S., Biometrics, FDA										

9.2 Study H7T-MC-TABL(Clinical Study Report: “PRasugrel IN Comparison to Clopidogrel for Inhibition of Platelet Activation and AggrEgation (PRINCIPLE) – TIMI 44”) (Study Dates: August 24, 2006 – June 20, 2007) (Date of Report: October 1, 2007)

9.2.1 Protocol, Amendment, and Post Hoc Changes

The study description was based on the original protocol dated February 28, 2006 and Protocol Amendment (a) dated May 11, 2006. Protocol Amendment (a) was completed prior to enrollment of subjects in the study and included the following changes:

1. The 15 minute sampling times were excluded for the following Phase 1 Platelet Function Measures:
 - a. IPA to 20 μ M ADP
 - b. IPA to 5 μ M ADP
 - c. Maximum platelet aggregation to 20 μ M ADP
 - d. Maximum platelet aggregation to 5 μ M ADP
 - e. Final extent of platelet aggregation (at 6 minutes after ADP addition) to 5 or 20 μ M ADP
2. Under “Myonecrosis Measures,” troponin I was changed to troponin.

9.2.2 Study Design

This was a multicenter, randomized, parallel, double-blind, double-dummy, cross-over, active comparator-controlled study in subjects undergoing elective cardiac catheterization with planned percutaneous coronary intervention (PCI) with coronary stenting. The study had two phases. Phase 1 included study drug loading dose, cardiac catheterization, PCI (if indicated), and daily maintenance dose for 14 ± 2 days in subjects undergoing PCI. In Phase 2, subjects were crossed over to the alternative daily maintenance dose for an additional 14 ± 2 days.

9.2.3 Study Population

The study population included subjects undergoing cardiac catheterization with planned elective PCI with coronary stenting.

9.2.4 Objectives

Primary Objectives:

The primary objectives of the study were

- to compare the inhibition of platelet aggregation (IPA) to 20 μ M adenosine disphosphate (ADP) measured at 6 hours (± 30 minutes) after prasugrel 60 mg loading dose versus clopidogrel 600 mg loading dose (LD) in subjects in the “on treatment population” who did not receive a GPIIb/IIIa inhibitor
- to compare the IPA to 20 μ M ADP measured after 14 ± 2 days of prasugrel 10 mg daily maintenance dose versus the IPA after 14 ± 2 days of clopidogrel 150 mg daily maintenance dose (MD) in the “on treatment population” who have received PCI (this includes subjects receiving clopidogrel and prasugrel in either order during the crossover phase)

Secondary Objectives:

The secondary objectives of the study were

- to measure the inhibition of platelet aggregation to 20 μ M ADP measured at approximately 2 hours after prasugrel 60 mg loading dose versus clopidogrel 600 mg loading dose in subjects in the “on treatment population” who did not receive a GPIIb/IIIa inhibitor
- to compare overall safety and tolerability of prasugrel 60 mg LD and 10 mg daily MD versus clopidogrel 600 mg LD and 150 mg daily MD after 14 ± 2 days in treated subjects who have received PCI. Safety measures

include, but are not limited to, the following: non-CABG-associated TIMI Major Bleeding, non-CABG related TIMI life-threatening bleeding, and non-CABG-related TIMI Minor Bleeding.

- to compare overall safety and tolerability of the following dosing regimens: prasugrel 60 mg LD and 10 mg daily MD for 14 ± 2 days with crossover to clopidogrel 150 mg daily MD for 14 ± 2 days versus clopidogrel 600 mg LD and 150 mg daily MD for 14 ± 2 days in treated subjects who have received PCI. Safety measures include but are not limited to the following: Non-CABG-associated TIMI Major Bleeding, non-CABG-related TIMI life-threatening bleeding, and non-CABG-related TIMI Minor Bleeding.
- to compare prasugrel (60 mg LD, 10 mg MD) versus clopidogrel (600 mg LD, 150 mg MD) in the occurrence of Major Adverse Cardiac Events (MACE) after 14 ± 2 days in treated subjects who have received PCI.
- to compare prasugrel versus clopidogrel on additional measures of platelet inhibition including, but not limited to, thienopyridine hyporesponsiveness, vasodilator-stimulated phosphoprotein (VASP), biomarkers of inflammation, and biomarkers of platelet activation
- to compare prasugrel (60 mg LD, 10 mg MD) versus clopidogrel (600 mg LD, 150 mg MD) in measures of myonecrosis [creatin kinase-MB isoforms (CK-MB), troponin]

9.2.5 Inclusion/Exclusion Criteria

Inclusion Criteria (Reproduced from Sponsor, page 879)

Subjects are eligible to be entered in the study if they meet the following criteria only:

1. Subjects ≥ 18 years of age undergoing cardiac catheterization with planned percutaneous coronary intervention (if coronary anatomy is suitable) for an indication of chest pain +/- anginal equivalent felt by the treating physician to be related to coronary ischemia
2. At least one of the following (a through c)
 - a. Functional study (exercise, or pharmacologic) within the past 8 weeks consistent with ischemia as manifested by at least one of the following:
 - i. a reversible defect on nuclear imaging
 - ii. a reversible wall-motion abnormality by echocardiography
 - iii. horizontal or down-sloping ST-depressions > 1 mm on electrocardiogram (ECG) (if no imaging performed)
 - b. Prior coronary revascularization (PCI or coronary artery bypass grafting (CABG))
 - c. A cardiac catheterization with at least one coronary artery lesion amenable to PCI (not yet performed) within 14 days prior to enrollment

Exclusion Criteria (Reproduced from Sponsor, page 879)

Subjects cannot be entered and will be excluded from the study if they meet **any** of the following criteria:

Cardiovascular Exclusion Criteria

1. Known creatine kinase-myocardial bands (CK-MB) or cardiac troponin greater than the upper limit of normal (ULN) at the time of screening
2. Have a planned PCI procedure as initial treatment for an acute myocardial infarction (MI) (STEMI or NSTEMI), or a planned PCI within 48 hours of fibrinolytic therapy for STEMI
3. Have cardiogenic shock at the time of screening (systolic blood pressure < 90 mm Hg associated with clinical evidence of end-organ hypoperfusion, or subjects requiring vasopressors to maintain systolic blood pressure over 90 mm Hg and associated with clinical evidence of end-organ hypoperfusion)
4. Have refractory ventricular arrhythmias
5. Have New York Heart Association (NYHA) Class IV congestive heart failure (CHF)

Bleeding Risk Exclusion Criteria

6. Have active internal bleeding or history of bleeding diathesis
7. Have clinical findings, in the judgment of the investigator, associated with an increased risk of bleeding

8. Have any of the following:
 - a. Prior history of hemorrhagic stroke
 - b. Intracranial neoplasm, arteriovenous malformation, or aneurysm
 - c. Ischemic stroke \leq 3 months prior to screening
9. Have an International Normalized Ratio (INR) known to be > 1.5 at the time of screening
10. Have a platelet count of $< 100,000/\text{mm}^3$ at the time of screening
11. Have anemia (hemoglobin [Hgb] < 10 gm/dl) at the time of screening

Prior/Concomitant Therapy Exclusion Criteria

12. Have received one or more doses of a thienopyridine (ticlopidine or clopidogrel) ≤ 5 days prior to PCI
13. Have been administered a GPIIb/IIIa inhibitor within the past 7 days or plans to use a GPIIb/IIIa inhibitor during PCI
14. Are receiving or will receive oral anticoagulation or oral antiplatelet therapy (other than aspirin) that cannot be safely discontinued for the duration of the study
15. Are receiving daily treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX2) inhibitors that cannot be discontinued or are anticipated to require > 2 weeks of daily treatment with NSAID or COX2 inhibitors during the study

General Exclusion Criteria

16. Are investigative site personnel directly affiliated with the study or are immediate family of investigative site personnel directly affiliated with the study. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted
17. Are employed by Eli Lilly & Company, Ube Industries Limited, Daiichi Sankyo company Limited, The TIMI Study Group, or the contract research organization (CRO) (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 studies 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.
18. Have received treatment within the last 30 days with a drug or device that has not received regulatory approval for any indication at the time of study entry or are presently enrolled in another drug or device study
19. Have previously completed or withdrawn from this study or any other study investigating prasugrel
20. Are women who are known to be pregnant, who have given birth within the past 90 days, who are breastfeeding, or of child-bearing potential who test negative for pregnancy at Period 1, but refuse to use a reliable method of birth control (that is, barrier, hormonal, or abstinence) during the study
21. Have a concomitant medical illness (for example, terminal malignancy or severe hepatic dysfunction) that in the opinion of the investigator is associated with reduced survival over the expected treatment period (maximum of 35 days)
22. Have a condition associated with poor treatment compliance, including alcoholism, mental illness, or drug dependence
23. Have a history of intolerance or allergy to aspirin or approved thienopyridines (ticlopidine or clopidogrel)

9.2.6 Study Plan

The study had two phases. Phase 1 included study drug loading dose, cardiac catheterization, PCI (if indicated), and daily maintenance dose for 14 ± 2 days in subjects undergoing PCI. In Phase 2, subjects were crossed over to the alternative daily maintenance dose for an additional 14 ± 2 days.

Approximately 180 subjects were to be randomly assigned in parallel fashion to either a dosing regimen of prasugrel plus aspirin or to clopidogrel plus aspirin. Subjects were to receive either prasugrel 60 mg or clopidogrel 600 mg LD in a double-blind, double-dummy fashion. The LD was to be given as a pretreatment approximately 1 hour and no less than 30 minutes prior to the time that cardiac catheterization was expected to begin.

After randomization and prior to study drug, subjects were to undergo sampling for platelet measures and biomarkers. Subjects were to subsequently receive either prasugrel 60 mg or clopidogrel 600 mg LD in a double-blind, double-dummy fashion. The LD was to be given as a pretreatment approximately 1 hour (>30 minutes) prior

to the time that cardiac catheterization was expected to begin. Treated subjects were to undergo platelet function measures at 30 minutes (\pm 5 minutes). Additionally, 2 hours (\pm 10 minutes) after the LD or following completion of diagnostic angiography, treated subjects were also to undergo platelet function measures.

Subjects who did not undergo PCI, were to have platelet function measures at 6 hours (\pm 30 minutes) following the LD and a telephone call for the Day 15 visit to assess clinical endpoints and adverse events.

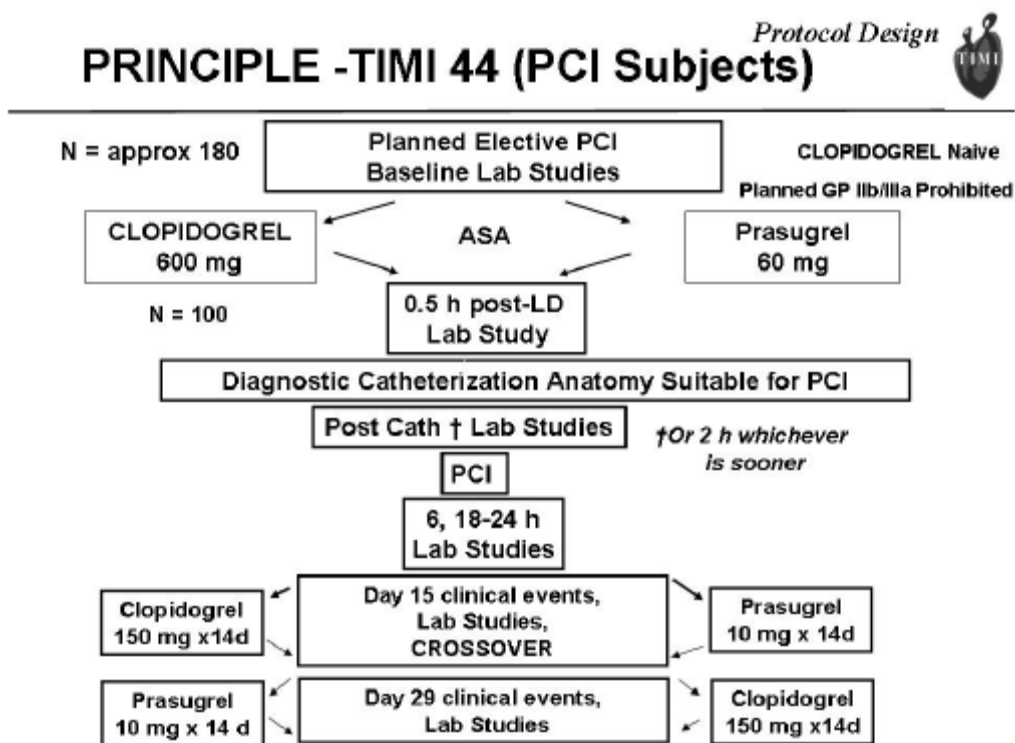
Subjects who were treated and underwent PCI were to have platelet function measures at 6 hours (\pm 30 minutes) and 18-24 hours following the LD. These patients were to receive once daily maintenance dosing of either prasugrel 10 mg or clopidogrel 150 mg per LD assignment and were to follow-up at Day 15 for platelet function measures, inflammatory biomarkers, and clinical endpoint and safety assessments. The first maintenance dose was to be given after the Day 2 platelet measures (18 to 24 hours after loading dose).

At the Day 15 visit, the subject would be "crossed over" to the alternative regimen so that patients previously on clopidogrel would receive prasugrel 10 mg daily and patients previously on prasugrel would receive clopidogrel 150 mg daily for an additional 14 ± 2 days. Subjects would report for a follow-up visit on Day 29.

Procedural anticoagulation with unfractionated heparin, low molecular weight heparin, or bivalirudin was at the discretion of the investigators; however, planned use of glycoprotein (GP) IIb/IIIa receptor inhibitors was prohibited.

The study design is displayed in Figure 28.

Figure 28. Study Design (Protocol H7T-MC-TABL)



(Reproduced from Sponsor, Figure 1, page 876 of 1590)

Oral enteric coated aspirin (325 to 500 mg) was recommended to be administered with the LD of study drug in subjects not receiving chronic aspirin therapy. Subsequently, each subject was to receive a daily enteric coated aspirin (75 to 325 mg).

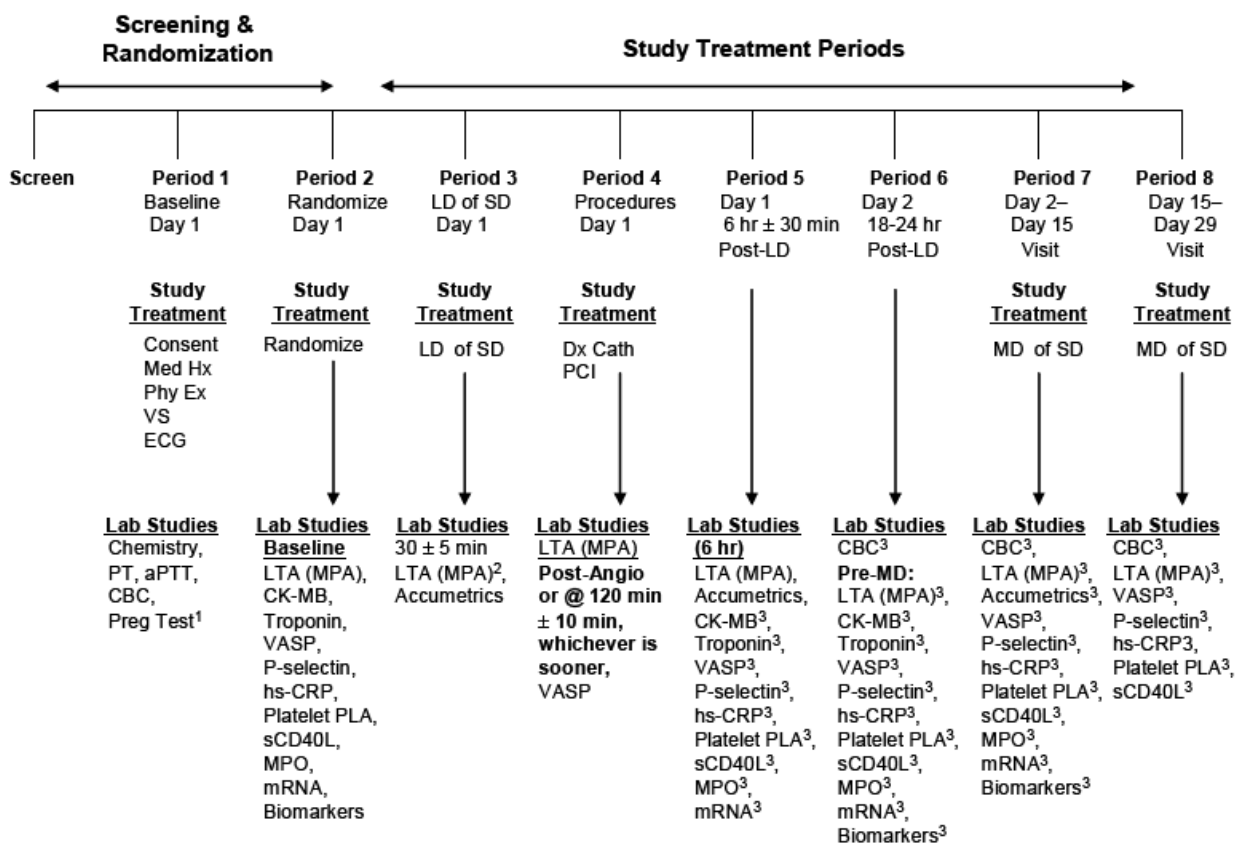
If unfractionated heparin was used during PCI, the recommended target ACT was between 200 to 300 seconds

If the subject required an emergency or urgent CABG or another urgent surgical procedure, study drug was to be temporarily discontinued and restarted when the investigator thought it was safe to do so. If a subject had an elective surgical procedure, including CABG, the study drug was to be discontinued at least 5 days before surgery.

9.2.7 Schedule of Evaluations and Procedures

The schedule of evaluations and procedures is displayed in Figure 29.

Figure 29. Schedule of Evaluations and Procedures (Protocol H7T-MC-TABL)



Abbreviations: Angio=angiography; aPTT=activated partial thromboplastin time; cath=catheterization; Dx=diagnostic; ECG=12-lead electrocardiogram; hr=hour; LD=loading dose; hs-CRP=high sensitivity C-reactive protein; IPA=inhibition of platelet activation; LTA=light transmittance aggregometry; MD=maintenance dose; Med Hx=medical history; min=minute; MPA=mean platelet aggregation; MPO=myeloperoxidase; mRNA=mononuclear cell mRNA; PCI=percutaneous coronary intervention; Phy Ex=physical exam; PLA=Platelet-Leukocyte aggregates; Preg Test=pregnancy test; PT=protime; SD=study drug; VASP=vasodilator-stimulated phosphoprotein; VS=vital signs.

¹Pregnancy test for female subjects of child-bearing potential. ²If the cardiac catheterization is unexpectedly delayed, IPA is also measured at 120 minutes (± 10 minutes).

³Subjects who received PCI.

(Reproduced from Sponsor, Figure TABL.9.2, page 52 of 1590)

Table 52. Study Schedule Protocol PRINCIPLE - TIMI 44 (TABL)

	Screen	Obtain Signed Consent	Randomization	Medical History	Phy Exam and VS	12-lead ECG	Study Drug	Chemistry, PT, aPTT	CBC	LTA (MPA)	Accumetrics (AA, P2Y12)	CK-MB / Troponin	Platelet/Inflammatory Markers ^b	VASP	mRNA	Biomarkers ^k
Screening to Consent	X															
Period 1 (Consent to Randomization)		X		X	X	X		X ^a	X							
Period 2 (Randomization to SD Administration)			X							X		X	X	X	X	X
Period 3 (LD to dx Cath)							X			X ^{c,d}	X ^c					
Period 4 (Cath to PCI)										X				X		
Period 5 (6 hr ± 30 minutes post-LD)										X ^e	X ^e	X ^{e,f}	X ^{e,f}	X ^{e,f}	X ^{e,f}	
Period 6 – Day 2 (18-24 hr post-LD)									X ^f	X ^f		X ^f	X ^f	X ^f	X ^f	X ^f
Period 7/Day 15 (1 st MD to Day 15) ^j							X ^{h,f}		X ^g	X ^g	X ⁱ		X ^g	X ^g	X ⁱ	X ⁱ
Period 8/Day 15 to Day 29							X ^f		X ^g	X ^g			X ^g	X ^g		

Abbreviations: AA = Aspirin Assay; aPTT = activated partial thromboplastin; CBC = complete blood count; Cath = cardiac catheterization; CK-MB = creatine kinase-MB isoform; dx = diagnostic; ECG = electrocardiogram; hsCRP = high sensitivity C-Reactive Protein; IPA = inhibition of platelet aggregation; LD = loading dose; LTA = light transmittance aggregometry; MPA = maximum platelet aggregation; MD = maintenance dose; MPO = myeloperoxidase; mRNA = mononuclear cell mRNA; PCI = percutaneous coronary intervention; Phy = physical; PLA = platelet leukocyte aggregates; PT = prothrombin; sCD40L = soluble CD40 Ligand; SD = study drug; VASP = vasodilator-stimulated phosphoprotein; VS = vital signs.

^a This also includes a pregnancy test for female subjects of child-bearing potential (see [Appendix 16.1.1](#)).

^b P-selectin, hs-CRP, PLA, sCD40L, MPO (MPO will not be drawn on Day 29).

^c Labs to be drawn at 30 minutes (± 5 minutes).

^d If the cardiac catheterization is unexpectedly delayed, IPA is also measured at 120 minutes (± 10 minutes).

^e Labs to be drawn at 6 hours (± 30 minutes). If 6 hours (± 30 minutes) occurs during PCI, samples may be obtained immediately following PCI.

^f For those subjects who received PCI.

^g Labs to be drawn once on Day 15 and once on Day 29.

^h Daily MD of study drug. At Day 15, subjects will be crossed over to the alternate therapy.

ⁱ To be drawn once on Day 15.

^j For a subject who was treated and did not receive PCI, a telephone call will be performed for Day 15.

^k Serum and plasma samples will be stored. These samples may be used to measure markers relevant to the study of subjects with coronary artery disease. The samples will be destroyed within 20 years after last patient visit for the study. The samples will be stored in the United States by the TIMI Study Group at Brigham and Women's Hospital in Boston, Massachusetts.

Note: Shading denotes core labs.

(Reproduced from Sponsor, Table TABL.9.2, pages 60-61 of 1590)

9.2.8 Endpoints

9.2.8.1 Primary Efficacy Measures

1. Inhibition of platelet aggregation (IPA) to 20 μ M adenosine diphosphate (ADP) by light transmission aggregometry (LTA) at 6 hours (\pm 30 minutes) after loading dose of study drug. IPA is defined as $(1 - [\text{maximal platelet aggregation at time } x \text{ after drug treatment}] / [\text{maximal platelet aggregation before drug treatment}]) \times 100$.
2. IPA to 20 μ M ADP measured after 14 ± 2 days of prasugrel 10 mg daily maintenance dose (MD) and the IPA after 14 ± 2 days of clopidogrel 150 mg daily MD (this includes subjects receiving clopidogrel and prasugrel in either order during the crossover phase)

9.2.8.2 Additional Efficacy Measures

Phase 1

1. Platelet Function Measures

- IPA to 20 μ M ADP at 30 min, 2 hours, 18 to 24 hours following loading dose of study drug
- IPA to 5 μ M ADP at 30 min, 2 hours, 6 hours, 18 to 24 hours following loading dose of study drug
- Maximum platelet aggregation (MPA) to 20 μ M ADP at 30 min, 2 hours, 6 hours, 18 to 24 hours following loading dose of study drug
- MPA to 5 μ M ADP at 30 min, 2 hours, 6 hours, 18 to 24 hours following loading dose of study drug
- Final extent of platelet aggregation (at 6 minutes after ADP addition) to 5 or 20 μ M ADP at 30 min, 2 hours, 6 hours, 18 to 24 hours following loading dose of study drug
- Thienopyridine hyporesponsiveness defined as IPA to 20 μ M ADP $< 20\%$ at 2 hours, 6 hours, and 18 to 24 hours following loading dose of study drug
- Vasodilator-stimulated phosphoprotein (VASP) phosphorylation ratio at 2 hours, 6 hours, 18 to 24 hours and 14 ± 2 days following loading dose of study drug
- sCD40L at 6 and 18 to 24 hours after loading dose of study drug and after 14 ± 2 days of maintenance therapy with study drug
- Peak sCD40 ligand (L) during follow-up (out to 14 ± 2 days)
- Platelet P-selectin at 6 and 18 to 24 hours after loading dose of study drug and after 14 ± 2 days of maintenance therapy with study drug
- Peak platelet P-selectin during follow-up (out to 14 ± 2 days)
- Platelet-leukocyte aggregates (PLA) at 6 and 18 to 24 hours after loading dose of study drug and after 14 ± 2 days of maintenance therapy with study drug
- Peak PLA during follow-up (out to 14 ± 2 days)

2. Inflammation Measures

- hs-CRP, myeloperoxidase (MPO) at 6 and 18 to 24 hours after loading dose of study drug and after 14 ± 2 days of maintenance therapy with study drug
- Peak hs-CRP, MPO during follow-up (out to 14 ± 2 days)

3. Myonecrosis Measures

- Creatine kinase-myocardial bands (CK-MB), troponin at 6 and 18 to 24 hours
- CK-MB $> 1 \times$ upper limit of normal (ULN) during the first 24 hours after PCI
- CK-MB $> 2 \times$ ULN during the first 24 hours after PCI
- CK-MB $> 3 \times$ ULN during the first 24 hours after PCI
- CK-MB $> 5 \times$ ULN during the first 24 hours after PCI
- CK-MB $> 10 \times$ ULN during the first 24 hours after PCI

- Troponin > ULN during the first 24 hours after PCI
 - Troponin > decision limit for myocardial infarction (MI) during the first 24 hours after PCI
 - Peak CK-MB, troponin during follow-up
4. The major clinical efficacy measure is MACE, a composite of cardiovascular (CV) death, myocardial infarction (MI), stroke, during 14 ± 2 days of maintenance therapy in subjects who were treated and received PCI.
5. Other clinical endpoints during 14 ± 2 days of maintenance therapy in subjects who were treated and received PCI:
- Subacute stent thrombosis
 - Urgent target vessel revascularization (UTVR)
 - Individual components of MACE

Phase 2

1. Platelet Function Measures

- IPA to 5 μ M ADP at the end of the second phase (pooled subject data from both crossover periods)
- Final extent of platelet aggregation to 5 or 20 μ M ADP at the end of the second phase
- Thienopyridine hyporesponsiveness defined as IPA to 20 μ M ADP < 20% at the end of the second phase
- VASP phosphorylation ratio at the end of the second phase
- sCD40L level at the end of the second phase
- Platelet P-selectin level at the end of the second phase
- PLA level at the end of the second phase
- hs-CRP at the end of the second phase

9.2.9 Safety Measures

9.2.9.1 Primary Safety Measure

Non-CABG related TIMI significant bleeding defined as the occurrence of TIMI major or minor bleeding in the treated population at the Day 15 visit

9.2.9.2 Other Prespecified Safety Measures

1. Non-CABG-related TIMI Major bleeding
2. Non-CABG-related TIMI life-threatening bleeding
3. Non-CABG-related TIMI Minor bleeding

9.2.10 Definitions

- **Non-CABG-related TIMI major bleeding:** any intracranial hemorrhage (ICH) OR any clinically overt bleeding (including bleeding evident on imaging studies) associated with a fall in hemoglobin (Hgb) of ≥ 5 gm/dL from baseline (accounting for the effect of transfusions on change in Hgb, defined as one unit packed red blood cells = 1 gm/dL Hgb = 3% hematocrit [Hct])
- **Non-CABG-related TIMI life-threatening bleeding:** any non-CABG-related TIMI major bleeding that is fatal, leads to hypotension that requires treatment with intravenous inotropic agents, OR requires surgical

intervention for ongoing bleeding, OR necessitates the transfusion of 4 or more units of blood (whole blood or packed red blood cells [RBC]) over a 48-hour period, OR any symptomatic ICH

- **Non-CABG-related TIMI minor bleeding:** any clinically overt bleeding (including bleeding evident on imaging studies) associated with a fall in Hgb of ≥ 3 gm/dL but < 5 gm/dL from baseline (accounting for the effect of transfusions on change in Hgb, defined as one unit packed red blood cells = 1 gm/dL Hgb = 3%).

Table 53. TIMI Hemorrhage Criteria

TIMI Hemorrhage Criteria ^a			
	ICH	Clinically Overt (including imaging)	Hgb Drop ^{b,c} (g/dL)
Major Bleeding	×	×	≥ 5
Minor Bleeding	-	×	3 to < 5
Minimal Bleeding	-	×	< 3

Abbreviations: Hgb = hemoglobin; ICH = intracranial hemorrhage; TIMI = The TIMI Study Group.

^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% hematocrit (Hct).

^c Hgb drop must be associated with clinically overt bleeding.

(Reproduced from Sponsor, Table 2, page 893)

- **Cardiovascular Death (CV Death):** death due to documented cardiovascular cause. Additionally, death not clearly attributable to noncardiovascular causes will be considered CV death.
- **Nonfatal Myocardial Infarction (MI):** the definition of MI is adapted from the standard ACC definition. The biomarker levels required for the diagnosis of MI are dependent on relationship to cardiac procedures. If the suspected event is within 48 hours of PCI, the CK-MB value must be $> 3x$ the ULN, on a single measurement; no symptoms are required.

If the suspected event is within 48 hours of CABG, the CK-MB value (on a single measure) must be $> 10x$ the upper limit of normal; no symptoms are required.

If the suspected event is not within 48 hours of PCI or CABG, the diagnostic criteria are met if the subject has CK-MB or cardiac troponin $> ULN$ and the presence of either chest pain > 20 minutes in duration or ST-segment deviation > 1 mm on the ECG. If cardiac biomarkers are elevated at the time of suspected onset of an MI, there must be demonstration that biomarkers were falling prior to the suspected event and that the peak post-event CK-MB is $> 50\%$ higher than the previous trough value.

In any clinical circumstance, the appearance of new Q-waves on the electrocardiogram (ECG) distinct from the baseline electrocardiogram (ECG) distinct from the baseline ECG or pathologic evidence (such as autopsy) showing a new myocardial infarction felt to have occurred after loading dose of study drug would be considered appropriate evidence for MI, as would ST-segment elevation (> 1 mm in 2 contiguous leads) lasting for more than 20 minutes and accompanied by ischemic chest pain or hemodynamic decompensation.

- **Stroke:** the rapid onset of new-persistent neurologic deficit lasting more than 24 hours. In the case of clinical diagnosis of stroke, computed tomography (CT) or magnetic resonance imaging (MRI) scan imaging is strongly recommended. Stroke will be classified as either ischemic or hemorrhagic based on imaging data, if available or uncertain cause if imaging data is not available.

- **Urgent Target Vessel Revascularization (UTVR):** PCI or CABG for recurrent ischemia that, in the investigator's opinion, cannot be delayed for more than 24 hours and is defined by the investigator as a non-elective procedure. Revascularization, either with PCI or CABG, must include the vessel(s) dilated at the initial procedure.
- **Subacute Stent Thrombosis (SAT):** documented stent occlusion within 30 days following the completion of the index procedure felt to be thrombotic in nature by the treating physician. Thrombosis occurring during the index procedure will not be considered SAT.
- **Major Adverse Cardiac Event (MACE):** the occurrence of any of the following: CV death, MI, stroke, or UTVR.

9.2.11 Statistical Considerations

The primary endpoint was the between treatment comparison of mean inhibition of platelet aggregation (IPA) to 20 μ M ADP 6 hours (\pm 30 minutes) after the LD of study drug. The IPA at 6 hours was the relative decrease in maximum platelet aggregation (MPA) from the baseline to MPA at 6 hours after the loading dose multiplied by 100. The primary comparison was the IPA with prasugrel 60 mg LD with clopidogrel 600 mg relative to the primary endpoint at a two-sided significance level of 0.05. The primary analysis was analysis of covariance (ANCOVA), with factors for treatment group and study site (pooled, where necessary) and a covariate for MPA at baseline, in the "on treatment population" who did not receive GP IIb/IIIa inhibitors (receiving as bailout).

The sponsor was also interested in evaluating the "on treatment population" undergoing PCI who did not receive GP IIb/IIIa inhibitors.

There were no adjustments for multiple comparisons.

In Protocol Amendment (a) dated May 11, 2006, the "on treatment population" was defined as

"all randomized subjects who [had] received study therapy according to the protocol. For measures within the first 24 hours of therapy, this [would] include all subjects who received the full loading dose of study drug. For the follow-up visits (Day 15 visit and Day 29 visit), this [would] include subjects who [had] missed no more than 2 doses within the 14 days prior to the follow-up date and who [had] taken at least one dose of medication within 24 hours of the follow-up visit."

In the Statistical Analysis Plan (SAP) dated July 25, 2007, the definitions of the study populations to be analyzed were defined as follows:

- **On-treatment population:** consisted of all subjects that received the loading dose of the study medication. This was defined as subjects where the start time of study medication had been provided, or it had otherwise been confirmed that the subject took the study medication.
- **Acute phase population:** consisted of subjects in the "on-treatment population" who did not receive a glycoprotein (GP) IIb/IIIa antagonist. This population would be used for all analyses of IPA within 24 hours after the LD

Analysis of IPA measurements within 24 hours after the LD would be repeated amongst all subjects in the "acute phase population" that underwent a PCI after receiving the loading dose of study medication.

- The "chronic phase population" would consist of subjects in the "on-treatment population" that received a PCI irrespective of whether they received a GP IIb/IIIa inhibitor. This population was to be used for all analyses of IPA more than 24 hours after the LD.

In the Clinical Study Report dated October 1, 2007, the “on-treatment population” is defined as

“All subjects that received the loading dose of the study medication. This is defined as subjects where the start time of study medication was provided, or it was otherwise confirmed that the subject took the study medication.”

The sponsor estimated that 96 subjects undergoing PCI and not receiving a GP IIb/IIIa inhibitor assigned equally between prasugrel and clopidogrel would provide 90% power to demonstrate higher IPA for prasugrel. Sample size calculations were based on the following assumptions:

1. prasugrel 60 mg yields 15% (absolute) higher mean IPA compared to clopidogrel 600 mg at 6 hours
2. intersubject standard deviation (within a laboratory) of 25% exists for clopidogrel and 15% for prasugrel

The sponsor estimated that about 180 subjects would need to be randomized so that 100 subjects would undergo PCI and there would be at least 96 evaluable subjects with baseline and 6 hour sampling for light transmission aggregometry (LTA).

No interim analysis was planned for the study.

9.2.12 Results

9.2.12.1 Sites, Investigators, and Study Dates

The study was conducted from August 24, 2006 to June 20, 2007. There were 15 principal investigators at a total of 14 study centers in 4 countries.

9.2.12.2 Good Practice, Monitoring, and Protocol Deviations

The study was conducted in accordance with Good Clinical Practices and the Declaration of Helsinki.

There were a total of 19 (9.5%) subjects with protocol violations including 8 (7.8%) in the prasugrel/clopidogrel group and 11 (11.1%) in the clopidogrel/prasugrel group. Two subjects in each treatment group were in serious violation and required withdrawal of their data from the analysis. The protocol violations are summarized in Table 54.

Table 54. Protocol Violations (TABL)

	Prasugrel/Clopidogrel N=102	Clopidogrel/Prasugrel N=99	Total N=201
Any Protocol Violations	8 (7.8%)	11 (11.1%)	19 (9.5%)
Retrospectively found to violate any of the entry criteria	2	6	8
Failed to provide written informed consent	0	0	0
Received any prohibited medications	5	5	10
Did not attend all of the study visits	1	1	2
Did not receive the correct study drug	1	0	1
Poorly compliant with the study drug	1	3	4

	Prasugrel/Clopidogrel N=102	Clopidogrel/Prasugrel N=99	Total N=201
Any Significant Protocol Violations	2 (2.0%)	2 (2.0%)	4 (2.0%)
<p>MD = maintenance dose; N = number of subjects. Note: Poor compliance defined as percentage compliance < 80% or > 120%. Notes: No protocol violations were identified that necessitated excluding a subject from the entire study. The following subjects violated the protocol in a manner that could have compromised individual assessments; these subjects were excluded from the analysis of all efficacy measurements at the relevant time point(s):</p> <ul style="list-style-type: none"> • Subject TABL-102-0008 received open-label clopidogrel for 3 days between the Day 2 and Day 15 visits (Day 15 data was excluded) • Subject TABL-301-0055 received open-label clopidogrel and phenprocoumon (for a serious adverse event of atrial fibrillation 5 days post LD) on an ongoing basis after Day 2 (Day 15 and Day 29 data was excluded) • Subject TABL-301-0059 received open-label clopidogrel for 5 days between the Day 2 and Day 15 visits (Day 15 data was excluded) • Subject TABL-302-0003 received the incorrect MD for 8 days between the Day 2 and Day 15 visits (Day 15 data was excluded) • Source: Table TABL.14.5 <p>(Reproduced from Sponsor, Table TABL.10.3, Protocol Violations, page 83 of 1590)</p>			

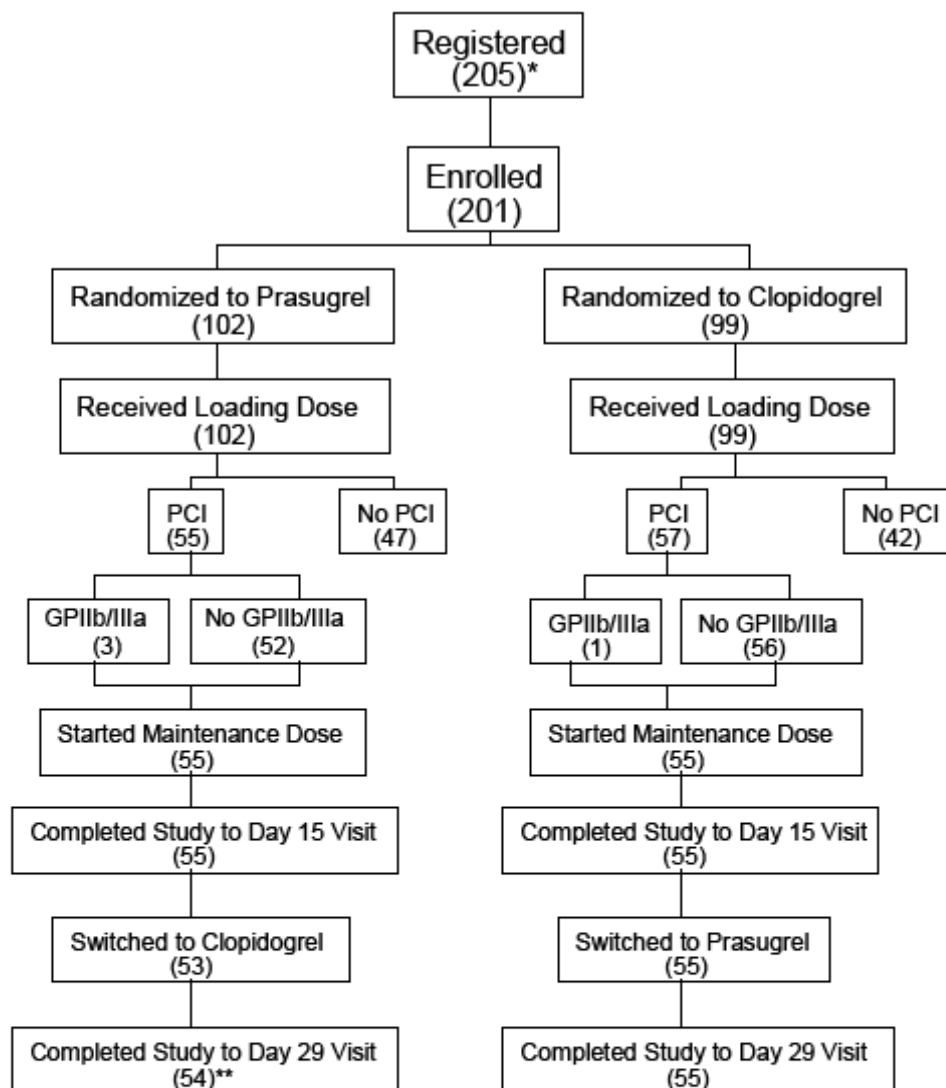
9.2.12.3 Disposition of Subjects

A total of 205 subjects were registered in the study via the interactive voice response system (IVRS) and 201 subjects were enrolled, including 102 subjects randomized to prasugrel and 99 subjects randomized to clopidogrel. Of the 102 subjects in the prasugrel treatment group, 54 subjects (52.9%) completed the trial, compared to 55 subjects (55.6%) out of the 99 subjects in the clopidogrel treatment group.

Four subjects withdrew from the study prior to taking study drug LD. One subject withdrew consent due to elevated cardiac enzymes, which was an exclusion criterion. Another subject was referred for stress echocardiography between enrollment and cardiac angiography and required coronary artery bypass grafting with mitral valve replacement. The last two subjects withdrew because one decided not to participate in the study after a discussion with his physician and the other withdrew consent after several unsuccessful attempts at phlebotomy.

Subject disposition is displayed in Figure 30.

Figure 30. Subject Disposition (TABL)



Abbreviations: GPIIb/IIIa = glycoprotein IIb/IIIa; PCI = Percutaneous Coronary Intervention

*Four subjects were registered via the Interactive Voice Response System (IVRS), but withdrew from the study prior to administration of the allocated study drug loading dose (LD; see [Section 10.1](#)). No further data were collected from these subjects and they were not considered to have been enrolled into the study.

**One subject ceased study drug on Day 10 on the advice of The Thrombolysis in Myocardial Infarction (TIMI) Study Group medical hotline and did not provide any further efficacy data. The subject did not take clopidogrel during the second maintenance dose (MD) period; however, all other study data was complete and the subject was considered to have completed the study.

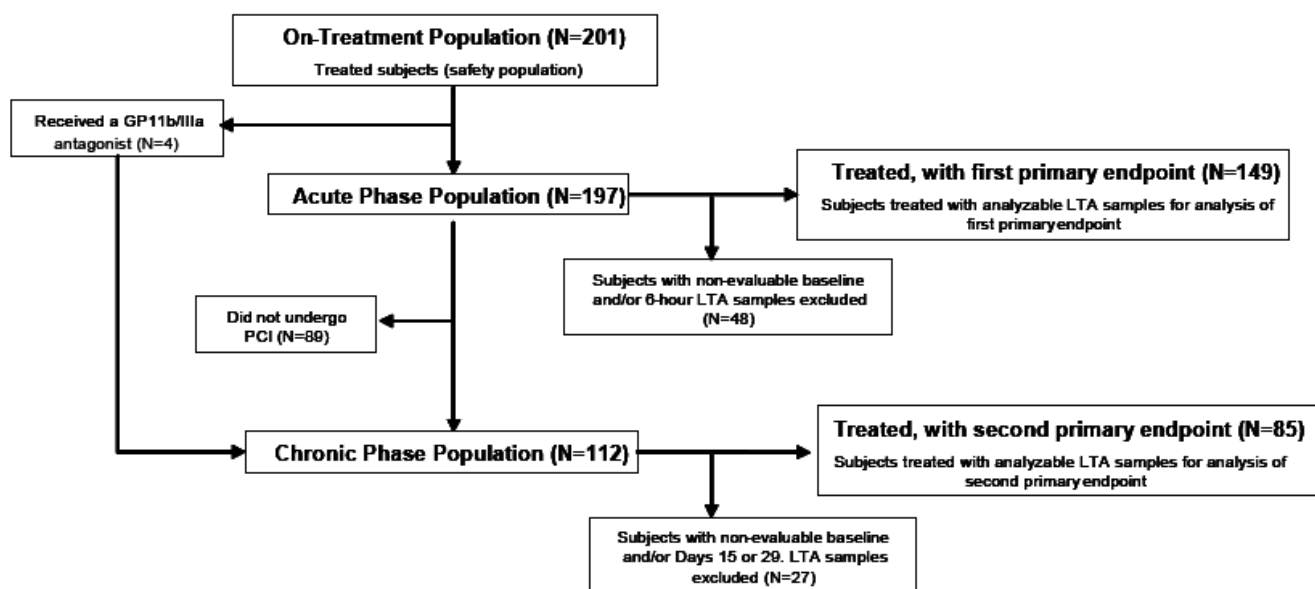
(Reproduced from Sponsor, Figure TABL.10.1, Subject Disposition, page 79 of 1590)

Fours subjects (2%) received GP IIb/IIIa inhibitors, including three subjects (2.9%) in the prasugrel/clopidogrel treatment group and one subject (1.0%) in the clopidogrel/prasugrel treatment group. Therefore, a total of 197 subjects were in the acute phase population, including 99 subjects in the prasugrel/clopidogrel group and 98 subjects in the clopidogrel/prasugrel group. Of the 99 subjects in the prasugrel/clopidogrel group, 52 subjects underwent PCI. Of the 98 subjects in the clopidogrel/prasugrel group, 56 subjects underwent PCI.

The “chronic phase population,” defined as all subjects in the on-treatment population who underwent PCI, regardless of the use of a GPIIb/IIIa antagonist, was comprised of 112 subjects, including 55 (53.9%) in the prasugrel/clopidogrel group and 57 (57.6%) in the clopidogrel/prasugrel group. Of the 55 subjects in the prasugrel/clopidogrel group, all subjects started their first MD period (Day 2 through Day 15 visits), 53 started the crossover MD period, and 54 completed the study. On the advice of the Thrombolysis in Myocardial Infarction (TIMI) medical hotline, one subject discontinued study drug on Day 10. Although the subject did not take clopidogrel during the second maintenance dose (MD) period, the sponsor considered the subject to have completed the study because all other study data was complete.

The study populations, including the “on treatment population,” “acute phase population,” and “chronic phase population” are summarized in Figure 31.

Figure 31. Study Populations (TABL)



Abbreviations: GP11b/111a = glycoprotein 11b/111a; IVRS = Interactive Voice Response System; LD = loading dose; LTA = light transmission aggregometry;
N = number of subjects; PCI = percutaneous coronary intervention

(Reproduced from Sponsor, Figure TABL.11.1, Study Populations, page 85 of 1590)

9.2.12.3.1 Premature Discontinuations

In addition to the four subjects who discontinued from the study prior to LD, three subjects (1.5%) prematurely discontinued from the study, including one subject in the prasugrel treatment group (1.0%) and two subjects in the clopidogrel treatment group (2.0%). All subjects withdrew consent to follow-up.

Of the 112 subjects who underwent PCI, five subjects (4.5%) prematurely discontinued study drug but completed the study visits. In the prasugrel treatment group, two (3.6%) of the 55 subjects prematurely discontinued study drug, compared to three (5.3%) of the 57 subjects in the clopidogrel treatment group. In the prasugrel treatment group, one subject experienced the adverse event of deep venous thrombosis during the first maintenance dose

period, leading to study drug discontinuation on the recommendation of the TIMI Study Group. Additionally, one subject did not want to continue to take study drug when crossed over to clopidogrel.

Of the 3 clopidogrel/prasugrel subjects who underwent PCI but prematurely discontinued study drug, two subjects did not receive a MD of study drug (one failed to meet the entry criteria and one elected to discontinue study drug) and one subject elected to stop taking study drug during the second (prasugrel) MD period.

9.2.12.4 Demographics and Baseline Characteristics

With the exception of subjects randomized to prasugrel loading dose having lower weights and heights, the baseline characteristics seemed to be similar between treatment groups. The demographic data are summarized in Table 55.

Table 55. Demographic and Baseline Characteristics (TABL)

Characteristics		Prasugrel/Clopidogrel (N= 102)	Clopidogrel/Prasugrel (N=99)	Total (N=201)
Sex	Male	73 (71.6%)	77 (77.8%)	51 (25.4%)
Age (years)	N	102	99	201
	Mean	64.0	63.8	63.9
	SD	10.73	9.38	10.06
	≥ 75 years	16 (15.7%)	13 (13.1%)	29 (14.4%)
Race	Caucasian	97 (95.1%)	94 (94.9%)	191 (95.0%)
Weight (kg)	N	102	98	200
	Mean	82.73	88.12	85.37
	SD	16.91	19.66	18.46
Height (cm)	N	102	97	199
	Mean	169.8	172.9	171.3
	SD	8.48	8.95	8.83
Prior MI		31 (30.4%)	28 (28.3%)	59 (29.4%)
Prior PCI		42 (41.2%)	37 (37.4%)	79 (39.3%)
Prior CABG		17 (16.7%)	22 (22.2%)	39 (19.4%)
Hypertension		87 (85.3%)	77 (77.8%)	164 (81.6%)
Congestive Heart Failure		36 (35.3%)	35 (35.4%)	71 (35.3%)
Peripheral Arterial Disease		9 (8.8%)	8 (8.1%)	17 (8.5%)
Cerebrovascular Disease (any)		8 (7.8%)	7 (7.1%)	15 (7.5%)
Dyslipidemia		92 (90.2%)	86 (86.9%)	178 (88.6%)
Diabetes Mellitus		33 (32.4%)	29 (29.3%)	62 (30.8%)
Family h/o premature CAD		38 (38.2%)	35 (35.4%)	74 (36.8%)

Characteristics		Prasugrel/Clopidogrel (N= 102)	Clopidogrel/Prasugrel (N=99)	Total (N=201)
Smoking	Current	18 (17.6%)	16 (16.2%)	34 (16.9%)
	Former	32 (31.4%)	35 (35.4%)	67 (33.3%)
	Never	52 (51.0%)	48 (48.5%)	100 (49.8%)
Reproduced from Sponsor, Table TABL.11.2, page 89 of 1590)				

9.2.12.5 Compliance

There were no instances of poor compliance during the LD period; however, one subject taking prasugrel and three subjects taking clopidogrel were poorly compliant (percentage compliance < 80% or > 120%) during the MD period.

9.2.12.6 Sampling

During the study, each subject contributed 1 blood sample for each time point. There were 149 non-evaluable samples from 79 subjects for maximal platelet aggregation (MPA) to 20 µM adenosine disphosphate, including 94 from the prasugrel/clopidogrel group (44 subjects) and 55 from the clopidogrel/prasugrel group (35 subjects). However, the percentages of evaluable samples for IPA and MPA were not significantly different between prasugrel and clopidogrel at each LTA time point.

9.2.12.7 Primary Efficacy Endpoint

9.2.12.7.1 IPA with 20 µM ADP by LTA at 6 hours (± 30 minutes) after LD of study drug.

As shown in Table 56, prasugrel significantly inhibited platelet aggregation at 6 hours post loading dose compared to clopidogrel (p < 0.0001). However, the standard deviation between treatment groups was also statistically significant (p < 0.0001).

Table 56. Sponsor's Analysis: IPA by LTA with 20 µM ADP 6 Hours post LD (Acute Phase Population) (TABL)

Timing		Prasugrel/ Clopidogrel (N=99)	Clopidogrel/ Prasugrel (N=98)	Difference Prasugrel – Clopidogrel (95% CI)	p-value
6 hours post LD	N	72	77		
	Mean	74.81	31.77	43.21 (38.04, 48.38) ^a	<0.0001 ^a
	SD	13.01	21.07		<0.0001*
	Median	77.03	31.43		
ANCOVA=analysis of covariance; CI=confidence interval; LD=loading dose. ^a Group means for data analyzed using an ANCOVA model with factors for study treatment and pooled study site, and a covariate for baseline MPA, assuming unequal group variances. *p-value to compare group variance obtained from an F-test. Reproduced from Sponsor, Table TABL.11.5, page 95 of 1590.					

9.2.12.7.2 IPA to 20 µM ADP at 14 ± 2 days

As shown in Table 57, the prasugrel treatment group had significantly higher inhibition of platelet aggregation and significantly higher least-squares mean inhibition of platelet aggregation over the 14 ± 2 days. The sponsor found no carry-over effect ($p = 0.9675$).

Table 57. Sponsor's Analysis: IPA to 20 µM ADP at 14 ± 2 days (Chronic Phase Population) (TABL)

Timing		Prasugrel/ Clopidogrel (N=99)	Clopidogrel/ Prasugrel (N=98)	Difference Prasugrel – Clopidogrel (95% CI)	p-value
Day 15 visit (14 ± 2 days)	N	40	46		
	Mean	61.94	45.40	15.72 (9.24, 22.20) ^a	< 0.0001 ^a
	SD	17.91	19.89		0.5054*
	Median	63.45	49.68		
Maintenance Dose (14 ± 2 days)	N	85 ^b	86 ^c		
	LS Mean	55.48	40.55	14.93 (10.60, 19.26) ^d	<0.0001 ^d
Treatment order					0.9675 ^d
<p>ANCOVA=analysis of covariance; CI=confidence interval; LSM=least-squares mean. ^aGroup means for data analyzed using an ANCOVA model with factors for study treatment and pooled study site, and a covariate for baseline MPA, assuming unequal group variances. ^bThis number represents the total number of evaluable samples from subjects that received prasugrel in each MD period (40 from the Day 15 visit and 45 from the Day 29 visit). ^cThis number represents the total number of evaluable samples from subjects that received clopidogrel in each MD period (46 from the Day 15 visit and 40 from the Day 29 visit). ^dGroup means for combined Day 15 and Day 29 data analyzed using an ANCOVA model with factors for pooled study site, and a covariate for baseline MPA, assuming unequal group variances. *p-value to compare group variance obtained from an F-test. Reproduced from Sponsor, Table TABL.11.5, page 95 of 1590.</p>					

9.2.12.8 Additional Efficacy Measures

9.2.12.8.1 IPA to 20 µM ADP at 30 min, 2 hours, 18 to 24 hours Following Loading Dose of Study Drug

Subjects in the prasugrel treatment group had significantly greater inhibition of platelet aggregation to 20 µM ADP at 30 minutes, 2 hours, and 18 to 24 hours post loading dose, compared to the clopidogrel treatment group. However, the standard deviations between treatment groups were significant at all time points.

Table 58. Sponsor's Analysis: IPA to 20 µM ADP at 30 min, 2 hours, 18 to 24 hours Following Loading Dose of Study Drug

Timing		Prasugrel/ Clopidogrel (N=99)	Clopidogrel/ Prasugrel (N=98)	Difference Prasugrel – Clopidogrel (95% CI)	p-value
30 minutes post LD	N	70	73		
	Mean	30.79	4.92	26.04 (18.91, 33.16) ^a	<0.0001 ^a
	SD	29.02	13.19		<0.0001*
	Median	32.24	6.74		

Timing		Prasugrel/ Clopidogrel (N=99)	Clopidogrel/ Prasugrel (N=98)	Difference Prasugrel – Clopidogrel (95% CI)	p-value
2 hours post-LD	N	74	78		
	Mean	64.54	20.32	44.75 (38.35, 51.15) ^a	< 0.0001 ^a
	SD	20.43	20.22		0.9294*
	Median	70.06	18.39		
6 hours post-LD	N	72	77		
	Mean	74.81	31.77	43.21 (38.04, 48.38) ^a	< 0.0001 ^a
	SD	13.01	21.07		<0.0001*
	Median	77.03	31.43		
18 to 24 hours post-LD	N	39	46		
	Mean	69.25	32.62	36.40 (29.04, 43.76) ^a	< 0.0001 ^a
	SD	13.97	19.85		0.0284*
	Median	71.62	32.39		
ANCOVA=analysis of covariance; CI=confidence interval; LD=loading dose; N=number of subjects; SD=standard deviation. ^aGroup means for data analyzed using an ANCOVA model with factors for study treatment and pooled study site, and a covariate for baseline MPA, assuming unequal group variances. *p-value to compare group variance obtained from an F test. Reproduced from Sponsor, Table TABL.11.5, page 95 of 1590.					

9.2.12.8.2 IPA to 5 μ M ADP at 30 min, 2 hours, 6 hours, 18 to 24 hours Following Loading Dose of Study Drug
As shown in Table 59, there was a significantly higher mean IPA for prasugrel compared to clopidogrel at all time points. However, the standard deviations between treatment groups were statistically significant for all time points except 2 hours post loading dose.

Table 59. Sponsor's Analysis: Inhibition of Platelet Aggregation with 5 μ M Adenosine Diphosphate (Acute Phase Population) (TABL)

Timing		Prasugrel/ Clopidogrel (N=99)	Clopidogrel/ Prasugrel (N=98)	Difference* Prasugrel – Clopidogrel (95% CI)	p-value*
30 minutes post LD	N	68	72		
	Mean	34.70	4.32	29.68 (22.10, 37.27)	<0.0001
	SD	28.21	18.067		0.003
	Median	37.87	5.57		
2 hours post-LD	N	74	75		
	Mean	66.19	23.95	42.61 (35.80, 49.43)	<0.001
	SD	20.82	21.97		0.6461
	Median	72.81	24.42		
6 hours post-LD	N	71	76		
	Mean	76.21	36.80	39.38 (33.49, 45.28)	<0.0001
	SD	13.11	23.17		<0.0001
	Median	77.78	37.14		

Timing		Prasugrel/ Clopidogrel (N=99)	Clopidogrel/ Prasugrel (N=98)	Difference* Prasugrel – Clopidogrel (95% CI)	p-value*
18 to 24 hours post-LD	N	39	48		
	Mean	70.97	34.48	36.36 (28.67, 44.05)	< 0.0001
	SD	12.58	21.85		0.0007
	Median	72.84	33.79		
ANCOVA=analysis of covariance; CI=confidence interval; LD=loading dose; N=number of subjects; SD=standard deviation. *Group means analyzed using an Analysis of Covariance model with factors for study treatment and pooled study site, and a covariate for baseline MPA, assuming unequal group variances. p-value to compare group variances obtained from an F-test. Reproduced from Sponsor, Table TABL.14.44, pages 279-280 of 1590.					

9.2.12.8.3 Maximum Platelet Aggregation to 20 µM ADP at 30 min, 2 hours, 6 hours, and 18 to 24 hours Following Loading Dose of Study Drug

Maximum platelet aggregation was significantly lower in the prasugrel treatment group, compared to clopidogrel, at 30 minutes, 2 hours, 6 hours, and 18 to 24 hours following the loading dose. However, standard deviations for most time points were significant, and the confidence interval for the difference between the prasugrel-clopidogrel treatment groups was large at Day 15, making these results less certain.

Table 60. Sponsor's Analysis: Maximum Platelet Aggregation to 20 µM ADP at 30 minutes, 2 hours, 6 hours and 18 to 24 hours following Loading Dose of Study Drug (Acute Phase Population) (TABL)

Timing		Prasugrel/ Clopidogrel (N=99)	Clopidogrel/ Prasugrel (N=98)	Difference* Prasugrel – Clopidogrel (95% CI)	p-value
Pre-treatment	N	84	84		
	Mean	75.86	76.95		0.5140*
	SD	11.87	9.727		
	Median	74.50	76.00		
30 minutes post LD	N	70	74		
	Mean	52.40	72.51	-20.26 (-25.72, -14.79) ^a	<0.001 ^a
	SD	21.72	9.96		<0.0001**
	Median	51.00	73.00		
2 hours post-LD	N	74	79		
	Mean	26.76	60.70	-33.95 (-38.71, -29.20) ^a	<0.0001 ^a
	SD	15.36	14.53		0.6289**
	Median	20.00	60.00		
6 hours post-LD ^c	N	72	77		
	Mean	18.86	52.05	-33.11 (-37.05, -29.16) ^a	<0.0001 ^a
	SD	9.49	16.06		0.0326**
	Median	17.50	50.00		

Timing		Prasugrel/ Clopidogrel (N=99)	Clopidogrel/ Prasugrel (N=98)	Difference* Prasugrel – Clopidogrel (95% CI)	p-value
18 to 24 hours post-LD	N	39	47		
	Mean	23.21	51.09	-27.37 (-32.87, -21.87) ^a	<0.0001 ^a
	SD	10.22	14.39		0.0326**
	Median	21.00	54.00		
Day 15 visit ^c	N	40	47		
	Mean	28.50	41.53	-12.13 (-16.18, -7.44) ^a	0.0001 ^a
	SD	12.88	14.12		0.5578**
	Median	26.50	40.00		
<p>ANCOVA=analysis of covariance; CI=confidence interval; LD=loading dose; MPA=maximum platelet aggregation; N=number of subjects; SD=standard deviation.</p> <p>^aGroup means for data analyzed using an ANCOVA model with factors for study treatment and pooled study site, and a covariate for baseline MPA, assuming unequal group variances.</p> <p>^bThis number represents the total number of evaluable samples from subjects that received prasugrel in each MD period (40 from the Day 15).</p> <p>^cKey secondary endpoint per SAP dated July 25, 2007 (but not prespecified in the Protocol or Protocol Amendment).</p> <p>*p-value obtained from 2-sample t test.</p> <p>**p-value to compare group variance obtained from an F-test.</p> <p>Source: TABL 14.47 and TABL 14.49.</p> <p>Reproduced from Sponsor, Table TABL.11.6, page 99 of 1590.</p>					

9.2.12.8.4 Maximum Platelet Aggregation to 5 µM ADP at 30 minutes, 2 hours, 6 hours, and 18 to 24 hours Following Loading Dose of Study Drug

The results for the MPA to 5 µM ADP, as seen in Table 61, were consistent with the 20 µM results.

Table 61. Sponsor's Analysis: Maximal Platelet Aggregation to 5 µM Adenosine Disphosphate (Acute Phase Population) (TABL)

Timing		Prasugrel/ Clopidogrel (N=99)	Clopidogrel/ Prasugrel (N=98)	Difference* Prasugrel – Clopidogrel (95% CI)	p-value*
Pre-treatment	N	81	83		
	Mean	68.65	67.88		0.6803
	SD	12.94	11.05		
	Median	68.00	70.00		
30 minutes post LD	N	69	73		
	Mean	44.71	64.67	-20.58 (-25.73, -15.44)	<0.0001*
	SD	19.17	12.65		0.0006*
	Median	42.00	65.00		
2 hours post-LD	N	75	76		
	Mean	23.00	51.12	-28.87 (-33.24, -24.51)	<0.0001
	SD	13.57	14.47		0.5838
	Median	18.00	51.00		

Timing		Prasugrel/ Clopidogrel (N=99)	Clopidogrel/ Prasugrel (N=98)	Difference* Prasugrel – Clopidogrel (95% CI)	p-value*
6 hours post-LD	N	71	77		
	Mean	16.38	42.61	-26.44 (-30.36, -22.52)	<0.0001*
	SD	9.27	15.53		<0.0001*
	Median	15.00	44.00		
18 to 24 hours post-LD	N	39	48		
	Mean	19.74	43.13	-23.69 (-28.67, -18.71)	<0.0001*
	SD	9.20	14.05		0.0084*
	Median	19.00	45.50		
<p>*p-value to compare baseline values obtained from a 2 sample t-test. Group means analyzed using an Analysis of Covariance model with factors for study treatment and pooled study site, and a covariate for baseline MPA, assuming unequal group variances. p-value to compare group variances obtained from an F-test.</p>					

9.2.12.8.5 Final Extent of Platelet Aggregation (at 6 minutes after ADP addition) to 5 or 20 μ M ADP at 30 min, 2 hours, 6 hours, 18 to 24 hours Following Loading Dose of Study Drug

All results were reviewed.

9.2.12.8.6 Mean VerifyNow™ P2Y₁₂ Percent Inhibition Data at 6 Hours and at the Day 15 Visit

Although this endpoint was not initially prespecified in the Protocol or Protocol Amendment, the endpoint was considered to be a key secondary endpoint in the SAP dated July 25, 2007. Interpretability of these results is limited, given the lack of baseline values in both treatment groups.

Table 62. Sponsor's Analysis: VerifyNow™ P2Y₁₂ Percent Inhibition Data

Timing		Prasugrel/ Clopidogrel (N=99)	Clopidogrel/ Prasugrel (N=98)	Difference* Prasugrel – Clopidogrel (95% CI)	p-value*
30 minutes post LD	N	77	88		
	Mean	45.6	11.0	34.6 (26.7, 42.5) ^a	<0.0001 ^a
	SD	34.7	8.5		<0.0001 ^a
	Median	37.0	12.0		
6 hours post-LD	N	83	90		
	Mean	89.5	38.4	51.4 (45.5, 57.4) ^a	<0.0001 ^a
	SD	10.5	26.1		<0.0001 ^a
	Median	95.0	30.5		
Day 15 Visit	N	50	53		
	Mean	83.3	65.1	18.9 (11.7, 26.1) ^a	<0.0001 ^a
	SD	16.0	23.1		0.0115*
	Median	90.5	67.0		
<p>ANCOVA=Analysis of Covariance; CI=confidence interval; LD=loading dose; N=Number of subjects; SD=standard deviation. ^aGroup means analyzed using an ANCOVA model with factors for study treatment and pooled study site, assuming unequal group variances. Note that the model did not contain a covariate for baseline value, as no</p>					

pretreatment VerifyNow P2Y₁₂ percent inhibition measurements were taken.

***p-value to compare group variances obtained from an F-test.**

Source: Table TABL. 14.54.

Reproduced from Sponsor, Table TABL.11.7, page 101 of 1590.

9.2.12.8.7 Thienopyridine Hyporesponsiveness

In the SAP dated July 25, 2007, prespecified endpoints in Phase 1 included

- Thienopyridine hyporesponsiveness defined as IPA to 20 μ M ADP < 20% or IPA to 5 μ M ADP < 25% at 2 hours, 6 hours, and 18 to 24 hours following loading dose of study drug. The comparison would be evaluated by Pearson Chi-square test or Fisher exact test as appropriate.

Per the SAP, prespecified endpoints in Phase 2 included

- Thienopyridine hyporesponsiveness defined as IPA to 20 μ M ADP < 20%, IPA to 5 μ M ADP < 25%, or less than observed 25th percentile of IPA response after 14 \pm 2 days of clopidogrel 150 mg daily MD following 14 \pm 2 days of study medication. The comparison would be conducted by Prescott's test or exact Prescott's test as appropriate.

The results for these endpoints are displayed in Table 63. Thienopyridine hyporesponsiveness was significantly lower in the prasugrel treatment group at 2 hours, 6 hours, and 18 to 24 hours post loading dose, compared to clopidogrel. However, the number of samples available for the 18 to 24 hour time point was lower than for the other time points. Additionally, at the Day 15 Visit (14 \pm 2 days), thienopyridine hyporesponsiveness, defined as IPA with 20 μ M ADP < 20%, was not statistically significant between treatment groups. However, thienopyridine hyporesponsiveness, defined as IPA with 20 μ M ADP < 25th %IPA was significantly higher in the clopidogrel treatment group, compared to prasugrel. The number of samples at the Day 15 visit was lower when compared to the samples available for the first 6 hours following the loading dose of study drug.

Table 63. Sponsor's Analysis: Thienopyridine Hyporesponsiveness to 20 μ M ADP After LD and During MD

	Prasugrel/Clopidogrel N=99	Clopidogrel/Prasugrel N=98	p-value
30 minutes post LD (N)	70	73	
IPA with 20 μ M ADP < 20%	30 (42.9%)	64 (87.7%)	<0.0001 ^a
2 hours post LD (N)[†]	74	78	
IPA with 20 μ M ADP < 20%	2 (2.7%)	43 (55.1%)	<0.0001 ^a
6 hours post LD (N)[†]	72	77	
IPA with 20 μ M ADP < 20%	0 (0.0%)	21 (27.3%)	<0.0001 ^a
18 to 24 hours post LD (N)[†]	39	46	
IPA with 20 μ M ADP < 20%	0 (0.0%)	14 (30.4%)	0.0002 ^a
Day 15 Visit (N)[†]	40	46	
IPA with 20 μ M ADP < 20%	1 (2.5%)	7 (15.2%)	0.0629 ^b
IPA with 20 μ M ADP < 25 th %IPA (clopidogrel)	3 (7.5%)	11 (23.9%)	0.0397 ^b
Day 29 visit (N)	40	45	
IPA with 20 μ M ADP < 20%	4 (10.0%)	1 (2.2%)	0.1827 ^b
IPA with 20 μ M ADP < 25 th %IPA (clopidogrel)	11 (27.5%)	3 (6.7%)	0.0097 ^b
Day 15 visit and Day 29 visit (N)^d	37	43	0.0215^c
IPA with 20 μ M ADP < 20% at Day 15	0 (0.0%)	6 (14.0%)	
IPA with 20 μ M ADP < 20% at Day 29	4 (10.8%)	1 (2.3%)	

	Prasugrel/Clopidogrel N=99	Clopidogrel/Prasugrel N=98	p-value
IPA with 20 µM ADP < 20% at both Day 15 and Day 29	0 (0.0%)	0 (0.0%)	
IPA with 20 µM ADP < 20% at neither Day 15/Day 29	33 (89.2%)	36 (83.7%)	
IPA with 20 µM ADP < 25 th %IPA (clop) at Day 15	1 (2.7%)	8 (18.6%)	0.0017 ^c
IPA with 20 µM ADP < 25 th %IPA (clop) at Day 29	9 (24.3%)	1 (2.3%)	
IPA with 20 µM ADP < 25 th %IPA (clop) at both Day 15 and Day 29	1 (2.7%)	2 (4.7%)	
IPA with 20 µM ADP < 25 th %IPA (clop) at neither Day 15/Day 29	26 (70.3%)	32 (74.4%)	
ADP=adenosine diphosphatase; clop=clopidogrel; IPA=inhibition of platelet aggregation; %IPA (clop)=percentile of IPA response after 14 ± 2 days of clopidogrel daily 150 mg MD; LD=loading dose; MD=maintenance dose; N=number of subjects. ^a p-value (30 minutes to 18 to 24 hours) is obtained from a Pearson's chi-squared test. ^b p-value (Day 15 and Day 29) is obtained from a Pearson's chi-squared test when total count ≥ 10 from a Fisher's exact test, otherwise. ^c p-value for the combined data is obtained from exact Prescott's test for the comparison of prasugrel versus clopidogrel. ^d Includes subjects with evaluable samples at both the Day 15 and Day 29 visits. Source: Table TABL.14.64 and Table.14.66. †Prespecified analyses in the SAP dated July 25, 2007.			

9.2.12.8.8 Vasodilator-Stimulated Phosphoprotein (VASP) Phosphorylation Ratio at 2 hours, 6 hours, 18 to 24 hours and 14 ± 2 days Following Loading Dose of Study Drug

VASP results are displayed in Table 64. At all time points, subjects receiving prasugrel had significantly lower VASP platelet reactivity indices, compared to clopidogrel.

Table 64. Sponsor's Analysis: VASP Platelet Reactivity Index (PRI %) Throughout Study

		Prasugrel/ Clopidogrel N=99	Clopidogrel/ Prasugrel N=98	Difference Prasugrel-Clopidogrel (95% CI)	p-value
Pretreatment	N	89	89		
	Mean	88.1	86.4		0.1301 ^a
	SD	7.10	7.48		
	Median	90.0	88.0		
2 hours post LD	N	93	88		
	Mean	21.5	75.0	-54.3 (-61.2, -47.4) ^b	<0.0001 ^b
	SD	27.06	16.91		
	Median	13.0	79.0		
6 hours post LD	N	68	68		
	Mean	7.4	68.4	-60.5 (-67.1, -54.0) ^b	<0.0001 ^b
	SD	16.66	21.18		
	Median	6.5	74.5		

		Prasugrel/ Clopidogrel N=99	Clopidogrel/ Prasugrel N=98	Difference Prasugrel-Clopidogrel (95% CI)	p-value
18 to 24 hours post LD	N	48	54		
	Mean	10.3	64.3	-56.2 (-63.2, -49.2) ^b	<0.0001 ^b
	SD	15.63	18.72		
	Median	8.5	68.0		
Day 15 visit	N	50	52		
	Mean	21.7	39.7	-17.9 (-26.6, -9.1) ^b	0.0001 ^b
	SD	18.97	21.90		
	Median	16.5	40.5		
Day 29 visit	N	51	50		
	Mean	48.0	25.1	-21.7 (-31.0, -12.4) ^b	<0.0001 ^b
	SD	24.06	19.47		
	Median	49.0	24.0		
<p>ANCOVA=analysis of covariance; CI=confidence interval; LD=loading dose; LS=least square; MD=maintenance dose; N=number of subjects; PRI=platelet reactivity index; SD=standard deviation; VASP=vasodilator-stimulated phosphoprotein.</p> <p>^ap-value to compare baseline values obtained from a 2 sample <i>t</i> test.</p> <p>^bGroup means (30minutes to 18 to 24 hours) analyzed using an ANCOVA model with factors for study treatment and laboratory, and a covariate for baseline value, assuming unequal group variances.</p> <p>^cThis number represents the total number of evaluable samples from subjects that received prasugrel in each MD period (50 from the Day 15 visit and a50 from theDay 29 visit).</p> <p>^dThis number represents the total number of evaluable samples from subjects that received clopidogrel in each MD period (52 from theDay 15 visit and 51 from the Day 29 visit).</p> <p>^eGroup means for combined Day 15 visit and Day 29 visit data analyzed using an ANCOVA model with factors for study treatment, study phase, treatment order, subject within-treatment order as a random effect and laboratory, and a covariate for baseline value, assuming unequal group variances.</p> <p>Source: Table TABL.14.61 and Table TABL.14.62.</p> <p>Reproduced from Sponsor, Table TABL. 11.9, page 105 of 1590.</p>					

9.2.12.8.9 Additional Platelet Function and Inflammatory Measures

The results are summarized as follows:

- There was no significant difference between treatment groups in sCD40L at 6 and 18 to 24 hours after loading dose of study drug and after 14 ± 2 days of maintenance therapy with study drug.
- At 6 hours and 18 to 24 hours, as well as at the Day 15 visit, prasugrel had significantly lower values for monocyte-platelet aggregates and neutrophil-platelet aggregates to 20 µM adenosine diphosphatase.
- At 18 to 24 hours post loading dose and at the Day 15 visit, the clopidogrel treatment group had significantly lower mean values of interferon gamma, compared to prasugrel.
- At the Day 15 visit, there was a significantly lower mean value of interleukin 13 in the clopidogrel treatment group, compared to prasugrel.
- At 18 to 24 hours post loading dose, there was a significantly lower mean interleukin 15 value in the clopidogrel treatment group, compared to prasugrel.
- At the Day 15 visit, there was a significantly lower mean value of interleukin 18 in the clopidogrel treatment group, compared to prasugrel.
- 6 hours post loading dose, tumor necrosis factor was significantly reduced in the clopidogrel treatment group compared to prasugrel.
- At 6 hours and 18 to 24 hours post loading dose and at the Day 15 visit and Day 29 visit, platelet P-selectin % Positive Platelets to 20 µM adenosine diphosphatase was significantly lower in the prasugrel treatment group, compared to clopidogrel.

- At 6 hours and 18 to 24 hours post loading dose, high-sensitivity C-reactive protein was significantly lower in the clopidogrel treatment group.
- At 6 hours and 18 to 24 hours post loading dose, myeloperoxidase was significantly lower in the prasugrel treatment group.

9.2.12.8.10 Myonecrosis Measures

There was no significant correlation between IPA with 20 μ M ADP at 6- and 18- to 24-hours post loading dose and CK-MB, except that CK-MB exceeding 1x ULN at 6 hours post LD was negatively correlated in the clopidogrel treatment group ($p = 0.0449$). However, the number of samples with positive enzymes in this study were small, so no definitive conclusions should be drawn from this analysis.

9.2.12.9 Major Adverse Cardiac Events (MACE)/Other Clinical Endpoints

MACE was a composite of cardiovascular death, myocardial infarction, and stroke during the first 14 ± 2 days of MD therapy in treated subjects who received PCI. Three subjects (2.9%) in the prasugrel/clopidogrel treatment group and one subject (1.0%) in the clopidogrel/prasugrel treatment group experienced the MACE endpoint, as displayed in Table 65. There were no deaths or strokes during the study.

Other clinical endpoints during 14 ± 2 days of maintenance therapy in subjects who were treated and underwent PCI were subacute stent thrombosis, urgent target vessel revascularization, and the individual components of MACE. The results of these clinical endpoints are also displayed in Table 65.

Table 65. Sponsor's Analysis: Clinical Efficacy Measures Occurring at any Time During the Study (On-Treatment Population) (TABL)

	Prasugrel/Clopidogrel # Reports	N = 102 # Subjects	Clopidogrel/Prasugrel # Reports	N = 99 # Subjects
MACE endpoint	3	3 (2.9%)	1	1 (1.0%)
Cardiovascular death	0	0 (0.0%)	0	0 (0.0%)
Myocardial infarction	3	3 (2.9%)	1	1 (1.0%)
Stroke	0	0 (0.0%)	0	0 (0.0%)
Subacute stent thrombosis	0	0 (0.0%)	1	1 (1.0%)
Urgent Target Vessel Revascularization	0	0 (0.0%)	1	1 (1.0%)
Reproduced from Sponsor, Table TABL.14.131, page 516 of 1590. Analysis verified by Karen A. Hicks, M.D.. Please note that Subject 301-0032 in the clopidogrel treatment group had subacute stent thrombosis 4 days after index stent placement, requiring urgent target vessel revascularization. This subject was counted under “subacute stent thrombosis” as well as “urgent target vessel revascularization.”				

9.2.12.10 Exposure

Study drug exposure was similar in each treatment group.

Table 66. Exposure to Study Medication (On Treatment Population) (TABL)

		Prasugrel/ Clopidogrel N=102	Clopidogrel/ Prasugrel N=99	Total N=201	p-value*
Received LD		102 (100%)	99 (100%)	201 (100%)	
MD between Day 2 and Day 15					
Took at least 1 MD of study drug		55(53.9%)	55 (55.6%)	110 (54.7%)	
Number of days of study drug	N	54 ^a	55	109	
	Mean	13.9	14.2	14.0	0.1919
	SD	1.17	1.30	1.24	
	Median	14.0	14.0	14.0	
MD between Day 15 and Day 29					
Took at least 1 MD of study drug		53 (52.0%)	55 (55.6%)	108 (53.7%)	
Number of days of study drug	N	53	55	108	
	Mean	13.7	13.8	13.8	0.8563
	SD	2.04	1.61	1.83	
	Median	14.0	14.0	14.0	
N=number of subjects; SD=standard deviation; LD=loading dose; MD=maintenance dose. *p-value obtained from a 2-sample <i>t</i> test. ^aOne subject (prasugrel) did not attend the Day 15 visit. The subject was hospitalized for 21 days after study drug LD. The investigator confirmed that the subject had taken study drug through the Day 15 visit; however, the site did not get quantity of drug returned or number of days exposure. The subject missed study drug for 4 days. The subject was given 1 dose of open-label clopidogrel on the 4th day of missing study drug and then started study drug (clopidogrel) while in hospital on the following day. Source: Table TABL.14.143. Reproduced from Sponsor, Table TABL.12.1, page 114 of 1590.					

9.2.12.11 Primary Safety Measure

The primary safety measure was non-CABG TIMI significant bleeding defined as the occurrence of TIMI major or minor bleeding in the treated population at the Day 15 visit. There were no TIMI major bleeds in either treatment group up to Day 15.

Table 67. Sponsor's Analysis: Non-CABG-Related TIMI Clinically Significant Bleeding Events up to Day 15 Visit (Number and Percentage of Subjects) (On-Treatment Population) (TABL)

	Prasugrel/Clopidogrel (N=102)		Clopidogrel/Prasugrel (N=99)	
	# reports	# subjects	# reports	# subjects
TIMI major or minor bleeding events	2	2 (2.0%)	0	(0.0%)
TIMI major bleeding events	0	0 (0.0%)	0	0 (0.0%)

	Prasugrel/Clopidogrel (N=102)		Clopidogrel/Prasugrel (N=99)	
	# reports	# subjects	# reports	# subjects
TIMI minor bleeding events	2	2 (2.0%)	0	0 (0.0%)
CABG=coronary artery bypass graft; TIMI=Thrombolysis In Myocardial Infarction. Note: # reports refers to the number of events that occurred; # subjects refers to the number of subjects who reported at least 1 event and is followed by the percent of total in parenthesis. Source: TABL.14.147, TABL.14.148, TABL.14.149. Reproduced from Sponsor, Table TABL.12.3, page 119 of 1590. Analysis verified by Karen A. Hicks, M.D.				

In the clopidogrel treatment group, there were no adjudicated hemorrhages; however, in the prasugrel treatment group, there were 5 unique hemorrhages, including (2) TIMI minor bleeds (Subjects 102-0003 and 301-0033), and (3) non-CABG related minimal bleeds (Subjects 102-0020, 201-0001, and 301-0026). Additionally, subject 301-0016, randomized to prasugrel, experienced a drop in hemoglobin from 13.7 to 8.2 g/dl, but there was no overt bleeding and no reason for the drop in hemoglobin could be identified.

9.2.12.12 Other Prespecified Safety Measures

Other prespecified safety measures included non-CABG related TIMI major bleeding, non-CABG-related TIMI life-threatening bleeding, and non-CABG-related TIMI minor bleeding. The TIMI major or minor bleeding events up to Day 15 are summarized in Table 67. There were no TIMI life-threatening bleeding events. After the Day 15 visit, there were no TIMI major or minor bleeding events.

9.2.12.13 Overview of Adverse Events

There were no deaths during the study. The prasugrel/clopidogrel treatment group had a higher percentage of serious adverse events up to Day 15 and thereafter. One subject in the prasugrel/clopidogrel treatment group discontinued the study due to an adverse event.

In the prasugrel/clopidogrel treatment group, there were 101 reports of nonserious treatment emergent adverse events in 45 (44.1%) subjects occurring at any time during the study. Eighty-seven nonserious treatment emergent adverse events occurred in 40 (39.2%) subjects from randomization to the Day 15 visit, and 14 nonserious treatment emergent adverse events occurred in 12 (22.6%) subjects from the Day 15 Visit to the Day 29 Visit.

In the clopidogrel/prasugrel treatment group, there were 104 reports of nonserious treatment emergent adverse events in 42 (42.4%) subjects occurring at any time during the study. Eighty nonserious treatment emergent adverse events occurred in 40 (40.4%) subjects from randomization to the Day 15 visit, and 24 nonserious treatment emergent adverse events occurred in 16 (29.1%) subjects from the Day 15 Visit to the Day 29 Visit.

An overview of adverse events is displayed in Table 68.

Table 68. Sponsor's Analysis: Overview of Adverse Events (Number and Percentage of Subjects) (On-Treatment Population) (TABL)

	Prasugrel/ Clopidogrel N=102	Clopidogrel/ Prasugrel N=99
Death (entire study duration)	0 (0.0%)	0 (0.0%)
Treatment-Emergent Adverse Events (entire study duration)	45 (44.1%)	42 (42.4%)
Up to Day 15 visit ^a		
Number of Subjects	102	99
Non-CABG-related TIMI clinically significant bleeding events ^b	2 (2.0%)	0 (0.0%)
TIMI major bleeding events	0 (0.0%)	0 (0.0%)
TIMI minor bleeding events	2 (2.0%)	0 (0.0%)
Serious adverse events	8 (7.8%)	7 (7.1%)
Discontinuations due to an adverse event	1 (1.0%)	0 (0.0%)
Treatment-emergent adverse events	40 (39.2%)	40 (40.4%)
Post-Day 15 visit ^a		
Number of subjects	53	55
Non-CABG-related TIMI clinically significant bleeding events ^b	0 (0.0%)	0 (0.0%)
TIMI major bleeding events	0 (0.0%)	0 (0.0%)
TIMI minor bleeding events	0 (0.0%)	0 (0.0%)
Serious adverse events	3 (5.7%)	1 (1.8%)
Discontinuations due to an adverse event	0 (0.0%)	0 (0.0%)
Treatment-emergent adverse events	12 (22.6%)	16 (29.1%)
CABG=coronary artery bypass graft; N=number of subjects; TIMI=Thrombolysis in Myocardial Infarction.		
^aSubjects may be counted in more than 1 category and/or study period for a given category.		
^bNon-CABG-related TIMI clinically significant bleeding events include TIMI major and TIMI minor bleeding events.		
Reproduced from Sponsor, Table TABL.12.2, page 115 of 1590.		
TIMI major or minor bleeding events, serious adverse events, and discontinuations due to an adverse event were verified by Karen A. Hicks, M.D.		

9.2.12.14 Serious Adverse Events

Serious adverse events are summarized in Table 69.

Table 69. Sponsor's Analysis: Serious Adverse Events by System Organ Class and Preferred Term (Number and Percentage of Subjects) (All Randomized Subjects) (TABL)

	Prasugrel/Clopidogrel		Clopidogrel/Prasugrel	
	# reports	# subjects	# reports	# subjects
Serious adverse events up to Day 15 visit				
Number of Subjects		102		99
Total Events	8	8 (7.8%)	11	7 (7.1%)
Cardiac disorders	3	3 (2.9%)	3	3 (3.0%)
Atrial fibrillation	1	1 (1.0%)	0	0 (0.0%)
Bradycardia	1	1 (1.0%)	0	0 (0.0%)
Extrasystoles	0	0 (0.0%)	1	1 (1.0%)
Myocardial infarction	0	0 (0.0%)	1	1 (1.0%)
Ventricular fibrillation	1	1 (1.0%)	0	0 (0.0%)
Ventricular tachycardia	0	0 (0.0%)	1	1 (1.0%)
General disorders and administration site conditions	2	2 (2.0%)	3	2 (2.0%)
Chest discomfort	0	0 (0.0%)	1	1 (1.0%)
Chest pain	0	0 (0.0%)	1	1 (1.0%)
Non-cardiac chest pain	0	0 (0.0%)	1	1 (1.0%)
Vessel puncture site haematoma	2	2 (2.0%)	0	0 (0.0%)
Injury, poisoning, and procedural complications	1	1 (1.0%)	1	1 (1.0%)
Fall	0	0 (0.0%)	1	1 (1.0%)
Post-procedural myocardial infarction	1	1 (1.0%)	0	0 (0.0%)
Investigations	1	1 (1.0%)	0	0 (0.0%)
Blood glucose increased	1	1 (1.0%)	0	0 (0.0%)
Nervous system disorders	0	0 (0.0%)	2	1 (1.0%)
Syncope	0	0 (0.0%)	1	1 (1.0%)
Vlth nerve disorder (cranial nerve)	0	0 (0.0%)	1	1 (1.0%)
Respiratory, thoracic, and mediastinal disorders	0	0 (0.0%)	1	1 (1.0%)
Dyspnoea	0	0 (0.0%)	1	1 (1.0%)
Vascular disorders	1	1 (1.0%)	1	1 (1.0%)
Deep vein thrombosis	1	1 (1.0%)	0	0 (0.0%)
Hypotension	0	0 (0.0%)	1	1 (1.0%)
Serious adverse events post-Day 15 visit				
Number of Subjects		53		55
Total Events	4	3 (5.7%)	1	1 (1.8%)
Cardiac disorders	2	2 (3.8%)	0	0 (0.0%)
Acute coronary syndrome	1	1 (1.9%)	0	0 (0.0%)
Tachycardia	1	1 (1.9%)	0	0 (0.0%)
General disorders and administration site conditions	0	0 (0.0%)	1	1 (1.8%)
Non-cardiac chest pain	0	0 (0.0%)	1	1 (1.8%)
Infections and infestations	1	1 (1.9%)	0	0 (0.0%)
Borrelia infection	1	1 (1.9%)	0	0 (0.0%)
Respiratory, thoracic, and mediastinal disorders	1	1 (1.9%)	0	0 (0.0%)
Chronic obstructive pulmonary disease	1	1 (1.9%)	0	0 (0.0%)

Note: # reports refers to the number of events that occurred; # subjects refers to the number of subjects who reported at least 1 event.

Source: Table TABL.14.160 and Table TABL.14.162

(Reproduced from Sponsor, Table TABL.12.6, page 125 of 1590)

9.2.13 Summary (TABL)

Based on these study results, prasugrel appears to have a greater inhibitory effect on platelet aggregation than clopidogrel. However, variable reproducibility in light transmission aggregometry measurements and inter-laboratory variability can affect the interpretability of these results. In many cases, there were large standard deviations which were statistically significant between treatment groups, suggesting the results are not as clear. Furthermore, the sponsor has not correlated these results with clinical outcome.

Although the Accumetrics VerifyNow P2Y₁₂ assay appears to correlate with results from light transmission aggregometry, the device has its own limitations. In 2006, CDRH issued a recall for the Accumetrics VerifyNow P2Y₁₂ assay device because it could report an erroneous result instead of an error message when a sample was run from a patient with a low hematocrit. TABL was performed during this recall. In the current instructions for use (IFU), the sponsor states assay performance was not affected by hematocrit values between 33-52%, or platelet count values between 119,000-502,000/ μ l. The IFU also states that there was no assay interference when samples with fibrinogen levels between 171 and 599 mg/dL were tested. However, glycoprotein IIb/IIIa inhibitors, abciximab, eptifibatide, and tirofiban, significantly affect VerifyNow P2Y₁₂ assay results, and it is recommended that these patients not be tested until platelet function has recovered (approximately 14 days after discontinuation of abciximab and up to 48 hours for eptifibatide and tirofiban).

In TABL, three subjects undergoing PCI in the prasugrel treatment group and one subject undergoing PCI in the clopidogrel treatment group received glycoprotein IIb/IIIa inhibitors. Additionally, during Period 1 screening, there were 27 clopidogrel subjects with low hematocrits, and two of these subjects had hematocrits < 33%. In the prasugrel treatment group, there were 24 subjects with low hematocrits during Period 1 screening, and one subject with a hematocrit < 32%. However, these few subjects would not have a large impact on the overall findings.

Nevertheless, I believe this science of measuring platelet aggregation is still evolving. Therefore, although these data from TABL are interesting, I consider the results to be exploratory only.

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 $\geq 50\%$ (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 H₂ antagonist (for example, cimetidine, ranitidine, famotidine, nizatidine) within 2 hours before PCI (The use of an H₂ 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/mm³
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 H₂ 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

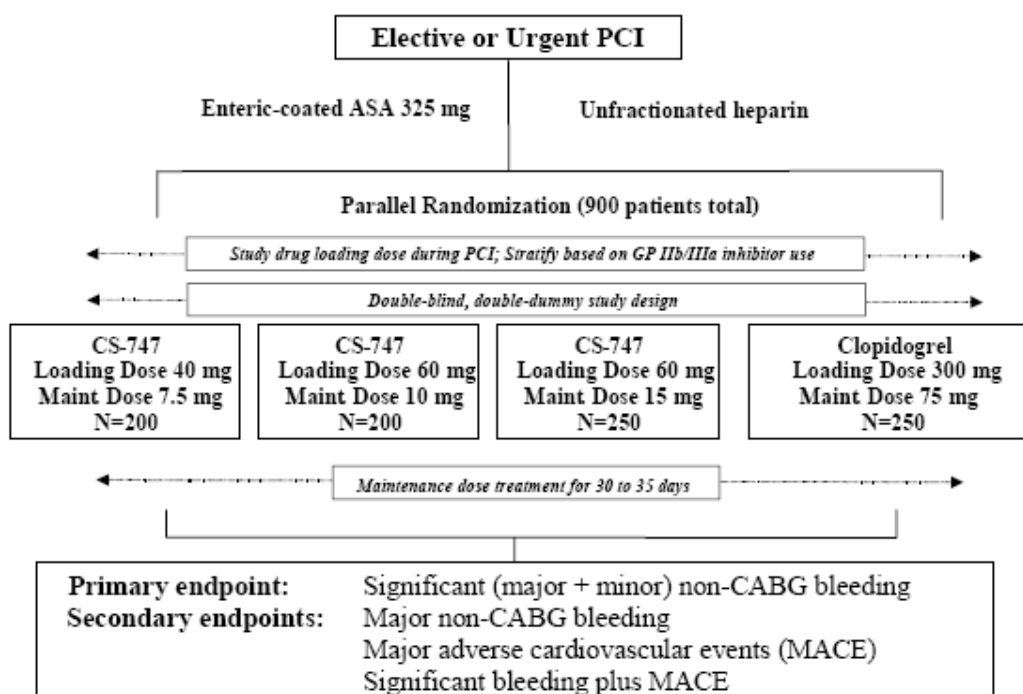


Figure TAAH.1. H7T-MC-TAAH study design.

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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Approved by Lilly: 31 January 2003

(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 ≤ 20 or BMI ≥ 25 versus BMI between 20 and 25)
- Male versus female
- Age (< 65 years versus ≥ 65 years)
- Use of any GP IIb/IIIa inhibitor
- TIMI Risk Score (TIMI score ≤ 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 if 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:

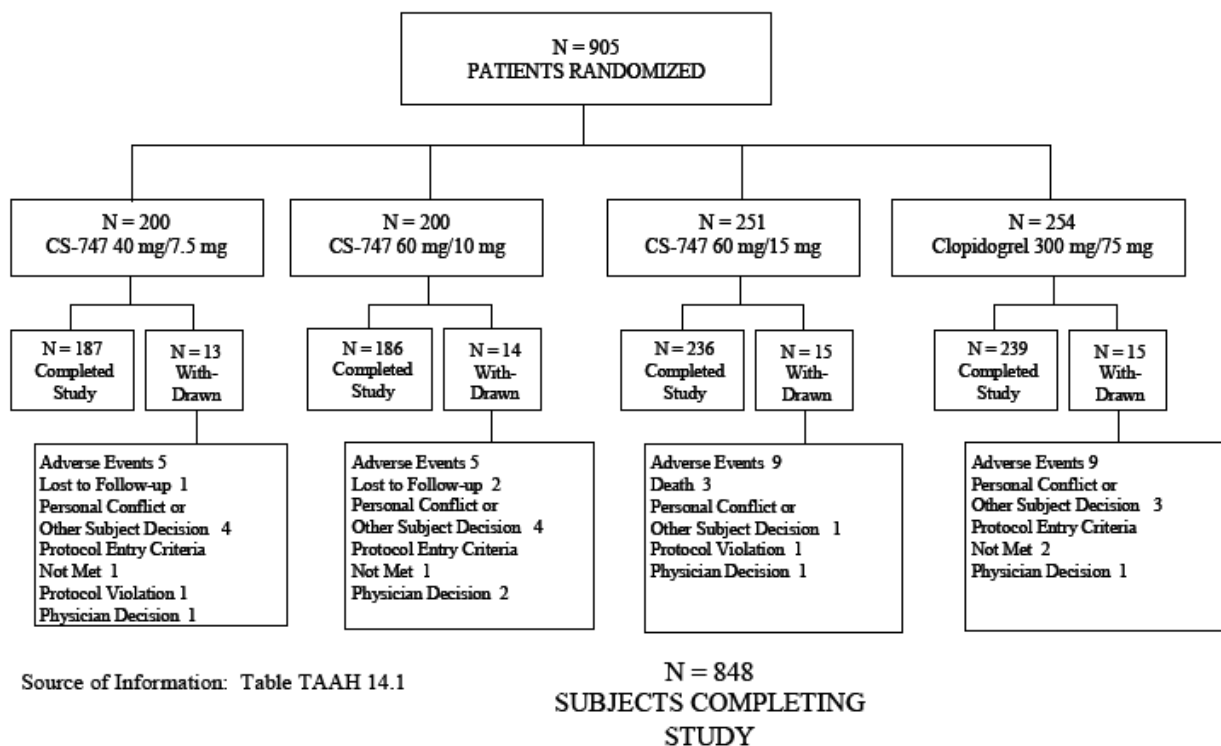
- Those who entered the study even though they did not satisfy the entry criteria (23 subjects)
- Those who developed withdrawal criteria during the study but were not withdrawn (37 subjects)
- Those who received the wrong treatment or dose (2 subjects) or
- Those who received an excluded concomitant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



(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)

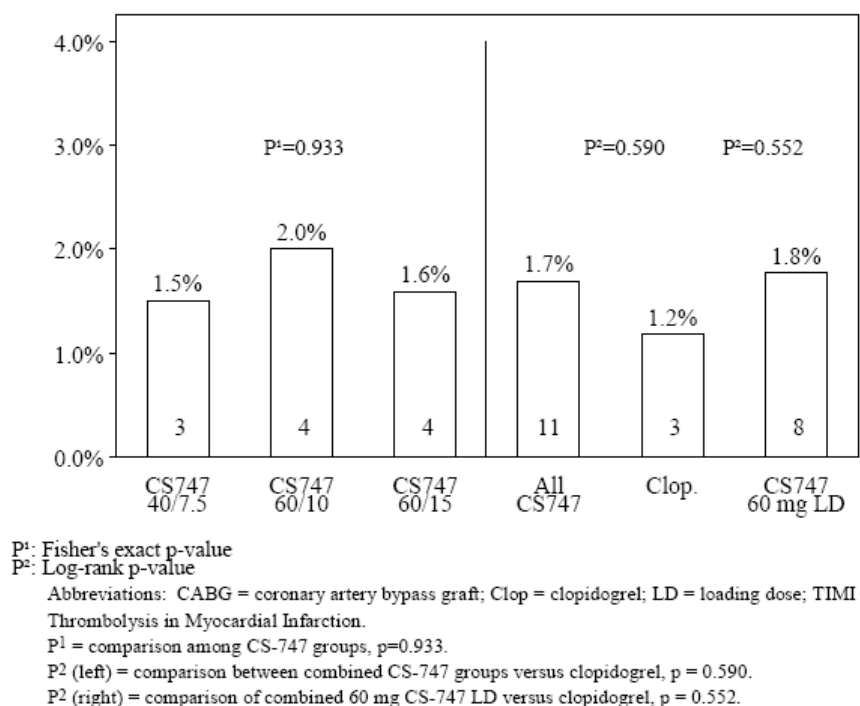
	CS-747				Clopidogrel	Total
	40/7.5 mg N=199	60/10 mg N=200	60/15 N=251	Subtotal N=650	300/75 mg N=254	N=904
Age (years)						
No. Subjects	199	200	251	650	254	904
>65	70 (35.2)	48 (24.0)	66 (26.3)	184 (28.3)	59 (23.2)	243 (26.9)
Mean (SD)	60.4 (8.72)	58.7 (9.15)	59.4 (8.97)	59.5 (8.96)	58.4 (9.17)	59.2 (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 (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 (%)



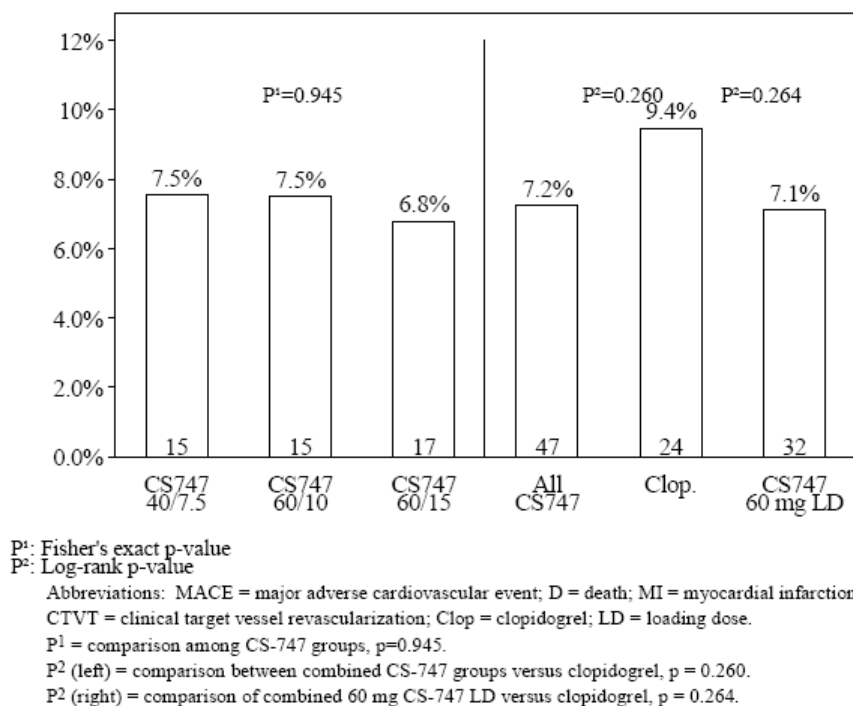
(Reproduced from Sponsor, Clinical Study Report, Figure TAAH.11.1, page 154)

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.

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



(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
12/28/2008 10:58:21 AM
MEDICAL OFFICER

1 EXECUTIVE SUMMARY

The purpose of the current document is to provide the Clinical Pharmacology background information of EFFIENT (Prasugrel Hydrochloride tablets – NDA 22307) for the Advisory Committee Meeting on Feb 2nd 2009.

1.1 RECOMMENDATIONS:

The Office of Clinical Pharmacology has reviewed the clinical pharmacology and biopharmaceutics (CPB) information submitted to NDA 22-307. The CPB information provided in NDA 22-307 is acceptable.

SPECIFIC RECOMMENDATIONS:

1. The proposed dose adjustment of prasugrel maintenance dose to 5 mg QD for patients with body weight less than 60 Kg is acceptable.
2. The proposed dose adjustment of prasugrel maintenance dose in patients with age ≥ 75 y is not acceptable.
3. Pre-treatment of at least 6 hrs for prasugrel or clopidogrel is not necessary to achieve maximum effectiveness. The loading dose for either prasugrel or clopidogrel should be administered at least within 30 minutes of the start of PCI.

The following comments should be properly addressed by the sponsor.

COMMENTS:

1. The sponsor should consider lowering the 60/10 dosing regimen of prasugrel in order to decrease the incidence of bleeding.
2. The sponsor should investigate the effects of a CYP2B6 inhibitor on the PK of prasugrel.
3. Not enough information is provided in the study reports in patients with ESRD. The sponsor is requested to provide additional information in order to better evaluate the study results and be able to provide labeling recommendations in this patient population.
4. The sponsor should address the problem of the conversion of the salt form into a free base. This differing amounts of conversion from lot to lot leads to differences in the peak plasma concentrations which might be clinically relevant.....
5. The labeling comments should be addressed by the sponsor.

1.2 PHASE IV COMMINTMENTS:.

.....

1.3 Summary of OCPB Findings

Pharmacokinetics

Absorption, Distribution, Metabolism, Excretion

Following oral administration, more than 79% of the dose is absorbed. The absorption and metabolism are rapid, with peak plasma concentrations (C_{max}) of the active metabolite occurring approximately 30 minutes after dosing. The active metabolite's exposure (AUC) increases slightly higher than proportionally over the therapeutic dose range. The administration of repeated doses of 10 mg does not lead to the accumulation of the active metabolite.

The parent drug is not detected in plasma following oral administration. It is rapidly hydrolyzed by hydroxysterases in the intestine to a thiolactone, which is then converted to the active metabolite by a single step primarily by CYP3A4 and CYP2B6 and to a lesser extent by CYP2C9 and CYP2C19.

The estimates of apparent volume of distribution of prasugrel's active metabolite ranged from 30 L to 84 L and the estimates of apparent clearance ranged from 73 L/hr to 266 L/hr in subjects with stable atherosclerosis.

The binding of the active metabolite to plasma proteins was not determined in vivo, and in vitro, it was 98% in a 4% human serum albumin solution in phosphate buffer, pH 7.4. All the inactive metabolites are highly bound to human plasma proteins.

Although the plasma-to-whole blood ratio measured by total radioactivity was generally greater than one, it does not prove that the penetration into red blood cell was limited to a specific molecular entity.

The active metabolite R-138727 contains 2 chiral centers, and thus is comprised of 4 enantiomers which possess different activities towards the platelet P2Y₁₂ ADP receptor, with the (R,R)/(R,S) pair being the most potent. In humans, the (R,R)/(R,S) pair comprised about 84% of the total active metabolite in plasma. The ratios of R-138727 enantiomers were consistent among all subjects.

Prasugrel is cleared both by the liver and the kidney: about 68% of the prasugrel dose is excreted in the urine and 27% in the feces, as inactive metabolites. The active metabolite has an elimination half life of about 7.4 hours (range 2 to 15 hours).

Pediatric Patients

The pharmacokinetics of prasugrel in children has not been studied in this NDA.

Intrinsic Factors

Body Weight

Dose adjustment to 5 mg QD in patients with body weight below 60 kg is acceptable. Trends of increased bleeding related adverse events were associated with increased exposures of R-138727. Exposure of R-138727 increased with decreasing body weight and the Thrombolysis in Myocardial Infarction (TIMI) Major bleeding risk was 2 fold higher in patients with body weight less than 60 Kg. Efficacy was similar across the body weight groups. Reducing the maintenance dose of prasugrel to 5 mg shifts more than 50% of patients with body weight less than 60 Kg to lower quartiles of exposure seen with 10 mg in patients with body weight greater than 60 kg.

Gender

No dose adjustment based on gender is recommended

Age

There is no need for the dose adjustment for the patients older than 75 years of age. Age ≥ 75 y was an independent predictor for increased risk of primary composite efficacy endpoint (Cardiovascular death, non-fatal myocardial infarction and non-fatal stroke CVD/ Non-fatal MI/Non-fatal Stroke) and TIMI Major bleeding. Even with 10 mg QD regimen, the risk of observing efficacy endpoint was ~2 fold higher in patients with age ≥ 75 y compared to patients below 75 y. Further the relative risk for TIMI major bleeding was 65% higher. However, prasugrel is shown to be better than clopidogrel in patients above 75 years age group. The impact of further dose reduction on the efficacy is not known. Hence dose reduction is not justified.

Race

The exposure to the prasugrel active metabolite in African, Hispanic, and Caucasian subjects were similar; however, the exposure were about 40-45% higher in Asian compared to Caucasian subjects. After adjusting for the population body weight and the effect of other covariates, C_{max} and AUC_{0-tlast} were still 20% higher in Asians than in Caucasians. The IPA response in the Asian subjects was stronger than in Caucasians. The highest incidence of bleeding-related adverse events was reported for Korean subjects.

The administration of prasugrel to subjects of Asian origin should be performed with caution.

Renal Impairment

After 60 and 10 mg doses of prasugrel, the exposure to R-138727 (both C_{max} and AUC_{0-tlast}) decreased by half in subjects with ESRD compared to that in healthy controls and subjects with moderate renal impairment. A conclusion about the MPA response in patients with ESRD is difficult to make due to the small sample size. The bleeding events were not assessed in these studies. The label should contraindicate prasugrel administration to ESRD patients.

Hepatic Impairment

The PK parameters estimated for the active metabolite R-138727 in healthy subjects and in subjects with moderate hepatic impairment were similar. The PD response measured as MPA to 20 mM ADP was similar in the groups of healthy subjects, and subjects with mild and moderate hepatic impairment.

A dose adjustment is not required for the patients with mild and moderate hepatic impairment. Prasugrel should be contraindicated in patients with severe hepatic impairment due to the potential risk of bleeding.

Extrinsic Factors

Food Effect

In a study of healthy subjects, AUC of the active metabolite was unaffected by a high fat, high calorie meal, but C_{max} was decreased by 49% and the time to reach C_{max} (T_{max})

was increased from 0.5 to 1.5 hours. Prasugrel can be administered without regard to food.

Drug-drug interaction information

The in vivo DDI studies with a CYP3A4 inhibitor (ketoconazole), a CYP3A4 inducer (rifampicin), and a CYP2B6 substrate (bupropion) did not reveal any clinically important interactions. A clinically significant pharmacodynamic drug-drug interaction: prolongation of the bleeding time was observed when prasugrel was co-administered with aspirin, warfarin and heparin. Caution should be exercised when these drugs are coadministered with prasugrel. Due to an increased incidence of liver enzyme elevation observed following coadministration of prasugrel and atorvastatin, this combination should be prescribed under close physician monitoring.

The potential role of prasugrel as a Pgp substrate was not evaluated in this NDA. Co-administration of prasugrel with digoxin reveals that prasugrel is not an inhibitor of Pgp, as digoxin clearance was not affected by prasugrel coadministration.

Exposure-Response Relationships

Effectiveness

Prasugrel showed a concentration dependent inhibition of the platelet aggregation (IPA). The exposures achieved with the proposed loading dose of prasugrel result in maximum inhibition of the platelet aggregation. However, the relationship between the inhibition of platelet aggregation and the clinical outcome (CVD/Non-fatal MI/Non-fatal Stroke) is not clearly understood. Further, in a double blind, randomized dose-ranging trial in patients undergoing percutaneous coronary intervention (PCI), no consistent relationship between the dose of prasugrel and the endpoint (major adverse cardiovascular event [MACE] at 30-day visit) was observed. However, it should be noted that this study was not designed to characterize dose-response and the sample size was small.

Lowest incidence of the primary efficacy endpoint was seen when the loading dose was administered within 30 minutes of the start of Percutaneous Coronary Intervention (PCI). The increased incidence of the primary efficacy endpoint when the loading dose was administered at least 6 hrs prior to the start of PCI was confounded with Prior Coronary Bypass Graft Surgery. The effect of timing of loading dose on the efficacy was seen independently for prasugrel and clopidogrel, suggesting that pre-treatment 6 hrs before the start of PCI may not be necessary.

Safety

A meta analysis of the pharmacokinetic data from 6 clinical pharmacology studies found that among subjects treated with prasugrel 10-mg MD, a trend towards a higher rate of bleeding-related adverse events in the highest quartile of exposure to the active metabolites. Further in a phase 1b study TAAD, the rate of epistaxis was higher in subjects treated with 15 mg prasugrel. Similar results indicating increased Thrombolysis in Myocardial Infarction (TIMI)/Major/Minor/Minimal bleeding rates were observed in

the phase II study TAAH indicating exposure bleeding relationship. In the phase II study TAAH in ACS patients, increasing doses of prasugrel resulted in increased Thrombolysis in Myocardial Infarction (TIMI)/Major/Minor/Minimal bleeding (5.2% with 60/15-mg MD versus 3.5% with 40/7.5-mg and 60/10-mg doses respectively). However, this difference was primarily in TIMI minimal bleeding. All these studies indicate towards a relationship between the exposure of R-138727 and bleeding.

Prasugrel was found not to prolong the QT interval.

Biopharmaceutics

Prasugrel particle size does not seem to affect the bioavailability of the active metabolite after coadministration with 30 mg lansoprazole.

Lots with differing amounts of prasugrel salt (78, 50 and 5%) were found to be bioequivalent. However, when these lots were co-administered with 30 mg lansoprazole. These lots were bioequivalent in terms of AUC but not CMAX. (30 % differences in means between the high and low conversion lots). This difference in CMAX translated into a greater than 10% difference in IPA at 0.5 and 1 hour postdose.

2 QUESTION BASED REVIEW

2.1 General Attributes

What are the proposed mechanisms of action and therapeutic indication?

Prasugrel's pharmacological action results from a covalent and irreversible binding of R-138727 to the P2Y₁₂ platelet adenosine diphosphate (ADP) receptor. Once bound, a platelet is rendered ineffective for its remaining lifespan. After prasugrel dosing is stopped, return to baseline platelet aggregation occurs only as new platelets are formed.

2.2 General Clinical Pharmacology

What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The investigation of prasugrel was performed under IND 63449. The clinical pharmacology program for NDA 22-307 includes 48 studies.

An assessment of prasugrel PK and PD in healthy subjects was performed in 8 clinical studies. The early studies investigated the base-formulation of the drug. A single and a multiple dose PK, a dose ascending, a mass-balance and a food-effect study were also performed. The influence of race, age, hepatic and renal impairment on prasugrel PK and PD were evaluated in 13 studies.

The PK and PD in subjects with atherosclerotic vascular disease were evaluated in 4 studies including the pivotal trial TAAL.

Drug-drug interaction PK and PD studies of prasugrel and aspirin, proton pump inhibitors, ketoconazole, rifampicin, atorvastatin, warfarin, bupropion, heparin, and digoxin were performed.

Also, protein binding, metabolism, and formation of the isomer sets (RS/RR and SR/SS) of R-138727, the active metabolites were studied in 7 in vitro studies.

Several studies describing the base formulation and also studies performed under the other investigation program in Japan were not reviewed.

In total, 36 studies submitted under the NDA 22-307 were reviewed.

Were the correct moieties identified and properly measured to assess clinical pharmacology?

Yes. The sponsor measured the concentrations of prasugrel metabolites since prasugrel is a prodrug and cannot be measured in plasma. In the majority of the clinical pharmacology studies, the active metabolite of prasugrel R138727 was measured as well as the inactive metabolites R-95913, R119251, and R106583. In the early studies, the other inactive metabolite R100932 was measured (instead of R119251). In order to measure the plasma concentrations of the active metabolite R-138787 of prasugrel, the sample should be derivatized immediately after the sample is taken. Due to the difficulties with the handling of blood samples, in the pivotal clinical study only inactive

metabolites were measured in plasma, and the active metabolite characteristics were estimated based on the proposed population PK model.

For the assessment of pharmacodynamics, the inhibition of platelet aggregation (IPA) by 5 and 20 mM of ADP was measured. Also, a few other methods were used, as VASP phosphorylation (flow cytometry), platelet reactivity index (PRI), bleeding time.

All assay methods were properly validated and are acceptable, chromatograms were shown.

EXPOSURE-RESPONSE RELATIONSHIP: EFFICACY

What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

The pharmacological response to clopidogrel or prasugrel is inhibition of platelet aggregation. A semi-mechanistic model was developed to describe relationship between the active metabolite concentrations of prasugrel or clopidogrel and inhibition of platelet aggregation. The active metabolites for both prasugrel and clopidogrel are reported to have similar affinities for binding to the P2Y₁₂ receptor of the platelets. Concentration dependent inhibition of platelet aggregation was seen as shown in Figure 1 below. Similarly a dose dependent increase in platelet aggregation was observed in Study TAAD.

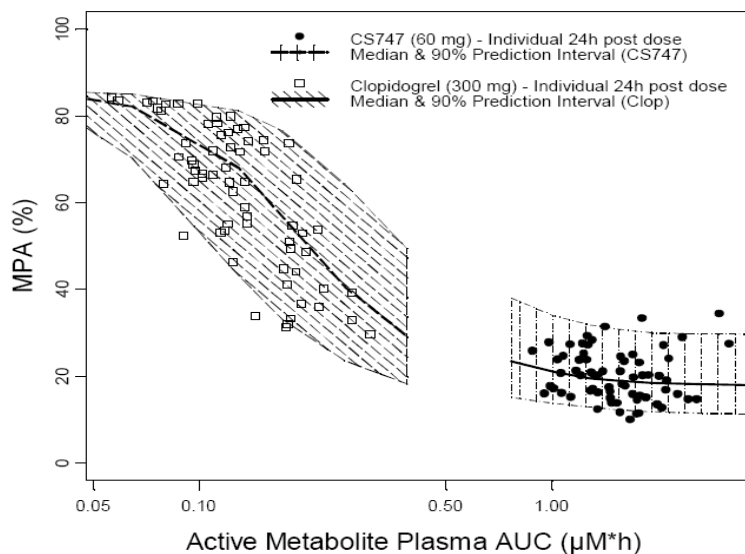


Figure 1 The inhibition of the platelet aggregation is dependent on the concentration of the active metabolites of prasugrel and clopidogrel (Source: Figure 2.5.3.3 of clinical-overview-us-pci.pdf)

The clinical endpoint for measuring the efficacy is a composite of Cardiovascular death (CVD), Non-fatal Myocardial Infarction and Non-fatal Stroke. Till date there is no established relationship between inhibition of platelet aggregation and the clinical endpoint. Since only one dose level of prasugrel (60 mg LD/10 mg MD) was studied in the pivotal trial, dose-response analysis could not be performed. However, in a double blind, randomized dose-ranging trial in patients undergoing percutaneous coronary intervention, no consistent relationship between the dose of prasugrel and the endpoint

(major adverse cardiovascular event [MACE] at 30-day visit) was observed as shown in Figure below. However, it should be noted that this study was not designed to characterize dose-response and the sample size was small (N=200 for 40/7.5 mg (LD/MD) and 60/10 mg groups and N=251 for 60/15 mg group).

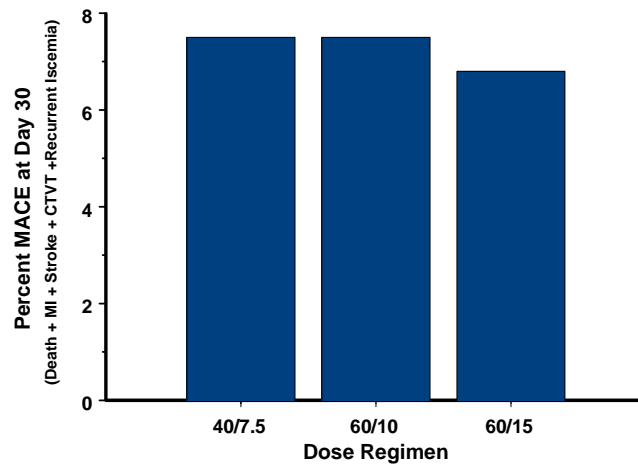


Figure 2 No relationship between dose and major cardiovascular events (MACE - Death+MI+Stroke+CTVT+Recurrent Ischemia at 30-day visit)

What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

A meta analysis of the pharmacokinetic data from 6 clinical pharmacology studies (TAAS, TAAZ, TABS, TABV and TACG) found that among subjects treated with prasugrel 10-mg MD, a trend towards a higher rate of bleeding-related adverse events in the highest quartile of exposure to the active metabolites as shown in Figure below.

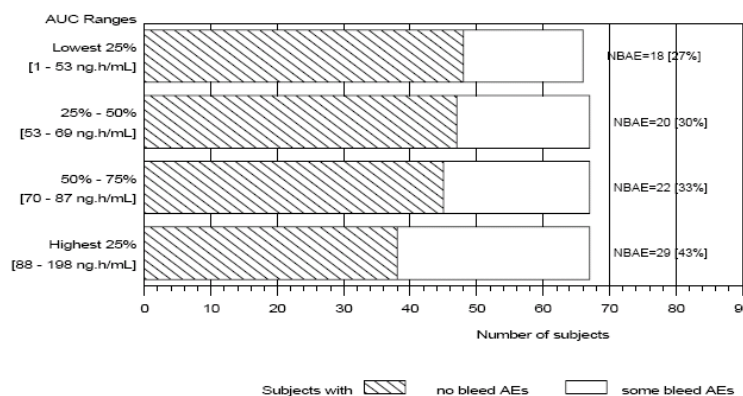


Figure 3 Increase in the active metabolite exposures trends to increase in number of bleeding adverse events (NBAE) (Source: Figure APP.2.7.4.4 of Sponsor's clinical-safety-summary-appendix-us-pci.pdf)

In the phase 1b study TAAD, in subjects with stable atherosclerosis, the rate of epistaxis was higher in subjects treated with prasugrel 15-mg MD (5%) than in subjects treated with prasugrel MD of 10 mg (1%), 7.5 mg (1%) or 5 mg (1%).

In the phase II study TAAH in ACS patients, increasing doses of prasugrel resulted in increased TIMI/Major/Minor/Minimal bleeding (5.2% with 60/15-mg MD versus 3.5% with 40/7.5-mg and 60/10-mg doses respectively). However, this difference was primarily in TIMI minimal bleeding.

All these studies indicate a relationship between the exposure of R-138727 and bleeding.

Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and is there any unresolved dosing or administration issues?

Dose selection for the pivotal trial was based primarily on the effect of prasugrel on the inhibition of platelet aggregation (IPA) and bleeding compared to clopidogrel in subjects with stable atherosclerosis.

In Study TAAD, 4 prasugrel LD/MD regimens were compared with the approved clopidogrel LD/MD regimen. As seen in Figure, both the 40-mg and 60-mg prasugrel LDs resulted in more rapid onset with significantly greater IPA to 20 μ M ADP from 2 to 6 hours after administration than the 300-mg LD of clopidogrel.

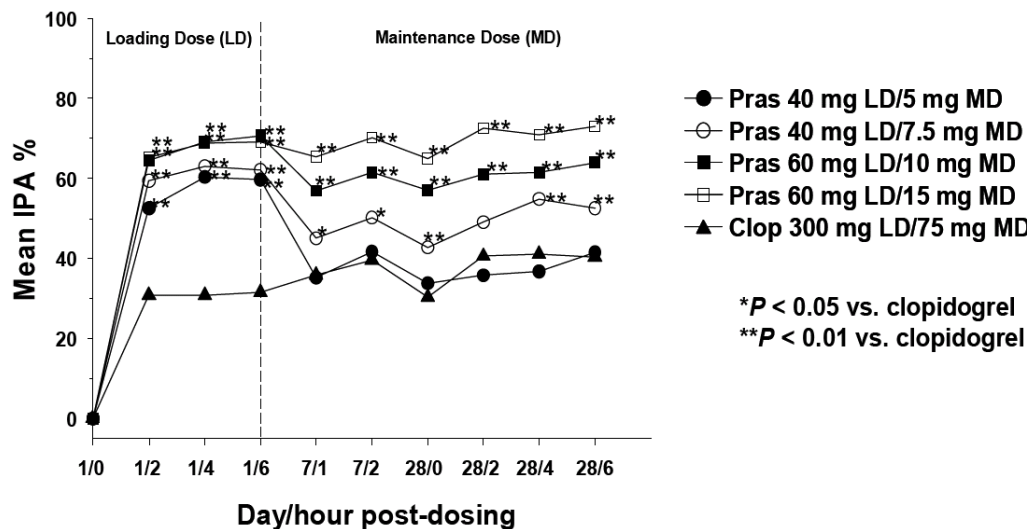


Figure 4 Prasugrel LD of 60 mg achieves highest IPA. Maintenance doses of 10 mg and 15 mg achieve significantly greater IPA compared to clopidogrel MD of 75 mg. (Source: Figure 2.5.1.1 of Sponsor's clinical-overview-us-pci.pdf)

The 60-mg prasugrel LD consistently achieved the highest level of platelet inhibition. Both the 10- and 15-mg prasugrel MDs achieved consistent and significantly greater IPA than the 75-mg clopidogrel MD. However, the 15-mg MD of prasugrel was associated with higher bleeding adverse events (AEs) hence 10-mg prasugrel MD was selected. This effect of increased trend for bleeding with 15-mg prasugrel MD compared to 10-mg

prasugrel MD was also observed in Study TAAH. Further, 10-mg prasugrel MD had 0% poor PD responders (as defined by IPA <20% to 20 μ M ADP) compared to about 20% with 7.5-mg prasugrel MD.

Hence, the dose regimen of a single 60-mg loading dose (LD), followed by a 10-mg once-daily maintenance dose (MD) was selected to be studied in the registration trial TAAL.

However, given the lack of consistent relationship between the inhibition of platelet aggregation and the risk for cardiovascular events, it is not known whether a mean 10% increased effect (prasugrel LD 60 mg Vs 40 mg) on platelet inhibition would translate into a meaningful incremental reduction of cardiovascular risk. Hence it is not known whether a lower dose would have provided similar benefit with decreased risk for bleeding. The current submission does not have enough data to explore the value of lower doses.

What is the impact of early loading dose (6 hours prior to the start of PCI) on the incidence of efficacy events?

The range for the time difference between loading dose and start of PCI across the octiles are shown in the table below:

Table 1 The range for the time difference between loading dose and start of PCI

Group	N	Range of Loading Dose Time – PCI Start Time (hrs)	Median (hrs)
1	1667	-234.83 - -0.12	-0.45
2	1703	-0.10 – 0.00	-0.05
3	1616	0.02 – 0.25	0.15
4	1658	0.27 – 0.43	0.35
5	1665	0.45 – 0.62	0.53
6	1773	0.63 – 0.83	0.73
7	1487	0.85 – 1.15	0.96
8	1699	1.17 – 530.00	1.45
<6 h*	231	-234.83 - -6.00	-19.82
>6 h*	13037	-5.9 0 – 530.00	0.45

* For comparing the range of differences in the loading dose time and the start of PCI in patients who were early pre-treated (<6 hrs Vs >6 hrs)

Irrespective of the treatment arms, the lowest incidence of CVD/Non-fatal MI/Non-fatal Stroke was observed when the loading dose was administered at the start of PCI or within 30 minutes of the start of the procedure as shown in Table 1.

The difference in the timing of the loading dose relative to the start of the PCI was not correlated with the risk factors associated with UA/NSTEMI or STEMI, such as prior history of CHF or MI or TIA/Stroke or Carotid/Vertebral Arterial disease or cerebrovascular accident. No correlation was observed with prior PCI. A weak but statistically significant correlation was observed with the use of GPIIb/IIIa antagonist, prior CABG and Stent use up to PCI or hospital discharge. However, it is not clear as to why the incidence of the events was higher when pre-treated, an observation that is not consistent with the current ACC/AHA 2007 guidelines for clopidogrel.

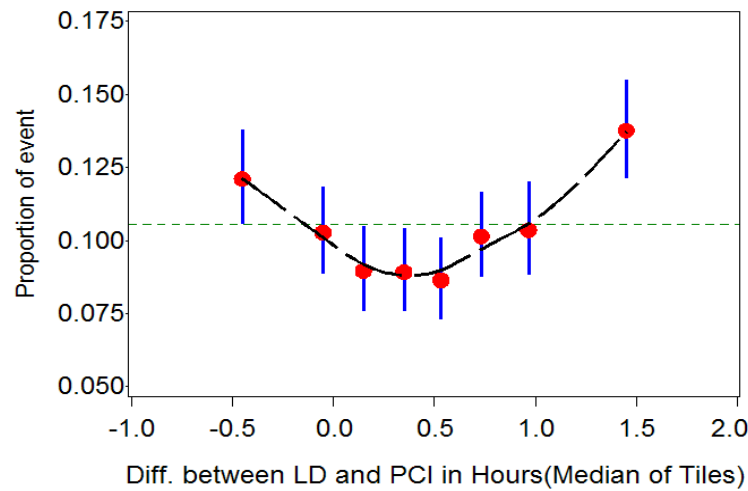


Figure 5: Maximum effectiveness is achieved when the loading dose is administered at the start or within 30 min of start of PCI (Red dots – represent proportion of events corresponding to the midpoints of the octiles; Blue bars – 95% Confidence interval; Black line – Smooth trend line; Green line – is the lowest confidence limit of the extremes)

Further the proportion of events were consistently higher when the time difference between the loading dose and the start of PCI were divided into groups based on whether the patient received the loading dose at least 6 hours or before as shown in the figure below.

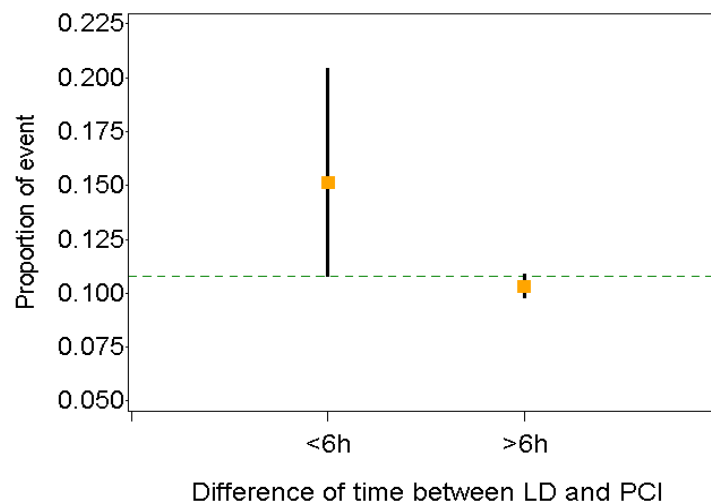


Figure 6 Pre-treatment with clopidogrel/prasugrel 6 hrs before the start of PCI results in decreased effectiveness compared to no pre-treatment (Orange squares – represent proportion of events; Black bars – 95% Confidence interval)

Similar relationship was seen across both the treatment arms as shown in the figure above.

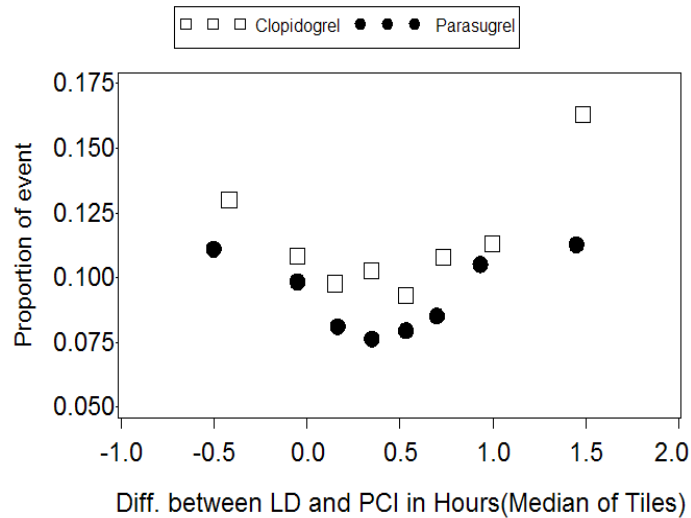


Figure 7 The effect of the timing of loading dose relative to the start of PCI is similar across prasugrel and clopidogrel

The value of administering the loading dose at the start of PCI is also evident from the Kaplan-Meier curves across the quartiles of difference between the loading dose and start of PCI as shown in Figure 8: The cumulative event rate of the efficacy endpoint is lower when the loading dose is administered at the start of PCI or within 30 minutes of the start of the PCI irrespective. Similar relationship was also seen when the data was divided into octiles instead of quartiles.

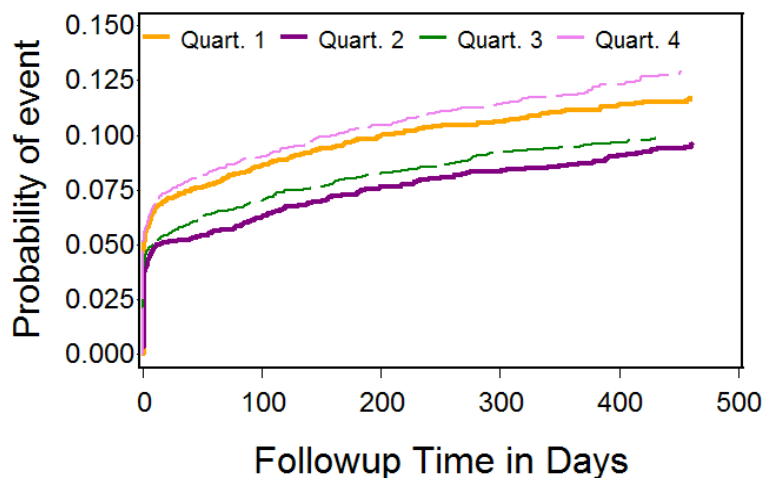


Figure 8: The cumulative event rate of the efficacy endpoint is lower when the loading dose is administered at the start of PCI or within 30 minutes of the start of the PCI irrespective

Cox Proportional regression shows that the relative risk for CVD/Non-fatal MI/Non-fatal Stroke is 28% and 24% lower for Quartiles 2 and 3 compared to Quartile 4. The details are presented in the table below:

Table 2 Comparison of Hazard Ratios for Quartiles

Quartile	N	Range of Loading Dose Time – PCI Start Time (hrs)	Hazard Ratio (95% Confidence Limit)	p-value
4*	3186	0.85 – 530.13	-	-
1	3370	-234.83 - 0	0.91 (0.79 – 1.05)	0.1858
2	3274	0.02 – 0.43	0.72 (0.62 – 0.84)	<0.0001
3	3438	0.45 – 0.83	0.76 (0.66 – 0.89)	0.0004

• Quartile – 4 was used as reference to compute the relative risk for rest of the quartiles.

This relationship was consistent between prasugrel and clopidogrel as shown in the figure above.

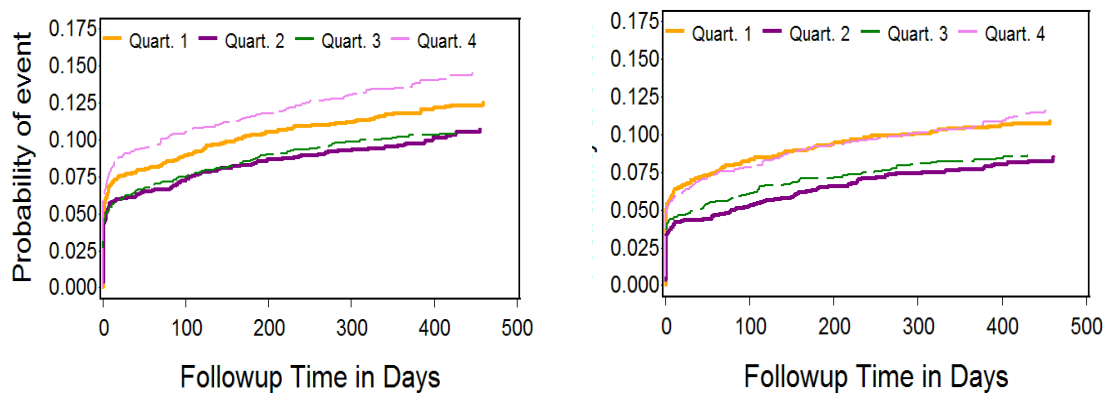


Figure 9 Cumulative event rate of the efficacy endpoint across quartiles of difference in time of loading dose and start of PCI is similar between clopidogrel (left) and prasugrel (right)

Exploratory analyses revealed a weak but statistically significant correlation was observed with the use of GPIIb/IIIa antagonist, prior CABG and Stent use upto PCI or hospital discharge.

Further, prior CABG was found to be a statistically significant predictor (χ^2 statistic $p < 0.0001$) of the timing of loading dose when a 2x2 contingency table was constructed between prior CABG and the timing of the loading dose (dichotomized by at least 6 hrs before PCI or not) in only those patients who received the loading dose before the start of PCI. After controlling for the prior CABG, no statistically significant association (CMH Statistics: General association $p = 0.1146$) was seen between timing of loading dose (at least 6hrs before PCI or not) and observing the efficacy endpoint. This could likely explain the reason for higher incidence of the primary endpoint when prasugrel or clopidogrel is dosed at least 6 hrs or before.

Hence with potent rapidly acting agents such as clopidogrel and prasugrel pre-treatment may not be necessary for achieving maximum effectiveness. However, the Loading Dose for either Prasugrel or Clopidogrel should be administered at least within 30 minutes of the start of the PCI.

Relationship between exposure and bleeding

A meta analysis of the pharmacokinetic data from 6 clinical pharmacology studies (TAAS, TAAZ, TABS, TABV and TACG) found that among subjects treated with prasugrel 10-mg MD, a trend towards a higher rate of bleeding-related adverse events in the highest quartile of exposure to the active metabolites.

In the phase 1b study TAAD, in subjects with stable atherosclerosis, the rate of epistaxis was higher in subjects treated with prasugrel 15-mg MD (5%) than in subjects treated with prasugrel MD of 10 mg (1%), 7.5 mg (1%) or 5 mg (1%).

In the phase II study TAAH in ACS patients, increasing doses of prasugrel resulted in increased TIMI/Major/Minor/Minimal bleeding (5.2% with 60/15-mg MD versus 3.5% with 40/7.5-mg and 60/10-mg doses respectively). However, this difference was primarily in TIMI minimal bleeding.

All these studies indicate towards a relationship between the exposure of R-138727 and bleeding.

Does prasugrel prolong the QT or QTc interval?

No. The sponsor performed a thorough QT study (TAAP) to assess the effect of prasugrel on QT and QTc prolongation.

The time course of mean $\Delta\Delta\text{QTcF}$ for R-138727 following 80-mg prasugrel and moxifloxacin (400 mg) is illustrated below in the figure below.

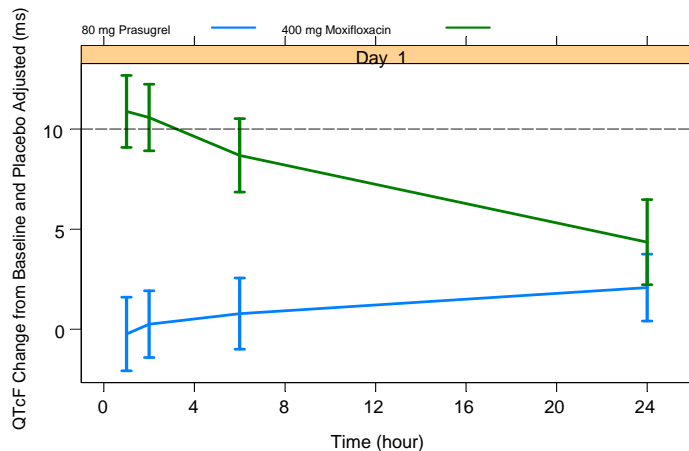


Figure 10 Time course of mean $\Delta\Delta\text{QTcF}$

There seems to be no significant relationship between R-138727 exposure and $\Delta\Delta\text{QTcF}$ from the figure below. The similar pattern for concentration- $\Delta\Delta\text{QTcF}$ was observed for other metabolites as well.

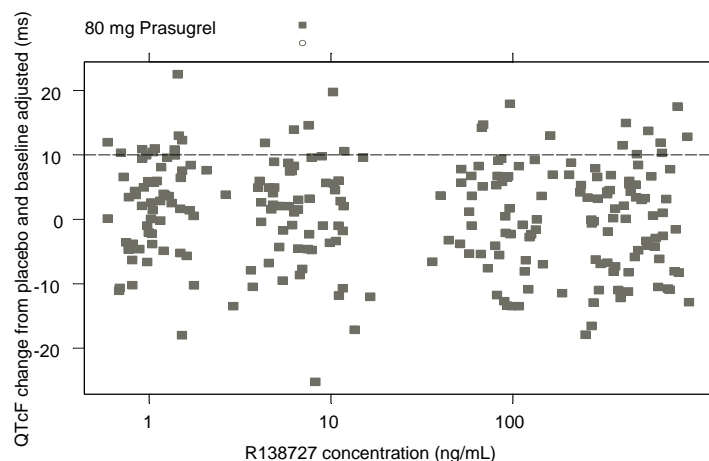


Figure 11 Log concentration- $\Delta\Delta$ QTcF relationship for R-138727

How does the plasma concentration of the inactive prasugrel metabolites correlate with QT?

Based on concentration-QT modeling, prasugrel metabolites do not exhibit any significant slope.

The inactive metabolites (R119521 and R106583) exposures achieved in a large Phase III clinical study TAAL were analyzed. After a 60-mg loading dose the exposures were much lower for R-106583 and similar for R-119521. In the population PK study of TAAL (1159 subjects) fewer than 2% of the subject had exposures of R-119521 higher than that observed in the QT study. With this information it could be said that the exposures of R-119521 were good enough in the present QT study to rule out any exposure-response relationship for R-119521 in spite of predicting the scenarios which might have higher exposure than in the present QT study. Furthermore, considering, that the 60-mg loading dose will be given in patient under clinical supervision, it would be reasonable to compare exposures of metabolites in this TQT study (80-mg prasugrel) to that following a 10-mg maintenance dose. In this case, the 80-mg dose would comfortably cover the exposures expected after a 10-mg maintenance dose. Moreover, no relationship was observed between concentration- $\Delta\Delta$ QTcF for any of the metabolites in the observed concentration ranges. Thus it can be said that prasugrel is unlikely to prolong QT interval after clinically relevant exposures.

PK CHARACTERISTICS OF THE DRUG AND ITS MAJOR METABOLITE(S)

What are the single dose and multiple dose PK parameters? How do the PK parameters change with time following chronic dosing?

The proposed dose regimen is associated with chronic administration after the loading dose. The comparison of the mean concentration vs. time profiles of R-138727 (active metabolite), and inactive metabolites following a single prasugrel 60-mg LD and during 10-mg MD is shown in the figure below.

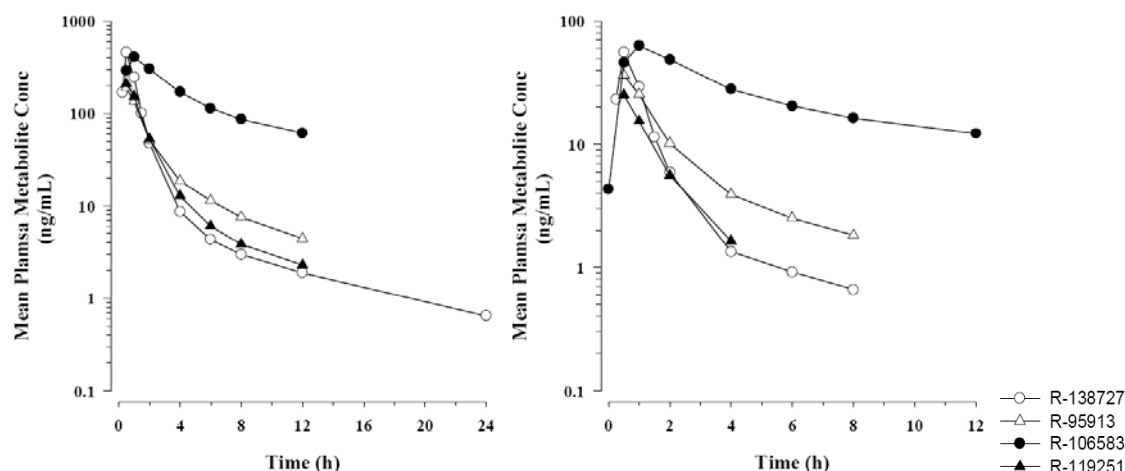


Figure 12. The mean concentration vs. time profiles of R-138727, R-95913, R-119251, and R-106583 following a single prasugrel 60-mg LD (left panel) and during 10-mg MD (right panel), Study TAAV.

The PK parameters of the prasugrel active metabolite after the LD and MD were calculated in healthy subjects (sponsor's meta-analysis) are listed in the table below.

Table 3 Pharmacokinetic Parameter Estimates for R-138727

Parameters	LS Geometric Mean (90% CI)		Variability (CV)		
	60-mg LD (N=437)	10-mg MD (N=284)	Within-Subject	Between-Subject	Between-Study
C_{max} (ng/mL)	475 (439, 514)	69.9 (64.3, 76.0)	38.1%	30.1%	14.9%
t_{max}^a (h)	0.5 (0.25, 2.07)	0.5 (0.25, 2.25)	NC	NC	NC
AUC(0- t_{last}) (ng•h/mL)	514 (478, 552)	67.5 (62.6, 72.7)	19.3%	27.6%	14.9%
$t_{1/2}^b$ (h)	7.36 (1.97, 14.6) ^c	NA	NC	24.4%	7.25%

LD = loading dose; MD = maintenance dose; N = number of subjects; NA = not available; NC = not calculated;

a Median (minimum, maximum). b Geometric mean (minimum, maximum). c Number of subjects=230.

How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The sponsor's meta-analysis of noncompartmental PK estimates from 16 Phase 1 studies compared the exposure estimates from 506 healthy male and female subjects and evaluated the effect of specific subject factors on exposure to the active metabolite. Noncompartmental analyses and the population PK analysis have produced results consistent across studies and between the 2 methods of analysis. The PK of R-138727 in subjects with stable atherosclerosis and subjects with ACS undergoing PCI also have been assessed by conventional noncompartmental methods and/or population PK methods in Studies TAAD, TABR, and TAAL. The exposures to the active metabolite in patients are very similar to those in healthy subjects (Table below).

Table 4. AUC values of R-138727 in Healthy Subjects and in Patients.

	R-138727 AUC (ng•h/mL)				
	Noncompartmental Analysis	Model-Predicted Analysis			
	PK meta-analysis	TAAJ	TAAD	TABR	TAAL ^a
	Healthy subjects	Healthy subjects	Stable atherosclerosis	Stable atherosclerosis	ACS undergoing PCI
60-mg LD					
N	437	66	40	55	1159
Median	528	526	530	394	478
5th-95th percentile	297-980	348-846	341-810	253-527	275-1021
10-mg MD					
N	284	—	19	55	1159
Median	70.5	—	88.7	59	79.6
5th-95th percentile	41.1-128	—	56.0-119	37.9-78.9	45.8-170

What are the characteristics of drug absorption (possible transporters and pH impact)?

Prasugrel is a prodrug, it is metabolized in vivo to the active metabolite which appears rapidly in plasma after oral dosing, reaching a peak concentration in about 30 minutes and then declining biphasically with a terminal half-life of about 7.4 hours. When prasugrel was coadministered with a proton pump inhibitor lansoprazole, and therefore, the gastric pH was elevated, the C_{max} values of the active metabolite decreased by 30% with no changes in AUC values. This indicates that the rate but not the extent of prasugrel dissolution decreased in the conditions of high pH in the stomach. This may delay the onset of effect after a LD but would not be relevant during MD. When prasugrel was coadministered with an H₂-receptor antagonist ranitidine, which also elevate gastric pH, the active metabolite's C_{max} and AUC decreased by about 20% after the LD with no changes occurring after the MD (see DDI section).

After oral administration to healthy subjects at least 79% of the prasugrel dose was absorbed.

What are the characteristics of drug distribution (including plasma protein binding?)

Prasugrel's active metabolite is extensively distributed into the tissues.

The estimates of apparent volume of distribution of R-138727 ranged from 30 L to 84 L in healthy subjects and subjects with stable atherosclerosis (Studies TAAD, TAAJ, and TABR).

The binding of the active metabolite to plasma proteins was not determined in vivo, and in vitro, it was 98% in 4% human serum albumin solution in phosphate buffer, pH 7.4. The inactive metabolites are highly bound to human plasma proteins. The fraction bound to plasma proteins at various concentrations, determined by ultracentrifugation, was 94.6% for R-95913 (50, 100, and 500 ng/mL), 95.1% for R-106583 (100 and 500 ng/mL), and 76.4% for R-119251 (100, 500, and 1000 ng/mL).

Although in the mass-balance study in 5 subjects, the plasma-to-whole blood ratio measured by total radioactivity was generally greater than one, it does not prove that the penetration into red blood cell was limited to a specific molecular entity.

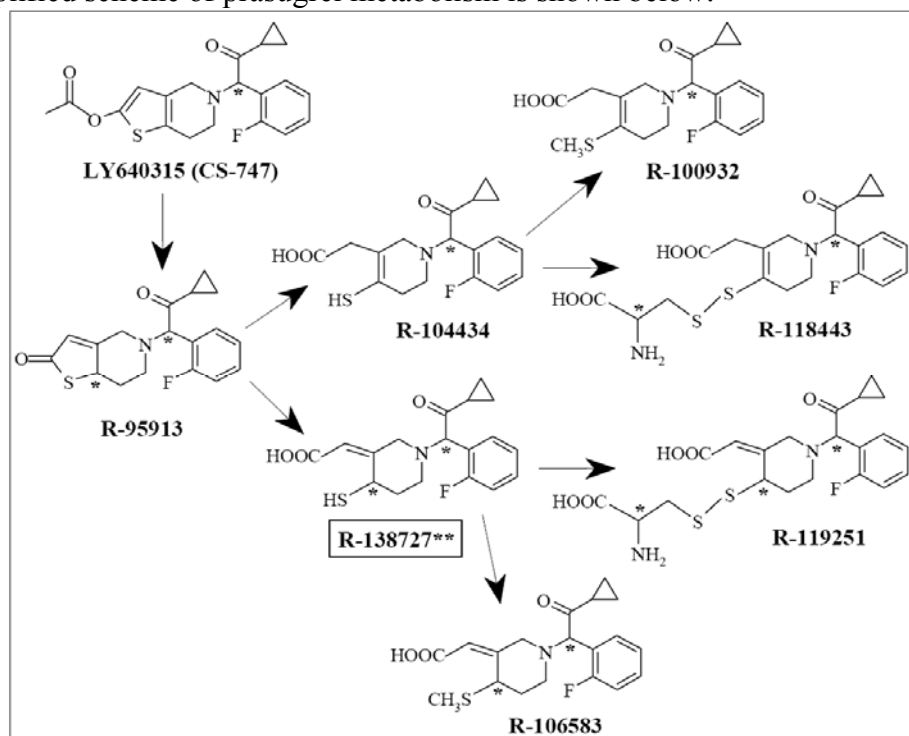
Does the mass balance study suggest renal or hepatic as the major route of elimination?

Prasugrel (prodrug) was metabolized rapidly in vivo and was not detected in plasma collected from the 5 subjects following the [14C] prasugrel dose (mass-balance study TAAB). The radiochemical profiles and mass spectral data confirmed the presence of 16 metabolites in plasma collected over the first 12 hours. R-106583 is the major metabolite in human plasma, followed by R-95913 and R-138727 which is a pharmacologically active metabolite.

About 90% of the total radioactivity was excreted in the urine over 240 hours, accounting 68% of the dose. A total of thirteen metabolites were identified in urine. The major metabolites observed in the urine were four diastereomers of M1 (m/z 336). The metabolites M1-A and M1-B and M1-C and M1-D were inter-convertible.

Approximately 27% of the 14C dose was eliminated in feces, 91% of which was recovered within the first 72 hours post-dose. Six metabolites were detected in feces, which were also observed in plasma.

The simplified scheme of prasugrel metabolism is shown below.



The estimates of apparent clearance of prasugrel's active metabolite ranged from 73 L/hr to 266 L/hr in healthy subjects and subjects with stable atherosclerosis (population PK analysis, Studies TAAD, TAAJ, and TABR).

What are the characteristics of drug metabolism?

Prasugrel is rapidly hydrolyzed in vivo and is not detected in plasma. In vitro studies showed that human carboxylesterases (hCE) 1 and 2, the dominant forms in the liver and intestinal tract, respectively, are capable of hydrolyzing prasugrel to R-95913, the precursor to prasugrel's active metabolite, and that hCE2 had a maximal hydrolysis rate approximately 26 times higher than that of hCE1. The results suggest that the hydrolysis of prasugrel to R-95913 is mediated efficiently by hCE2 prior to reaching the portal vein. The metabolism of R-95913 to the active metabolite R-138727 is catalyzed by several isoforms of CYP, with CYP3A and CYP2B6 being the main contributors to this oxidative step. Since CYP3A constitutes approximately 80% of the intestinal CYP enzymes, most of R-138727 form during first pass metabolism is probably formed by intestinal CYP3A during absorption. The active metabolite is further metabolized to 2 inactive compounds by S-methylation or conjugation with cysteine.

The active metabolite R-138727 contains 2 chiral centers, and thus is comprised of 4 enantiomers, (R,S), (R,R), (S,R), and (S,S). The R- and S-configurations at the 1' position interconvert in vivo, and therefore the 4 enantiomers of R-138727 can be considered to be 2 pairs, (R,S)/(R,R) and (S,R)/(S,S). The enantiomers possess different activities towards the platelet P2Y₁₂ ADP receptor, with the (R,R)/(R,S) pair being the most potent. In humans, the (R,R)/(R,S) pair comprised about 84% of the total active metabolite in plasma. The ratios of R-138727 enantiomers were consistent among subjects, regardless of dose, time of sample collection, or whether the blood was sampled after the first prasugrel dose or after 4 weeks of treatment. Therefore, the variation in enantiomeric ratios is not important in interpreting the clinical data.

The active metabolite's half-life is 7.4 hours. It further converts to the inactive metabolites. The comparison of the pharmacokinetic parameters of prasugrel metabolites in healthy subjects is shown in the Table below.

Table 5. Comparison of the Pharmacokinetic Parameters of Prasugrel Metabolites

Parameter	Geometric Mean (%CV)							
	Active Metabolite		R-95913		R-119251		R-106583	
	LD (N=34)	MD (N=32)	LD (N=34)	MD (N=32)	LD (N=4)	MD (N=32)	LD (N=34)	MD (N=32)
C _{max} (ng/mL)	453 (35)	56.5 (48)	190 (46)	36.2 (54)	216 (38)	24.0 (49)	399 (27)	63.5 (29)
t _{max} ^a (h)	0.50 (0.25-1.00)	0.50 (0.25-1.00)	0.50 (0.50-1.00)	0.50 (0.50-1.00)	0.50 (0.50-1.00)	0.50 (0.50-1.00)	1.00 (0.50-2.00)	1.00 (0.50-4.00)
AUC(0-t _{last}) (ng•h/mL)	460 (21)	54.5 (26)	324 (42)	59.6 (52)	317 (28)	30.6 (34)	1760 (30)	299 (30)
t _{1/2} ^c (h)	6.88 (26.4)	-- ^b	6.81 (25.7)	-- ^b	5.33 (50.4)	-- ^b	8.41 (25.2)	-- ^b

The concentration vs. time profiles of R-95913 (the precursor to the active metabolite) and of R-119251 (the cysteine conjugate of the active metabolite) parallel those of the active metabolite. These metabolites reach the peak plasma concentrations at the same time as the active metabolite. Their profiles decline in parallel with each other and with the active metabolite. This suggests that the elimination of the active metabolite and R-119251 are formation-rate limited and depend on the elimination rate of R-95913. The most abundant metabolite, the S-methyl conjugate R-106583, reach the peak of plasma concentration later, and decline slower than those of the active metabolite and 2 other

major inactive metabolites. These metabolites at concentrations of 100 μM and 300 μM did not significantly affect ADP-induced aggregation of human platelets in platelet-rich plasma. These metabolites do not accumulate during multiple dosing and have adequate margins of safety.

Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Prasugrel dose-proportionality was assessed in the studies S001, S004, TAAW and during the population PK data analyses. The first 2 studies used a base formulation and did not measure the plasma concentrations of the active metabolite. In the study TAAW, the measurements of the prasugrel metabolites R138727, R95913, R106583, and R119251 after low prasugrel doses (5-10 mg) were performed only up to 4 hours post-dose. Only metabolite R106583 was measurable through 24 hours post-dose. Therefore, a comparison of the AUC0-4 was performed for this study. AUC0-4 hours for all metabolites of prasugrel related to the absorption-early distribution state, hence, it is not appropriate to evaluate the dose proportionality based on this parameter. In this study the active metabolite's C_{max} was dose proportional over the 5-60 mg dose range and the AUC_{inf} and AUC0-4 increased more (26% and 18%) than dose proportional. The relationship between dose and the PK parameters of R138727 is shown in the figure below.

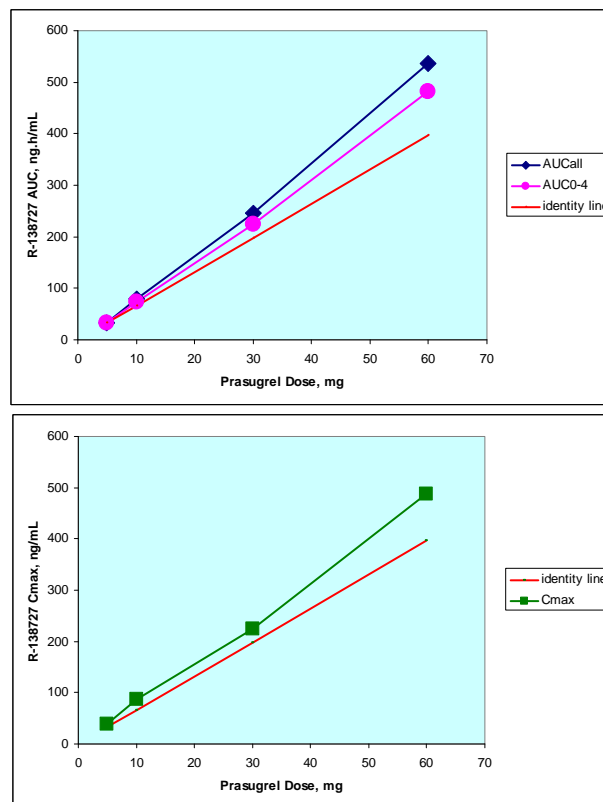


Figure 13. PK Parameters of R138727 vs. Prasugrel Dose, Study TAAW.

The assessment of dose-proportionality in the population PK did not find any disproportionality between doses (Appendix IV). The sponsor also performed a meta-analysis of the PK data which were reasonably combined from the different studies. Since for the general population the proposed dosing regimen includes only one dose of 60 mg followed by repeated 10 mg dose, slight disproportionality in AUC would not be of clinical significance. The administration of repeated doses of 10 mg does not lead to any accumulation of the active metabolite.

What is the inter- and intra-subject variability of the PK parameters, and what are the major causes of variability?

Prasugrel is a moderately variable drug.

The estimates of between-patient variability in apparent clearance in these studies have been moderate, ranging from 25% to 30%. Between-patient variability in apparent volume of distribution (Vd/F) was moderate at 28.5% in Study TAAD and 34.3% in Study TAAJ. The variability was explained by body weight, age, dose, co-administration of ketoconazole and food as significant factors relating to the differences between R-138727 and R-106853. (See PM review for details).

2.3 Intrinsic Factors

What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses? Based on what is known about exposure-response relationships, what dosage regimen adjustments, if any, are recommended for each subgroup listed below?

The effects of age, gender, race, and body weight was prospectively studied in the NDA.

Body Weight

In the sponsor's meta-analysis, body weight was found to significantly influence both C_{max} and AUC_{0-t_{last}} of R-138727.

Table 6. Effect of Body Weight on AUC and C_{max} of R-138727

Parameters (units)	Change of Body Weight (kg)	Ratio of LS Geometric Mean (90% CI)
		Compare to 85 kg
C _{max} (ng/mL)	From 85 to 60	1.49 (1.39, 1.59)
AUC(0-t _{last}) (ng•h/mL)	From 85 to 60	1.45 (1.38, 1.52)

The individuals with lower body weight have higher R-138727 exposures. Relative to a population mean of 85 kg in the target patient population (Studies TABR, TAAD, and TAAL), an approximately 25 kg decrease in body weight is predicted to result in an increase of 49% and 45% in R-138727 C_{max} and AUC, respectively, following LD or MD doses.

The apparent clearance of R-138727 decreased with decreasing body weight, which would produce increasing exposure as body weight decreases. Specifically, a 31% decrease in body weight from 84 kg to 58 kg produced an approximately 22% decrease in R-138727 CL/F and an increase of ≤ 10 percentage points in MPA.

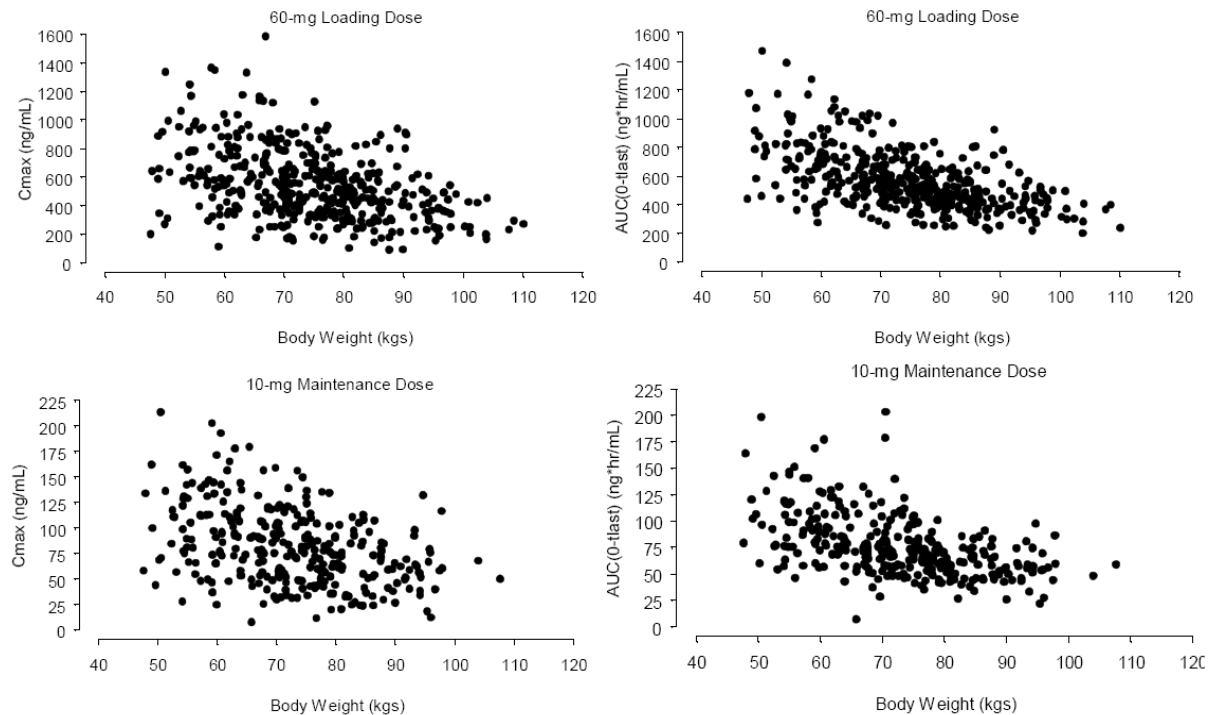


Figure 14. Observed AUC_{0-tlast} and C_{max} of R-138727 vs. body weight following a 60-mg LD or during 10-mg MD of prasugrel (Source: Figure APP.2.7.2.34 of Sponsor's clin-pharm-summary-appendix-us-pci.pdf)

Should the maintenance dose be reduced to 5 mg QD in patients with body weight below 60 Kg?

Dose adjustment to 5 mg QD in patients with bodyweight below 60 kg is acceptable. Trends of increased bleeding related adverse events were associated with increased exposures of R-138727. Exposure of R-138727 increased with decreasing body weight and the Thrombolysis in Myocardial Infarction (TIMI) Major bleeding risk was 2 fold higher in patients with body weight less than 60 Kg. Efficacy was similar across the body weight groups. Reducing the maintenance dose of prasugrel to 5 mg shifts more than 50% of patients with body weight less than 60 Kg to lower quartiles of exposure seen with 10 mg in patients with body weight greater than 60 kg.

Relationship between body weight and efficacy

The exploratory univariate Cox model showed inconsistent results for the impact of body weight on efficacy depending on whether it is used as a continuous or categorical

variable. Further, multivariate analysis did not reveal body weight as a significant predictor of risk for efficacy event in multivariate analyses.

Relationship between body weight and TIMI major bleeding

The risk for TIMI major bleeding with prasugrel was found to be higher in the lower body weight group as shown below in the Kaplan-Meier plot. The univariate Cox regression showed that the relative risk for TIMI major bleeding on prasugrel for patients with body weight less than 60 Kg was 4 fold higher (HR: 3.051 (2.013 – 4.623), $p < 0.0001$) compared to patients with higher body weight. Body weight was retained as the significant predictor of TIMI major bleeding risk in multivariate analyses too (HR: 2.826; $p < 0.0001$). Similar relationship was observed for the NCABG TIMI major bleeding.

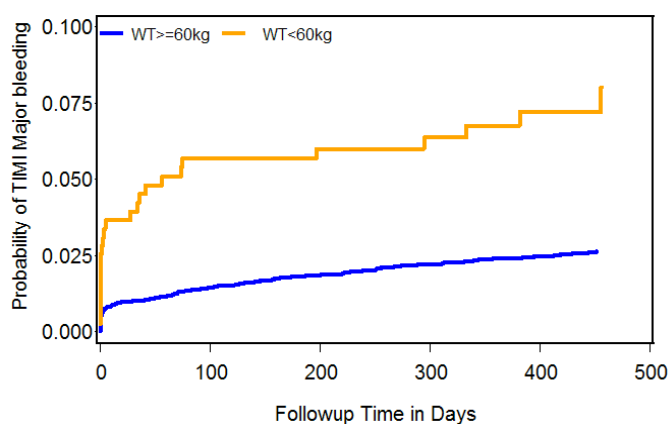


Figure 15 Risk for TIMI Major bleeding is higher in patients with body weight less than 60 Kg.

Relationship between body weight and exposure

The population pharmacokinetic analyses of studies TAAD and TABR reveal that the clearance of the active metabolite R-138727 increases with increase in the body weight as shown in the figure below. This indicates a decrease in exposures with increase in body weight.

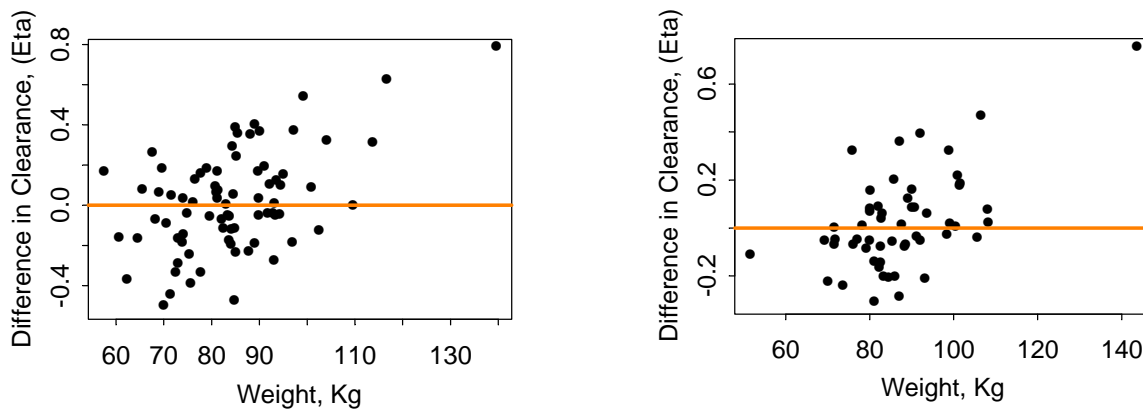


Figure 16 Clearance of R-138727 increases with increase in body weight (Left: Study TAAD; Right: Study TABR)

This decreased exposure with increase in bodyweight is also evident in the pivotal trial (Study TAAL) as shown in the figure below.

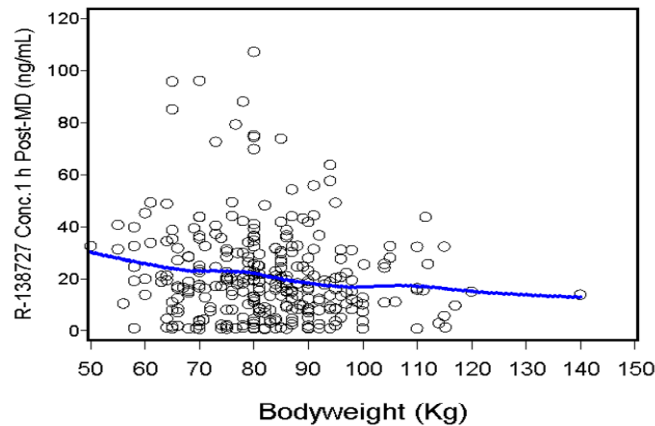


Figure 17 **Decreased Exposures of R-138727 with increased body weight in Study TAAL.** (Circles represent plasma concentrations 0.75-1.25 h post MD; Blue line is a smooth trend line)

Simulation of R-138727 exposure (model based AUC for the maintenance dose) show that the proposed dose adjustment of 5 mg MD by the sponsor is able to shift the exposure of the majority of subjects with body weight less than 60 Kg from the upper quartile to the lower quartile of those seen in patients with body weight greater than 60 Kg.

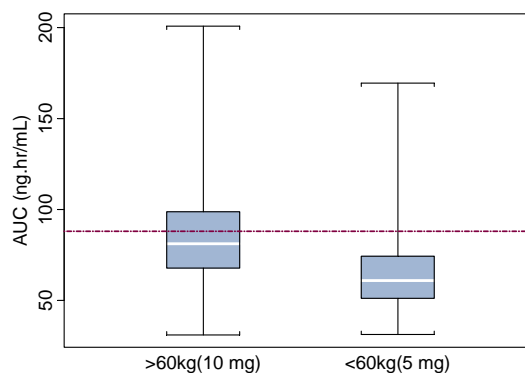


Figure 18 **Simulation (N=2000) of the proposed dose of 5 mg in patients with body weight < 60kg will result in exposures predominantly corresponding to lower two quartiles of those expected with 10 mg MD in patients with body weight >60 kg.** (The red dashed line represent the concentration range beyond which the bleeding related

adverse events were highest from Figure 3). ($CL = 123 \times (WT/85)^{0.798}$; Between-subject variability (%CV) = 24% - Obtained from Reviewer's POPPK analysis of TABR for Simulation)

Age and Gender

A gender effect was not detected in the population PK data analysis performed for the pivotal study TAAL. The sponsor's meta-analysis concluded that R-138727 PK is not clinically significantly affected by age with a range of 18 to 80 years, nor is R-138727 PK affected by gender.

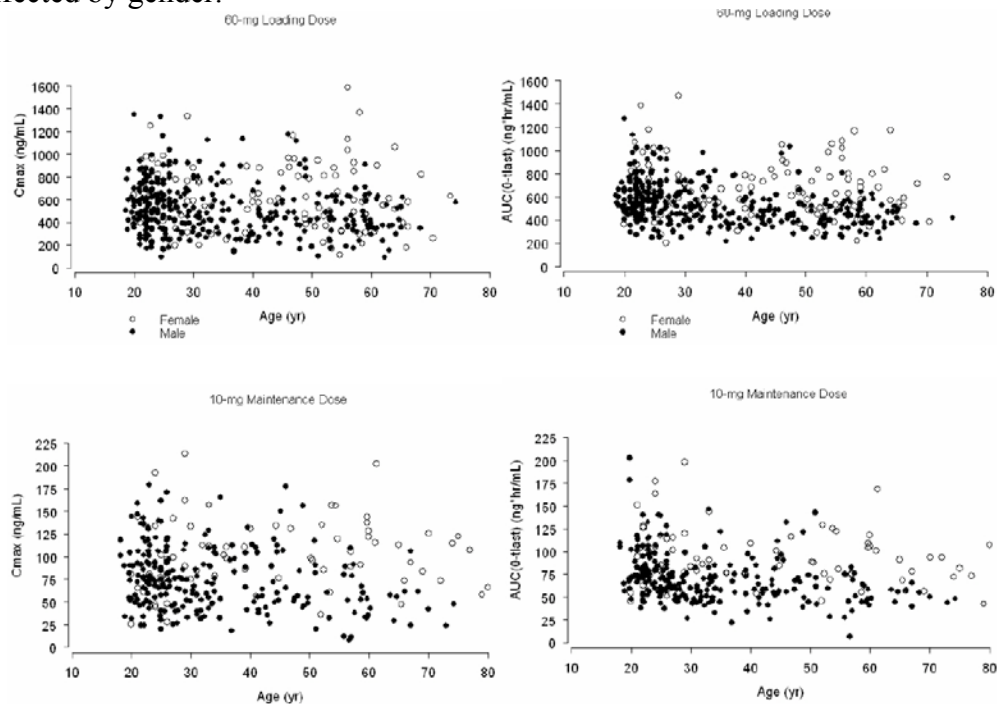


Figure 19 Effect of age by gender on observed R-138727 Cmax and AUC0-tlast following a 60-mg LD and daily 10-mg MD of prasugrel Figure APP.2.7.2.4 of Sponsor's clin-pharm-summary-appendix-us-pci.pdf)

No dose adjustment should be made based on gender.

In the sponsor's analysis, the older male subjects had lower exposure, specifically a 20% lower AUC0-tlast compare to men 65 years old.

The data from the studies in patients were reanalyzed, and the results are shown below:

Should the maintenance dose be reduced to 5 mg QD in patients with age \geq 75 years?

Relationship between age and efficacy

Age was found to be a significant predictor of the CVD/Non-fatal MI/Non-fatal stroke (HR: 1.031, $p < 0.0001$). When age was tested as a categorical covariate, the risk for CVD/Non-fatal MI/Non-fatal Stroke on prasugrel for patients with age greater than 75 years was 98%% higher (HR: 1.982 (1.647 – 2.386), $p < 0.0001$) compared to patients with age less than 75 years. The Kaplan-Meier curve depicting the effect of age is shown in Figure 20. This effect of age was also evident in the multivariate Cox proportional

model (HR: 1.98; $p < 0.0001$). Similar relationship was observed for the clopidogrel treatment arm.

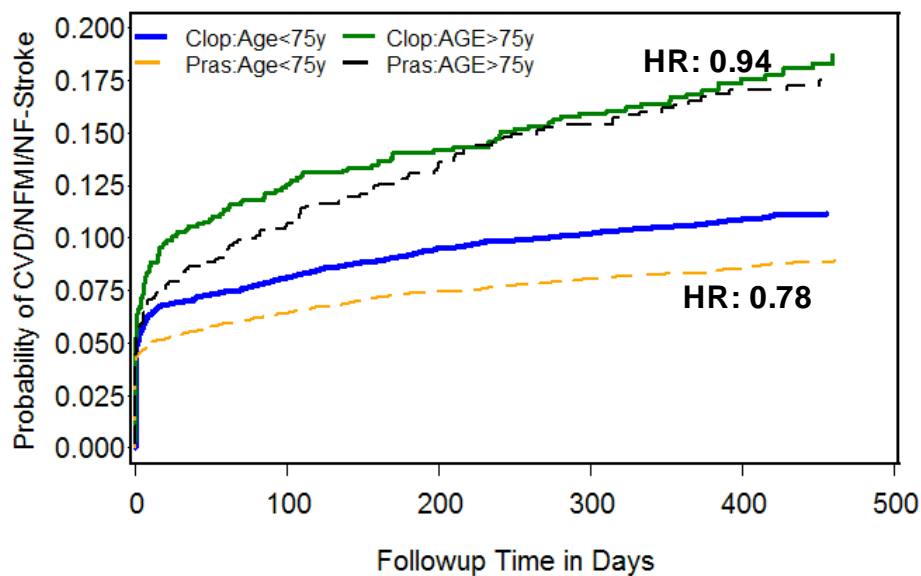


Figure 20: Risk for CVD/Non-fatal MI/ Non-fatal Stroke is high in patients above 75 years of age compared to patients below 75 years. (The Hazard Ratios are for Prasugrel compared to Clopidogrel in each of the age groups)

Relationship between age and TIMI major bleeding

Univariate analysis with age as a continuous measure was found to be a significant predictor of TIMI Major bleeding risk with 3.2% increase in risk per year (HR:1.032; $p < 0.0001$). When tested as a categorical covariate (cutoff 75 years) the relative risk for TIMI major bleeding with prasugrel was significant (HR: 1.818 (1.265 – 2.612); $p = 0.00120$). The Kaplan-Meier curves showing the effect of age on bleeding risk is shown in Figure 21. Age was found to be an independent predictor of TIMI major bleeding risk in multivariate analyses too (HR: 1.650; $p = 0.0069$). Similar relationship was observed for the NCABG TIMI major bleeding in a multivariate analysis.

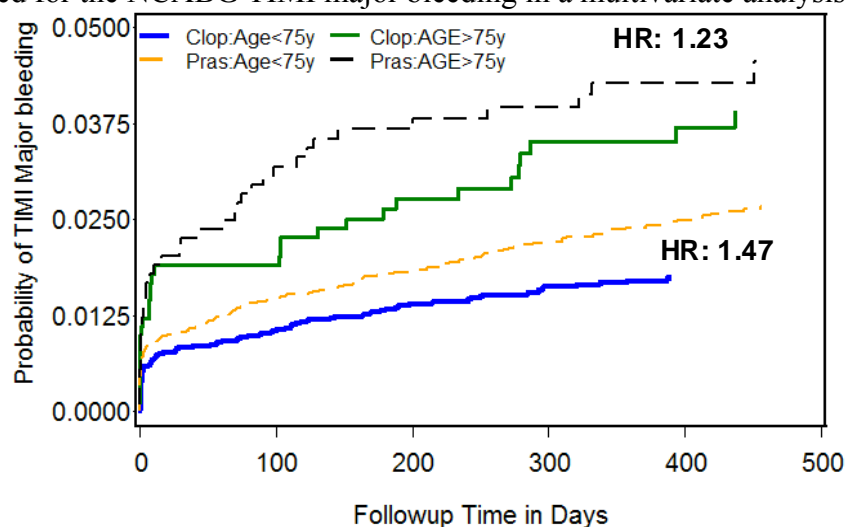


Figure 21 Risk for TIMI Major bleeding is high in patients above 75 years of age compared to patients below 75 years. (The Hazard Ratios are for Prasugrel compared to Clopidogrel in each of the age groups)

Since the risk of decrease of efficacy is higher with the existing dosing regimen in patients above 75 years of age, any further reduction in dose aimed at reducing the risk for bleeding might result in reduced efficacy. Based on the reviewer's analysis, prasugrel does not appear to provide safe and effective therapy to patients above 75 years compared to those below 75 years. Hence, prasugrel should not be the treatment of choice in patients above 75 years. Similar results were observed with clopidogrel. Hence P2Y₁₂ antagonists such as clopidogrel and prasugrel should be avoided in elderly patients (age \geq 75 years).

Race, in particular differences in exposure and/or response in Caucasians, African Americans, and/or Asians

There were 96% Caucasian subjects in the pivotal study TAAL. The sponsor performed 2 studies to assess the effect of Asian ethnicity on the pharmacokinetics and pharmacodynamics of prasugrel. The effect of other ethnic background was evaluated by means of meta-analysis performed by the sponsor.

The C_{max} and AUC_{0-tlast} values in subjects of African and Hispanic descent were similar to Caucasian subjects, and the Asian subjects had higher exposures than Caucasians. In every dose group, there was a 40-45% increase of C_{max} and AUC values in Asian compared to Caucasian subjects. As a population, Asians have lower average body weight; therefore, a 65-kg Asian subject is predicted to have an exposure that is approximately 40% higher compared to a 77-kg Caucasian subject. After adjusting for body weight and effect of other covariates, C_{max} and AUC_{0-tlast} values were approximately 20% higher in Asians than in Caucasians. Within Asian populations (Study TABZ), the exposures to prasugrel were similar among Chinese, Japanese, and Korean subjects.

The figure below shows the comparison of the exposure parameters per population per dose of prasugrel.

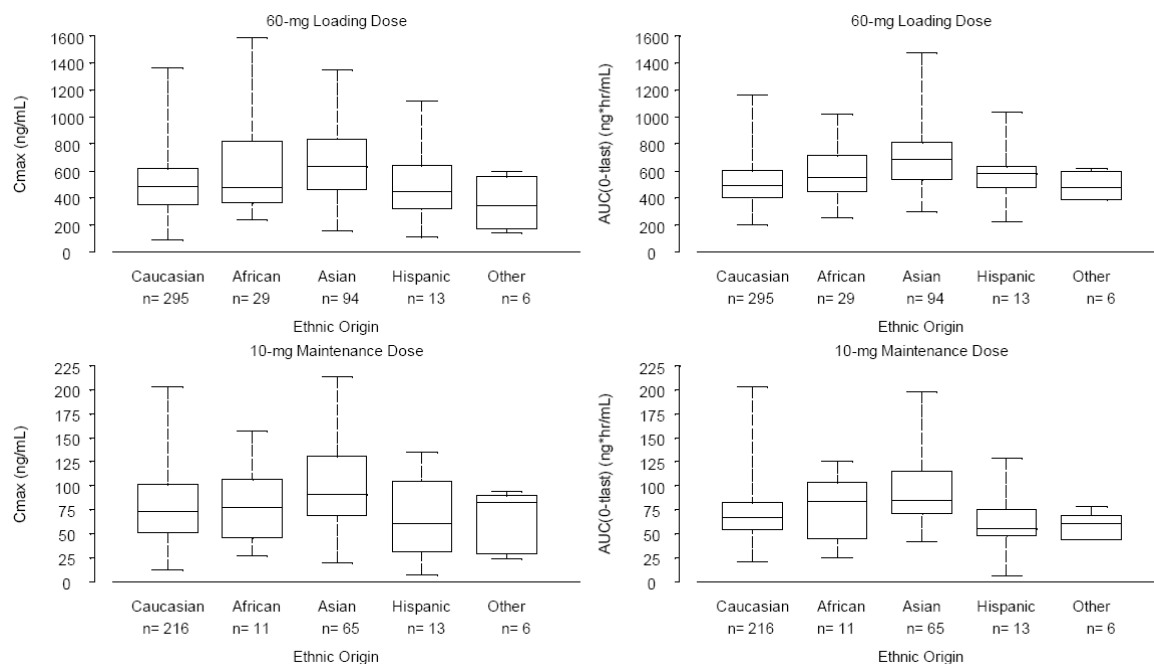


Figure 22 Box plots compare the observed AUC0-tlast and Cmax values of R-138727 by ethnic group following 60-mg LD or 10-mg MD of prasugrel

The IPA response in the Asian subjects was stronger than in Caucasians although the differences between all groups were not significant. The high variability of the method could mask the differences. The highest incidence of bleeding-related adverse events was reported for Korean subjects 20 out of 33, and the lowest incidence reported for Japanese subjects, 9 out of 10. For each ethnic group, the bleeding-related events were most frequently reported following the 10-mg MDs. The bleeding events analyses are performed in the clinical review.

The information related to the development of prasugrel in Japan under the other indication and IND was submitted with NDA 22,307. There were 8 PK and PD studies of prasugrel which were not reviewed except for their synopses. The excessive bleeding was associated with a administration lower dose (30 mg) administered to the Japanese subjects than it is proposed in this NDA.

Similar differences were observed after the multiple 10mg/day and 5mg/day doses of prasugrel

In the Package Insert, it should be mentioned that the administration of prasugrel to subjects of Asian origin should be performed with caution.

Renal Impairment

The impact of renal impairment on the PK of prasugrel was assessed in 3 studies. The two studies used 4 and 5 subjects in the ESRD group and were stopped early. After the 60 and 10 mg doses of prasugrel, the exposure to R-138727 (both Cmax and AUC(0-tlast)) decreased by half in subjects with ESRD compared to that in healthy controls and subjects with moderate renal impairment. The sponsor concluded that the differences in mean MPA values at each time point between subjects with moderate renal impairment and healthy matched subjects and between subjects with ESRD and healthy matched

subjects were not statistically significant. However, at each time point, including the baseline, ESRD subjects had less than maximal platelet aggregation (vs. healthy) with differences between 3 and 19%. It is not clear if this is an indication of increased IPA due to the low baseline MPA values in ESRD group. The statistical conclusion about the MPA response in patients with ESRD is difficult to make due to the small sample size, and the sponsor did not provide any recommendations regarding their dose adjustment. The label should contraindicate prasugrel administration to ESRD patients.

Hepatic Impairment

The PK parameters estimated for the active metabolite R-138727 in healthy subjects and in subjects with moderate hepatic impairment were very similar (Studies TAAN and TABV). Only 4 subjects with mild hepatic impairment were studied. The PD response measure as MPA to 20 mM ADP was similar in the groups of healthy subjects, and subjects with mild and moderate hepatic impairment. The effect of hepatic impairment on the prolongation of bleeding time and the frequency of the bleeding events was not evaluated in the two studies performed in subjects with hepatic impairment. A dose adjustment for the hepatically impaired subjects is not required.

Does the pharmacogenomic data support the label claim: “In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving EFFIENT, there was no relevant effect of genetic variation in CYP3A5, CYP2B6, CYP2C9, or CYP2C19 on the pharmacokinetics of EFFIENT or its inhibition of platelet aggregation.”?

This claim is linked to an accurate assessment of the link between patient genotype and the pharmacokinetics of EFFIENT. This claim was tested through the *de novo* analysis of the anonymized genotyping data reported by the sponsor.

Genotyping data were reported from three clinical studies. In the IGA study, the effects of variation in genes encoding CYP enzymes involved in thienopyridine metabolism on PK and PD in response to LD or MD of Prasugrel or Clopidogrel were studied in healthy subjects. The TAAL PK study examined the relationship between variation in the genes encoding CYP2C19 and CYP2C9 and Prasugrel AUC estimates of active metabolite derived from a subset of patients. The TABR study covered the relationship between variation in the genes encoding CYP2C19 and CYP2C9 and Prasugrel AUC estimates of active metabolite derived from aspirin-treated patients with stable atherosclerosis.

The genomic data analysis strategy for the IGA study focused on application of linear mixed-effects models for the analyses of PK and PD as a function of genotype for mutations in CYP3A5, CYP2B6, CYP2C9 and CYP2C19. Results for independent analyses with binning for CYP2C9 and CYP2C19 were also confirmed. In the TAAL study, a multi-linear regression correlation model was used to estimate AUC from the predicted R-138727 Prasugrel active metabolite concentrations during loading and maintenance dosing. The genomic data analysis strategy for the TABR study was analogous to that for IGA, but it included results for measurement of platelet aggregation by several methods, and selective application of linear regression and logistic regression models. The results of this review for data from these studies confirm the conclusion

reported by the sponsor that there was no relevant effect of genetic variation on the pharmacokinetics of Prasugrel.

In healthy subjects, patients with stable atherosclerosis and patients with ACS receiving Prasugrel, there was no clinically significant effect of genetic variation in CYP3A5, CYP2B6, CYP2C9, or CYP2C19 as defined by active metabolite exposure levels. In healthy subjects, no effect of genetic variation in CYP3A5, CYP2B6, CYP2C9, or CYP2C19 genes on PD measures of platelet function was observed. In patients with ACS, these evaluations suggest there is no effect of genetic variation on the primary efficacy measures in prasugrel treated patients for any individual CYP enzyme.

2.4 Extrinsic Factors

What extrinsic factors (herbal products, smoking, and alcohol use) influence dose-exposure and/or- response and what is the impact of any differences in exposure on response?

The sponsor addressed the effects of smoking and alcohol use in the meta-analysis. About 20% of subjects were identified as smokers and 70% as consuming alcohol, based on self-reported information. While a statistically significant effect of smoking on the AUC(0-tlast) of R-138727 was detected, the magnitude of the difference between smokers and non-smokers was not clinically relevant. The ratio of LS geometric mean was 0.918 and 90% CI (0.871, 0.967) for R-138727 AUC(0-tlast) and the range of exposure values in smokers and non-smokers overlaps. Smoking status had no significant effect on Cmax. Alcohol consumption did not significantly affect R-138727 PK.

Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes.

Prasugrel is a pro-drug which is hydrolyzed in vivo and is not detected in plasma. In vitro studies showed that the hydrolysis of prasugrel to R-95913 (precursor of the active metabolite) is mediated efficiently by human carboxylesterase hCE2 prior to reaching the portal vein. The metabolism of R-95913 to the active metabolite R-138727 is catalyzed by the 4 cytochromes most capable of forming R-138727, in rank order: CYP3A4 > CYP2B6 > CYP2C9 ~ CYP2C19. The values of the apparent Michaelis-Menten constant (Km) for CYP2B6 (2.3 µM, 761 ng/mL) and CYP2C19 (3.8 µM, 1258 ng/mL) suggest that these enzymes have higher affinities for R-95913 conversion to R-138727 than does CYP2C9 (11 µM, 3641 ng/mL) and CYP3A4 (21 µM, 6951 ng/mL). Considering the abundance of CYP3A, the sponsor hypothesized that the most of R-138727 forms during first pass metabolism intestinal CYP3A during absorption. Inhibition of CYP2B6 (by a monoclonal antibody) and CYP3A (by ketoconazole), in incubations with human liver microsomes, substantially inhibited R-138727 formation, while inhibition of CYP2C9 (by sulfaphenazole) and CYP2C19 (by omeprazole) produced minor and more variable inhibition of R-138727 formation. Additionally, in vitro data showed that CYP3A4 and CYP3A5 may be similarly efficient in converting R-95913 to R-138727.

What drug-drug interaction studies were performed based on the in vitro information?

Prasugrel is metabolized in vitro by CYP3A4 and CYP2B6. The sponsor evaluated the interaction of prasugrel with the following drugs:

1. CYP3A4 inhibitor (ketoconazole),
2. CYP3A4 inducer (rifampicin), and
3. CYP2B6 substrate (bupropion).
- 4.

Although C_{max} of the prasugrel active metabolite was reduced by 34% when coadministered with ketoconazole, there was no change in AUC; therefore, the clinical drug interactions of prasugrel with other CYP3A4 inhibitors will not be of major concern and no dose adjustment is recommended. There was no significant interaction found between prasugrel and rifampicin. Prasugrel coadministration with a single dose of bupropion decreased its hydroxylation (C_{max} by 32% and AUC by 24%). Dose adjustment of bupropion is not needed after coadministration with prasugrel.

Is prasugrel a substrate and/or inhibitor of P-glycoprotein transport processes?

The potential role of prasugrel as a Pgp substrate was not evaluated in this NDA. Co-administration of prasugrel with digoxin reveals that prasugrel is not an inhibitor of Pgp, as digoxin clearance was not affected by the prasugrel coadministration.

In vivo studies with medications that are likely to be administered for the treatment of ACS

Aspirin, warfarin, heparin and atorvastatin are the drugs which may be administered to patients for the treatment of the reduction of atherothrombotic events, stent thrombosis in ACS (acute coronary syndrome), and patients with stable angina.

A significant pharmacodynamic drug-drug interaction, prolongation of the bleeding time was observed when prasugrel was co-administered with aspirin, warfarin and heparin.

At 24 hours post-dose, bleeding time ratio (BTR) increased by 41% in patients who received the 60/10 mg of prasugrel and 150 mg aspirin (compared to the prasugrel arm). An additional administration of 900 mg of aspirin has not changed BTR in this study. At 48 hours post-dose, BTR increased by 73% in patients who received 60/10mg prasugrel and a single 15 mg dose of warfarin (compared to the warfarin arm). At 4 and 6 hours post-dose BTR increased by 36% in the warfarin/prasugrel (compared to the prasugrel arm). The BTR at 4 and 6 hours post-dose was increased by 28% and 16% respectively in the prasugrel + UFH arm compared to the prasugrel alone arm. The increase in BTR was even higher when the prasugrel +UFH arm was compared with the UFH alone arm: 167% and 154% at 4 and 6 hours post-dose.

Based on the serious adverse effects observed following atorvastatin administration in subjects on prasugrel, the combination should be prescribed under close physician monitoring.

Are there other metabolic/transporter pathways that may be important?

No.

2.5 General Biopharmaceutics

The significant, unresolved issues related to in vitro dissolution or in vivo BA and BE

Is the HCL salt formulation of prasugrel bioequivalent to the prasugrel base formulation?

The sponsor investigated the extent of conversion of the salt to the base in 2 bioequivalence studies where lots with high extent of conversion (70%), intermediate extent of conversion (58%) and low extent of conversion (5 %) were compared with and without the coadministration of 30 mg lansoprazole. The low medium and high extent of conversion lots were found to be bioequivalent to each other. However, when given with lansoprazole, the low medium and high extent of conversion were found to be bioequivalent to each other with respect to AUC but not to CMAX. There was on average a 29% difference (90% confidence interval 0.62-083) in CMAX between the low conversion and the high conversion lot. The difference between the medium and high conversion lot was less pronounced (10% with a 90 % CI of 0.77-1.04). This difference between these lots translated into differences in mean IPA of greater than 10% at 0.5 and 1 hour post dose. These differences can be potentially clinically significant. This difference can be attributed to difference in dissolution characteristics at higher pH between the base and the salt form. At higher pH the dissolution of the HCL salt is faster than the prasugrel base resulting in faster absorption rates explaining the 30% difference in CMAX.

The sponsor was made aware of the Agency's concern with regards of not being able to control the amount of conversion from the salt form to the base resulting in highly variable peak plasma concentrations from lot to lot.

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Does the particle size of prasugrel have an effect on bioavailability?

The effect of particle size on the bioavailability of prasugrel was tested in a bioequivalence study The results show that the difference in surface area did not have any effect on the extent of absorption as measured by AUC but had a slight effect on the rate of absorption as measured by CMAX as the 90% CI were slightly outside the 80-125% limits on the lower side (79-114% for the low and high surface area ratio and 78-112% for the medium to high surface area ratio). This slight difference in CMAX is not expected to be clinically significant.

What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Except for Studies S002 (pilot study, 6 subjects) and TAAF, clinical pharmacology and pivotal TAAL studies were conducted in fasted subjects. In Study TAAF,

coadministration of a single 15-mg prasugrel dose with a high-fat high-calorie meal C_{max} was reduced by nearly half, t_{max} was delayed from 0.5 to 1.5 hours but not the extend of absorption. The figure below shows the effect of food on the kinetics of R138727.

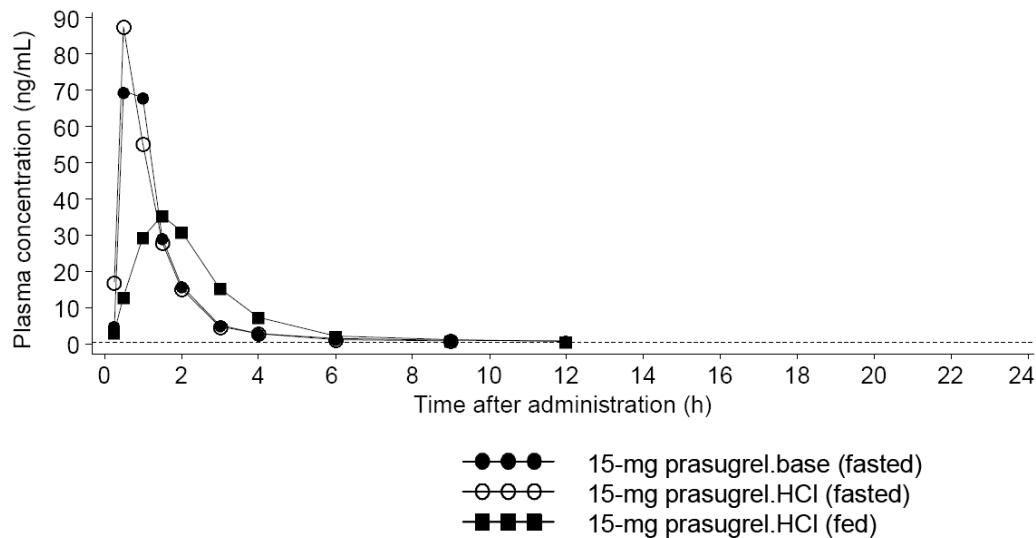


Figure 23. R138727 Plasma Concentrations vs Time. Food Effect

When prasugrel was administered with a high fat food breakfast, the disposition of all prasugrel metabolites changed (Table below).

For the inactive metabolite R-95913, food intake increased $AUC(0-\infty)$ between 13% and 34% (90% CI) and similarly for $AUC(0-t_{last})$. For the active and other inactive metabolites measured (R-119251 and R-106583), both $AUC(0-\infty)$ and $AUC(0-t_{last})$ are bioequivalent in the fed and fasted conditions. For all metabolites, food intake decreased the C_{max} values, and increased median t_{max} from 0.5 to 1.5 hours.

Because PCI is usually performed in the fasted state, the food effect may be not clinically relevant and therefore, prasugrel can be administered with or without food.

Table 7. Fed vs Fasted PK Parameters for Prasugrel Metabolites

Metabolites	PK Parameter (unit)	Geometric mean ^a (90% CI) [CS-747.HCl (Fed)]	Geometric mean ^a (90% CI) [CS-747.HCl (Fasted)]	Ratio of Geometric mean ^a (90% CI) [CS-747.HCl (fed) vs CS-747.HCl (fasted)]
R-138727	AUC (0-∞) (ng·h/ml)	122 (108, 138)	129 (114, 146)	0.949 (0.893, 1.01)
	AUC (0-t _{last}) (ng·h/ml)	118 (105, 134)	124 (110, 141)	0.952 (0.890, 1.02)
	C _{max} (ng/ml)	63.6 (53.7, 75.4)	124 (105, 147)	0.512 (0.428, 0.612)^b
R-95913	AUC (0-∞) (ng·h/ml)	144 (127, 163)	117 (103, 133)	1.23 (1.13, 1.34)^b
	AUC (0-t _{last}) (ng·h/ml)	133 (117, 151)	107 (93.8, 121)	1.25 (1.14, 1.36)^b
	C _{max} (ng/ml)	50.4 (43.8, 58.1)	62.8 (54.5, 72.4)	0.803 (0.680, 0.948)^b
R-119251	AUC (0-∞) (ng·h/ml)	69.0 (59.9, 79.4)	75.1 (65.4, 86.3)	0.918 (0.849, 0.993)
	AUC (0-t _{last}) (ng·h/ml)	63.4 (54.9, 73.1)	70.8 (61.3, 81.7)	0.896 (0.827, 0.970)
	C _{max} (ng/ml)	27.3 (23.1, 32.3)	53.6 (45.3, 63.4)	0.510 (0.427, 0.609)^b
R-106583	AUC (0-∞) (ng·h/ml)	789 (686, 907)	741 (645, 852)	1.06 (1.02, 1.11)
	AUC (0-t _{last}) (ng·h/ml)	691 (604, 791)	660 (577, 755)	1.05 (0.998, 1.10)
	C _{max} (ng/ml)	98.2 (86.0, 112)	121 (106, 139)	0.810 (0.741, 0.885)^b

How the elevated gastric pH affect the prasugrel bioavailability?

Prasugrel's dissolution in vitro is faster at pH 1 than at pH 6.8 and is intermediate at pHs in between. Therefore, treatment with drugs that increase gastric pH could slow the rate and/or extent of dissolution and absorption of a prasugrel dose. Treatment with such gastric pH modifiers is common in patients with ACS. In Study TAAL, 41% of subjects took a PPI and 15% took a H2-receptor antagonist through 3 days after the LD.

Therefore, any effect occurring when given with prasugrel could be clinically relevant. The different classes of gastric pH modifiers had different magnitudes of effect on the rate of prasugrel absorption.

Effect of PPIs: Lansoprazole given with a prasugrel LD or MD reduced the C_{max} of prasugrel's active metabolite by nearly 30%, did not change t_{max} and did not affect the AUC(0-8) of prasugrel's active metabolite (Study TAAI).

It is likely that the lower C_{max} with PPIs will delay the onset of platelet inhibition when prasugrel is given to a patient taking a PPI, but will not affect the level of platelet inhibition during MD.

Since a 30% differences in C_{max} for the active metabolite of prasugrel did not change the PD response, this differences probably would not of clinical significance, and no dose adjustment of prasugrel is required when administered with lansoprazole.

Effect of H2 Antagonists: Oral ranitidine was studied with a prasugrel LD or MD (Study TABS). Ranitidine reduced the rate of absorption, the C_{max} of prasugrel's active metabolite decreased by 14%, although it did not change t_{max} and did not affect the AUC(0-t_{last}) of prasugrel's active metabolite. This effect on active metabolite C_{max} was less than that measured during treatment with lansoprazole. The platelet aggregation

assessments included early time points that were lacking in the PPI Study TAAI. The assessment of ranitidine interaction in Study TABS showed no statistically significant difference in IPA at any time point except for 0.5 hours after the prasugrel LD + ranitidine. The reduction in IPA at 0.5 hours was 12 percentage points, which was associated with a 9 percentage point increase in MPA to 20 μ M ADP. Prasugrel can be coadministered with or without a H₂-receptor antagonist.

2.6 Analytical section

How the active moieties are identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Plasma samples collected in clinical studies were analyzed for prasugrel active (R-138727) and/or inactive (R-119251, R-106583, and R-95913) metabolites using validated liquid chromatography with tandem mass spectrometric detection (LC/MS/MS) methods. The methods for quantifying prasugrel metabolites in human plasma were first developed at Lilly Laboratory for Bioanalytical Research (LLBR). The methods were transferred to Advion BioServices, and the LLBR and Advion methods were successfully cross-validated.

In the drug-drug interaction studies, the assay validations for all measured moieties were provided.

What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The lower limit of quantitation was 0.5 ng/mL for R-138727 and 1 ng/mL for R-119251, R-106583, and R-95913. The upper limit of quantitation was 250 ng/mL for R-138727 and 500 ng/mL for R-119251, R-106583, and R-95913. Samples above the limit of quantitation were diluted and reanalyzed to yield results within the calibrated range. The sponsor described each method used in the clinical studies, their cross-validation methods, as well as the validated standard curve range, intra/inter-assay precision, and intra/inter-assay accuracy for each method. Storage conditions and freeze/thaw stability data for prasugrel are also summarized in this appendix.

Derivatization of R-138727 in blood with 2-bromo-3-methoxyacetophenone within 30 seconds after collection was required to ensure the stability of the active metabolite during sample processing and storage.

The LC/MS/MS method used R138727-MP-d4 (3'-methoxyphenacyl derivative of deuterated R138727) as an internal standard for R-138727. Due to these difficulties, it was not possible to determine the plasma concentrations of the prasugrel active metabolite in the pivotal study TAAL which was performed at the multiple centers. The sponsor instead determined the inactive metabolites plasma concentrations and used plausible pharmacokinetic modeling to predict the concentrations of the active metabolite.

What analytical methodologies were used to assess pharmacodynamic action?

Many of the studies that evaluated the PK of prasugrel's metabolites also evaluated the effect of prasugrel on platelet function. The primary method used to determine the PD response to prasugrel was light transmittance aggregometry (LTA) using 20 μ M ADP as the agonist; 5 μ M ADP was also used. Prasugrel administration results in inhibition of the platelet aggregation response to ADP, a result that may be reported as either a change in MPA, which decreases with increasing PD response, or inhibition of platelet aggregation (IPA), which increases with increasing PD response. Duplicate determinations of MPA were included in Studies TAAD, TAAJ, and TACJ, permitting the reproducibility of the LTA assay to be assessed. In addition to LTA, the PD response to prasugrel was also explored with additional assays as described in the sponsor's Table APP.2.7.1.5. They were VASP (platelet reactivity index) phosphorylation, serum thromboxane B2, activated partial thromboplastin time, factor Xa inhibition and activated clotting time values of anti-Xa.

The bleeding time assessment using a modified Ivy technique is a standard test. A pressure of 40 mmHg was applied using a blood pressure meter cuff inflated around the subject's arm. Three punctures were made on the subject's forearm at 5 second intervals using an Accu-check Softclix lancing device (Roche). A single sheet of filter paper was used to dab the outer perimeter of the three puncture wounds every 15 seconds. Bleeding time was recorded as the time from puncture to when a small clot formed.

Were the validation characteristics of the assays acceptable?

Yes. In all studies the assays have their validation reports, they are acceptable. See individual study reviews.

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Secondary Review of Cancer Adverse Events and Risk/Benefit



NDA: 22,307
Drug: prasugrel (Effient)
Indication: reduction of atherothrombotic events and stent thrombosis in acute coronary syndromes managed by percutaneous coronary intervention
Sponsor: Eli Lilly and Company
Review date: December 31, 2008
Reviewer: Thomas A. Marciniak, M.D.
Medical Team Leader

Background

This review is a special secondary review of the findings in this NDA submission related to cancer adverse events and risk/benefit. I initiated the analyses because of my assignment as the clinical reviewer for the prasugrel IND, a professional interest in exploring cancer rates in large outcome trials, and the suggestive results (in my interpretation) of the mouse carcinogenicity study. Because my preliminary analysis raised the issue of increased cancer rates with prasugrel in a large outcome study, the Cross Discipline Team Leader for this submission requested that I complete and formally submit my analyses. For a general background on prasugrel and this NDA submission and discussions of the formulation issues, please see the primary clinical review, the other discipline primary reviews, and the Cross Discipline Team Leader review. This version is an updated version based on a series of exchanges with the sponsor regarding the cancer events and includes the data collected by the sponsor in response to those exchanges; it replaces all prior versions.

Recommendation and Conclusions

I recommend approval of prasugrel for the indication of reduction in myocardial infarctions in acute coronary syndromes managed by percutaneous coronary interventions with a boxed warning regarding cancer and a duration of treatment limited to 30 days. In the large outcome study TAAL, new solid cancer rates were more than 40% higher in the prasugrel group than in the clopidogrel control group. The solid cancer rates began diverging after about 4 months and continued diverging for the duration of the study. They were associated with substantial death rates. It is impossible to decide whether these findings are real drug effects or artifactual or chance variations from TAAL alone; another study is needed. Until such a study is completed I believe it is prudent to approve prasugrel, because of its beneficial impact upon an important endpoint (myocardial infarction), but to limit its duration of use. The sponsor is planning another large outcome study in acute coronary syndrome patients who are medically managed. A description of the TAAL cancer results must be incorporated into the informed consent for the new trial, patients with a history of solid cancers must be excluded, complete follow-up for cancer events must be detailed, and the trial must be sized (including a blinded interim analysis of cancer event rates with resizing if needed) to have 90% power of detecting a 50% increase in the rate of development of new solid cancers.

Materials Used in Review

1. Submissions for NDA 22,307, particularly the reports and data sets for the rodent carcinogenicity studies, the data sets and case report forms for the large TAAL outcome trial, and the supplementary regulatory responses on neoplasms from March 25 through November 12, 2008
2. Primary Clinical review by Karen A. Hicks, M.D., dated April 28, 2008
3. Statistical Review of the Rodent Carcinogenicity Studies by Mohammad Atiar Rahman, Ph.D., dated February 19, 2008
4. Pharmacology/Toxicology Review by Belay Tesfamariam, Ph.D., dated April 26, 2008

Relevant Chemistry and Metabolism

Prasugrel is a thienopyridine prodrug for an irreversible antagonist of the platelet P2Y₁₂ receptor. It is functionally and structurally similar to the approved thienopyridine platelet P2Y₁₂ receptor antagonist clopidogrel and, in fact, the large TAAL outcome trial in this submission compared prasugrel to clopidogrel rather than placebo. However, prasugrel is neither structurally nor metabolically identical to clopidogrel as shown in the structure diagrams in Figure 1 and Figure 2 and the metabolic pathways of prasugrel in Figure 3 and the major and active metabolites of clopidogrel in Figure 4.

Figure 1: Prasugrel Structural Formula

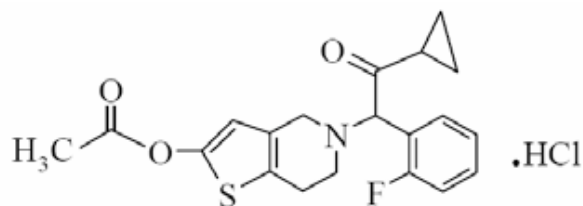


Figure 2: Clopidogrel Structural Formula

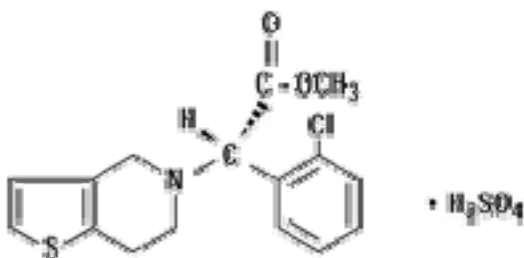


Figure 3: Prasugrel Proposed Metabolic Pathways

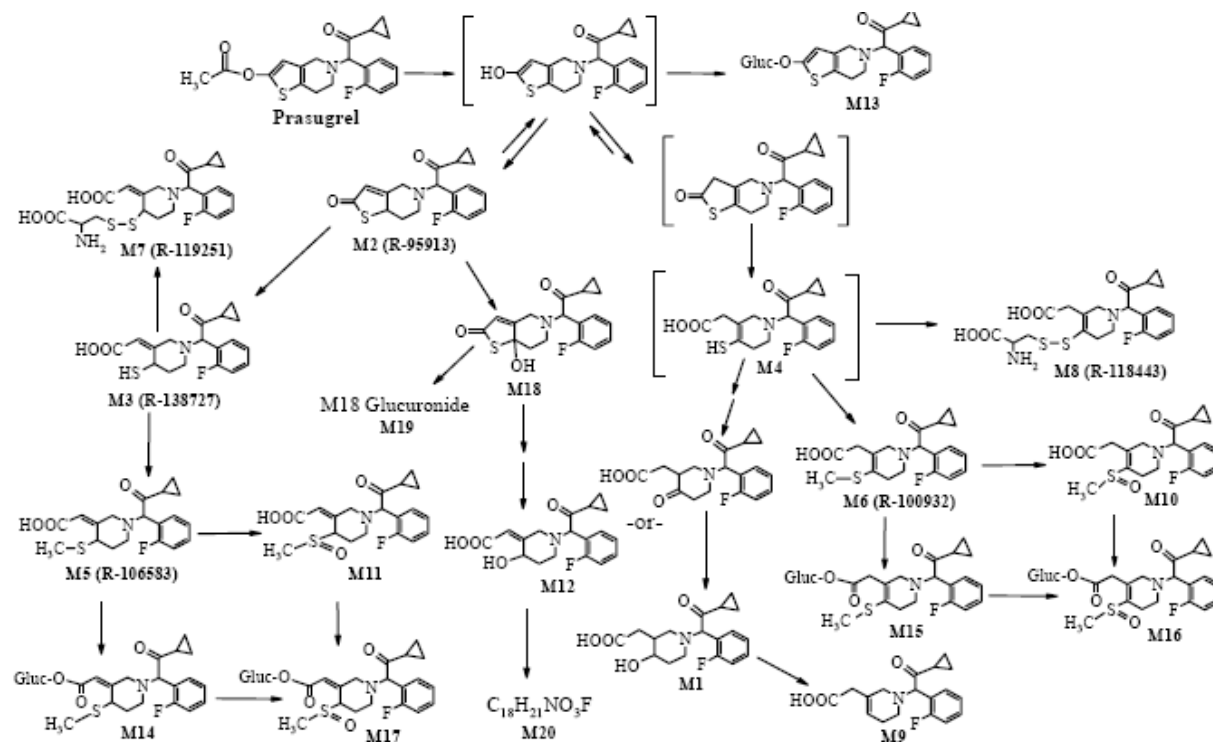
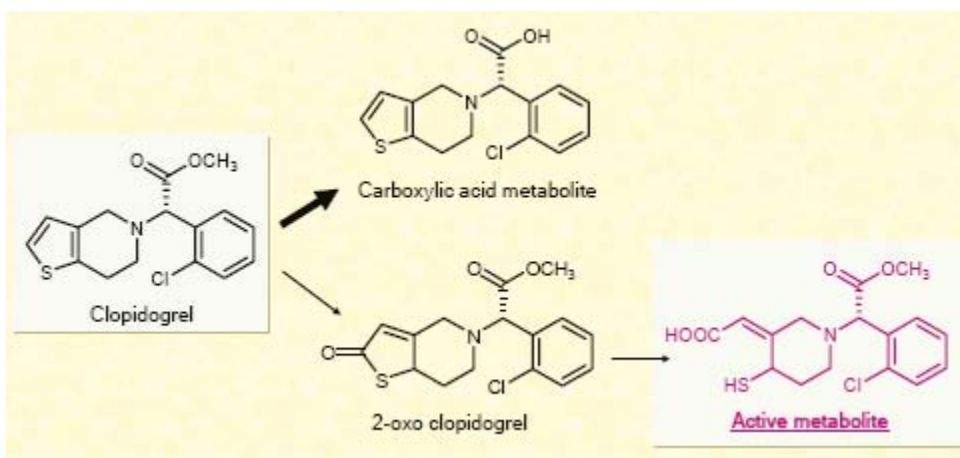


Figure 4: Clopidogrel Major and Active Metabolites*



*from http://www.inertsil.com/Technical_Data/Titansphere/ASMS2006/A061099.pdf

Both prasugrel and clopidogrel are prodrugs. Prasugrel is rapidly hydrolyzed to the inactive metabolite R-95913. R-95913 is then converted by various CYP isoenzymes to the thiol active metabolite R-138727. Clopidogrel undergoes rapid hydrolysis to its carboxylic acid derivative, the major metabolite in plasma. It also undergoes an alternate pathway of oxidation through CYP isoenzymes to a thiol active metabolite. Both prasugrel and clopidogrel undergo extensive other metabolism.

COMMENT: While structurally similar, there are sufficient structural and metabolic dissimilarities between prasugrel and clopidogrel such that an adverse effect of one can not be automatically assumed to be an adverse effect of the other. The metabolic pathways of each are diverse enough that one can not elucidate from typical clinical or pre-clinical studies what metabolite can produce an adverse effect.

Rodent Carcinogenicity Studies

Included in the NDA submission are two two-year carcinogenicity studies, one in mice and one in rats. The studies are similar, each with 55 animals per dosing and control groups, except that the dosages are lower in the rat study because of a lower tolerability limit in rats compared to mice: The mice dosages tested were 30, 100, and 300 mg/kg and the rat dosages were 10, 30, and 100 mg/kg. The suggestive carcinogenicity findings are predominantly in the mouse study. I show the distributions of neoplasms (benign and malignant) by site, sex, and dosing group in Table 1 and by sex and dosing group for both sexes combined in Table 2.

Table 1: Neoplasms with Frequency > 4 by Site, Sex, and Dosing Group in the Prasugrel Mouse Carcinogenicity Study (NOTE: All Group Sizes Were 55)

Group	Female				Male			
	Control	30	100	300	Control	30	100	300
Harderian gland	5	3	7	6	5	8	2	2
Intestinal cancer	0	2	2	1	1	0	0	2
Liver adenoma	5	5	20	39	20	11	26	44
Liver carcinoma	1	4	2	5	11	12	13	16
Liver cancer*	2	6	3	5	11	15	14	17
Liver hemangioma	1	2	0	0	6	3	1	1
Lung adenoma	1	2	4	3	5	5	5	6
Lung cancer	2	2	1	2	3	3	8	4
Lymphorecticular ca	19	24	20	16	5	12	4	6
Pituitary adenoma	2	3	4	3	1	0	0	0
Skin benign	2	0	0	1	2	0	0	1
Skin cancer	4	1	2	2	0	0	1	0
Spleen sarcoma	1	3	0	1	0	0	1	0
Spleen hemangioma	2	3	0	1	4	0	1	0
Uterus neoplasm†	1	3	3	2	0	0	0	0

*including hemangiosarcoma, hepatoblastoma; †one carcinoma in 30 mg/kg group, the rest polyps

Table 2: Neoplasms with Frequency > 4 by Site and Dosing Group in the Prasugrel Mouse Carcinogenicity Study

Group	Control	30	100	300
Harderian gland	10	11	9	8
Intestinal cancer	1	2	2	3
Liver adenoma	25	16	46	83
Liver carcinoma	12	16	15	21
Liver cancer*	13	21	17	22
Liver hemangioma	7	5	1	1

Group	Control	30	100	300
Lung adenoma	6	7	9	9
Lung cancer	5	5	9	6
Lymphorecticular ca	24	36	24	22
Pituitary adenoma	3	3	4	3
Skin benign	4	0	0	2
Skin cancer	4	1	3	2
Spleen sarcoma	1	3	1	1
Spleen hemangioma	6	3	1	1
Uterus neoplasm†	1	3	3	2

*including hemangiosarcoma, hepatoblastoma; †one carcinoma in 30 mg/kg group, the rest polyps

In addition to the neoplasms, there were two other hepatic histologic findings worth noting, shown in Table 3.

Table 3: Other Hepatic Histologic Findings in the Prasugrel Mouse Carcinogenicity Study

Group	Female				Male			
	Control	30	100	300	Control	30	100	300
Central hypertrophy	0	0	0	0	0	0	9	22
Altered cell focus, eosinophilic	6	6	18	36	9	17	23	24

Prasugrel is an enzyme inducer that, in mice, produces an increase in liver size. The central hepatocytic hypertrophy seen in the male mice at the higher dosages (mild to moderate at the 100 mg/kg dosage and moderate in 7 mice at the 300 mg/kg dosage) is attributed to this enzyme induction. (See also the discussion regarding carcinogenicity in the Comment below.) The National Toxicology Program has suggested that presence of the altered cell foci may form part of weight-of-evidence considerations used by regulatory bodies when accompanied by a concomitant liver tumor response. (Maronpot, Harada et al. 1989)

COMMENT: The most striking finding is the increase in liver adenomas. This neoplasm appears to have a high background rate in this species—note the 20 adenomas in the male control group, although this number appears to be anomalously high. While the increase in adenomas is the most statistically significant finding, the increase in the closely related liver carcinomas is also striking. Whether one counts only carcinomas or all cancers (there were also more cases of hemangiosarcomas and hepatomas in the prasugrel groups) the increase in liver malignancies is roughly 50% with prasugrel. There are also more cases of lung cancer and intestinal cancer in the prasugrel groups with suggestions of dose-response relationships.

The FDA's statistical reviewer of these studies judged the increases in adenomas and combined adenomas and carcinomas to be statistically significant: The standard statistical analysis showed statistically significant positive dose-response relationship in the incidence of hepatocellular adenoma and combined incidences of hepatocellular adenoma and hepatocellular carcinoma in both sexes. Pairwise comparisons showed statistically significantly increased incidence of hepatocellular adenoma and combined incidences of hepatocellular adenoma and hepatocellular carcinoma in high dose group in males, and mid and high dose groups in females

compared to their respective controls. (Per the Society of Toxicologic Pathology the incidences of benign and malignant neoplasms arising from the same cell type are usually combined for statistical analyses. (Boorman, Dixon et al. 2004)) The Executive CAC judged the mouse study to be positive for hepatocellular adenomas in both sexes.

I have the following additional comments on this study:

- *An increase in the rates of the most prevalent cancers of 50% or more is not consistent with the sponsor's explanation of the findings, that the liver adenoma increases are the result of enzyme induction similar to that seen with phenobarbital.*
- *The increase in uterine neoplasms, mainly polyps, by itself wouldn't appear very concerning or even unlikely—one more polyp in the control group would make all of the groups indistinguishable. However, it is consistent with the one suggestive finding in the rat study.*
- *The increase rates of altered cell foci may be consistent with the increased rates of adenomas. However, the triumvirate of liver adenoma increases, altered cell foci increases, and cancer increases appears consistent with a tumor promotion effect.*
- *Skin cancers and combined skin neoplasms were more frequent in the control group.*

While the increases in cancers with prasugrel are not statistically significant, they do not appear to be random effects. There are no comparable random increases in cancers for the placebo group. The neoplasms for which the count in the placebo group is higher are skin neoplasms, liver hemangiomas, and spleen hemangiomas. The fewer liver and spleen hemangiomas in the prasugrel groups are hardly reassuring because there are more hemangiosarcomas in these organs in the prasugrel groups.

The prasugrel rat carcinogenicity study does not show an increased rate of liver adenomas. Nor does it show any increased rates of cancers with prasugrel, either by site or in total. To the contrary, it showed lower rates with prasugrel for two malignancies: large granular lymphocytic leukemia and mesothelioma as shown in Table 4. The one finding consistent with the mice study findings is a higher rate of uterine neoplasms (due to high rates of polyps) in the prasugrel groups as also shown in Table 4.

Table 4: Neoplasms Differing by Dosing Group in the Prasugrel Rat Carcinogenicity Study

Group	Female				Male			
	Control	10	30	100	Control	10	30	100
Leukemia	14	13	6	1	8	8	3	2
Mesothelioma	0	0	0	0	4	3	1	1
Uterus neoplasm	20	26	29	30				

Exposure to prasugrel and its metabolites differed between the two rodent carcinogenicity studies. The exposures for the active metabolite and the main human metabolite are shown in Table 5.

Table 5: Exposure (Mean AUC₀₋₂₄ µg·h/mL) for Main/Active Metabolites in the Prasugrel Carcinogenicity Studies (Compared to Human 0.3/0.05 for 10 mg Daily Dose)

	Female				Male			
	10	30	100	300	10	30	100	300
Mouse		23/6	85/26	201/68		23/2	87/16	206/41
Rat	4/7	18/28	43/59		4/5	7/14	22/58	

Main human metabolite R-106583/active metabolite R-138727

In addition to the neoplasms, the similar findings to the two other hepatic histologic findings found in the mouse study were also observed in the rat study as shown in Table 6.

Table 6: Other Hepatic Histologic Findings in the Prasugrel Rat Carcinogenicity Study

Group	Female				Male			
	Control	10	30	100	Control	10	30	100
Diffuse hypertrophy	0	0	0	15	0	0	0	20
Altered cell focus, eosinophilic	27	31	31	36	43	41	44	51

COMMENT: The rat carcinogenicity does not support the mouse study in suggesting that prasugrel is carcinogenic. Alone it might be interpreted as suggesting that prasugrel has a protective effect, e.g., the lower rates of leukemia. There are some similarities between the two studies for other findings, such as the endometrial polyps and the hepatocytic hypertrophy. There are also definite differences in exposure, both regarding the higher high dose exposure in the mice and the different ratios of active to main metabolite.

Because of the highly significant difference in hepatic adenomas, the moderately suggestive trend in hepatic cancers, the weakly suggestive trends in intestinal and lung cancers, the supportive data of the altered cell foci, and the absence of any tumors showing a clear reverse trend, I would still interpret the mouse study as suggestive of a carcinogenic effect of prasugrel in one species. The difference in measured exposures between the mouse and humans is not completely reassuring because we have no idea of what metabolite could be carcinogenic. The rat study is not supportive of carcinogenicity but neither does it contradict the possibility. However, by itself the results of the mouse study do not prohibit approval—the critical issue is what the human studies show. Regardless, these studies are very useful for hypothesis generation: The hypothesis they suggested to me is that prasugrel may be a tumor promoter for a variety of solid cancers—it is this hypothesis that I tested in my initial analysis of the TAAL study data.

Cancer Adverse Events in TAAL

The only human study in the submission large and long enough to provide any insight into cancer rates is TAAL. Hence I limit my analyses to that study.

TAAL (or TRITON) was a large, international, multicenter, randomized, double-blind, double dummy, active-controlled (vs. clopidogrel) of prasugrel in patients with ACS undergoing PCI. The labeled regimen for clopidogrel (300 mg loading, 75 mg maintenance) was compared to prasugrel 600 mg loading, 10 mg maintenance. About 13,608 patients (74% male) were randomized 1:1 and followed for 6-15 months. Baseline characteristics were well-balanced

between the two groups except for slightly more males in the prasugrel group (75.4% vs. 73.5%). For details regarding TAAL conduct and patient characteristics, disposition, and other outcomes please see the primary clinical review.

For all of my analyses I worked from the raw data sets, checking for incomplete data against the case report forms (CRFs). The data submitted for TAAL were typical of most NDA submissions with four exceptions:

1. The original submission did not include the raw data corresponding to what the investigator originally recorded for CRF fields but only the final values that may have been changed through an iterative, multi-step data clarification process. In a few instances the data clarifications were bizarre, e.g., an initial recording of lung cancer (squamous cell cancer on a lung biopsy) was changed to squamous cell cancer and coded as skin cancer.
2. The CRFs employed a consecutive ID (E01, E02, etc.) for adverse events (AEs). The investigator was supposed to use the same ID for the same adverse event at subsequent visits despite recording AEs on different pages. Not surprisingly, investigators made mistakes and used the same ID on different pages for different AEs. The sponsor's computer system overwrote the old AE with a different AE if the investigator mistakenly used the same AE ID for different AEs, e.g., replacing "(L) breast cancer" (at baseline) with "no reflow". The sponsor at our request later submitted a data set providing the original and final descriptions for all AE IDs, but other overwritten AE fields (date of onset, severity, etc.) were not provided.
3. The CRFs collected cardiac and cardiac related baseline conditions with checkboxes on specific CRFs. For other non-cardiac baseline conditions, the CRF form was similar to the AE forms, including using the same AE IDs. The investigator was supposed to record only ongoing conditions, so not all histories of cancers were captured. The investigator was also supposed to re-record all baseline ongoing conditions at the final visit, indicating if the severity had changed. These directions were not followed perfectly. Some investigators recorded histories of cancers at baseline and baseline conditions at subsequent visits, and some repeated baseline conditions at multiple visits.
4. Coding of AEs was not very accurate. Coding for a few records were bizarre, e.g., "mycosis of the skin (fungi)" and "inguinal mycosis both groins" were coded as "mycosis fungoides". Transcriptions of handwritten entries also caused a few problems, e.g., "metastasis change", coded as "metastasis", was eventually resolved as "mental status change".

For all the above reasons, I have recoded all potential cancer adverse events using the original investigator terms and checked ambiguous data against the CRFs and against any additional data provided by the sponsor. The analyses below are based on the best available data, and I tried to assign derived variables without knowledge of treatment group.

Because I have refined the accuracy of assignments, the analyses in this review replace any of my preliminary analyses quoted in the original primary clinical review or in consults. Because this is a very complex submission, I may have a few remaining errors or I may have missed some additional information provided by the sponsor. However, please note that the results have changed little from my original analyses despite substantial refinements.

In the following analyses, when I refer to “solid cancers” I mean all malignancies excluding hematological malignancies, non-melanoma skin cancers, and primary brain tumors (malignant and benign). Non-melanoma skin cancers do not carry the same dire prognoses as most other adult malignancies, ascertainment may be erratic, and multiple cancers over years are not uncommon, making determination of new impossible. Skin cancers and neoplasms were less frequent in the prasugrel groups than in the control group in the mouse carcinogenicity study. Also, in the analyses below, I classified “squamous cell carcinomas” as skin cancers unless I found a record of a non-skin site. Brain tumors raise issues of metabolites crossing the brain-blood barrier and are sufficiently infrequent (1 new malignancy in this study) that including or excluding them does not change results significantly. Hematological malignancies also deserve separate treatment because their pathogenetic mechanisms differ from solid tumors, e.g., they are not dependent upon angiogenesis. Prasugrel also appears to have differential effects upon them in the rodent carcinogenicity studies.

For “new cancers”, I prospectively counted a cancer as new if the date of definitive diagnosis was after the randomization date. I believe this definition is most consistent with how incidence dates of cancers are usually determined and consistent with trying to detect tumor promoter effects. The sponsor has counted cancer cases for which there was a sign of a tumor (mass, x-ray lesion) preceding the randomization date as not treatment emergent (not new) regardless of whether the date of definitive diagnosis was after the randomization date. After internal discussions with other FDA staff and cancer case adjudication meetings with the sponsor, I have been persuaded to present additionally a modified definition that allows cases to be counted as recurrent cancers if the evidence is strong that the cancer was active prior to randomization, e.g., a fracture occurring prior to randomization that was biopsy proven after randomization to be a pathologic fracture due to metastatic prostatic cancer. I continue to have misgivings about this latter definition because of the subjectivity of determining whether the evidence is strong enough. Furthermore, solid cancer development is well established to be a lengthy process such that we have good reason to believe that all of the “new” solid cancers diagnosed in TAAL were present prior to randomization. Hence the most relevant measure is all new cancers plus recurrent ones having a new cancer-related event or intervention post-randomization, and I show the analyses for this latter categorization (“new and worse”) as well. I will note that, despite believing the latter to be most relevant, my prospective endpoint was new cancers because of a suspicion that combining new and worse cancers might produce a noisier endpoint.

Baseline Cancers

Before considering the cancer results, it is appropriate to examine the subjects’ baseline cancer data. TAAL was a large study, so substantial baseline imbalances should be rare, and demographics and other baseline characteristics were well-balanced between the two groups as noted above and detailed in the primary clinical reviewer’s review. The TAAL exclusion criteria did not exclude patients with cancer histories; investigators were to exclude patients only if the life

expectancy was reduced, i.e., less than 15 months. Furthermore, the protocol and case report forms did not require that investigators record the patients' histories of cancers; the investigators recorded "on-going" medical problems as discussed above. Hence no one can determine how many TAAL patients have a history of cancer (although, for patients who subsequently developed a cancer problem, the CRFs usually document whether the cancer had been diagnosed prior to randomization.) The statistics that are ascertainable are how many patients had an on-going cancer problem and the types of cancers that investigators considered to be on-going. Patients with any on-going malignancy or brain tumor were well-balanced between the two groups: clopidogrel 175 and prasugrel 174, about 2.6%. I show the breakdown by cancer site in Table 7.

Table 7: Patients with On-going Malignancies and Brain Tumors at Baseline in TAAL

site*	clopidogrel	prasugrel
bladder	12	8
brain	6	5
breast	13	12
cervix	5	1
colorectal	14	16
esophagus	1	0
eye	0	1
head & neck	2	4
kidney	3	4
leukemia	6	6
lung	7	9
lymphoma	14	5
melanoma	9	5
myelodysplasia	4	5
ovary	2	0
pituitary	0	2
prostate	46	61
sarcoma	0	1
skin	20	18
squamous	2	1
stomach	2	3
testis	3	3
thyroid	3	2
unknown	0	1
uterus	1	1
Total	175	174

* 8 clopidogrel and 4 prasugrel patients had multiple on-going cancers at baseline

Most sites are well-balanced between the two groups, with the exceptions of slight excesses of lymphomas, melanomas, and cervical cancers in the clopidogrel group and prostate cancers in the prasugrel group. None of the site imbalances are nominally statistically significant even ignoring the multiple comparisons. Patients with solid cancers excluding non-melanoma skin and brain were also reasonably well balanced between the two groups (clopidogrel 123 and prasugrel 132).

COMMENT: Baseline imbalances in patient characteristics or on-going cancers do not appear to explain the subsequent differences in cancer rates.

Investigator-Reported Cancers

Because the pre-specified data collection in TAAL was whether the investigator judged the cancer to be on-going and not whether the patient had a history of cancer, it should be informative to examine the rates of patients having subsequent cancer AEs for which the investigator did not report an on-going cancer of the same type at baseline. Most new cancer events were reported in patients who did not have a corresponding on-going cancer reported at baseline. The few new events in patients with the same cancer reported on-going at baseline were overwhelmingly in the prasugrel group (7 vs. 1). I show the new cancer events without a corresponding on-going cancer reported at baseline in Table 8 and the types of malignancies in Table 9.

Table 8: Investigator-Reported New Cancer Events without an On-going Cancer Reported at Baseline in TAAL

	clopidogrel	prasugrel	RR	p*
solid cancers except non-melanoma skin, brain	58	88	1.52	0.013
malignancies except non-melanoma skin	65	92	1.42	0.031
all malignancies including skin	81	108	1.33	0.050

*by Chi-square

Table 9: Types of Investigator-Reported Malignancies without an On-going Cancer Reported at Baseline in TAAL

	clopidogrel	prasugrel
bladder	6	6
breast	1	6
colorectal	9	21
esophagus	2	4
gall bladder	0	2
head & neck	2	1
kidney	3	2
leukemia	4	2
lung	11	17
lymphoma	1	2
melanoma	2	2
mesothelioma	0	1
myelodys	2	0
ovary	0	1
pancreas	2	2
prostate	11	11
sarcoma	0	2
skin	14	15
squamous	2	1
stomach	7	6
unknown	1	4
uterus	1	0
Total	81	108

The mortality rate was substantially higher for patients who experienced a new cancer event (excluding non-melanoma skin cancers), about 38% in the prasugrel group and 34% in the clopidogrel group vs. < 3% in patients without a new cancer event.

COMMENT: It should be very clear from Table 8 and the mortality statistics why these preliminary analyses of the investigator-reported cancers immediately raised serious concerns. Note that colorectal, breast, and lung cancer events are more frequent in the prasugrel group. Because TAAL CRFs did not capture histories of cancer and because the investigator reports of adverse events were inadequate to confirm malignancy in some cases, we and the sponsor scrutinized all potential cancer events and the sponsor collected operative reports, path reports, and follow-up information on these cases. The remainder of my analyses included these post-hoc data manipulations. However, note that the sponsor, in a “White Paper: Neoplasm” dated September 18, 2008 stated that “The Sponsors feel strongly that the neoplasm data should be analyzed as reported by the investigators.” The above statistics are the neoplasm data as reported by the investigators; they are extremely concerning.

Reviewer-Adjudicated Cancers

The hypothesis I wished to test based on my interpretation of the rodent carcinogenicity studies was whether prasugrel is a promoter for a variety of solid cancers. Initially I decided to analyze as the primary analysis new cancers on the assumption that recurrent cancers or progression of existing cancers would introduce noise, i.e., cancers already poised to progress may not be affected as significantly by a cancer promoter. Of course, this assumption may not be valid, so as the secondary analysis I also planned to examine combined new and worse cancers.

Classifying a cancer as new requires a convention: Cancers may initially present as vague symptoms or masses that could be benign. They may be detected initially on imaging with uncertainty about the malignancy status. They usually eventually have a histologic diagnosis, but not always. I adopted the usual convention of counting a cancer as new if the date of first clinical diagnosis was after the randomization date. Two cases, both in the prasugrel group, had highly suspicious imaging (mammogram, chest x-ray) prior to randomization but refused further workup; I counted these cases as not new. A third case, also in the prasugrel group, had sclerotic changes on imaging suggestive of malignancy about the time of randomization with confirmation of malignancy shortly thereafter; I also counted this case as not new.

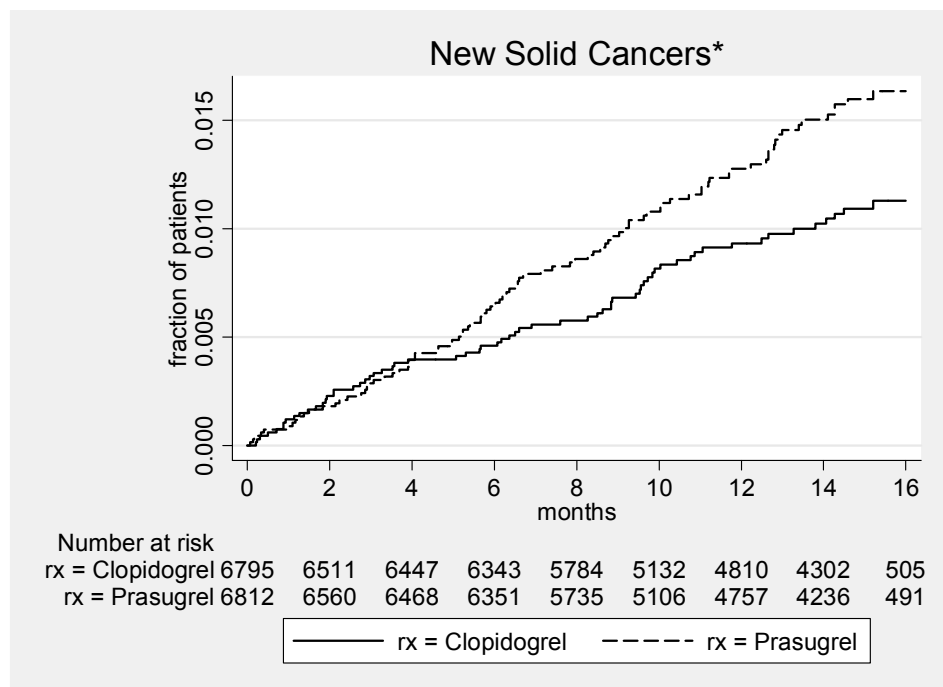
One relatively common neoplasm presented difficulties regarding malignancy status: Villous adenomas had varying histologic descriptions of mild dysplasia through severe dysplasia and invasive carcinoma. Differentiating severe dysplasia from carcinoma-in-situ is unreliable. (Terry, Neugut et al. 2002) Because severe dysplasia behaves similarly to carcinoma-in-situ (and in Japan and in an international guideline the two categories are lumped into one), I classified villous adenomas with severe dysplasia or carcinoma noted in the path report as new cancers. (Riddell 1999; Arumugam, Joseph et al. 2002; Stolte 2003)

Another site presented a different dilemma: squamous cancers near the lip could be classified as skin cancers if they primarily involve the skin and head and neck cancers if they involve the mucosa. The one such case in a prasugrel patient I counted as a skin cancer, hence excluded from my solid cancers analyses. Finally, there were two suspicious prasugrel cases for which the available data are inadequate: one a 55-year-old male who had an AE of “radiation burns” at day

104 and a “lesion removed from neck” at day 384; and the other a 71-year-old male who had an AE of “radiation burn on back” on day 30.

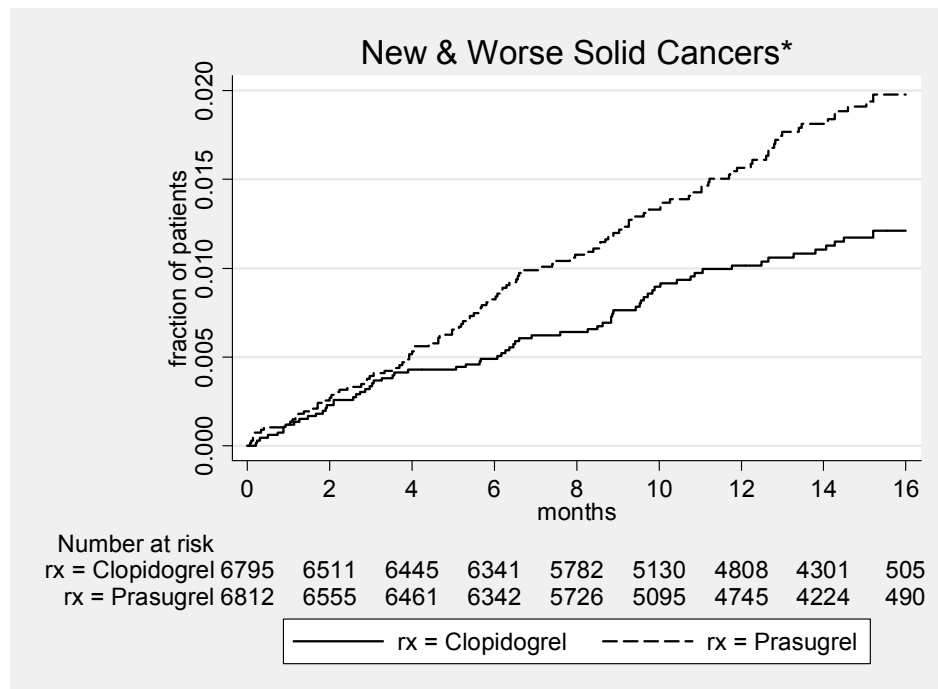
I show in Figure 5 the Kaplan-Meier (K-M) incidence plots by treatment for all new solid cancers (excluding non-melanoma skin and brain tumors) in TAAL by the conventions just discussed and in Figure 6 for new and worse solid cancers. I show the breakdown for new cancers and brain tumors by site and treatment in Table 10.

Figure 5: K-M Incidence Plot for New Solid Cancers (Excluding Skin and Brain) in TAAL



*excluding non-melanoma skin cancers and brain tumors; $p = 0.024$ by log rank

Figure 6: K-M Incidence Plot for New and Worse Solid Cancers (Excluding Skin and Brain) in TAAL



*excluding non-melanoma skin cancers and brain tumors; $p = 0.0013$ by log rank

Table 10: Numbers of New and Worse Malignancies by Site and Treatment in TAAL

site/patients	new		new and worse	
	clopidogrel	prasugrel	clopidogrel	prasugrel
bladder	7	7	8	8
breast	1	4	1	6
cervix	0	1	0	1
colorectal	10	22	10	22
esophagus	2	4	2	4
gall bladder	0	2	0	2
head & neck	2	1	2	1
kidney	4	5	4	6
liver	1	0	1	0
lung	12	15	14	19
melanoma	2	3	2	3
mesothelioma	0	1	0	1
ovary	0	2	0	2
pancreas	3	2	3	2
prostate	9	8	11	18
sarcoma	0	2	0	2
stomach	8	7	8	8
thyroid	0	1	0	2
unknown	2	5	2	5
uterus	1	0	1	0

site/patients	new		new and worse	
	clopidogrel	prasugrel	clopidogrel	prasugrel
solid cancers*	64	92	69	112
brain	1	0	1	0
leukemia	1	2	2	2
lymphoma	1	2	1	2
myelodysplasia	1	0	1	0
myeloma	0	1	0	1
skin	15	15	15	17
squamous	2	1	2	1
other malignancies	21	21	22	23

*excluding brain and non-melanoma skin

The relative risk a new solid cancer was about 1.44 and for a new or worse solid cancer was about 1.62 for prasugrel compared to clopidogrel. There was only one new brain malignancy and new hematologic and non-melanoma skin malignancies were relatively evenly distributed between the two groups. As with the investigator-reported cancers, new solid cancers were associated with a high mortality rate, about 30%, compared to <3% in patients without cancers. The mortality rate was slightly higher for patients with solid cancers in the prasugrel group such that there were substantially more deaths in prasugrel patients with new solid cancers (37 vs. 25) and in prasugrel patients with new and worse solid cancers (43 vs. 28).

COMMENT: Note the divergence of the K-M solid cancer incidence plots at four months with continuing divergence throughout the duration of the study. The divergence at four months would not seem to be a collection date artifact because the initial post-hospitalization visits were done at about 30, 90, and 180 days. It could be related to delaying doing invasive procedures after the ACS event.

New malignancies other than solid cancers excluding non-melanoma skin and brain appear to be balanced between the two groups. Including them dilutes the significance of the solid cancer findings but does not eliminate it: $p=0.045$ by log rank for all new malignancies, $p=0.0038$ for all new and worse malignancies.

For new solid cancers only colorectal appear clearly higher in the prasugrel group (with some suggestion that unknown primaries and breast may be higher as well.) For new and worse solid cancers the signal for breast cancer is stronger and prostate and lung cancers also are increased in the prasugrel group.

The high mortality rate in the patients with cancer, slightly higher in the prasugrel group, remains highly concerning. If, as the sponsor alleges, the differences are due to a detection bias due to more bleeding with prasugrel, we would expect the mortality rate from cancers with prasugrel to be lower than with clopidogrel. We would also expect the incidence curves to diverge initially and then converge. Observing slightly higher mortality in prasugrel new cancer patients and a continuing divergence of the incidence curves argues strongly against the TAAL findings being due to a detection bias.

Reconciliation of Cancers with Sponsor

Because of the serious implications of the above findings, we and the sponsor attempted to come to an agreement about the classification of non-skin cancer cases with ambiguous features. The changes from my classifications above were reclassifying all tubular adenomas with severe dysplasia as not malignant and reclassifying some cancer cases with signs or symptoms preceding the randomization date as not new. For four cases I may have differences in classification from the sponsor's:

1. A 68-year-old male in the prasugrel group was hospitalized after more than a year on-study with an enlarged hard, anechoic nodular liver and sepsis. The patient died before a biopsy was done and no autopsy was done. The investigator reported the event as a malignancy and the CEC adjudicated the event as a malignancy death. I believe this case should be classified as a new malignancy while the sponsor proposes to reclassify it as not malignant.
2. A 44-year-old male in the clopidogrel group had an event reported of "recurrent bladder tumor" at about 3 months with a clear history of prior bladder tumors. I believe this case should be classified as a not new, but worse, cancer while the sponsor proposes to reclassify it as new because the initial diagnosis of bladder tumor was six years prior to randomization, although the operative report refers to a "history of superficial bladder tumors" and it is not recorded whether there were any other recurrences. The surgeon gave a clinical diagnosis of "superficial bladder cancer", although the investigator reported the event and history as histology unknown and a path report was not submitted.
3. A 73-year-old female in the clopidogrel group had a rectal polyp removed that showed high-grade dysplasia. Because all other adenomas with severe dysplasia were classified as not malignant, I believe this case should be classified as not malignant, while at last reconciliation the sponsor classified this case as malignant.
4. A 75-year-old female in the prasugrel group had low back pain at randomization but was not tentatively diagnosed as multiple myeloma until 3 months later. Low back pain is a non-specific symptom, so I believe this case should be classified as a new malignancy.

Using the classifications for the three solid cancer cases discussed above and the rest of the classifications reconciled with the sponsor, I count 86 new solid cancers in the prasugrel group and 61 in the clopidogrel group, for a relative risk for prasugrel of 1.41, $p = 0.038$ by log rank. For new and worse solid cancers the corresponding numbers are 110 and 67, for a relative risk for prasugrel of 1.64, $p = 0.0011$ by log rank. For new malignancies excluding non-melanoma skin the corresponding numbers are 90 and 65, for a relative risk for prasugrel of 1.38, $p = 0.043$ by log rank. It is only if non-melanoma skin cancers are included that the relative risk becomes nominally non-statistically significant (relative risk 1.29, $p = 0.08$ by my calculations.)

Table 11: Comparison of Reviewer’s and Reconciled New and Worse Solid Cancers (excluding Non-Melanoma Skin and Brain) in TAAL

	clopidogrel	prasugrel	relative risk	p*
new solid cancers (except non-melanoma skin and brain)				
investigator	58	88	1.52	0.013
reviewer	64	92	1.44	0.024
reconciled	61	86	1.41	0.038
new and worse solid cancers (except non-melanoma skin and brain)				
investigator	59	95	1.61	0.0035
reviewer	69	112	1.62	0.0013
reconciled	67	110	1.64	0.0011

*by log rank

COMMENT: While the numbers of total new solid cancers is reduced slightly by the reconciliation and the p value declines correspondingly, the relative risk remains about the same. For new and worse solid cancers there is virtually no change, and the relative risks among the three different classifications are remarkably similar. Because none of the solid cancers presenting as clinical problems in TAAL were really new, the new and worse cancer rates are the best measures of the promoter potential of prasugrel. I believe these statistics still document a serious potential problem for prasugrel.

The sponsor in “Supplemental Regulatory Response Concerning Neoplasms” dated November 7, 2008, rejects my conclusion that the data suggest a serious potential problem for prasugrel based predominantly on two arguments: (1) all malignancies, including skin cancers should be included in the analyses; and (2) “the higher incidence of nonbenign neoplasms observed in prasugrel-treated subjects results from detection/ascertainment bias related to the higher incidence of bleeding observed in prasugrel-treated subjects.”

The sponsor proposes several arguments for including skin cancers. I summarize each argument below in italics followed immediately by my response:

- *“Exclusion of any specific type of cancer would be post-hoc and subject to bias” and “The only scientific rationale to exclude a tissue from analysis is that the tissue has no exposure to the drug.”* However, my exclusion of skin cancers was done *pre hoc* based on my interpretation of the animal carcinogenicity studies (as well as experience with the SEER cancer registries, which similarly exclude non-melanoma skin cancers). A preliminary decision based on animal data is scientific—see Table 2 above for the evidence that, if anything, skin cancers were less frequent in the prasugrel treated mice than the control mice. Secondly, safety analyses are frequently post hoc. If a strong signal were detected for all malignancies, it would be greatly concerning just as this strong signal in solid cancers is greatly concerning, although the existing strong signal in solid cancers is doubly concerning because the analysis was pre-specified by me. Finally, for purposes of estimation of statistical significance of the TAAL cancer analyses, it makes no difference whether my interpretations of the animal carcinogenicity studies are reasonable or completely flawed.

- *Some carcinogens cause skin cancers and some skin tumors are sensitive to some promoters.* But most carcinogens are site-specific, as a perusal of the Carcinogenic Potency Database will confirm. (Carcinogenic_Potency_Project 2008) Ideally we would like to know in advance exactly what cancers a carcinogen or promoter affects. In the case of prasugrel we can look to the animal data for some hints—which is what I did.
- *Skin would be a good signal tumor to detect tumor promotion because skin is an active mitotic organ and skin tumors are likely to have a lower probability of providing false negatives.* No data are presented to support these assertions. Because skin cancers are not as serious as other cancers and are usually handled without hospitalizations, reporting of them is more erratic than for other cancers. (Karagas 1994) Skin cancer data are noisy and may mask real effects.
- *Recent assessment of the role of drugs in cancer promotion include melanotic and nonmelanotic skin cancers (ezetimibe/Vytorin – Peto et al, 2008)* For ezetimibe there are no pre-clinical studies suggesting sites to examine, so inclusion in skin is reasonable. However, it may also illustrate my contention that skin cancer data are noisy because the greatest difference in rates in the one study (SEAS) in which more cancers were reported in the ezetimibe group was for skin cancers, and the difference for skin cancer rates favors ezetimibe in the other studies. (Peto, Emberson et al. 2008) Regardless, a signal of increased cancers with or without skin cancers is highly concerning. The ezetimibe SEAS data are of low concern only because there are other large trials with ezetimibe that do not show increased cancer rates. Prasugrel, too, needs other large trials (or at least one) not showing increased cancer rates.

COMMENT: I believe I have excellent justification for excluding skin cancers. I discuss cancer and bleeding next.

Cancer and Bleeding

Bleeding reporting is complicated because there were three sources for capturing bleeds: (1) the adverse event CRFs; (2) the bleeding endpoint CRFs; and (3) Clinical Endpoint Committee (CEC) added bleeds that are not recorded on the AE or bleeding endpoint CRFs but were mentioned on other documents provided to the CEC. For the following analyses I have used the data for bleeding events from all three sources. Because most common bleeds (epistaxis, bruises, etc.) would not initiate a cancer workup, I analyzed bleeds that would be likely to initiate a cancer workup (GI, hemoptysis, hematuria, vaginal, breast) as well as all bleeds and site-specific bleeds.

For patients with new solid cancers, 54% of the prasugrel and 41% of the clopidogrel patients had a preceding bleed of any type. About 33% in each group had a preceding bleed of a type likely to lead to a cancer workup. I show the rates of site-specific prior bleeds for the solid cancers for which bleeding is a common presentation, plus breast cancer because its rates are different in the two treatment groups, in Table 12.

Table 12: New Solid Cancers and Site-Specific Prior Bleeds in TAAL

	new cancers		# with prior site specific bleed		% with prior site specific bleed	
	clopidogrel	prasugrel	clopidogrel	prasugrel	clopidogrel	prasugrel
breast	1	4	0	0	0%	0%
colorectal	10	22	6	12	60%	55%
gi*	20	33	11	16	55%	49%
lung	12	15	0	2	0%	13%
kidney/bladder	11	12	7	5	64%	42%
cervix/uterus	1	1	1	1	100%	100%

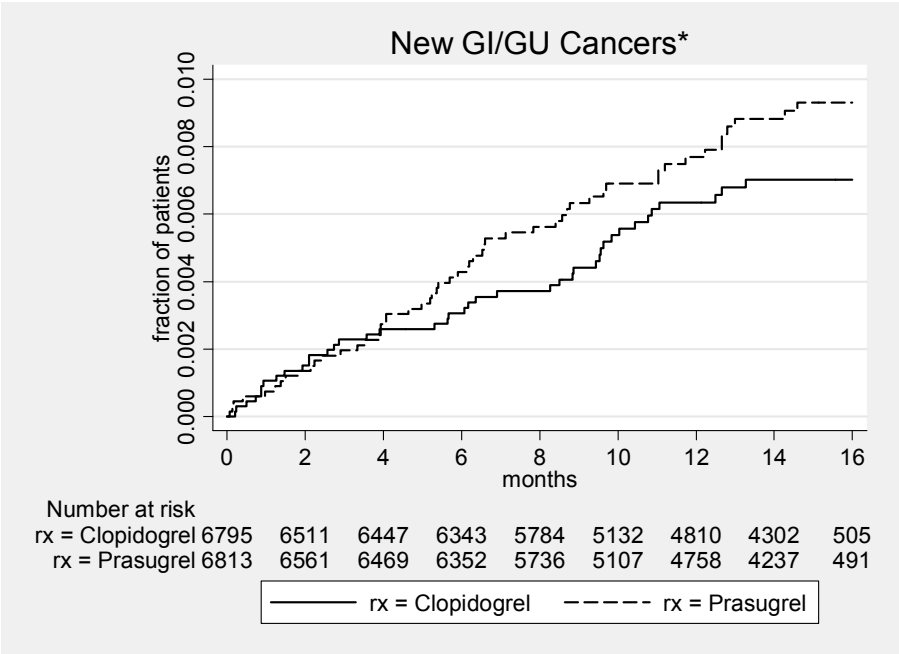
*includes colorectal, stomach, esophagus but not pancreas, liver, gall bladder

COMMENT: For the site (colorectal) with the largest difference in cancers and the one the sponsor argues that the difference is due to a detection bias, there is no difference in preceding site-specific bleeding. For kidney and bladder the prior bleeding also leans towards clopidogrel. The sponsor's analyses that suggest such a bias include neoplasms other than solid cancers and benign tumors and the common bleeds such as epistaxis, ecchymoses, and superficial hematomas that are unlikely to lead to a cancer search. Regardless, demonstrating more bleeding prior to cancer detection is not very reassuring: I would expect cancers stimulated to grow would bleed more readily, so we can not be certain that more bleeding is due to some cancer effect, e.g., increased angiogenesis, or platelet inhibition or both. The appropriate criterion for whether a cancer is serious is not whether it is preceded by bleeding but whether it is followed by serious consequences, e.g., death. The excess prasugrel cancers are serious by this latter, vital criterion.

To explore further the hypothesis of ascertainment bias due to bleeding, I examined the incidence curves for cancers that commonly present with bleeding. I show the K-M incident plot for GI/GU cancers in

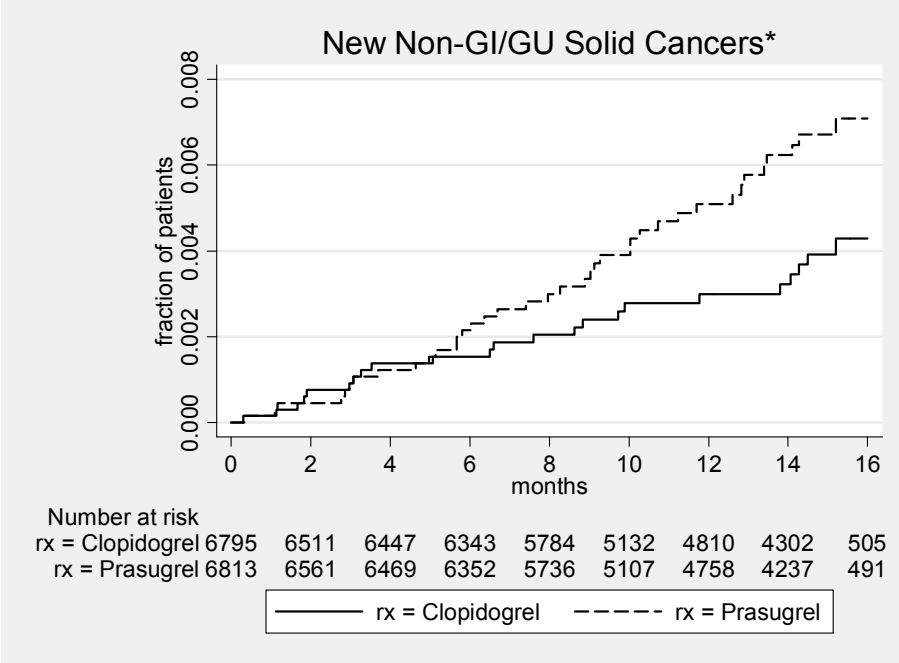
Figure 7, for non-GI/GU cancers in Figure 8, for GI cancers alone in Figure 9, and for GU cancers alone in Figure 10. (For these analyses I have not counted ovarian or testicular cancers as GU cancers or pancreas, gall bladder, or liver cancers as GI cancers because they do not usually present by bleeding.) For comparison, I show the bleeding rates by month in TAAL in Figure 11.

Figure 7: K-M Incidence Plot for New GI/GU Cancers in TAAL



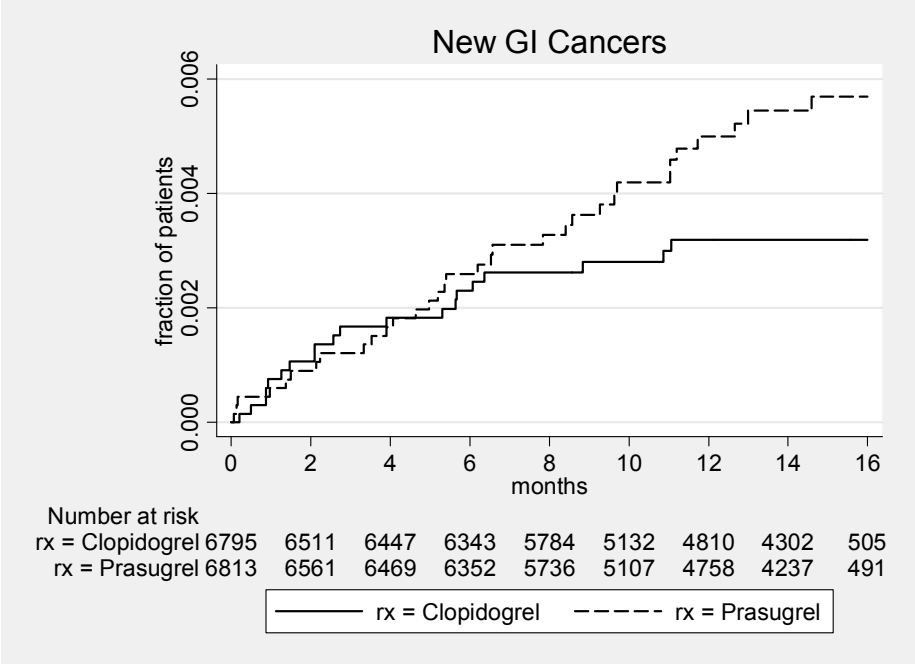
*ovarian, testicular, hepatic, GB, and pancreatic cancers excluded; p = 0.18 by log rank

Figure 8: K-M Incidence Plot for New Non-GI/GU Solid Cancers in TAAL



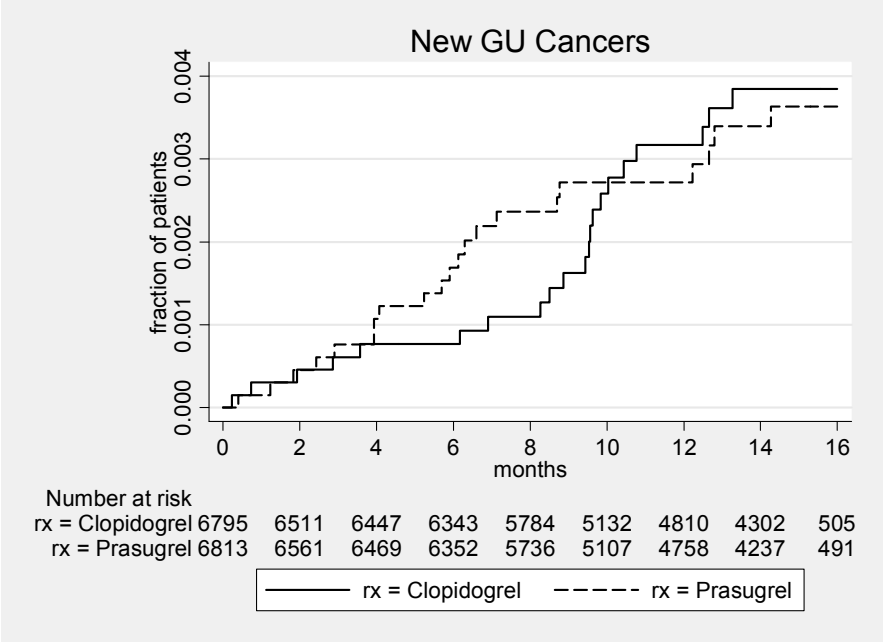
*excluding non-melanoma skin cancers and brain tumors; p = 0.053 by log rank

Figure 9: K-M Incidence Plot for New GI Solid Cancers in TAAL



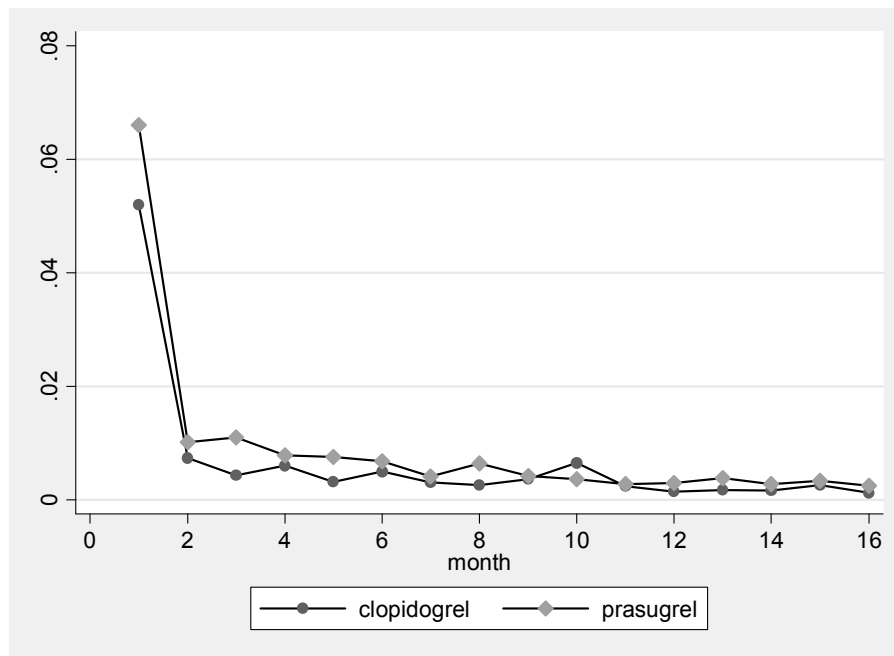
p = 0.074 by log rank

Figure 10: K-M Incidence Plot for New GU Cancers in TAAL



p = 0.99 by log rank

Figure 11: Bleeding Event Rates by Treatment and Month in TAAL



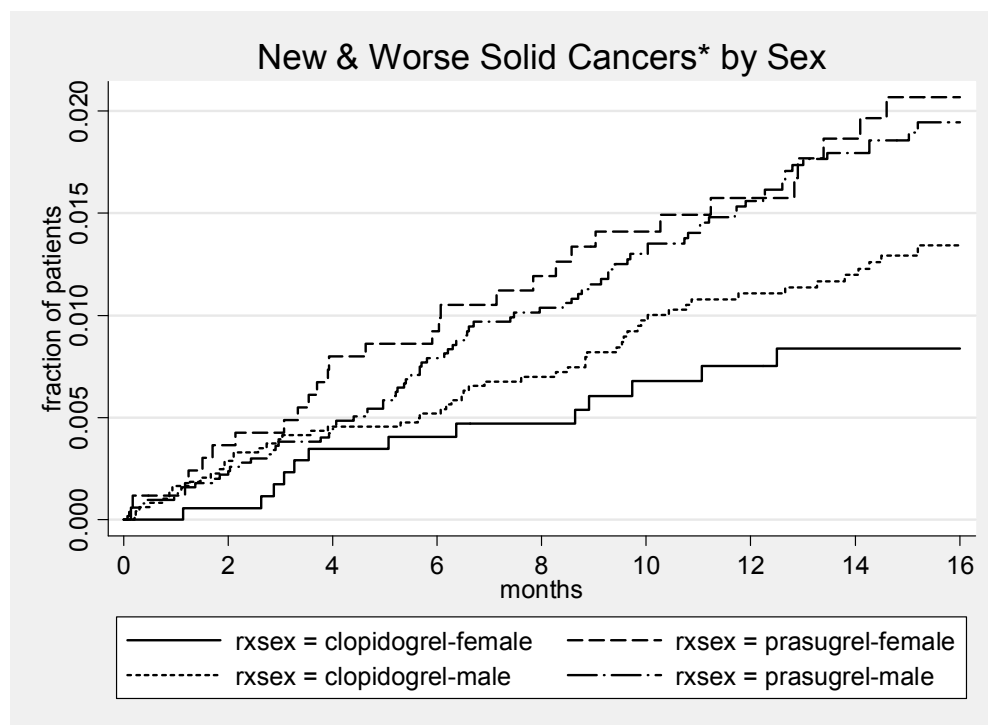
COMMENT: The site-specific incidence plots for GI/GU cancers diverge at four months and then almost converge at about 12 months. However, they do not diverge early when many bleeding events occur (as shown in Figure 11.) Non-GI/GU cancers show a continuing divergence as do GI cancers, leaving only GU cancers for which the ascertainment bias due to bleeding remains plausible. Both the incidence plots for GI solid cancers (Figure 9) and for non-GI/GU cancers (Figure 8) suggest that the diagnosis rates for non-GU cancers were higher in the first four months than later, particularly for clopidogrel. I would speculate that this difference is due to the increased surveillance initially due to the hospitalization for the ACS event.

Other Cancer Issues

Cancer and Gender

Based on preliminary analyses of all solid cancers by sex, the primary clinical reviewer has noted that increases in new solid cancers with prasugrel were greater in women than in men. I show the incidence plots for new and worse cancers by sex in Figure 12. Note that TAAL patients were predominantly male (74%).

Figure 12: K-M Incidence Plot for New and Worse Solid Cancers (Excluding Skin and Brain) by Sex in TAAL



*excluding non-melanoma skin cancers and brain tumors

COMMENT: There is some variation in new and worse cancer rates by sex, with females on clonidogrel having the lowest rate and females on prasugrel having the highest. However, for each sex cancer rates are higher with prasugrel. I attribute the variations to the smaller numbers of female patients in TAAL.

Early Cancers

There is no biologic plausibility for cancers diagnosed shortly after randomization to be causally related to study drug. There were reasonable numbers of cancer AEs in TAAL in the immediate months following randomization as shown in the incidence plots above. During internal discussions within the Division of the cancer findings in TAAL, we discussed excluding cancers for some short, arbitrary period after randomization to eliminate biologically implausible incident cancers. I show the effects of varying early cancer diagnosis exclusions in Table 13.

Table 13: New Solid Cancers (excluding Non-Melanoma Skin and Brain) in TAAL Excluding Early Diagnoses

cutoff	clonidogrel	prasugrel	RR*	p†
none	64	92	1.44	0.024
>7 days	62	89	1.44	0.027
>14 days	60	87	1.45	0.025
> 30 days	56	86	1.54	0.011

*RR = relative risk prasugrel/clonidogrel; † by log rank

COMMENT: Not surprisingly, given the superimposed incident curves for the first four months, whether one excludes or includes very early solid cancers makes little difference in the analysis. Because a 7-day (or 14-day, or any length) exclusion is arbitrary, the occurrences of non-study drug related cancers should be reasonably balanced by the randomization, and handling these cases differently breaks the randomization, I would not exclude early cancers from the analyses. The one complicating factor is the possible effect of bleeding that I address next.

Cancer by Region

The sponsor has also argued that the cancer results are inconsistent in subgroups, e.g., by country. I have classified the geographic sources of patients into four regions (US, Eastern and Western Europe, and other) yielding reasonable number of patients in each region. I show the rates of new solid cancers by region in Table 14.

Table 14: Rates of New Solid Cancers by Region in TAAL

Region	Patients		New solid cancers	
	Clopidogrel	Prasugrel	Clopidogrel	Prasugrel
E Europe	1,665	1,657	0.8%	1.4%
Other	1,342	1,342	0.7%	1.3%
US	2,020	2,039	1.0%	1.4%
W Europe	1,768	1,775	1.1%	1.2%
Total	6,795	6,813	0.9%	1.4%

COMMENT: New solid cancer rates with prasugrel are higher in all regions, with only Western Europe showing a small effect size. The US, the region of greatest interest to us, show rates very similar to the entire study. Overall the variations in this table are consistent with random subgroup variations. I did not find convincing evidence for subgroup inconsistencies either by region or by sex.

Clopidogrel and Cancer

Because an excellent and critical question is whether carcinogenicity could be a class effect, I also examined the data we have available for large outcome trials using clopidogrel. For reference I have summarized the study features in Table 15.

Table 15: Clopidogrel Studies

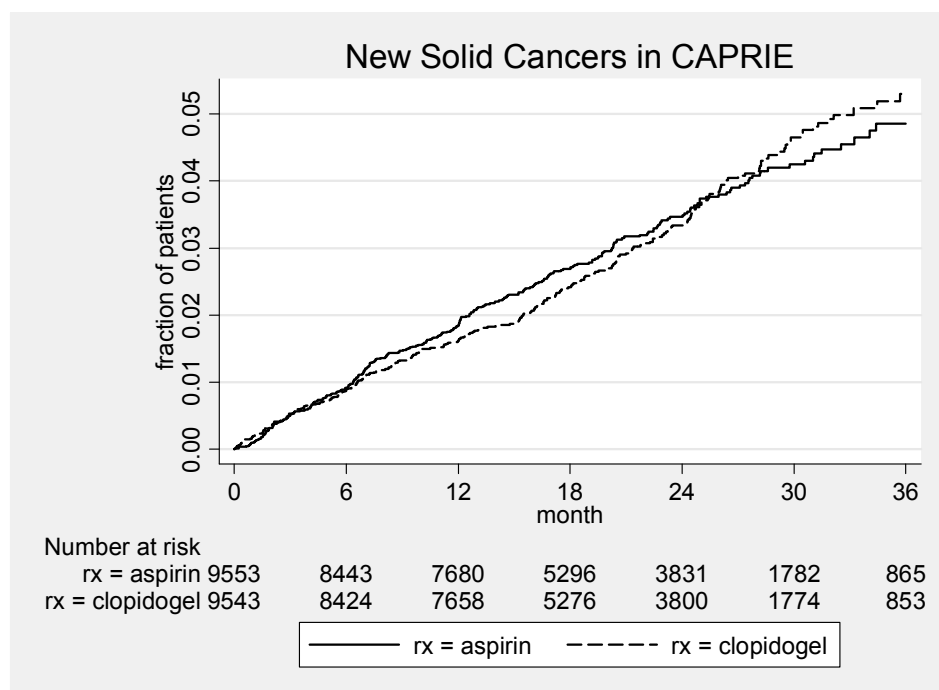
Study	Population	Aspirin	Median age	n	Median months
CAPRIE	high CV risk	325 control	63	19,185	20
CREDO	PCI	325 then 81-325	61	2,116	12
CURE	ACS NSTEMI	75-325	65	12,562	9
CHARISMA	high CV risk	75-162	64	15,603	28

Note that CAPRIE used aspirin only in the control group, while the other studies involved adding clopidogrel to background aspirin at dosages selected by the investigators. CURE and CREDO are the smaller studies with more limited follow-up, so I will summarize briefly their findings but present CAPRIE and CHARISMA in more detail.

In CURE there was a slight excess of solid cancers (48 vs. 42) with clopidogrel due to higher rates of colorectal (16 vs. 8) and lung (12 vs. 7) but slightly higher rates for breast, prostate, bladder, and unknown in the placebo group. In CREDO there was a 5 vs. 0 excess of lung cancers (*post hoc* $p = 0.03$ commented upon in the study report) but overall new solid cancers were less frequent with clopidogrel (20 vs. 12). Hematologic malignancies and brain tumors did not show any noteworthy variations except a 4 vs. 1 excess of lymphomas in the placebo group in CURE.

I show the new solid cancer incidence plots for CAPRIE in Figure 13 and for CHARISMA in Figure 14; I show the types of cancers for CAPRIE in Table 16 and for CHARISMA in Table 17.

Figure 13: K-M Incidence Plot of New Solid Cancers in CAPRIE



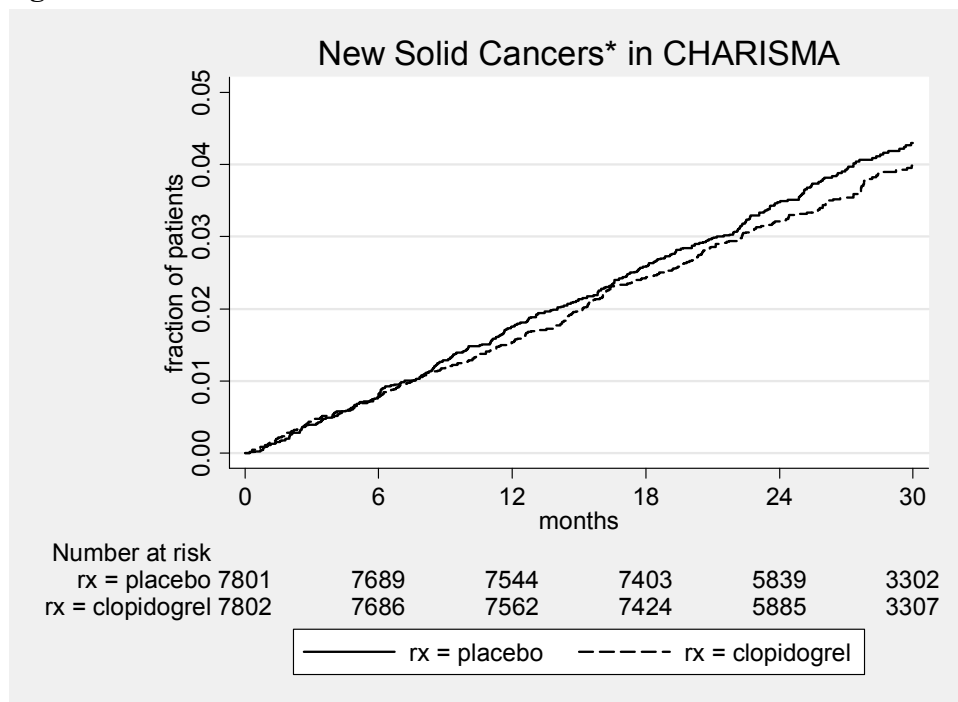
*excluding non-melanoma skin cancers and brain tumors; $p = 0.9$ by log rank

Table 16: Numbers of Cancers by Site and Treatment in CAPRIE

	aspirin	clopidogrel
patients	9599	9586
bladder	28	26
breast	15	11
cervix	2	2
colorectal	40	33
esophagus	4	4
gall bladder	3	0
head & neck	11	16
kidney	10	10
liver	4	3
lung	74	72
melanoma	13	11

	aspirin	clopidogrel
mesothelioma	0	1
ovary	1	3
pancreas	11	3
prostate	46	61
sarcoma	1	4
stomach	5	13
unknown	11	8
uterus	5	1
total new solid cancers	284	282
skin	71	76
pituitary	4	0
brain	3	9
leukemia	4	5
lymphoma	12	7
myeloma	0	4
polycythemia	4	3

Figure 14: K-M Incidence Plot for New Solid Cancers in CHARISMA



*excluding non-melanoma skin and brain; p = 0.35 by log rank

Table 17: Numbers of Cancers by Site and Treatment in CHARISMA

	clopidogrel	placebo
patients	7,802	7,801
bile duct	3	1
bladder	26	19
breast	13	22

	clopidogrel	placebo
cervix	0	2
colon	0	1
colorectal	41	39
esophagus	6	5
gall bladder	0	1
gi	2	0
head & neck	16	22
kidney	11	13
liver	5	7
lung	70	63
melanoma	9	13
mesothelioma	2	1
myeloma	4	2
other	2	1
ovary	1	3
pancreas	5	10
pelvis	2	1
prostate	52	52
sarcoma	1	0
small intestine	3	2
stomach	8	10
testis	2	0
thyroid	1	1
unknown	9	15
uterus	3	4
vagina	0	1
total new solid cancers	297	311
brain	7	3
leukemia	9	4
lymphoma	4	15

The K-M incidence plots show no significant differences in the rates of new solid cancers in either CAPRIE or CHARISMA. The plot for CAPRIE looks like it might be starting to trend unfavorably for clopidogrel but the plot for CHARISMA looks like it might be trending favorably for clopidogrel. The distributions of cancer types by treatment group also show random differences in the rates, e.g., slightly more prostate and stomach cancers with clopidogrel in CAPRIE but less colorectal cancer; more bladder and lung cancers with clopidogrel in CHARISMA but less breast cancer.

One final comment about CHARISMA: bleeding rates were higher in the clopidogrel group as shown in Table 18.

Table 18: Bleeding in CHARISMA

Type of Bleeding (GUSTO)	No. % With Event		Difference Clopidogrel - Placebo (%) (95% CI)	p-Value
	Clopidogrel (N=7802)	Placebo (N=7801)		
Any	2827 (36.23)	1616 (20.72)	15.52 (14.12,16.91)	<0.001
Severe/Moderate ^a	290 (3.72)	197 (2.53)	1.19 (0.65,1.74)	<0.001
Severe ^a	130 (1.67)	104 (1.33)	0.33 (-0.05,0.71)	0.087
Moderate ^{ab}	164 (2.10)	101 (1.29)	0.81 (0.40,1.21)	<0.001
Other bleeding ^c	2646 (33.91)	1487 (19.06)	14.85 (13.49,16.22)	<0.001

COMMENT: Clopidogrel does not appear to have an appreciable effect upon cancer rates. The exposure in the clopidogrel studies is much higher than that for prasugrel in TAAL and should be sufficient for detecting an effect comparable to that seen in TAAL. I believe the clopidogrel studies are good examples of what variations in results to expect when analyses like those I performed for TAAL are done for a drug that has good substantiation of a lack of carcinogenic potential. Furthermore, the fact that in CHARISMA there was substantially more bleeding in the clopidogrel group than in the control group but similar cancer rates does not support the hypothesis that increased bleeding leads to a cancer ascertainment bias.

Prasugrel Efficacy Robustness

Because I have been asked to recommend approvability of prasugrel and labeling for it, I also performed some independent analyses of prasugrel efficacy in TAAL. I was interested in understanding the robustness of the prasugrel effect for comparison to the risk of cancer promotion. The sponsor's analyses of the TAAL use Clinical Endpoint Committee (CEC) adjudications of site-reported and lab value-triggered events. As a measure of robustness I analyzed the TAAL results using site-reported events only.

CEC Adjudication

The CEC adjudicated all important endpoint events, including MIs, strokes, and CV deaths as well as stent thromboses, and bleeding events for TAAL. What the study report and reviews do not state prominently is that there were two distinct paths for an event to be referred to the CEC: (1) by the site; and (2) "triggered" by a review of adverse events or lab values. (In addition, the CEC could find an event in a CRF or other documentation submitted for a different type of event, but such CEC-detected events were rare.) For MIs the majority of triggered events were peri-procedural MIs (PPMIs). There were far more potential PPMI events adjudicated by the CEC (2,583) than investigator reported MI events (483). However, because the CEC adjudicated the minority of potential PPMIs as MIs, the number of adjudicated MIs submitted in some fashion by the sites (705—in addition to MIs the sites also submitted other potential cardiac ischemic events) exceeded the number of adjudicated MIs based on PPMI triggers (512, with 11 additional MIs being otherwise triggered or CEC determined.)

The CEC adjudicated higher percentages of clopidogrel events as MIs than prasugrel events as shown in Table 19.

Table 19: CEC MI Adjudications by Type of Referring Event

referring event	clopidogrel		prasugrel	
	n	% MI	n	% MI
site MI event	303	80%	180	76%
site other ischemic event	984	19%	903	15%
triggered PPMI*	1022	21%	1049	19%

*PPMI = peri-procedural myocardial infarction

Note also that site referred MI events were substantially higher in the clopidogrel group than in the prasugrel while triggered potential PPMIs were equal between the two groups. However, there are problems with the determination of MI adverse events as I describe later.

Adjudication in a clinical study always raises at least three sets of issues: (1) whether the adjudication rules were pre-specified and appropriate; (2) whether referral for adjudication was comparable; and (3) whether the adjudication was performed fairly or, at least, how adjudication affects the results. Regarding the first set of issues, the criteria for the endpoint definitions, including the definition of an MI, were provided in the original protocol. One MI criterion was changed during the study as discussed in the primary clinical review: The original definition of peri-procedural myocardial infarction required an elevation of creatine kinase-myocardial band (CK-MB) to $> 3x$ upper limit of normal (ULN) on a minimum of two samples within 48 hours of PCI. The modified definition, specified in Protocol Amendment (a) dated January 10, 2006, maintained the original definition but extended periprocedural myocardial infarctions to a CK-MB $> 5x$ ULN on one sample if it was the last available sample and was drawn ≥ 12 hours after PCI. While this change does not appear to be problematic, there is an inconsistency in the PPMI definition that is: While the protocol and study report state the post-PCI and CABG CK-MB criteria without qualifications, the CEC Charter adds as a footnote that they “Cannot be determined within 12 hours of onset of qualifying STEMI.” How PPMIs are adjudicated is critical because on day 0 there were 36 more PPMIs adjudicated for clopidogrel than for prasugrel. The first two PPMIs I checked (010003 10565 and 10966) had CEC Adjudication: Cardiac Ischemic Events forms with the type of event sections filled out but the Section A: Adjudication of Myocardial Infarction section not filled out and no signatures by CEC reviewers. How the PPMI cases were adjudicated is not well documented in the materials submitted to the NDA.

Regarding referral for adjudication, the CEC Charter includes an appendix describing the algorithms for Triggers for Identifying Events Not Reported by the Sites. The charter also describes the screening for triggered events being performed by the Contract Research Organization (CRO) but otherwise how or when the algorithms were developed and how they were implemented is not detailed. The referral of site-determined events is complicated by another problem: Sites were to assign an “AEID” (e.g., E01, E02, etc.) to each active medical problem at baseline and to each adverse event. Despite the AEIDs being required on many different forms filled out at many different times, the sites were not supposed to use the same AEID for different events or problems. Not surprisingly, sites made mistakes. In the original NDA submission for the adverse event data sets, if the sites erroneously re-used an AEID, the entries for the later event replaced those for the earlier ones. For cancer events we later obtained a file with both the original and final event data for every AEID and based our cancer analyses

on the more complete records of events. How this AEID problem affected referrals for adjudication I do not know, but I performed the following analyses to attempt to elucidate the impact.

In this first data set provided by the sponsor with initial and final values (AETERMCH), I counted 201 MI events for which the final value was not an MI. I counted 724 final MI events so that about 21% (201/925) of the MI events may have been lost. However, the potential loss does not appear to be biased because a similar percentage of the potential loss cases were clopidogrel (54%) as of the final value cases (56%). This first data set did not provide other details of the cases such as event dates so that further analysis of it is not helpful.

The sponsor submitted later more complete data sets of initial and final values (OEVENTSA and OVENTSB split because of size—I combined them into one data set OEVENTS). OEVENTS is the most complete description of adverse events for TAAL submitted by the sponsor. I classified MI and stroke events in OEVENTS by both the originally reported and final event terms. As a check of the completeness of the referral for adjudication of potential events, I cross-checked the MI events from OVENTS with the adjudicated events in the CEC adjudication dataset and with the investigator-reported events in CIE1. I found 62 MI events from OEVENTS that did not have records in CEC. Of these 62 events 61% were in clopidogrel patients, 85% had a flag set (CRF field) that they had been submitted for adjudication, and 25% of the prasugrel cases and 12.5% of the clopidogrel cases were not classified as having an MI based on another event. Hence the absolute number of cases that may have missed adjudication is small (10 cases for MIs by this analysis).

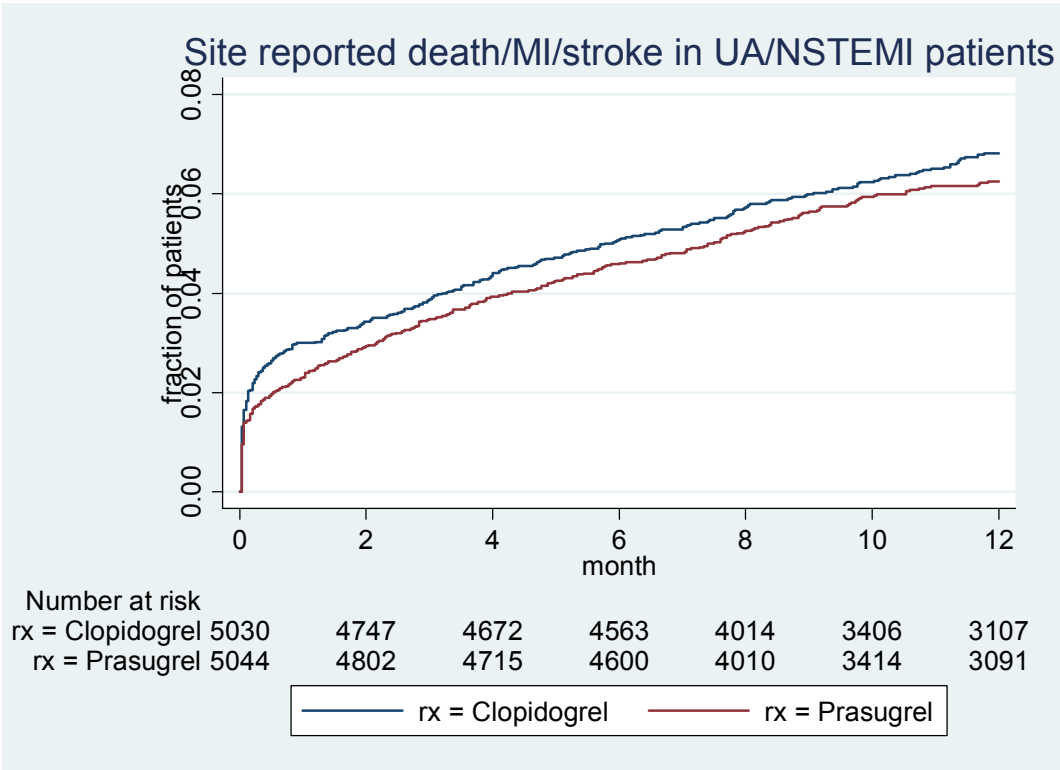
I also analyzed OEVENTS for an endpoint identical to the primary endpoint but not utilizing the CEC adjudications. I did the OEVENTS analyses as sensitivity analyses to determine the robustness of the results and to compare the site-reported results with the adjudicated results. The endpoint I tested was the composite of all-cause mortality, site-reported MIs, and site-reported strokes. I present the results below.

Site-Reported Endpoint Results

For the following analyses I accepted the site's description of the event as reported in the verbatim term, i.e., AEMODIFY in the SAS data sets. Sites reported many events as MIs and I counted them as such; however, for some cardiac events the sites described the events as “new Q wave”, “acute coronary syndrome”, “cardiac ischemia”, or “LAD thrombosis”. The CEC adjudicated the latter events and classified some of them as MIs; for the following analyses I counted the latter reports as not MIs (although note that vessel thrombosis reports were sometimes accompanied by a clinical event of MI.)

Based on site reports the endpoint most similar to the pre-specified primary endpoint (except avoiding adjudication—the composite of all cause mortality, site-reported MIs, and site-reported strokes) for the pre-specified primary analysis (time-to-event tested by the Gehan-Wilcoxon test for the unstable angina/non-ST elevation MI (UA/NSTEMI) subgroup (about 74% of the study population) shows early improvement but not a statistically significant benefit with prasugrel. I show the Kaplan-Meier (K-M) failure plot in Figure 15.

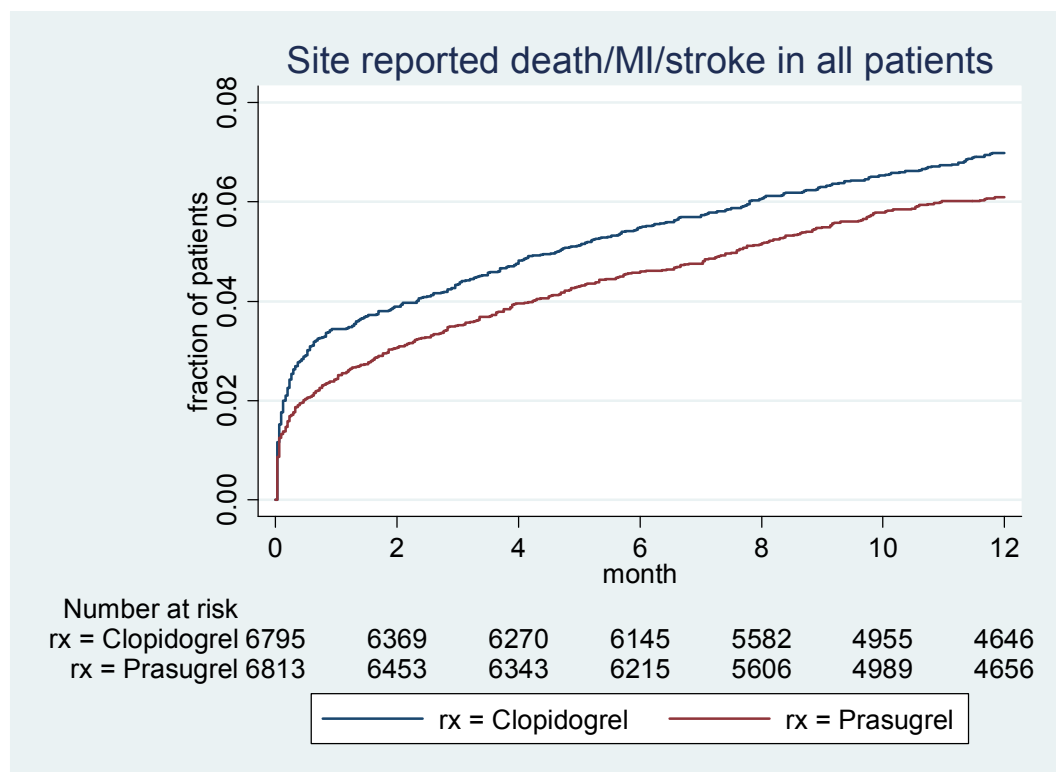
Figure 15: Site-reported Death/MI/Stroke in TAAL UA/NSTEMI Patients



p = 0.24 by Gehan test, 0.35 by log rank test

While the benefit with prasugrel is not statistically significant in this “noisy”, site-reported and unadjudicated sensitivity analysis, there does appear to be a lower rate for early events. While the sponsor pre-specified the UA/NSTEMI subgroup as the primary analysis, the early lower rate of events is better shown in the whole study population in Figure 16.

Figure 16: Site-Reported Death/MI/Stroke in All TAAL Patients

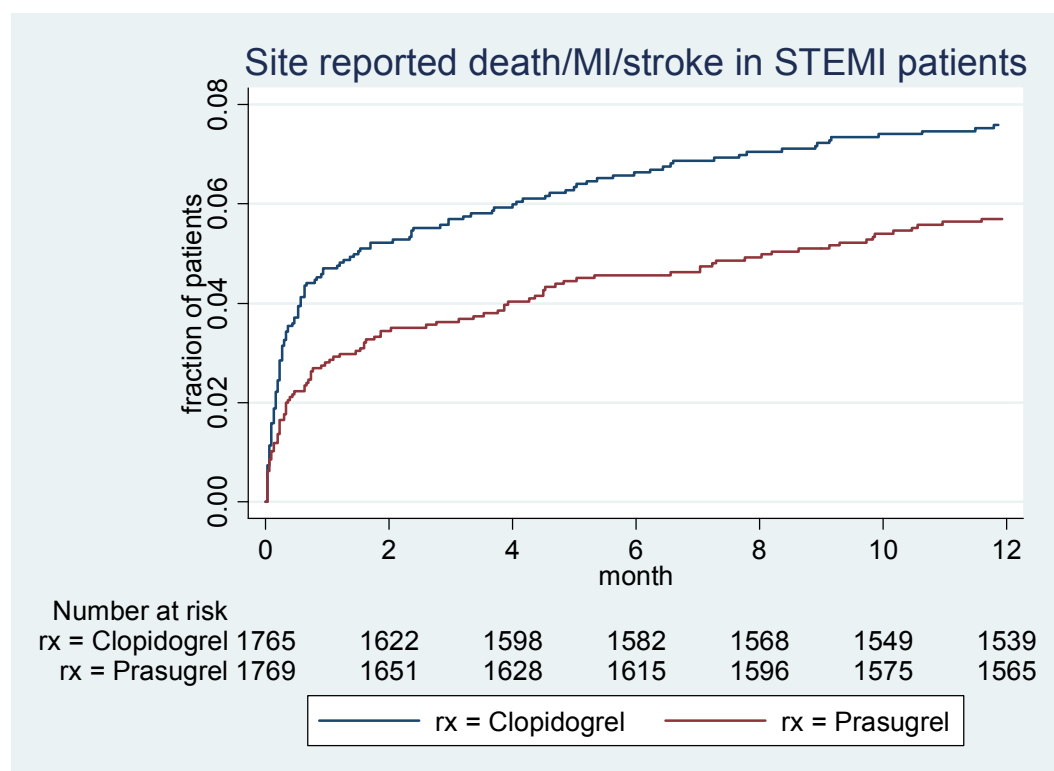


p = 0.12/0.04 (stratified/unstratified) by Gehan test, 0.08/0.07 by log rank test

The results for the primary site-reported endpoint are not statistically significant by the Gehan test stratified by ACS type, i.e., UA/NSTEMI vs. STEMI, or by the log rank test stratified or non-stratified. They are by the unstratified Gehan test. The Gehan test is more sensitive to the early part of the survival or failure curve compared to the log rank test. That event rates are highest immediately after an ACS event may be the reason the sponsor pre-specified using the Gehan rather than the log rank test. This pre-specification was accepted by the Division when the statistical analysis plan was submitted.

The prasugrel benefit appears greater for the STEMI subgroup as shown in Figure 17.

Figure 17: Site-Reported Death/MI/Stroke in TAAL STEMI Patients



p = 0.07 by Gehan test, 0.06 by log rank test

Note the much wider separation of the curves, still mainly early, in the STEMI subgroup. While the sponsor likely picked the UA/NSTEMI group as the group more likely to benefit based on the clopidogrel studies, prasugrel appears to show more benefit in the STEMI population.

The distribution of first site-reported event types is different from that for the CEC-adjudicated events. I show the site-reported first event types in Table 20.

Table 20: Site-Reported First Event Types

	UA/NSTEMI			STEMI			all		
	clopidogrel	prasugrel	Δ	clopidogrel	prasugrel	Δ	clopidogrel	prasugrel	Δ
MI	235	175	60	62	48	14	297	223	74
stroke	43	43	0	24	22	2	67	65	2
death	83	113	-30	58	49	9	141	162	-21

While prasugrel's benefit in all patients is due to a reduction in MIs, first events of all-cause deaths go in opposite directions in the two subgroups. Whether this latter dichotomy is a real difference or a subgroup variation due to chance is difficult to judge, but the dichotomy suggests that mortality differences should not be ignored.

The CEC-adjudicated events were the pre-specified primary endpoint and, if the adjudication really works, should be more discriminatory regarding risks. The latter can be evaluated

regarding risk of death, and I show the death rates for CEC-adjudicated and site reported MIs in Table 21.

Table 21: CEC-Adjudicated vs. Site-Reported MIs and Death Rates

		CEC-adjudicated			site-reported	
		no MI	PPMI only	MI event	no MI	MI event
clopidogrel	n	6,155	265	375	6,500	298
	% died	2.4%	4.5%	13.3%	2.4%	18.8%
prasugrel	n	6,327	231	255	6,588	226
	% died	2.8%	2.6%	11.4%	2.7%	14.2%

The site-reported MIs appear to be better predictors of death than the CEC-adjudicated MIs. The patients with only PPMIs in the prasugrel group actually had a rate of death comparable to those without MIs. While one might attribute these results to a benefit of prasugrel, the death rate for prasugrel patients without adjudicated MIs is not confirmatory of a prasugrel benefit.

Besides the overall assessment of benefit, the other question of critical importance for prasugrel use is the time course of the benefit. This question is critical because of the potential for tumor promotion, which should be related to duration of treatment. I show the cumulative difference in site-reported death/MI/stroke events per 100 patients in Figure 18. For comparison I show in Figure 19 the corresponding CEC-adjudicated results and in Figure 20 the results for the major adverse effect of bleeding.

Figure 18: Cumulative Site-Reported Death/MI/Stroke Difference in All TAAL Patients

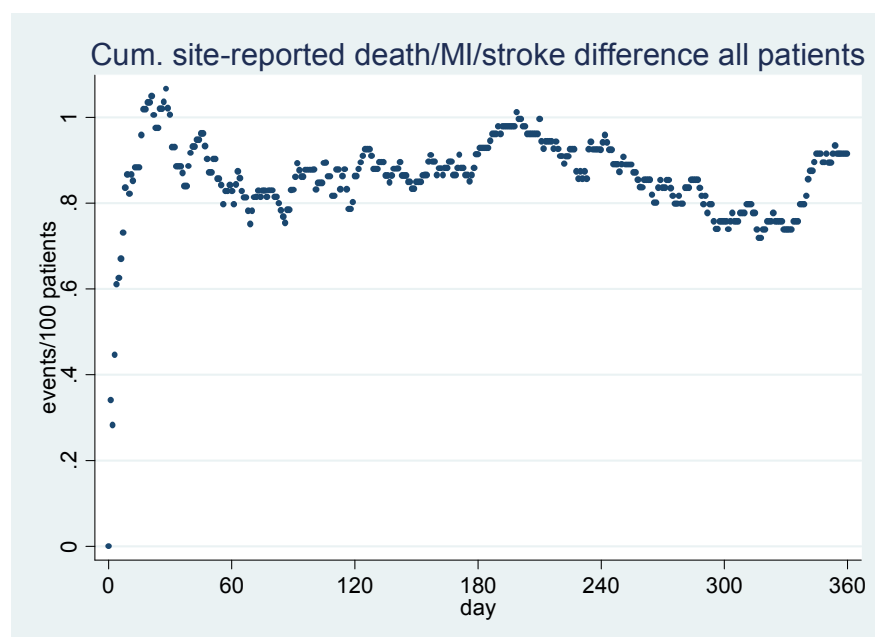


Figure 19: Cumulative CEC-Adjudicated CV Death/MI/Stroke Difference in All TAAL Patients

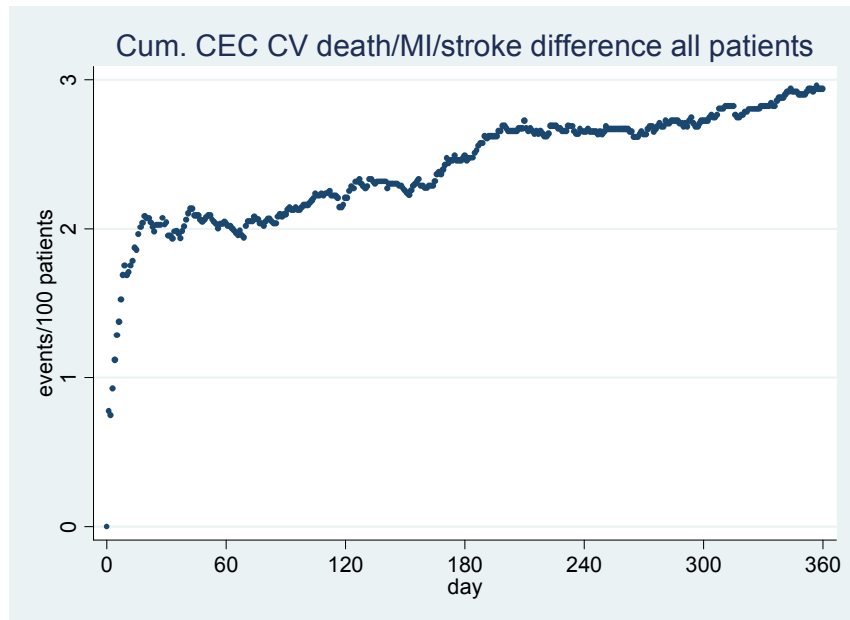
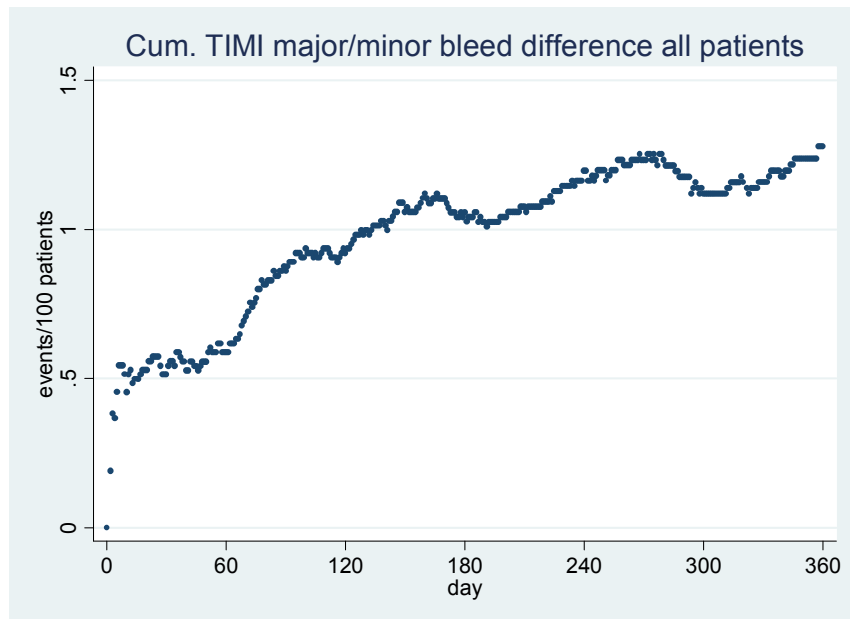


Figure 20: Cumulative TIMI Major/Minor Bleed Difference in All TAAL Patients

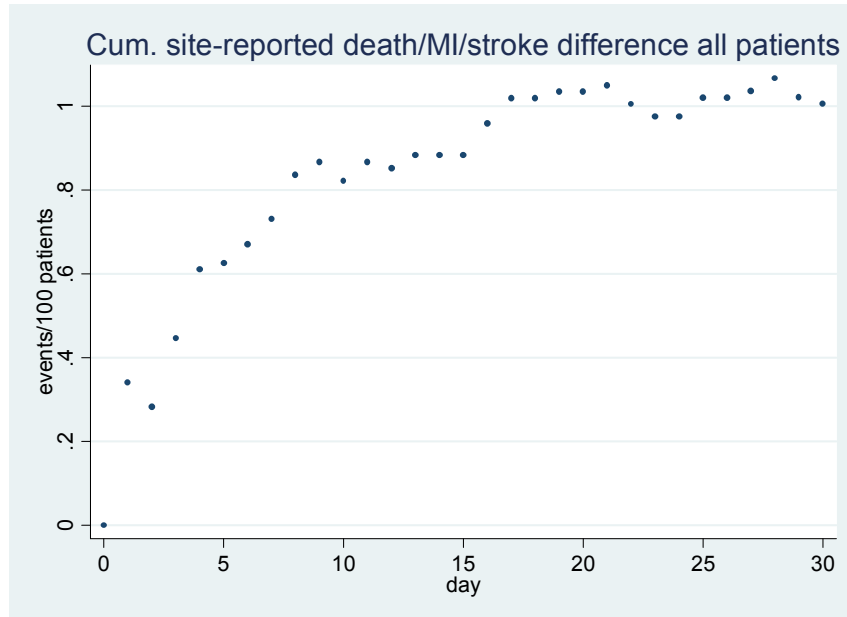


NOTE: The difference is reversed from the efficacy graphs:
 There were more bleeds with prasugrel than with clopidogrel.
 TIMI major/minor bleeding = hemoglobin drop of ≥ 3 gm/dL.

For site-reported events the benefit all appears to be early, i.e., within less than 30 days. Hence I show event differences through 30 days in Figure 21. The benefit appears to be close to maximal

at 3 weeks. Note also that the net efficacy benefit in site-reported events, about 1 event/100 patients, is matched by the net detriment in bleeding events between 2 and 4 months.

Figure 21: Cumulative Site-Reported Death/MI/Stroke Difference in All TAAL Patients



TAAL included two related but possibly distinct study populations: patients with UA/NSTEMI and those with STEMI. In fact, the sponsor pre-specified the primary efficacy analysis to be done in the UA/NSTEMI subgroup alone. Hence I show the site-reported composite endpoint results of UA/NSTEMI patients in Figure 22 and for STEMI patients in Figure 23. For all patients the MI benefit occurs early as shown in Figure 25.

Figure 22: Cumulative Site-Reported Death/MI/Stroke Difference in TAAL UA/NSTEMI Patients

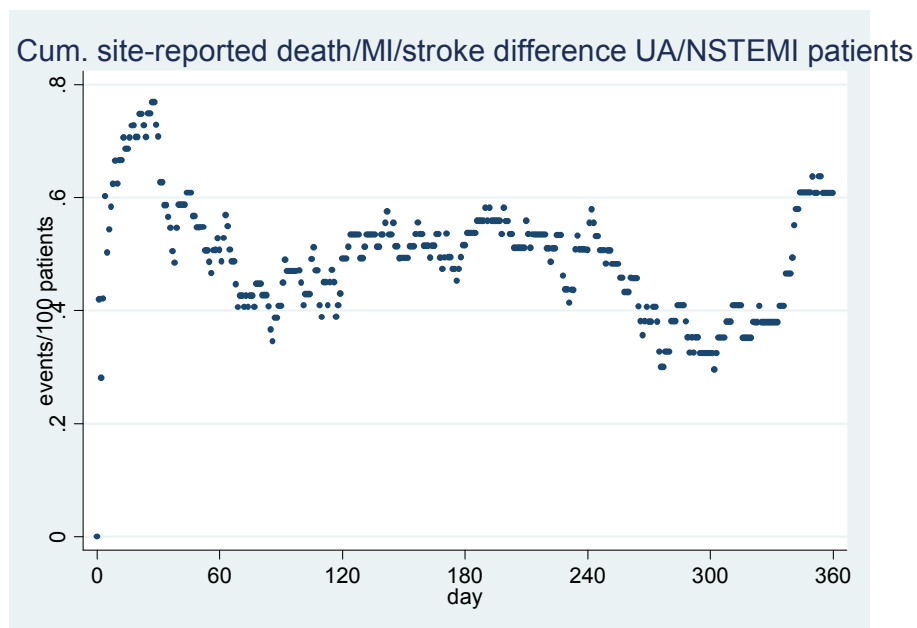
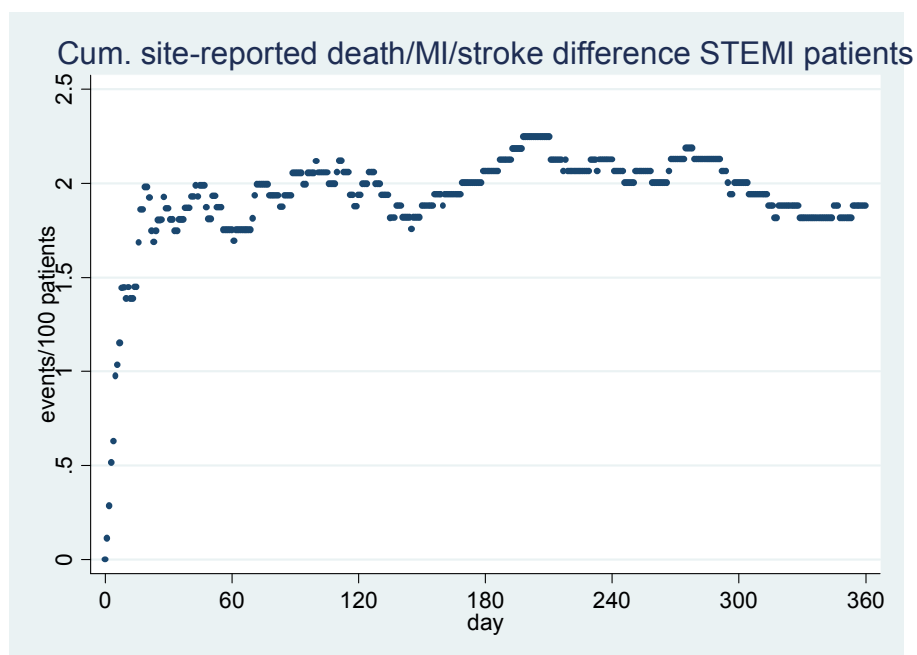


Figure 23: Cumulative Site-Reported Death/MI/Stroke Difference in TAAL STEMI Patients



For UA/NSTEMI patients there appears to be an early benefit that converts to a slight detriment as time progresses; for STEMI patients there appears to be a larger early benefit that improves

little with passing time. The late detriment for UA/NSTEMI patients occurs despite a continuing slight benefit for fewer MIs as shown in Figure 24.

Figure 24: Cumulative Site-Reported MI Difference in TAAL UA/NSTEMI Patients

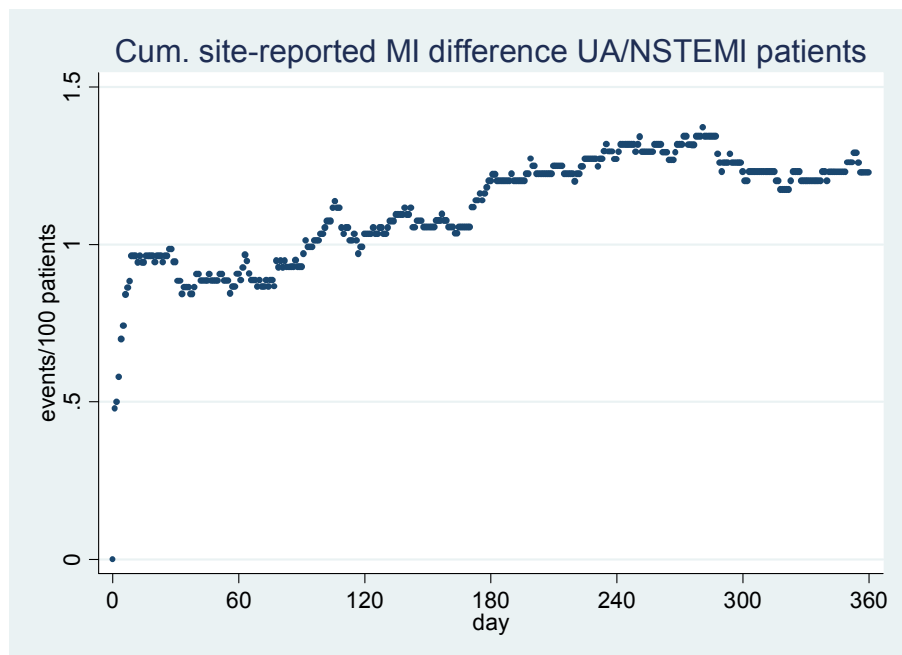
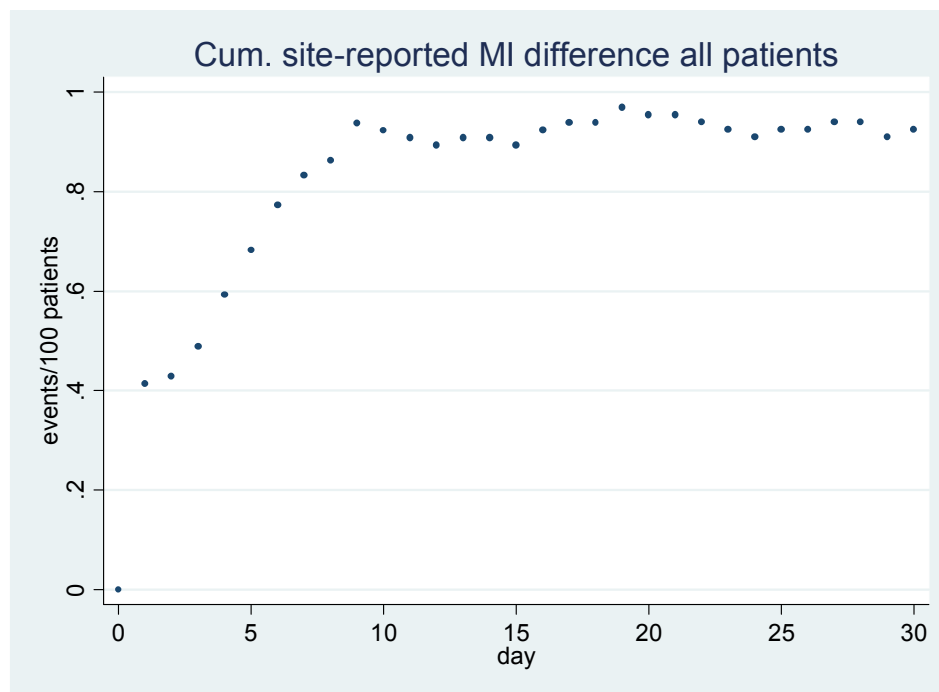


Figure 25: Cumulative Site-Reported MI Difference in All TAAL Patients



COMMENT: The site-reported events portray a slightly different picture of prasugrel benefit than the CEC adjudications. For the composite site-reported endpoint (all cause death/MI/stroke) corresponding to the CEC-adjudicated primary endpoint (CV death/MI/stroke), the TAAL results are not statistically significant for the pre-specified primary analysis in UA/NSTEMI patients. However, in the UA/NSTEMI patients the point estimate is beneficial for prasugrel and in all patients there is a statistically significant improvement in the site-reported death/MI/stroke endpoint by unstratified analysis. The benefit in all analyses appears to be a reduction in MIs. However, the site-reported events show a lower absolute benefit, a suggestion that deaths may be problematic, and little evidence of benefit beyond 15-30 days.

I interpret these efficacy results as showing that prasugrel has a small (in the order of one event/100 patients) early (< 30 days) benefit related to reduction in MIs. Whether the benefit increases beyond 30 days is less clear but it is very clear that significant bleeding increases continuously with time and the potential for tumor promotion remains a serious question for long term use.

Discussion

I interpret all of these results as follows: The preclinical studies suggest, but are not conclusive, that prasugrel is a tumor promoter in mice. The clinical results in TAAL are also suggestive of a promoter effect. While it is tempting to dismiss the clinical findings as due to ascertainment bias due to increased bleeding with prasugrel, the delay in the divergence of the incidence plots for four+ months, the continued divergence of most plots through 16 months, the lack of evidence for an ascertainment bias for solid tumors other than GU, the cancer deaths leaning in the wrong direction, and the lack of a similar ascertainment bias in CHARISMA do not support the ascertainment bias hypothesis.

Besides drug effect, one other possible explanation is a play of chance resulting in more cancer prone individuals ending up in the prasugrel group. While this remains possible, I think it is unlikely because of the size of TAAL, the excellent balance in cancers reported as on-going at baseline, and the significant p values for the most relevant comparisons (0.024 and 0.0013). While these p values do not have the same strength of evidence as that of a pre-specified primary efficacy endpoint, neither were they picked as unusual from data dredging the trial results. The p value of 0.024 is generated by the initial analysis I had envisioned based on my review of the pre-clinical data.

One limitation of TAAL is the quality of the data. TAAL was not pre-specified to examine cancer rates, although cancer events are routinely captured in most CV trials and were captured prospectively in TAAL. TAAL did not capture prospectively a complete history of all cancers. However, from a patient perspective, a cancer recurrence is as deadly as or usually more deadly than a new cancer—prasugrel looks as bad for new and worse solid cancers as it does for new solid cancers. So the data quality issue (the lack of cancer histories) that some reviewers have viewed as insurmountable does not make the TAAL cancer results uninterpretable. TAAL raises a serious safety concern. I don't think that safety concern can be put to rest by manipulating TAAL data; another study is needed.

I am not impressed at all by the counterargument that the finding lacks biologic plausibility because we have never seen a similar pattern before. We have no large randomized trials of documented tumor promoters in humans. We should not assume that we know exactly what to expect based on animal studies. The evidence for a problem is far stronger in TAAL than it was at NDA submission times for the recent withdrawals from market, such as Vioxx and Zelnorm.

The efficacy data from TAAL document a reasonable benefit on reduction in MIs. However, there is no overall mortality benefit and there is little evidence of a benefit beyond 15-30 days. I can argue that the short term benefit justifies immediate approval, although only for short term use, but I can also argue that approval should be delayed until the planned trial in medically managed ACS addresses the cancer promotion issue.

One issue that I have not discussed is the formulation problem of conversion from salt to base form. Please see the FDA CMC and CDTL reviews for the details on this problem. Because I would project that cancer promotion should not have a steep dose-response relationship, the formulation problem is not important for the cancer issue. It could affect other safety and efficacy and hence is relevant to risk/benefit analyses. My overall judgment is that, because TAAL showed efficacy and acceptable non-cancer related safety despite a less than ideal formulation, the formulation problem should not be an absolute bar to approval. However, it is another factor that argues for delaying full approval until the sponsor addresses all outstanding issues with new data and a new formulation.

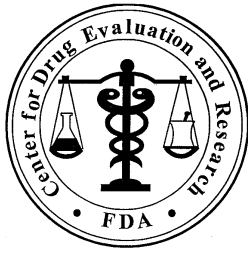
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/s/

Thomas Marciniak
12/31/2008 02:15:55 PM
MEDICAL OFFICER
This review replaces completely my review from June 2008.



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: January 8, 2009

To: Norman Stockbridge, M.D., Ph.D., Director
Division of Cardiovascular and Renal Products (DCRP)

Through: Henry Francis, MD, Deputy Director
Office of Surveillance and Epidemiology (OSE)

From: OSE EFFIENT Risk Management Review Team

Subject: **Background Package for Advisory Committee** NDA 22-307
EFFIENT™ (prasugrel hydrochloride) Tablets 5mg and 10 mg strengths

Sponsor: Eli Lilly and Company

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EXECUTIVE SUMMARY

Prasugrel is an orally bioavailable thienopyridine adenosine diphosphate (ADP) receptor antagonist. The proposed indication is for the reduction of acute myocardial infarction in acute coronary syndrome (ACS) patients with unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI) who are managed with percutaneous coronary intervention (PCI) and patients with ST-segment elevation myocardial infarction (STEMI) who are managed with primary or delayed PCI.

During the clinical trial prasugrel was shown to significantly reduce the rate of the combined endpoint of cardiovascular death, nonfatal myocardial infarction, or non-fatal stroke in the UA/NSTEMI, all ACS, and STEMI populations at a median follow-up of 12 months, compared to clopidogrel. Of note, overall mortality was not found to be significantly different between treatment groups. Although prasugrel has been shown to be more efficacious than the comparator, it is also associated with a significant increased risk of bleeding, including fatal bleeding. Additionally, during the review of this application, the Division became concerned regarding disproportionate numbers of malignancies in the prasugrel group compared to the clopidogrel group.

If approved, we believe that a boxed warning would be warranted to emphasize the increased risk of bleeding observed in patients treated with prasugrel, particularly in patients with a prior history of TIA or stroke and in patients older than ≥ 75 years. The boxed warning should emphasize the need to avoid the use of prasugrel in these two subgroups. We believe that the boxed warning should also convey an increased risk of bleeding in patients that are generally vulnerable including: 1) patients who are undergoing elective CABG or other surgical procedures and the need to discontinue use of prasugrel at least 7 days prior to surgical procedure and discourage using prasugrel when coronary anatomy is unknown and CABG is a possibility; 2) patients with body weight <60 kg (the sponsor should provide data to support their recommendation to reduce the maintenance dose of prasugrel from 10 mg to 5 mg daily); and 3) emphasize the increased risk of bleeding in patients on concomitant medications such as warfarin, heparin, fibrinolytics or chronic use of NSAIDS. The need to initiate therapy in the inpatient setting should also be included in the boxed warning.

We believe the potential risk of tumor stimulation associated with prasugrel use should be addressed in the warnings/precautions section of the label. We agree with the Review Division that one way to minimize the risk of malignancy, as well as the risk of bleeding, would be to limit the duration of therapy. However, specific dose conversions would need to be explicitly stated in the labeling. An overdose could occur if patients receive another loading dose of clopidogrel resulting in increased risk of bleeding. Patients may also be at an increased risk of thrombosis if the switch results in underdosing or if therapy is delayed. This is especially concerning in patients at risk of stent thrombosis. Until a determination is made regarding number of days of therapy and a dose conversion strategy or algorithm from prasugrel to clopidogrel, DMEPA reserves their comments on other potential sources of error.

Lilly proposes a risk evaluation and mitigation strategy (REMS) which will consist of a patient package insert (PPI) and a schedule for the assessment for the REMS. Given the four-fold increased risk of fatal bleeding events with prasugrel compared with clopidogrel, and the potential effect of prasugrel on tumor stimulation, we have determined that a REMS would be necessary to ensure that the benefits of the drug outweigh the risks. The REMS should consist of a Medication Guide, a communication plan, a timetable for assessments, and assessments of the REMS.

Lilly also plans to conduct post-launch active surveillance activities using large administrative claims databases or hospital in-patient electronic medical records databases to estimate and monitor the incidence of bleeding events and to identify and monitor subpopulations at risk for bleeding events in ACS patients treated with prasugrel. Lilly's active surveillance plan is likely to experience logistical and scientific problems as this product is initiated in the hospital and

continued for an unknown period of time in an outpatient setting necessitating long-term follow-up of patients in different settings.

Some members of the OSE prasugrel team recommend a public Advisory Committee meeting before general approval and marketing to discuss the benefit of prasugrel treatment over the current standard of care (clopidogrel) given the issues concerning the drug's reformulation, bleeding, and cancer.

1 INTRODUCTION AND BACKGROUND

This review follows the January 31, 2008 request from the Division of Cardiovascular and Renal Products (DCRP) for the Office of Surveillance and Epidemiology (OSE) to review Lilly's proposed risk management plan submitted on December 26, 2007.


Prasugrel, a thienopyridine adenosine diphosphate (ADP) receptor antagonist, is an orally administered prodrug whose active metabolite irreversibly inhibits platelet activation and aggregation. The proposed indication for prasugrel is for the reduction of acute myocardial infarction in ACS patients with unstable angina or NSTEMI who are managed with PCI and patients with STEMI who are managed with primary or delayed PCI. The recommended starting dose is a loading dose of 60 mg to be initiated in the hospital followed by 10 mg once daily dose. Prasugrel is available as 5 mg and 10 mg film coated unscored tablets. Currently, there are two thienopyridines approved for the treatment of ACS. These drugs are ticlopidine (Ticlid[®]) and clopidogrel (Plavix[®]). Similar to prasugrel, both are prodrugs requiring in vivo metabolism to form an active metabolite.

In the prasugrel NDA submission Lilly proposes a worldwide routine pharmacovigilance to manage the risks of this product. Additionally, for the U.S. the sponsor proposes a risk evaluation and mitigation strategy (REMS) which will consist of a patient package insert (PPI) and a schedule of assessment for the REMS.

1.1 REGULATORY HISTORY

Prasugrel is a new molecular entity (NME) that has not been approved for marketing in any country. During the clinical trial, prasugrel was shown to significantly reduce the rate of the combined endpoint of cardiovascular death, nonfatal myocardial infarction, or non-fatal stroke in the UA/NSTEMI, all ACS, and STEMI populations at a median follow-up of 12 months, compared to clopidogrel. Subjects appeared to receive much of the treatment benefit from prasugrel within the first several days of therapy. Based on the significant improvement demonstrated in the clinical trial with use of prasugrel over current standard of care (Plavix[®], clopidogrel bisulfate), the application was granted priority review with a 6-month review clock.

¹ Division of Cardiovascular and Renal Products. Importance of Prasugrel's Conversion from a Salt to the Base Form; dated September 12, 2008.



The sponsor submitted a major amendment dated June 20, 2008 that included a draft proposal of post marketing commitments and a risk management proposal.³ The document reiterated the commitments and timelines stated in the REMS document within the original application. The REMS submission was no different than the original proposal and included a PPI and a schedule for assessment. Inclusive of the risk management plan, the sponsor also stated there would be a pharmacovigilance plan with agreed upon surveillance terms, and surveillance of safety events relevant to special populations (such as, elderly, pregnant, patients of different racial or ethnic origin).

2 METHODS AND MATERIALS

2.1 DATA AND INFORMATION SOURCES

- 1) Proposed prasugrel “Risk Minimization Plan” submitted December 26, 2007 by Eli Lilly & Co.
- 2) Proposed prasugrel labeling submitted December 26, 2007 by Eli Lilly & Co.
- 3) Rahman MA, Lin K. Statistical Review and Evaluation – Carcinogenicity Studies, Division of Biometrics, FDA; dated February 19, 2008.
- 4) Analysis by Thomas A. Marciniak, M.D., Division of Cardiovascular and Renal Products, FDA; dated April 22, 2008.
- 5) Hicks KA. Clinical Review of Prasugrel, Division of Cardiovascular and Renal Products, FDA; dated April 28, 2008.
- 6) Mann BS. Carcinogenic potential for prasugrel, Division of Drug Oncology Products, FDA; dated April 24, 2008.
- 7) Mishina EV, Mada S. Clinical Pharmacology Review. DPEI and Cardio-Renal Drug Products, FDA; dated May 23, 2008.
- 8) Turner T. Proprietary Name, Label, and Labeling Review, Division of Medication Error Prevention, FDA; dated May 29, 2008.
- 9) Wysowski D. Cancer in Clinical Trials of Prasugrel, Division of Epidemiology, FDA; dated June 12, 2008.
- 10) Brinker A. Team Leader covering Memorandum, Division of Epidemiology, FDA; dated June 13, 2008.

² Mishina EV, Mada S. Clinical Pharmacology Review. DPEI and Cardio-Renal Drug Products, FDA; dated May 23, 2008.

³ Prasugrel: Submission of proposed post marketing requirements (NDA 22-307/Sequence: 0044) dated June 20, 2008.

- 11) Unger, EF. Division of Cardiovascular and Renal Products *Secondary Review*, FDA; dated July 10, 2008.
- 12) Division of Cardiovascular and Renal Products. Importance of Bleeding to Prasugrel's Risk Benefit Relation; draft dated September 23, 2008.
- 13) Division of Cardiovascular and Renal Products. Importance of Prasugrel's Conversion from a Salt to the Base Form; draft dated September 25, 2008.

2.2 ANALYSIS TECHNIQUES

The submission was assessed for risks associated with prasugrel use based primarily on the analysis of the pivotal Study TAAL (a study comparing prasugrel and clopidogrel in acute coronary syndrome subjects who are to undergo percutaneous coronary intervention). In Study TAAL (primary safety database), data were collected from 13,457 subjects (prasugrel: 6,741; clopidogrel 6,716) with ACS who were managed by PCI. Of the 6,741 subjects randomized to prasugrel, 4088 subjects were exposed to prasugrel for at least 1 year. The submission was reviewed for proposed risk mitigation strategies, as well as, conformance with the Food and Drug Administration Amendments Act of 2007.⁴

3 SAFETY CONCERNS

3.1 SPONSOR'S SAFETY CONCERNS

Prasugrel is an inhibitor of platelet aggregation and poses the risk of hemorrhagic events. The sponsor has identified important risks to include intracranial hemorrhage, gastrointestinal hemorrhage, intraocular hemorrhage, epistaxis, PCI-related hemorrhage, CABG-related hemorrhage, other procedure-related hemorrhage, and anemia. The sponsor has also identified important potential risks to include phototoxicity (ocular or skin), drug-induced hepatic injury, allergic reactions, thrombocytopenia, thrombotic thrombocytopenic purpura, and neutropenia. From the clinical trials three populations were identified by the sponsor as at risk population for hemorrhagic events when treated with prasugrel and are discussed below.

- Age ≥ 75 years was identified as a risk factor for hemorrhagic events among subjects on prasugrel. In Study TAAL, subjects age ≥ 75 years was associated with a higher incidence of Non-CABG-related Thrombolysis in Myocardial Infarction (TIMI) Major or Minor bleeding events in both treatment groups (8.98% prasugrel, 6.94% clopidogrel). Age ≥ 75 years was also associated with higher risk of Non-CABG-related TIMI Major Life-Threatening bleeding events (including fatal bleedings and symptomatic intracranial hemorrhage) for both treatment groups. Age ≥ 75 years was also associated with a higher risk of gastrointestinal hemorrhagic adverse events for both treatment groups. The sponsor concludes, though, that a statistically significant interaction between treatment and age ≥ 75 years was observed, which resulted in a statistically significant higher incidence of stroke in subjects aged ≥ 75 years treated with prasugrel compared to clopidogrel (2.89% versus 1.43%; $p=0.024$). The sponsor suggests, for patients ≥ 75 years of age, prasugrel should be given as a single 60 mg loading dose (LD) and consideration may be given to a 5 mg once daily dose as an alternative to 10 mg once daily dose.
- Body weight < 60 kg was identified as a risk factor for hemorrhagic events for subjects on prasugrel. For patients with body weight < 60 Kg, the sponsor recommends dose adjustment of prasugrel maintenance dose to 5 mg once daily following the 60 mg loading dose.

⁴ Food and Drug Administration Amendments Act of 2007. http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:pub1085.110

- Prior history of TIA or stroke was associated with a higher risk of Non-CABG-related TIMI major or Minor Life-Threatening bleeding events (including fatal bleeding and symptomatic intracranial hemorrhage). The sponsor opines that the clinical findings support the proposed prescribing information stating that, in patients with a known history of TIA or stroke (ischemic or hemorrhagic) prasugrel should be used with caution.

Additionally, the concomitant use of prasugrel with warfarin, heparin, fibrinolytics, or chronic use of NSAIDS (non ASA) was considered to increase the risk of hemorrhage. Subjects at increased risk of bleeding due to use of concomitant medications (for example, fibrin-specific fibrinolytic therapy <24 hours or nonfibrin-specific fibrinolytic therapy <48 hours prior to randomization) or clinical conditions, in the judgment of the investigator, associated with increase risk of bleeding were excluded in Study TAAL.

3.2 DCRP SAFETY CONCERNS

The Review Division identified several safety concerns. Below are summary of the identified risks based on the primary and secondary medical reviews.^{5,6}

3.2.1 Bleeding

TIMI major and TIMI minor or minor non-CABG related hemorrhages and CABG-related hemorrhage were statistically significantly higher in the ACS population for prasugrel subjects compared with clopidogrel subjects. According to the secondary review, prasugrel was associated with excess bleeding, irrespective of bleeding definition, seriousness, or location, and across most subgroups assessed. Many of the bleeding events occurred within the first 3 to 5 days of the index Procedure.

There were 21 and 5 fatal bleeding events in the prasugrel and clopidogrel non-CABG-related groups, respectively (RR = 4.19, 95% C.I.: 1.58, 11.1, p=0.002). For the clopidogrel group, all 5 fatal bleeding events were intracranial in location. For the prasugrel group, 9 bleeding events were intracranial, 5 were gastrointestinal (GI), 2 originated from puncture sites, 2 from surgical sites, 2 from retroperitoneal locations, and 1 from an intra-abdominal location. Dr. Ellis Unger stated in his review that none of the deaths in the clopidogrel group, but over half the deaths in the prasugrel group, were attributed to extra-cranial sites of hemorrhage.

The following subgroups were at particular risk of bleeding:

Patients with a prior history of a TIA or CVA

In all ACS subjects with a prior history of transient ischemic attack or stroke, there was a 38% increased risk of experiencing death, nonfatal myocardial infarction, or nonfatal stroke at a median of 12 months of follow-up on prasugrel, compared to clopidogrel.

Patients \geq 75 years of age

For subjects \geq 75 years of age, the RR of TIMI major or minor bleeding events was 1.35, which is similar to the RR in younger subsets. However, subjects \geq 75 years of age had a higher frequency of fatal and life-threatening bleeding events, and the RR was very unfavorable for prasugrel, i.e., fatal bleeding: 1.01% prasugrel, 0.11% clopidogrel; symptomatic intracranial hemorrhage: 0.79% prasugrel, 0.34% clopidogrel.

⁵ Hicks KA. Clinical Review of Prasugrel, Division of Cardiovascular and Renal Products, FDA; dated April 28, 2008.

⁶ Unger, EF. Division of Cardiovascular and Renal Products Secondary Review, FDA; dated July 10, 2008.

Patients who undergo CABG

The frequency of CABG-related TIMI major bleeding was higher in subjects treated with prasugrel compared to clopidogrel, and there was higher risk even when prasugrel was discontinued more than 7 days in advance of CABG. In the prasugrel group, there were 24 TIMI major bleeding events (11.3%, RR=3.50), of which 2 were fatal (0.9%) compared to the clopidogrel group, where there were 8 TIMI major bleeds, and none were fatal. Based on the reviewer's analysis, prasugrel should not be the drug of choice for patients in whom CABG surgery is anticipated and prasugrel is not well-suited for pre-treatment of patients in whom coronary anatomy is unknown.

In summary, the Review Division concluded that risk of bleeding is higher and specific information is merited in labeling for:

- patients ≥ 75 years of age (here the greater risk is for fatal and life-threatening bleeding)
- patients with a prior history of a transient ischemic attack or cerebrovascular accident (contraindication)
- patients who undergo CABG, or by extension, probably any surgical procedure

3.2.2 Malignancy

During the review of this application, neoplasia was also identified as an important risk by the medical reviewers in DCRP. Two carcinogenicity studies in the rat and in the mouse were reviewed. In the rat studies, no statistically significant dose response relationship or difference in survival between prasugrel treatment group and clopidogrel were observed in either sex. However, the mouse study showed statistically significant positive dose response relationship in the incidence of hepatocellular adenoma and combined incidences of hepatocellular adenoma and hepatocellular carcinoma in both sexes.⁷

DCRP conducted analyses of neoplasms cases in the pivotal study, TAAL. In Study TAAL, 4088 subjects were exposed to prasugrel for at least 1 year. In this study an increased rate of neoplasms, particularly solid tumors, in the prasugrel treatment group compared to clopidogrel ($p=0.006$) was observed.⁸ In the prasugrel treatment group, there were 104 nonskin, nonbrain cancers, compared to 69 in the clopidogrel group. A Kaplan-Meier plot for all new cancers (excluding skin and brain) after 7 days in TAAL showed a divergence between the drugs and higher rates beginning at four months for prasugrel. Cancer sites showing the largest difference between drugs included breast, colorectal, lung, and "unknown/other." Further analysis also suggested that cancers in women played an important role.

A consult was sent to the Division of Drug Oncology Products (DDOP) to assess the carcinogenic potential of prasugrel. DDOP agreed with DCRP that when the incidences of "all cancers" between the drugs were compared, a p value of < 0.05 was obtained. However, DDOP is not certain of the statistical or clinical significance of these findings given that the study was not designed to compare the cancer incidence between the study arms. Furthermore, based on the absence of well defined cancer screening at study entry and no specified follow up to detect specific cancer, DDOP concluded that the cancers diagnosed on study are more likely to be "incidental".⁹

⁷ Rahman MA, Lin K. Statistical Review and Evaluation – Carcinogenicity Studies, Division of Biometrics, FDA; dated February 19, 2008.

⁸ Analysis by Thomas A. Marciniak, M.D., Division of Cardiovascular and Renal Products, FDA; dated April 22, 2008.

⁹ Mann BS. Carcinogenic potential for prasugrel, Division of Drug Oncology Products, FDA; dated April 24, 2008.

The sponsor has related the excess cancers in the prasugrel group to ascertainment bias because prasugrel appears to cause earlier bleeding than clopidogrel, thus resulting in increased detection of cancer. Despite the sponsor's explanation, the Review Division remains concerned about the difference in cancer rates between the drugs. Based on the preliminary analysis as well as increased bleeding risk with prasugrel over time, the medical reviewer recommended limiting therapy with prasugrel to short-term use (i.e. 1 week) so that patients may receive the benefits of this therapy while avoiding some of the possible risks.

3.3 OSE SAFETY CONCERNS

Based on the identified and potential risks described by the sponsor, as well as the risks identified during the NDA review by DCRP, we note the following:

3.3.1 Bleeding

The risk identified by the sponsor of hemorrhagic events associated with prasugrel is a class effect of the thienopyridines, including clopidogrel and ticlopidine, and one that is well-known to prescribers. Typically, these risks are managed through routine pharmacovigilance plans and labeling consistent with the plan outlined by the sponsor. Clopidogrel and ticlopidine labeling consists of the package insert (PI) which addresses the risk of bleeding in the precautions and adverse reaction sections. However, prasugrel was associated with a significant increased risk of bleeding, including fatal bleeding compared to clopidogrel.

Based on the medical officer's review, there was a 36% increased risk of overall bleeding and a 46% increased risk of serious bleeding in the prasugrel treatment group compared to clopidogrel.¹⁰ The sponsor has identified increased risk of hemorrhagic events in certain at-risk subpopulations to include patients age ≥ 75 years, patients with body weight <60 kg, patients with prior history of TIA or stroke, and patients on concomitant medications such as warfarin, heparin, fibrinolytics or chronic use of NSAIDs. Additionally, the review team in DCRP identified patients who underwent CABG at an increased risk of prasugrel-associated bleeding.

Because of the four-fold increased risk of fatal bleeding events with prasugrel compared with clopidogrel, we believe that a boxed warning is warranted. The above mentioned at-risk subpopulations should be included in the boxed warning. Patients with previous history of stroke and/or transient ischemic attacks should be contraindicated to receive prasugrel. We agree with the medical reviewer that in patients ≥ 75 years of age, prasugrel should not be the treatment of choice. Therefore, age ≥ 75 years old should be identified as a risk factor for hemorrhagic events and use should be discouraged. Lower body weight of <60 kg should be included in the boxed warning as a risk factor. The sponsor should provide data to support their recommendation to reduce the maintenance dose of prasugrel from 10 mg to 5 mg daily. A significant pharmacodynamic drug-drug interaction, prolongation of the bleeding time, was observed when prasugrel was co-administered with aspirin, warfarin and heparin, and should be included in the boxed warning to emphasize the increased risk of bleeding. Finally, patients undergoing CABG or any surgical procedure are at increased risk of bleeding and should be included in the boxed warning.

The increased risk of both fatal and non-fatal bleeds associated with prasugrel might warrant additional communication such as a Medication Guide. A Medication Guide would advise patients about the risk of bleeding with prasugrel and ensure that patients in whom prasugrel is contraindicated are not receiving it. It would inform patients about the risk factors (e.g., age ≥ 75 years, body weight <60 kg) and the drug-drug interactions (e.g., NSAIDs, warfarin, heparin, and

¹⁰ Hicks KA. Clinical Review of Prasugrel, Division of Cardiovascular and Renal Products, FDA; dated April 28, 2008.

fibrinolytics). Additionally, a Medication Guide would inform patients of signs and symptoms of bleeding and the need to seek immediate medical attention as well as the need to discontinue prasugrel prior to elective surgery. Healthcare provider communication at product launch would also help familiarize prescribing physicians with important product information as described above to ensure appropriate patient selection and monitoring.

3.3.2 Malignancy

The risk of neoplasia has been raised and it remains questionable if this observed risk is “incidental” or real. Since the risk of malignancies cannot be ruled out, patients and prescribers need to be informed of this serious risk as it would directly affect the patients’ decision as to whether or not to use or to continue to use prasugrel, and the information is necessary for the prescribers to provide adequate oversight in patient selection and follow up. The risk of malignancy is particularly concerning if the product is used long term. The sponsor identified several possible “off-label” uses in one section of their risk management proposal which includes uses that might result in long term therapy:

- primary prevention of cardiovascular events;
- treatment of subjects with clinical history of coronary artery disease with no symptoms of ACS;
- treatment of other clinical manifestations of atherosclerotic disease such as previous myocardial infarction;
- peripheral arterial disease and ischemic stroke treatment of subjects with ACS for whom PCI is not indicated;
- prescription of higher than the recommended dose, under the belief that higher doses may confer greater efficacy.

In some of these mentioned circumstances, “off-label” use can be minimized if the package insert labeling is consistent with the proposed risk management plan and explicitly states that the loading dose should be given in a hospital setting. Consistency between the labeling and the risk management plan will also avert dosing confusion.¹¹

Some in DCRP have recommended limiting the duration of use of prasugrel as a strategy to minimize the potential risk of malignancy. Patients treated with prasugrel would be switched after an initial time frame to clopidogrel for the remainder of therapy. We agree that one way to minimize the risk of malignancy, as well as the risk of bleeding, would be to limit the duration of therapy. However, specific dose conversions would need to be explicitly stated in the labeling. An overdose could occur if patients receive another loading dose of clopidogrel resulting in increased risk of bleeding. Patients may also be at an increased risk of thrombosis if the switch results in underdosing or if therapy is delayed. This is especially concerning in patients at risk of stent thrombosis. Until a determination is made regarding number of days of therapy and a dose conversion strategy or algorithm from prasugrel to clopidogrel, DMEPA reserves their comments on other potential sources of error.

The Division of Epidemiology (DEPI) was consulted to comment on the usefulness of registries and to provide recommendations on the design of a study planned by the sponsor called TRILOGY ACS Study (previously called TABY) with respect to assessing prasugrel’s risk of neoplasia. Dr. Wysowski, Ph.D., DEPI, stated in her review that the question of cancer etiology in prasugrel users cannot be adequately answered using a registry.

¹¹ Turner T. Proprietary Name, Label, and Labeling Review, Division of Medication Error Prevention, FDA; dated May 29, 2008.

The review also outlined suggested analyses that should be performed by the sponsor on the available data from TAAL to resolve the question of tumor stimulation before the drug is approved for marketing.¹² Dr. Wysowski suggested that Lilly proceed with its proposed second randomized clinical trial, TRILOGY ACS Study. The study would need to be performed with enough power to detect prasugrel's effect on lung, breast, colon, and prostate cancers, and with careful collection of data on risk factors for lung, breast, colon, and prostate cancers. Collection of complete histories of cancer, symptoms of cancer, alcohol use, cigarette smoking, and medication use (including aspirin), and weight and body mass index, would be required.

3.3.3 Formulation (Salt to Base Conversion)

The clinical pharmacology analysis showed that concomitant use of 30 mg lansoprazole (proton pump inhibitor) reduced the C_{max} of prasugrel's active metabolite by nearly 30% and that the low, intermediate, and high rate of conversion tablets were not bioequivalent to each other since the C_{max} failed to meet the 90% confidence interval criteria of 80-125. The concern is that the differing amounts of conversion from lot to lot, in the presence of proton pump inhibitors (PPIs), leads to differences in the peak plasma concentrations which could be clinically significant. The review team in DCRP has assessed efficacy as a function of the age of the prasugrel lots in the presence and absence of PPI use and has determined that prasugrel's efficacy was at least comparable to clopidogrel for all lots, and efficacy was not importantly affected by pill age. The frequency of bleeding in prasugrel-treated subjects was also found to be very similar in subjects who did and did not receive a PPI, 2.5% and 1.7%, respectively.¹³



4 SPONSOR'S RISK MANAGEMENT PROPOSAL

The sponsor proposes labeling, routine pharmacovigilance, and continued safety assessment of the following specific adverse events of interest: general bleeding, epistaxis, intraocular bleeding, anemia, photosensitivity, hepatic abnormalities, allergic reactions, thrombotic thrombocytopenic purpura, thrombocytopenia, and neutropenia. Targeted surveillance activities with specific follow-up forms for general bleeding, epistaxis, intraocular bleeding, procedure related bleeding; evaluation of type, severity, seriousness, localizations, concomitant medication, and indication of use will be implemented. Of note, the aforementioned follow-up forms have not been submitted for review.

Lilly also plans to conduct post-launch active surveillance activities using large administrative claims databases or hospital in-patient electronic medical records databases to estimate and monitor the incidence of bleeding events and to identify and monitor subpopulations at risk for bleeding events in ACS patients treated with prasugrel. The details of these post-marketing surveillance activities have not been submitted.

¹² Wysowski D. Cancer in Clinical Trials of Prasugrel, Division of Epidemiology, FDA; dated June 12, 2008.

¹³ Division of Cardiovascular and Renal Products. Importance of Bleeding to Prasugrel's Risk Benefit Relation; dated September 15, 2008.

Additionally, the sponsor proposes, in the U.S., to distribute a patient package insert (PPI) for prasugrel and states that this will constitute a Risk Evaluation and Mitigation Strategy (REMS) and will be implemented in accordance with the REMS requirements. The assessment of the REMS will be submitted to the agency according to the following schedule:

- No later than 18 months after the REMS submission is approved;
- No later than 3 years after the REMS submission is approved;
- No later than 7 years after the REMS submission is approved, unless FDA waives this requirement after determination that serious risks of the drug have been adequately identified and assessed and are being adequately managed;
- When a supplemental application for a new indication for use is submitted to the agency;
- At other times, if requested by FDA;
- At other times, at the discretion of Lilly.

5 OSE'S ASSESSMENT OF THE ACTIVE SURVEILLANCE PLAN

Lilly submitted a brief section, 2.1.4, "Active (Additional) Surveillance Activities" and this was reviewed. The company stated that it plans to conduct additional surveillance of relevant special populations (e.g., pediatric, elderly, pregnant or lactating women, patients of different racial or ethnic origin) or particular conditions of use (e.g., outside a drug's current approved indications). If Lilly identifies a serious safety signal in a special population or condition of use, Lilly will conduct "further targeted assessments." No detail was provided about the nature of the targeted assessments.

Lilly also plans to conduct periodic data mining of its surveillance system and publically available versions of FDA's Adverse Event Reporting System database to evaluate patterns of disproportionate reporting of adverse events following exposure to prasugrel. In addition, the company plans to "conduct active surveillance activities using appropriate large administrative claims databases or hospital in-patient electronic medical records databases." They state that, "The estimation of background mortality incidence of and ascertainment of possible risk factors for bleeding events in ACS patients who are managed by PCI and in relevant subgroups within this population will be established." The company does not explain how it will estimate "background mortality incidence" and ascertain possible risk factors for bleeding events from spontaneously submitted reports. If prasugrel is approved by the FDA, the company should be asked to explain these statements and provide more detail and rationale.

Although prasugrel has been compared with clopidogrel in the TRITON-TIMI 38 (also called TAAL) randomized clinical trial and the reformulated prasugrel will be compared with clopidogrel in the randomized clinical trials called the TRIOLGY ACS study, active surveillance will identify adverse events in real world situations. However, the active surveillance that Lilly plans is likely to experience numerous logistical and scientific hurdles. The first administration of prasugrel in most, if not all, patients will be in a hospital. The drug will then be continued for an indefinite period of time on an outpatient basis. The onset of prasugrel's antiplatelet effect to reduce risk for myocardial infarction is rapid--within the first few days of treatment. Active surveillance of adverse events would have to begin in inpatient hospital settings, and to obtain representative data and incidence rates, a sample of hospitals would need to be drawn from hospitals that administer the drug. Patients administered prasugrel identified in the hospital setting would need to be followed for adverse events in the outpatient setting. Many of the serious adverse events of interest such as major bleeding would require assessment of data from emergency room treatment or hospital readmissions.

Aside from one known in-hospital database, administrative claims databases do not capture drugs administered in the hospital and would not include adverse events that occur during hospitalization if they are not entered as a discharge diagnosis. Consequently, a study using administrative claims data from most hospital systems would not capture in-patient prasugrel use.

To identify low frequency adverse events associated with prasugrel use in the postmarketing setting, a large representative sample of patients administered prasugrel would need to be followed from hospital administration through discharge and outpatient use. The study should document appropriate or inappropriate indication and use, deaths due or associated with bleeding, serious bleeding events and other adverse events. A sample of hospital medical records and discharge data would need to be obtained and there would need to be continued follow-up of patients outside of the hospital. Deaths and causes of death in patients lost to follow-up would need to be identified through the National Death Index of the National Center for Health Statistics.

The TRILOGY ACS Study, [REDACTED], will provide data on prasugrel and risk of cancer. It would be desirable to perform TRILOGY with enough statistical power to detect prasugrel's initiation or promotion effect on lung, breast, colon, and prostate cancers, and with careful collection of data on risk factors for these cancers. Collection of complete medical histories including histories of cancer, symptoms of cancer, social and reproductive history, family history, alcohol use, cigarette smoking, medication use (including aspirin), and weight and body mass index, would be required.

6 DISCUSSION

Available data suggest that there is a benefit and risk associated with prasugrel over the current standard of care, clopidogrel. In patients with acute coronary syndrome with scheduled percutaneous coronary intervention, prasugrel therapy was associated with reduced rates of ischemic events, but with an increased risk of major bleeding, including fatal bleeding. Overall mortality was not shown to differ significantly between treatment groups.

If approved, the increased risk of both fatal and non-fatal bleeds associated with prasugrel use warrants a boxed warning. The contraindicated conditions and risk factors that increase the risk of bleeding should be provided and use of prasugrel in patients with these risk factors should be discouraged. The identified at-risk subpopulations include patients with prior history of TIA or stroke, patients age ≥ 75 years, patients with body weight <60 kg, patients who are undergoing CABG or other surgical procedure, and patients on concomitant medications such as warfarin, heparin, fibrinolytics or chronic use of NSAIDs.

During the review of this application, the review team in DCRP also identified neoplasia as an important risk. DEPI was consulted on the issue of neoplasia and they do not believe that the etiology of tumor stimulation associated with the use of prasugrel can be adequately answered using a registry¹⁴, one possible strategy being considered by DCRP. DEPI also provided recommendations that outline specific analyses that should be performed on available data for TAAL and the proposed TRILOGY trial prior to approval of prasugrel to resolve the question of prasugrel's potential for tumor stimulation.

Because the risk of malignancies cannot be ruled out at this point, we recommend that information specific to the risk of malignancy observed in patients treated with prasugrel be included in the warnings/precautions section of the labeling. Given that most of the treatment benefit from prasugrel was observed within the first several days of therapy, some in DCRP have proposed to limit the duration of treatment. We agree that one way to minimize the risk of malignancy, as well as the risk of bleeding, would be to limit the duration of therapy. However, specific dose conversions would need to be explicitly stated in the labeling. An overdose could occur if patients receive another loading dose of clopidogrel resulting in increased risk of bleeding. Patients may also be at an increased risk of thrombosis if the switch results in underdosing or if therapy is delayed. This is especially concerning in patients at risk of stent thrombosis. Until a determination

¹⁴ Wysowski D. Cancer in Clinical Trials of Prasugrel, Division of Epidemiology, FDA; dated June 12, 2008.

is made regarding number of days of therapy and a dose conversion strategy or algorithm from prasugrel to clopidogrel, DMEPA reserves their comments on other potential sources of error.

Lilly has proposed a REMS which will consist of a patient package insert (PPI) and a schedule for assessment. Given the four-fold increased risk of fatal bleeding events with prasugrel compared with clopidogrel, we have determined that a REMS to include a Medication Guide and a communication plan would be necessary to ensure that the benefits of the drug outweigh the risks. Therefore, instead of a voluntary PPI, as currently proposed by the sponsor, we recommend that Lilly be required to develop and submit for review and approval, a Medication Guide that will be required to be provided to patients with each dispensed prescription.

A Medication Guide would advise patients about the risk of bleeding associated with prasugrel and ensure that patients in whom prasugrel is contraindicated are not receiving it. It would inform patients about the risk factors (e.g., age ≥ 75 years, body weight < 60 kg) and the drug-drug interactions (e.g., NSAIDs, warfarin, heparin, and fibrinolytics). Additionally, a Medication Guide would inform patients of signs and symptoms of bleeding and the need to seek immediate medical attention, as well as, the need to discontinue prasugrel prior to elective surgery. Healthcare provider communication at product launch would help familiarize physicians with the important product information as described above to ensure appropriate patient selection and monitoring.

Lilly also plans to conduct post-launch active surveillance activities using large administrative claims databases or hospital in-patient electronic medical records databases to estimate and monitor the incidence of bleeding events and to identify and monitor subpopulations at risk for bleeding events in ACS patients treated with prasugrel. Lilly's active surveillance plan is likely to experience logistical and scientific problems as this product is initiated in the hospital and continued for an unknown period of time in an outpatient setting necessitating long-term follow-up of patients in different settings. Active surveillance of prasugrel's appropriate use, including indications and dose, specific bleeding events, other adverse events should be undertaken.

7 CONCLUSION

If prasugrel is approved, we believe that a boxed warning is warranted to emphasize the increased risk of bleeding observed in patients treated with prasugrel, particularly in certain subgroup of patients. Given the four-fold increased risk of fatal bleeding events with prasugrel compared with clopidogrel, we have determined that in addition to appropriate labeling a REMS would also be necessary to ensure that the benefits of the drug outweigh risk of bleeding, including fatal bleeding. Because the risk of malignancies cannot be ruled out at this point, the potential risk of tumor stimulation associated with prasugrel should be addressed in the warnings/precautions section of the label and any REMS proposal would need to address this potential risk. The REMS proposal should include at a minimum a Medication Guide, a communication plan, a timetable for assessments, and assessment of the REMS.

Active surveillance of appropriate use, specific bleeding events, other adverse events, and prasugrel's use postmarketing including indications and dose would be useful. A large, cohort study of prasugrel users or a large, multicenter, observational cohort study of prasugrel compared with clopidogrel should be undertaken.

8 RECOMMENDATIONS

- Some members of the OSE prasugrel team recommend a public Advisory Committee meeting before general approval and marketing to discuss the benefit of prasugrel treatment over the current standard of care (clopidogrel) given the issues concerning the drug's reformulation, bleeding, and cancer.
- **Labeling:**
 - Requirement of a boxed warning to emphasize the increased risk of bleeding observed in patients treated with prasugrel and the need to initiate therapy in the inpatient setting.
 - Inclusion of the identified at-risk subpopulations in the boxed warning:
 - Contraindication in patients with prior history of TIA or stroke
 - Emphasis on avoiding use in patients age ≥ 75 years
 - Emphasis on increased risk of bleeding in patients with body weight <60 kg.
 - Discontinue use of prasugrel at least 7 days prior to elective CABG procedure or other surgical procedures
 - Use of prasugrel should be discouraged when coronary anatomy is unknown and CABG is a possibility
 - Emphasis on increased risk of bleeding in patients on concomitant medications such as warfarin, heparin, fibrinolytics or chronic use of NSAIDS.
 - The sponsor should provide data to support their recommendation to reduce the maintenance dose of prasugrel from 10 mg to 5 mg daily in patients with body weight <60 kg.
 - Information specific to the risk of malignancy observed in patients treated with prasugrel be included in the warnings/precautions section of the labeling.
 - The requirement of a Medication Guide rather than a voluntary PPI.
 - If the duration of prasugrel use were to be limited, the specific number of days of therapy and dose conversions would need to be explicitly stated in the labeling to prevent medication errors. Until a determination is made regarding number of days of therapy and the dose conversion from prasugrel to clopidogrel, DMEPA reserves their comments on other potential sources of error.
- **Active Surveillance:**
 - A large, cohort study of prasugrel users or a large, multicenter, observational cohort study of prasugrel compared with clopidogrel that focuses on appropriate or inappropriate use, deaths associated with or due to bleeding, and other serious bleeding events should be undertaken.
- **Formulation:**
 - [REDACTED]
- **REMS Elements:**

- Medication Guide rather than a PPI as stated above
- Communication Plan to healthcare providers that includes information:
 - appropriate patient selection (emphasizing patients that prasugrel should not be used in)
 - the risk of bleeding and potential risk of malignancies associated with Effient and the need for appropriate monitoring
 - the need to initiate prasugrel in the inpatient setting because of the increased risk of bleeding in the first 7 days

The Division of Risk Management will work with DCRP to draft language that can be inserted into a CR or IR letter requesting a REMS. Should DCRP raise further concerns with the risks outlined above or identify additional risks associated with prasugrel warranting more extensive risk management activities, please send a consult to OSE Division of Risk Management.

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/s/

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