CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-307

SUMMARY REVIEW

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

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

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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.

3. Chemistry Manufacturing and Controls

3.1. Conversion from Salt to Base Form

From the CMC perspective, the review team recommended the application for "approval." Their primary concern is the observed conversion of the prasugrel salt to free base, but pursuant to an Information Request and additional requests in a Discipline Review Letter, they opined that the sponsor has addressed this issue adequately.

The sponsor initiated the development program using the free base of the drug substance, but became aware that the hydrochloride (HCl) salt had better bioavailability at higher gastric pH. Gastric pH is an important issue in patients who use anti-platelet medications in the ACS setting, because a substantial fraction of these patients take proton pump inhibitors [PPI] or H2 receptor antagonists to reduce gastric acidity, with the goal of reducing gastrointestinal bleeding. Thus, with the concurrence of the Division, the sponsor decided to switch the manufacturing process to the HCl salt form of the drug substance, to enhance bioavailability at higher gastric pH.

Late in development, near the time that the pivotal efficacy study (TAAL) was completed, the sponsor discovered that an acid-base reaction (b) (4) was converting up to 86% of the salt form to the free base form. Using x-ray powder diffraction, the sponsor determined that conversion from salt to base was beginning at the initial (b) (4). Conversion continued during storage to some extent, reaching a plateau after approximately (b) (4). Relative humidity and storage temperature were key factors affecting conversion. Originally, the sponsor proposed to limit the form conversion in the finished product to Not More Than (NMT) (b) (4)

The Division issued a **Discipline Review Letter** on April 9, 2008, summarizing concerns related to form conversion. The sponsor then added several in-process controls as well as a desiccant to packaging, in order to limit form conversion of the to-be-marketed product to Not More Than (NMT) (b) (4).

The CMC team opined that the current specification would allow the sponsor to market a product with wide variability (i.e. NMT (b) (4) that is inelegant from a quality viewpoint. However, given the analyses of safety and efficacy of form conversion by other disciplines, **(b) (4)** . The main basis was:

- There have been extensive discussions with the Clinical Pharmacology and Clinical reviewers of this NDA, as well as with the Cross Discipline Team Leader, Division Director, and Office Director concerning the clinical implications of form conversion. The consensus

is that, although sub-optimal from a quality viewpoint, the presence of a mixture of salt and free base in prasugrel does not appear to have any bearing on safety or efficacy.

- The Clinical Pharmacology reviewer noted in her May 23, 2008, review that the 30% difference in C_{max} for the active metabolite in patients on PPI who received high-conversion tablets did not change the pharmacodynamic response and consequently may not have clinical significance.

- **(b) (4)**

3.2. Compliance

The three clinical sites selected for inspection were the largest sites in their respective countries/ continents, and showed the most favorable results for prasugrel. According to the Division of Scientific Investigations' overall assessment, the data were considered reliable in support of the proposed indication. The manufacturing facility was inspected by the Office of Compliance on September 6, 2008, and the Current Good Manufacturing Practice status was found to be acceptable.

3.3. Degradation Products

Several of the degradation products of the drug substance, e.g. (b) (4), (b) (4), have structural alerts for genotoxicity. In a Discipline Review Letter dated April 9, 2008, the CMC Team asked the sponsor: 1) to provide comprehensive analysis of these substances; 2) to determine the levels of these impurities detected under normal storage conditions; 3) to assess safety based on the Threshold of Toxicological Concern (EMEA Guidance) under recommended storage conditions; and 4) to provide justification for not monitoring these compounds in release and stability testing.

The sponsor provided a comprehensive analysis of specified and unspecified degradation products in the drug substance and drug product. All specified degradation products were found to have been products of metabolism or were determined to have been appropriately qualified. A number of unspecified degradation products were further evaluated for potential genotoxicity using quantitative structure-activity relationship (QSAR) methodology. None of the compounds were predicted to be genotoxic. Consequently, the sponsor's approach is to treat these according to ICH guidelines, and not the EMEA guideline for genotoxic impurities.

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. ^{14}C-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 hydroxyesterases 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] $\geq$ 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_{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.

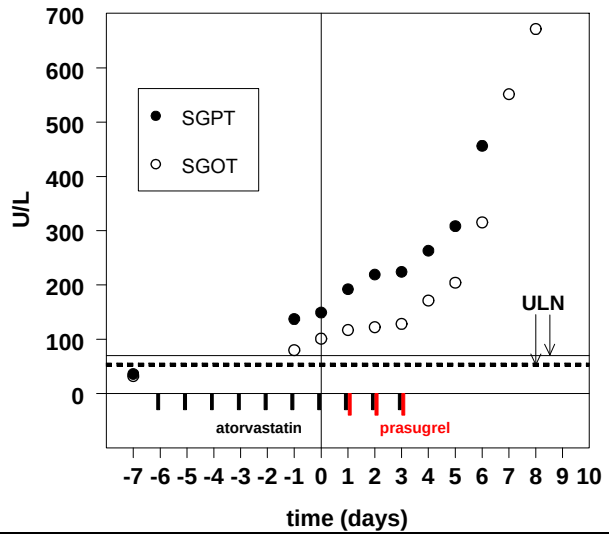
5.3.2. Drug-Drug Interaction Information

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 TAAD, 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	467	409	0.99	0.87	0.88
(424, 522)	(421, 518)	(368, 454)	(0.93, 1.06)	(0.82, 0.93)	(0.82, 0.93)
C_{max} (ng/mL)					
331	297	236	0.90	0.71	0.80
(285, 384)	(257, 344)	(204, 274)	(0.77, 1.04)	(0.62, 0.83)	(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 μM 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 μM 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 ± SD; calculated by CDER, Study TACS)

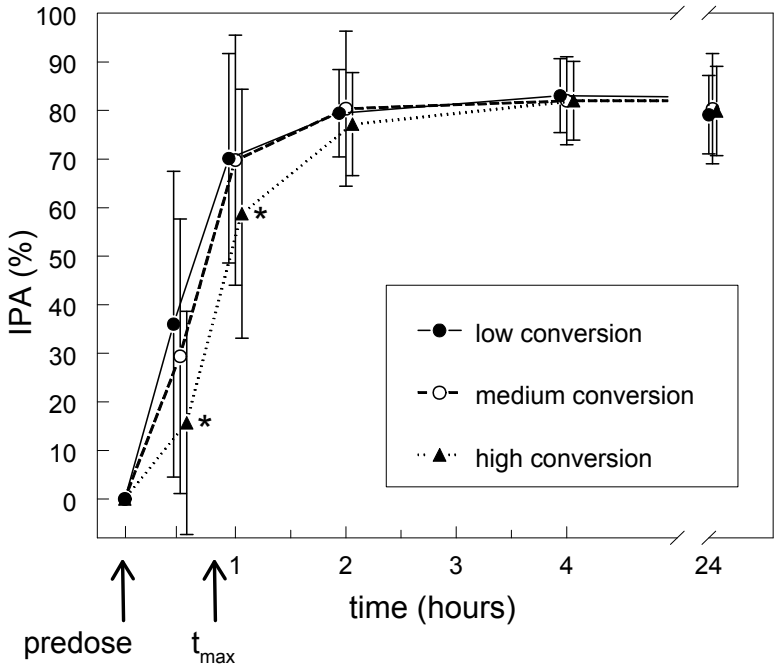
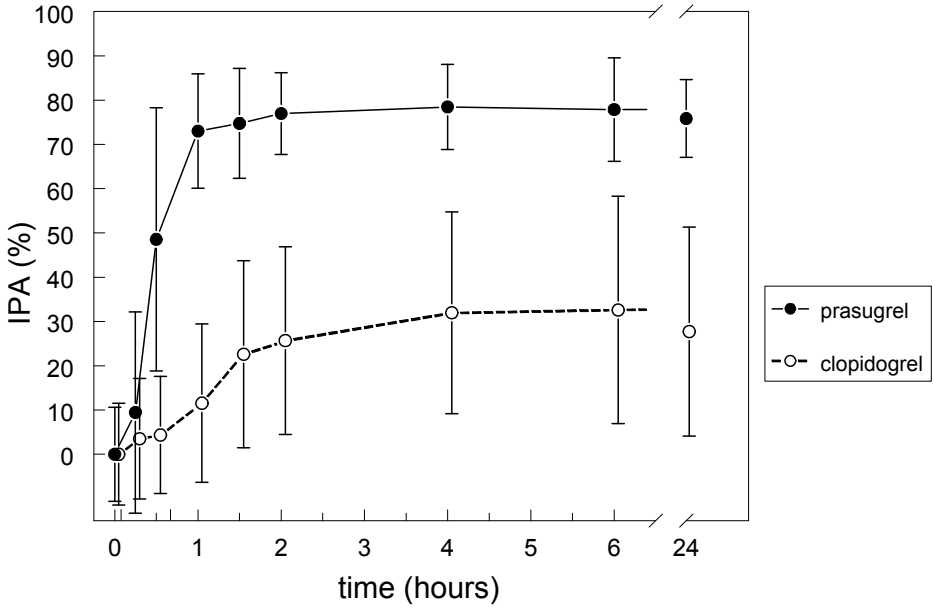


Figure 3: Inhibition of Platelet Aggregation (IPA) to 20 μM ADP, Following Loading Doses of Prasugrel 60 mg or Clopidogrel 300 mg (from Study TAAJ, mean ± SD)



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° 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 ≡ 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 ≡ 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 X ULN was acceptable.

- STEMI ≡ 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/mm^3
  - 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 ≡ 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 ≥ 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 ≡ 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) ≡ 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 ≡ 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" ≡ 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 ≡ 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

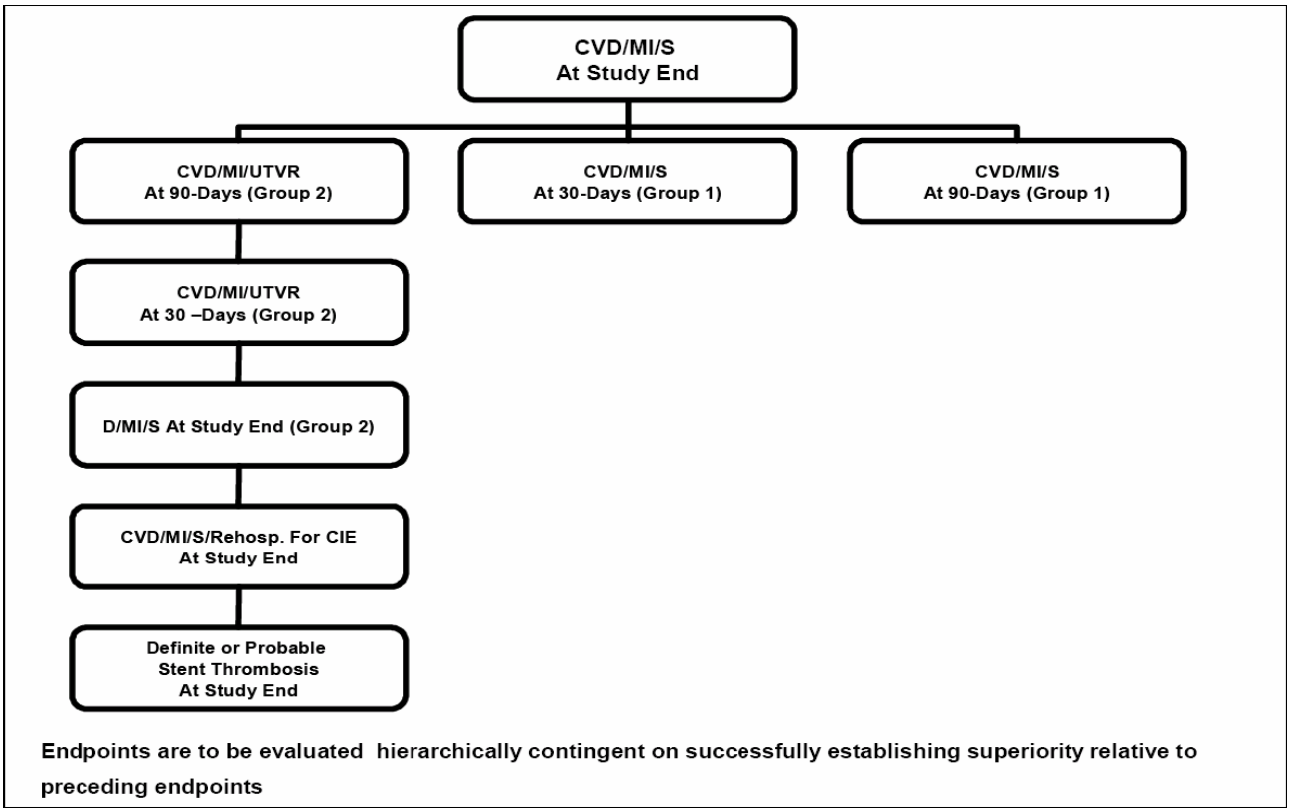
Both 2° endpoints in Group 1 were to be eligible for inclusion in labeling if the results were statistically significant.

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° 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 ≥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.

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

7.2.4. 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.

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 impairmant		
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.

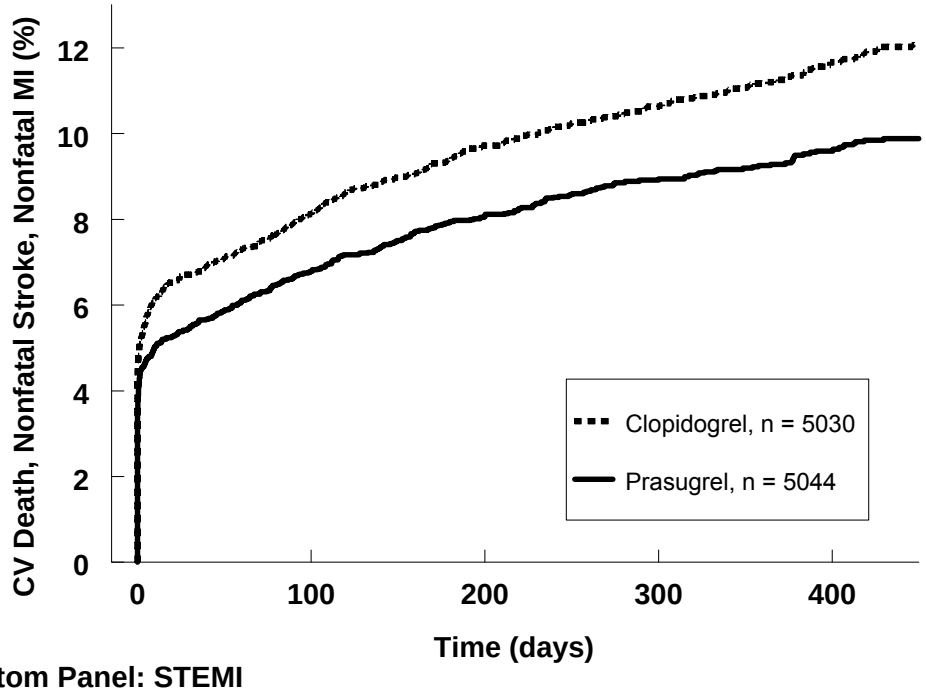
Table 6: Numbers and Percentages of Subjects Reaching 1° Composite Endpoint

	Prasugrel			Clopidogrel			Cox Proportional HR (95% C.I.)	p
subject population	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

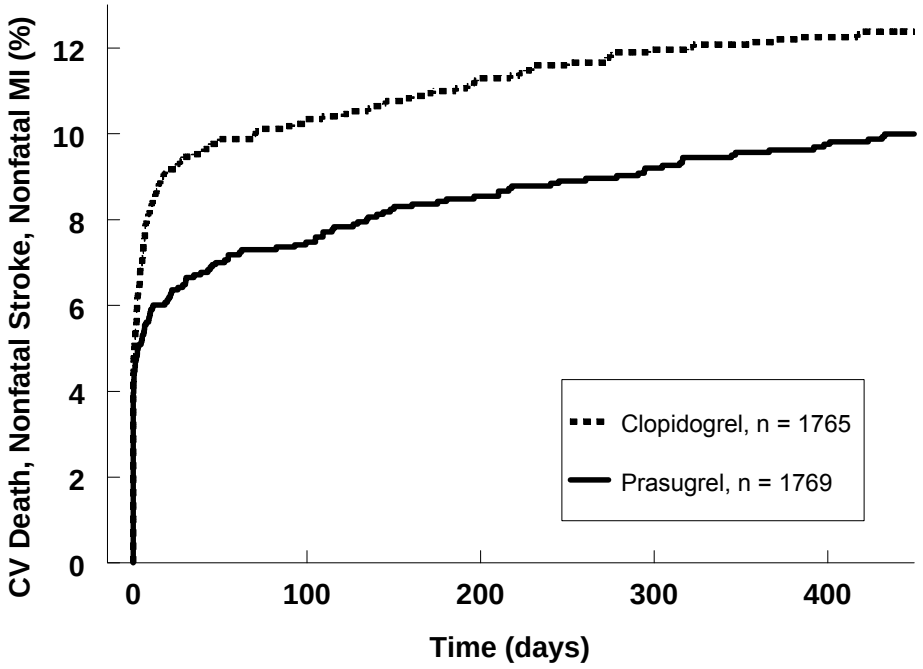
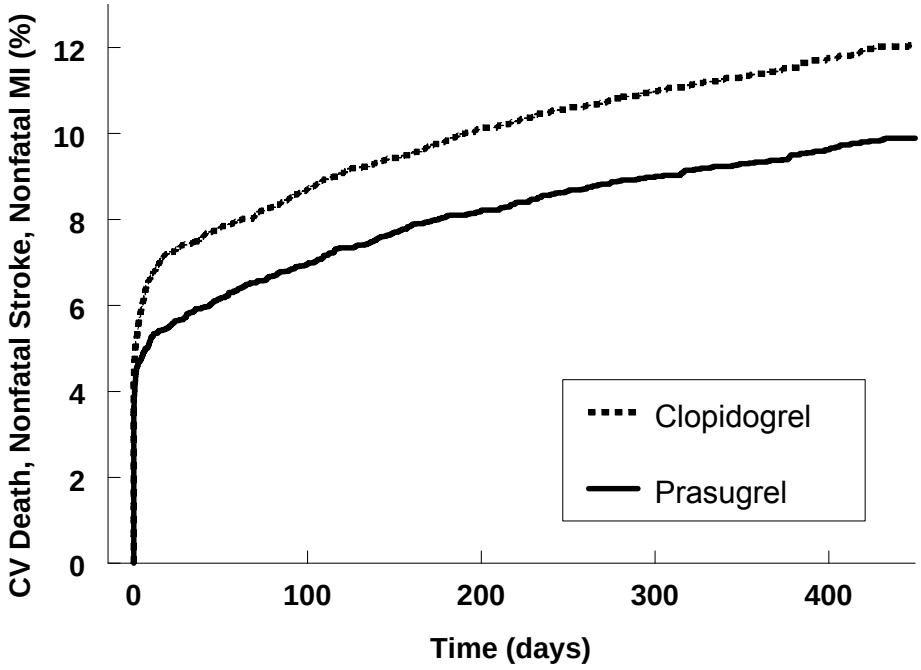


Figure 6: Kaplan-Meier Estimates of the 1° Efficacy Endpoint CV Death, Nonfatal MI, Nonfatal Stroke, All ACS Subjects

Top Panel: 0 – 450 Days;



Bottom Panel: 0 – 30 Days:

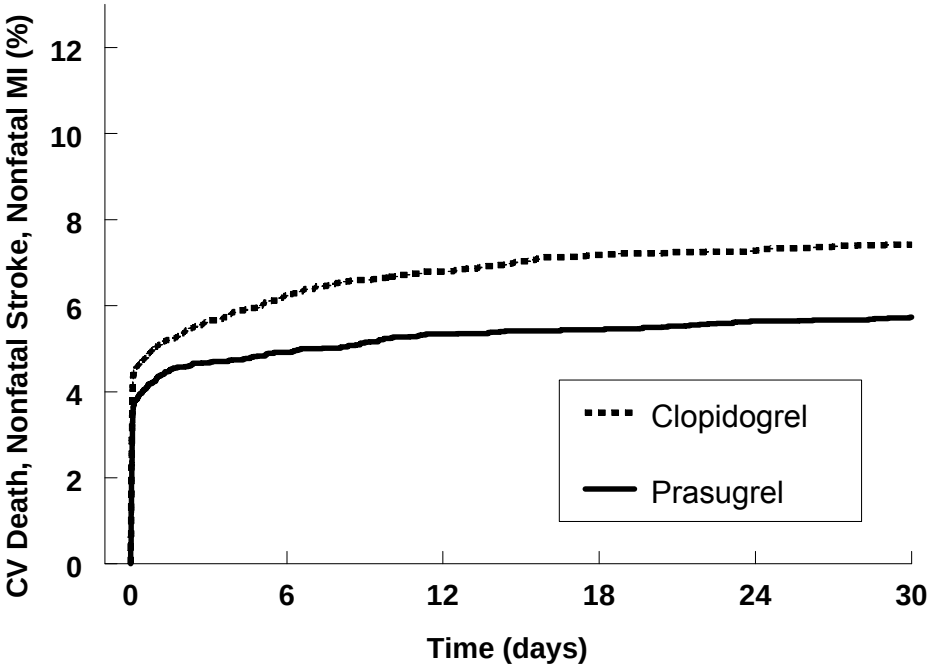
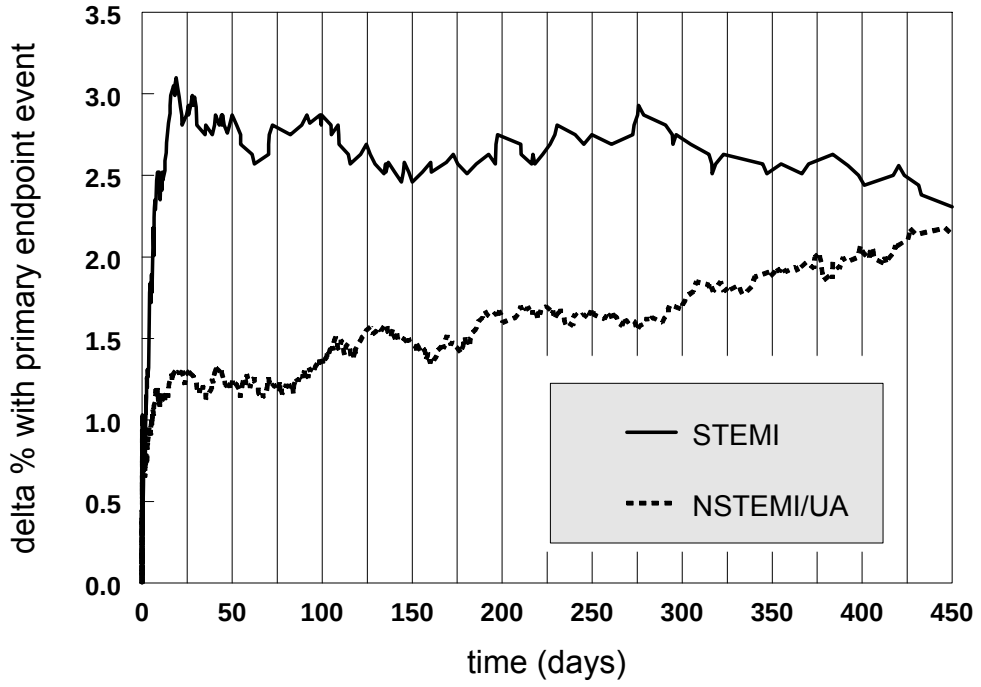


Figure 7: Kaplan-Meier Estimates of the 1° Efficacy Endpoint; Delta between Prasugrel and Clopidogrel, STEMI and NSTEMI/UA Populations



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.

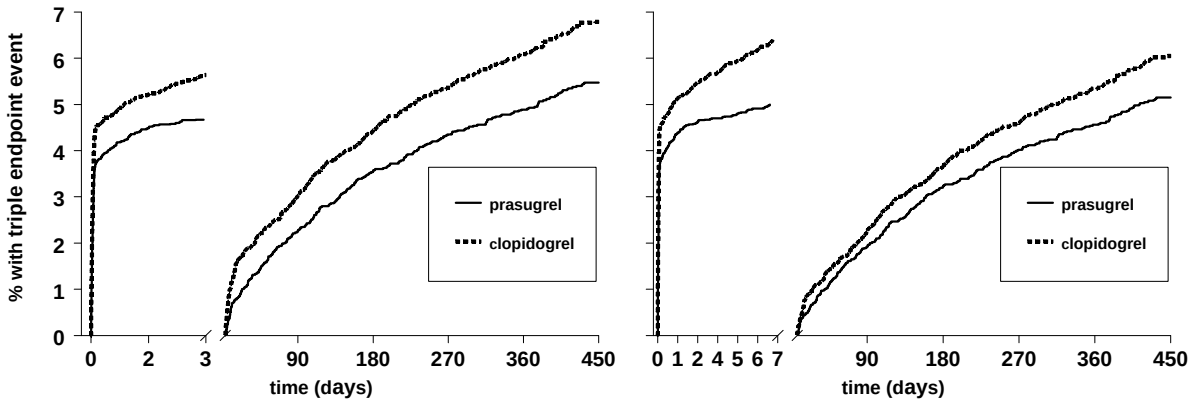
Landmark Analyses:
There is support for the concept that a clopidogrel LD of 600-mg is associated with more rapid inhibition of platelet aggregation than the standard LD of 300-mg (used in TAAL), and OASIS7 is being conducted to examine this hypothesis in a randomized controlled trial (ClinicalTrials.gov 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 asses 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

	clopidogrel		prasugrel	
referring event	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 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.

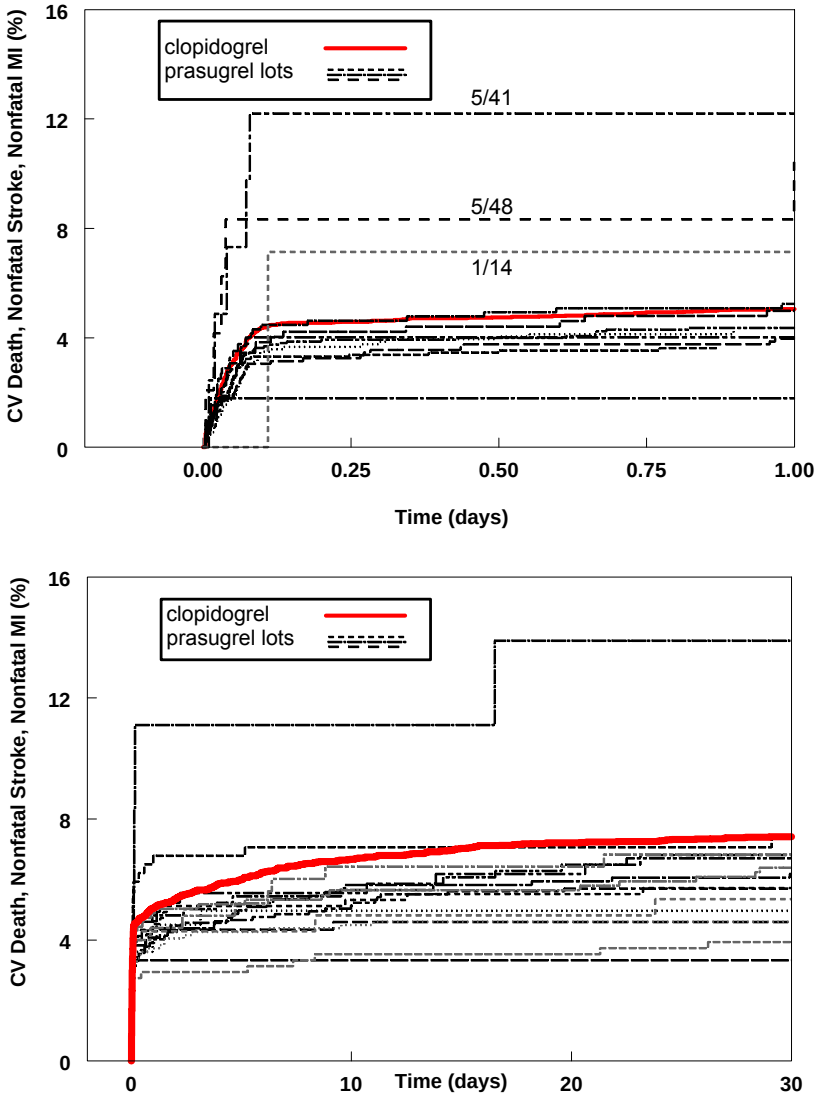
In summary, the results for the 1° efficacy endpoint are persuasive and robust to exploration. The overall treatment effect was driven by nonfatal MI. The CV death component shows a trend in favor of prasugrel in the STEMI population, but only a very weak trend in the overall population. The effect of 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.

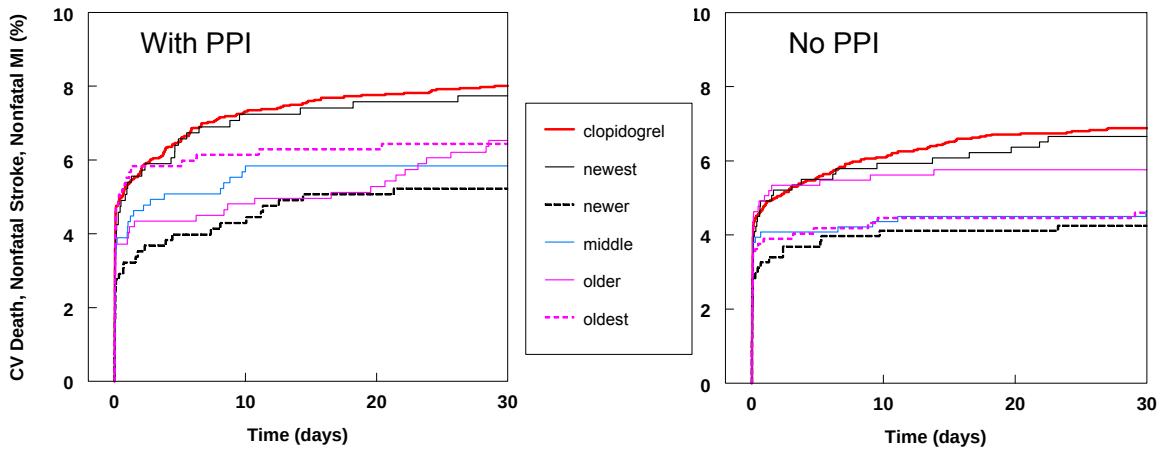
These issues notwithstanding, some estimate of the clinical importance of conversion can be gleaned through the following analyses: Although subjects obtained prasugrel from several lots during the course of the study, the loading dose (6 pills) was obtained from a single lot, and the initial month's 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:

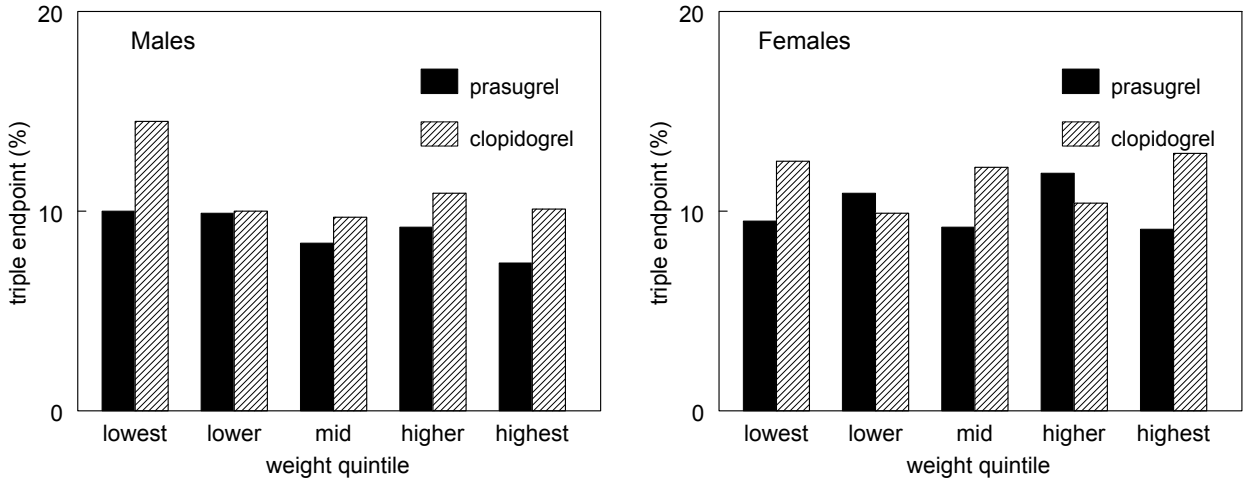
Given that the study employed a fixed dosing regimen (non-weight-adjusted), there is concern that subjects at higher weights may have received an insufficient dose of prasugrel. (There is also the concern that subjects at the lower fringes of weight may have received excess drug, but this is more an 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.

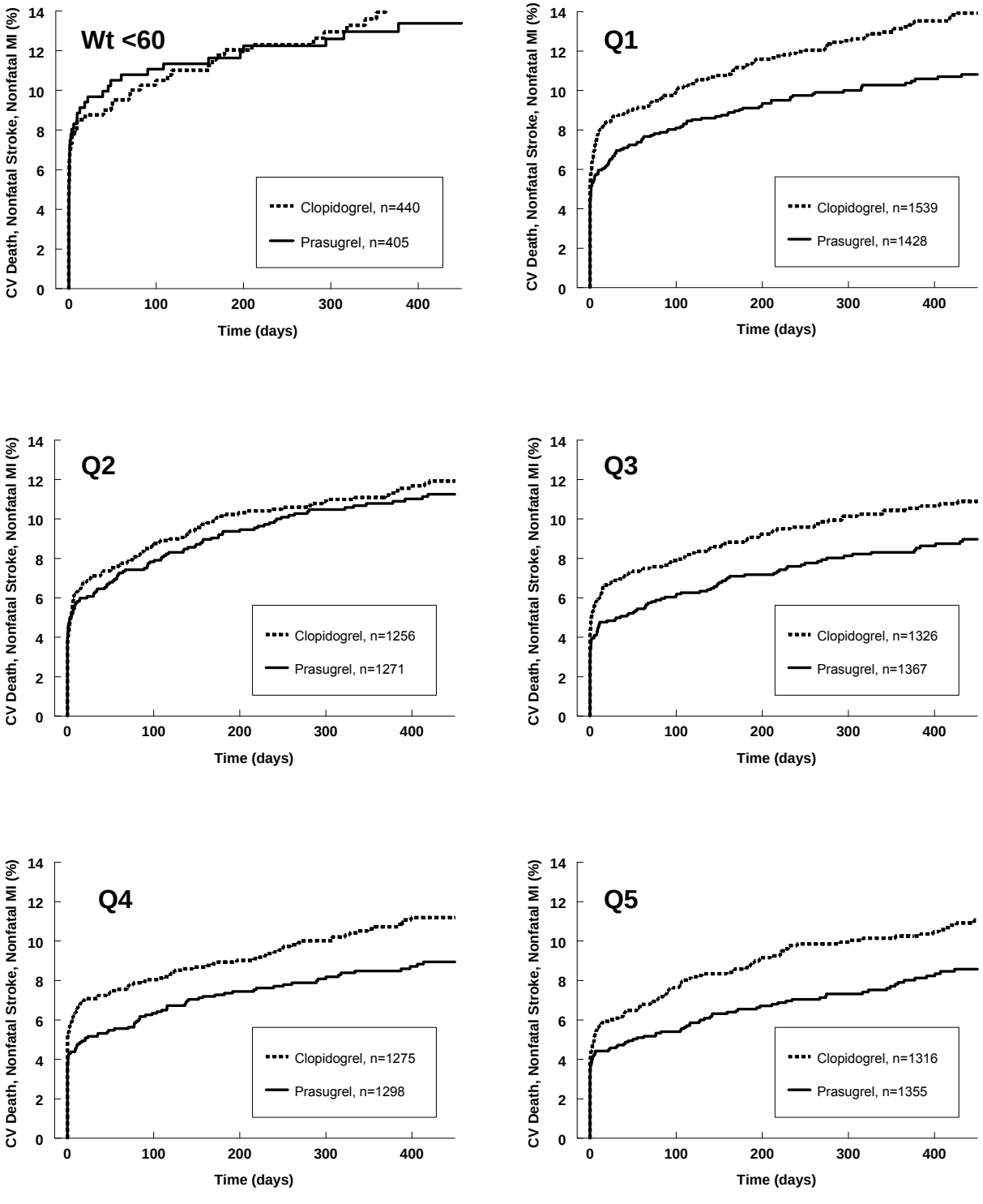
Figure 12 shows the results on the 1° endpoint for the overall ACS population by weight. The upper left panel shows the results for subjects weighing <60 kg. The effect of prasugrel was neutral in this small subgroup, comprising 6% of the overall subject population. The remaining panels show results 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.

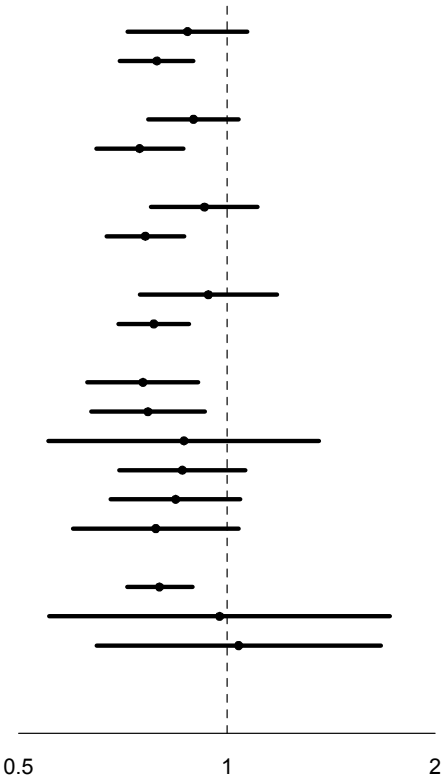
Figure 12: Primary Triple Composite Endpoint by Weight



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

	Prasugrel			Clopidogrel		
	N	n	%	N	n	%
female	1705	178	10.4	1818	215	11.8
male	5108	465	9.1	4977	566	11.4
age ≥ 65	2625	321	12.2	2661	361	13.6
age <65	4188	322	7.7	4134	420	10.2
age ≥ 70	1668	235	14.1	1699	257	15.1
age <70	5145	408	7.9	5096	524	10.3
age ≥ 75	901	144	16.0	908	154	17.0
age <75	5912	499	8.4	5887	627	10.7
North America	2164	199	9.2	2146	258	12.0
U.S.	2039	191	9.4	2020	244	12.1
South America	270	36	13.3	264	40	15.2
Western Europe	1779	164	9.2	1774	188	10.6
Eastern Europe	1657	153	9.2	1665	181	10.9
rest of world	943	91	9.7	946	114	12.1
Caucasian	6263	581	9.3	6274	720	11.5
African	205	25	12.2	187	23	12.3
Hispanic	269	36	13.4	256	33	12.9

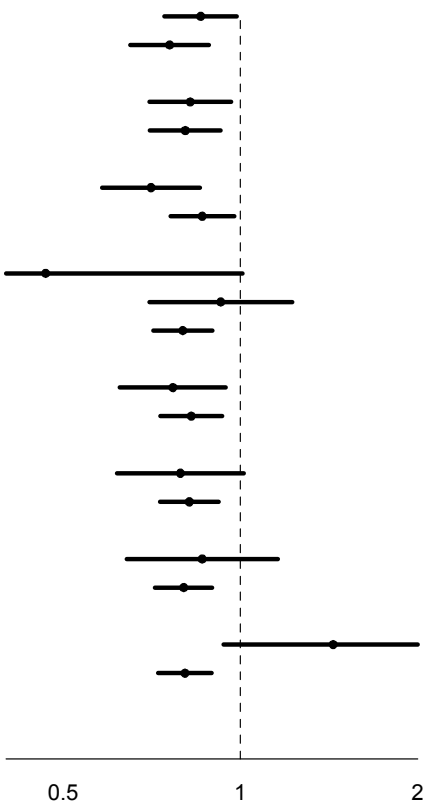


Event rates were fairly similar across geographic regions, except for South America, where event rates were higher. There, too, the odds ratio trended favorable for prasugrel.

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

	Prasugrel			Clopidogrel		
	N	n	%	N	n	%
Hx vascular disease	2907	358	12.3	2848	405	14.2
No Hx vascular disease	3906	285	7.3	3947	376	9.5
Metabolic syndrome	2966	279	9.4	2938	333	11.3
No metabolic syndrome	3847	364	9.5	3857	448	11.6
Diabetes	1576	180	11.4	1570	248	15.8
No dibetes	5237	463	8.8	5225	533	10.2
Ccr <30	51	11	21.6	54	21	38.9
Ccr 30-60	666	92	13.8	720	106	14.7
Ccr >60	5982	515	8.6	5907	630	10.7
Prior MI	1226	161	13.1	1208	201	16.6
No prior MI	5587	482	8.6	5587	580	10.4
Prior PCI	904	112	12.4	926	143	15.4
No prior PCI	5909	531	9.0	5869	638	10.9
Prior CABG	541	86	15.9	497	90	18.1
No prior CABG	6272	557	8.9	6298	691	11.0
Prior TIA or CVA	262	50	19.1	256	36	14.1
No prior TIA or CVA	6551	642	9.8	6539	786	12.0



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 stokes 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 use to make determinations of stent

Table 9: TAAL – Secondary Endpoints

endpoint	Patient population	Prasugrel			Clopidogrel			Total			Cox Proportional HR (95% C.I.)	p
		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° 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.

Table 10: Summary of Deaths in TAAL (adapter from sponsor's Table TAAL.11.10)

	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 (conponent 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.

Figure 15: Incidence of Non-CABG-Related TIMI Major or TIMI Minor Bleeding Events – All ACS Population

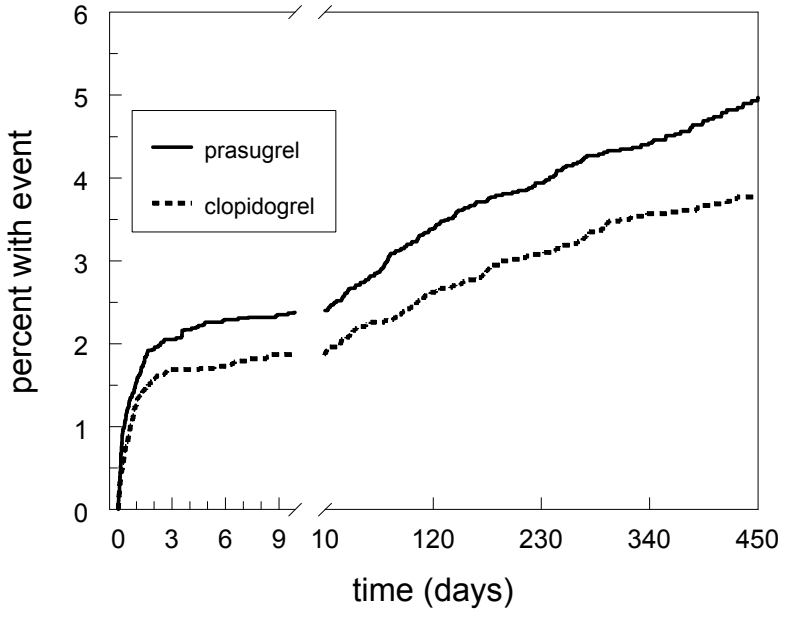


Table 11 summarizes the various categories of bleeding events in TAAL. Because some subjects experienced more than one bleeding event, they appear in more than one category. The last two categories of the upper section, "Worst: TIMI Minor" and "Worst: TIMI Minimal," represent the subjects in whom the 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 $\geq$ 3 g/dL, and 5.1 bleeding events associated with a decrease in hemoglobin of $\geq$ 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

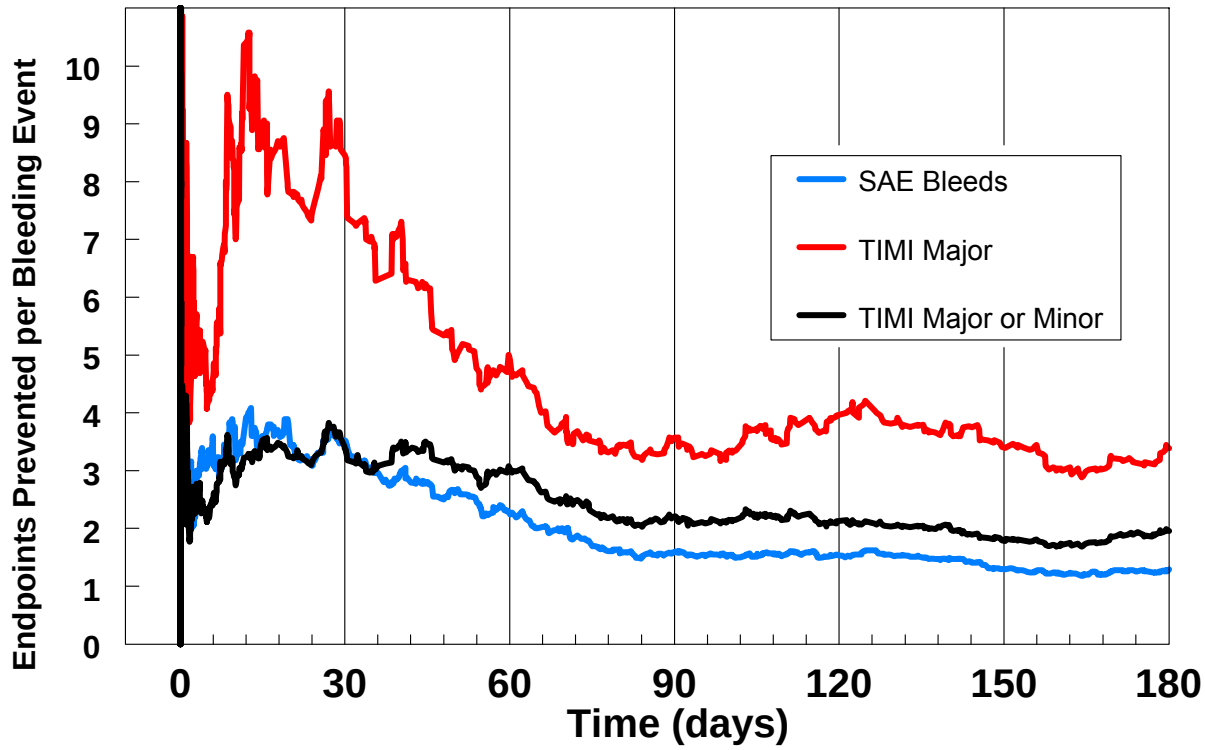
The fatality rate for intracranial hemorrhages was twice as high in the prasugrel treatment group compared to the clopidogrel treatment group.

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.

Table 13: Non-CABG-Related Spontaneous TIMI Major or Minor Bleeding Events From Symptom Onset through Days 3 by Concomitant Medication Use

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 Cmax 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**	

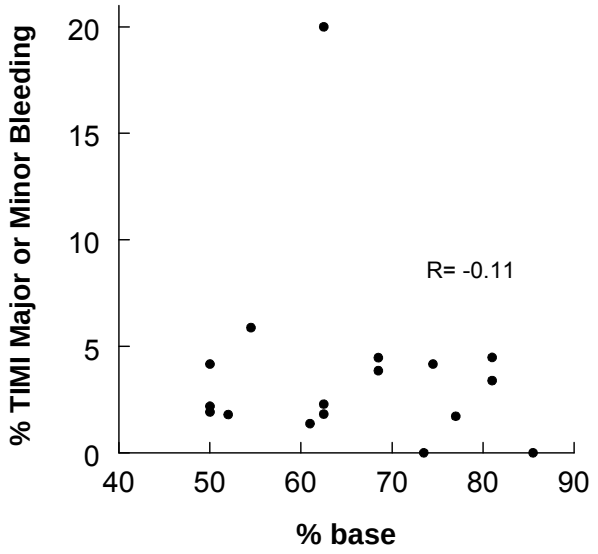
For both treatment groups, the incidence of bleeding was higher in subjects who received gastric pH-raising drugs than in those who did not. This may be related, in part, to the fact that PPI and H2 antagonist use was discretionary, and physicians may have been more willing to prescribe them for patients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

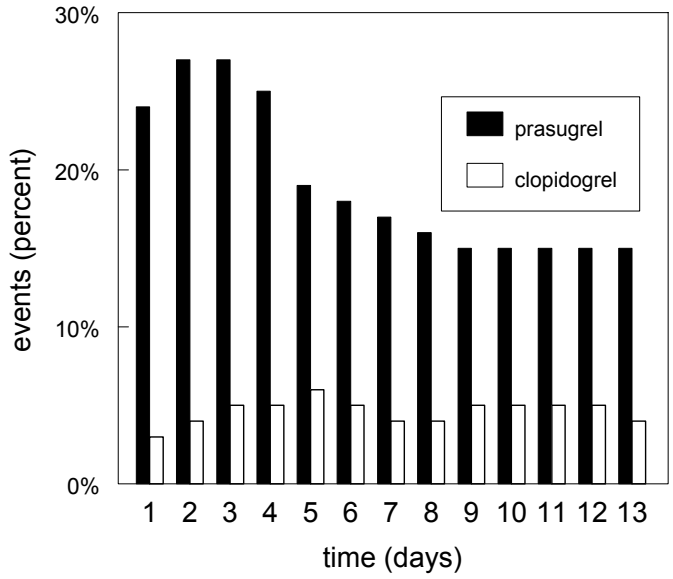
N = numbers of subjects who underwent CABG
N = numbers of bleedin events

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 x 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 $P2Y_{12}$ 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	Clopidogrel
	n (%)	n (%)
all	87 (1.29)	60 (0.89)
colon cancer	10 (0.15)	2 (0.03)
gastric cancer	6 (0.09)	7 (0.1)
prostate cancer	6 (0.09)	7 (0.1)
breast cancer	4 (0.06)	1 (0.01)
adenocarcinoma	2 (0.03)	0 (0)
bladder cancer	2 (0.03)	4 (0.06)
brain cancer	2 (0.03)	1 (0.01)
clear cell cancer of kidney	2 (0.03)	0 (0)
lung neoplasm malignant	2 (0.03)	2 (0.03)
lung squamous cell carcinoma	2 (0.03)	1 (0.01)
metastases to lung	2 (0.03)	0 (0)
metastatic neoplasm	2 (0.03)	0 (0)
non-small cell lung cancer	2 (0.03)	2 (0.03)
prostate cancer metastatic	2 (0.03)	1 (0.01)
renal neoplasm	2 (0.03)	0 (0)
squamous cell carcinoma	2 (0.03)	1 (0.01)
acute myeloid leukaemia	1 (0.01)	0 (0)
adenoma benign	1 (0.01)	0 (0)
basal cell carcinoma	1 (0.01)	1 (0.01)
benign lung neoplasm	1 (0.01)	0 (0)
bladder neoplasm	1 (0.01)	1 (0.01)
bladder papilloma	1 (0.01)	0 (0)
bone neoplasm	1 (0.01)	0 (0)
bronchial carcinoma	1 (0.01)	2 (0.03)
cervix carcinoma	1 (0.01)	0 (0)
chronic lymphocytic leukaemia	1 (0.01)	0 (0)
colon adenoma	1 (0.01)	1 (0.01)
colon neoplasm	1 (0.01)	0 (0)
colorectal cancer	1 (0.01)	0 (0)
gallbladder cancer	1 (0.01)	0 (0)
gastrointestinal carcinoma	1 (0.01)	2 (0.03)
gastrointestinal tract adenoma	1 (0.01)	0 (0)
haemangioma	1 (0.01)	0 (0)
lung adenocarcinoma	1 (0.01)	0 (0)
lung neoplasm	1 (0.01)	1 (0.01)
malignant ascites	1 (0.01)	0 (0)
mesothelioma malignant	1 (0.01)	0 (0)
metastases to bone	1 (0.01)	2 (0.03)
metastases to liver	1 (0.01)	1 (0.01)
nasal neoplasm	1 (0.01)	0 (0)
oesophageal adenocarcinoma	1 (0.01)	0 (0)
oesophageal cancer metastatic	1 (0.01)	0 (0)
oesophageal carcinoma	1 (0.01)	3 (0.04)
ovarian neoplasm	1 (0.01)	0 (0)
pancreatic carcinoma	1 (0.01)	1 (0.01)
papillary thyroid cancer	1 (0.01)	0 (0)
papilloma	1 (0.01)	0 (0)
peripheral t-cell lymphoma	1 (0.01)	0 (0)
pituitary tumour benign	1 (0.01)	0 (0)
prostatic adenoma	1 (0.01)	0 (0)
rectal cancer	1 (0.01)	0 (0)
rectal neoplasm	1 (0.01)	0 (0)
renal cell carcinoma	1 (0.01)	2 (0.03)
salivary gland neoplasm	1 (0.01)	0 (0)
sarcoma	1 (0.01)	0 (0)
small cell lung cancer	1 (0.01)	3 (0.04)
thyroid cancer	1 (0.01)	0 (0)
transitional cell carcinoma	1 (0.01)	0 (0)
uterine leiomyoma	1 (0.01)	0 (0)
adenocarcinoma pancreas	0 (0)	1 (0.01)
adrenal neoplasm	0 (0)	1 (0.01)
bladder transitional cell carcinoma	0 (0)	1 (0.01)
carcinoid tumour pulmonary	0 (0)	1 (0.01)
chronic myeloid leukaemia	0 (0)	1 (0.01)
colon cancer metastatic	0 (0)	1 (0.01)
gastric neoplasm	0 (0)	1 (0.01)
hepatic cancer metastatic	0 (0)	1 (0.01)
hepatic neoplasm	0 (0)	1 (0.01)
lymphocytic leukaemia	0 (0)	1 (0.01)
malignant melanoma	0 (0)	1 (0.01)
metastases to adrenals	0 (0)	1 (0.01)
myelodysplastic syndrome	0 (0)	1 (0.01)
non-hodgkin's lymphoma	0 (0)	2 (0.03)
small cell lung cancer metastatic	0 (0)	1 (0.01)
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 (%)
all	153 (2.27)	123 (1.83)
prostate cancer	16 (0.24)	7 (0.1)
colon cancer	11 (0.16)	2 (0.03)
lung neoplasm malignant	8 (0.12)	2 (0.03)
gastric cancer	6 (0.09)	8 (0.12)
bladder cancer	5 (0.07)	4 (0.06)
breast cancer	5 (0.07)	1 (0.01)
squamous cell carcinoma	5 (0.07)	5 (0.07)
lung neoplasm	4 (0.06)	8 (0.12)
prostatic adenoma	4 (0.06)	0 (0)
skin papilloma	4 (0.06)	1 (0.01)
colon adenoma	3 (0.04)	3 (0.04)
malignant melanoma	3 (0.04)	3 (0.04)
metastases to lung	3 (0.04)	0 (0)
metastatic neoplasm	3 (0.04)	1 (0.01)
renal neoplasm	3 (0.04)	1 (0.01)
skin cancer	3 (0.04)	4 (0.06)
adenocarcinoma	2 (0.03)	1 (0.01)
basal cell carcinoma	2 (0.03)	5 (0.07)
biliary neoplasm	2 (0.03)	1 (0.01)
brain neoplasm	2 (0.03)	1 (0.01)
chronic lymphocytic leukaemia	2 (0.03)	1 (0.01)
clear cell carcinoma of the kidney	2 (0.03)	0 (0)
gastric neoplasm	2 (0.03)	1 (0.01)
lung squamous cell carcinoma	2 (0.03)	1 (0.01)
metastasis	2 (0.03)	0 (0)
mycosis fungoides	2 (0.03)	1 (0.01)
non-small cell lung cancer	2 (0.03)	2 (0.03)
ovarian neoplasm	2 (0.03)	0 (0)
prostate cancer metastatic	2 (0.03)	1 (0.01)
thyroid neoplasm	2 (0.03)	2 (0.03)
acrochordon	1 (0.01)	1 (0.01)
acute myeloid leukaemia	1 (0.01)	0 (0)
adenoma benign	1 (0.01)	1 (0.01)
adrenal adenoma	1 (0.01)	0 (0)
benign lung neoplasm	1 (0.01)	0 (0)
bladder neoplasm	1 (0.01)	3 (0.04)
bladder papilloma	1 (0.01)	0 (0)
bladder squamous cell carcinoma	1 (0.01)	0 (0)
bladder transitional cell carcinoma	1 (0.01)	0 (0)
bone neoplasm	1 (0.01)	0 (0)
bone neoplasm malignant	1 (0.01)	0 (0)
breast cancer recurrent	1 (0.01)	0 (0)
bronchial carcinoma	1 (0.01)	2 (0.03)
cardiac neoplasm	1 (0.01)	0 (0)
cervix carcinoma	1 (0.01)	0 (0)
colon neoplasm	1 (0.01)	0 (0)
colorectal cancer	1 (0.01)	0 (0)
fibroadenoma of breast	1 (0.01)	0 (0)
gallbladder cancer	1 (0.01)	0 (0)
gastrointestinal carcinoma	1 (0.01)	2 (0.03)
gastrointestinal tract adenoma	1 (0.01)	0 (0)
haemangioma	1 (0.01)	0 (0)
hepatic neoplasm	1 (0.01)	1 (0.01)
lipoma	1 (0.01)	1 (0.01)
lung adenocarcinoma	1 (0.01)	0 (0)
lymphoma	1 (0.01)	1 (0.01)
malignant ascites	1 (0.01)	0 (0)
meso helioma malignant	1 (0.01)	0 (0)
metastases to bone	1 (0.01)	2 (0.03)
metastases to liver	1 (0.01)	1 (0.01)
metastases to lymph nodes	1 (0.01)	0 (0)
multiple myeloma	1 (0.01)	0 (0)
nasal cavity cancer	1 (0.01)	0 (0)
nasal neoplasm	1 (0.01)	1 (0.01)
oesophageal adenocarcinoma	1 (0.01)	0 (0)
oesophageal cancer metastatic	1 (0.01)	0 (0)
oesophageal carcinoma	1 (0.01)	3 (0.04)
oesophageal neoplasm	1 (0.01)	0 (0)
pancreatic carcinoma	1 (0.01)	1 (0.01)
papillary thyroid cancer	1 (0.01)	0 (0)
papilloma	1 (0.01)	1 (0.01)
peripheral T-cell lymphoma	1 (0.01)	0 (0)
pituitary tumour	1 (0.01)	0 (0)
pituitary tumour benign	1 (0.01)	0 (0)
rectal cancer	1 (0.01)	0 (0)
rectal neoplasm	1 (0.01)	1 (0.01)
renal cell carcinoma	1 (0.01)	3 (0.04)
salivary gland neoplasm	1 (0.01)	1 (0.01)
sarcoma	1 (0.01)	0 (0)
small cell lung cancer	1 (0.01)	3 (0.04)
thyroid cancer	1 (0.01)	0 (0)
transitional cell carcinoma	1 (0.01)	0 (0)
uterine leiomyoma	1 (0.01)	2 (0.03)
xanthoma	1 (0.01)	0 (0)
adenocarcinoma pancreas	0 (0)	1 (0.01)
adrenal neoplasm	0 (0)	1 (0.01)
bladder transitional cell carcinoma	0 (0)	1 (0.01)
carcinoid tumour pulmonary	0 (0)	1 (0.01)
chronic myeloid leukaemia	0 (0)	1 (0.01)
colon cancer metastatic	0 (0)	1 (0.01)
fibrous histiocytoma	0 (0)	1 (0.01)
haemangioma of liver	0 (0)	1 (0.01)
hepatic cancer metastatic	0 (0)	1 (0.01)
hypergammaglobulinaemia benign	0 (0)	1 (0.01)
monoclonal	0 (0)	1 (0.01)
laryngeal cancer	0 (0)	1 (0.01)
lentigo	0 (0)	1 (0.01)
lung carcinoma cell type	0 (0)	1 (0.01)
unspecified recurrent	0 (0)	1 (0.01)
lymphocytic leukaemia	0 (0)	1 (0.01)
melanocytic naevus	0 (0)	1 (0.01)
metastases to adrenals	0 (0)	1 (0.01)
myelodysplastic syndrome	0 (0)	1 (0.01)
myeloproliferative disorder	0 (0)	1 (0.01)
nasopharyngeal neoplasm benign	0 (0)	1 (0.01)
neoplasm	0 (0)	1 (0.01)
neoplasm malignant	0 (0)	1 (0.01)
non-hodgkin's lymphoma	0 (0)	2 (0.03)
ocular neoplasm	0 (0)	1 (0.01)
osteoma cutis	0 (0)	2 (0.03)
pyogenic granuloma	0 (0)	1 (0.01)
rectal adenoma	0 (0)	1 (0.01)
seborrhoeic keratosis	0 (0)	1 (0.01)
small cell lung cancer metastatic	0 (0)	1 (0.01)
squamous cell carcinoma of skin	0 (0)	2 (0.03)
thymoma	0 (0)	1 (0.01)
tongue neoplasm malignant	0 (0)	1 (0.01)

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 has 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

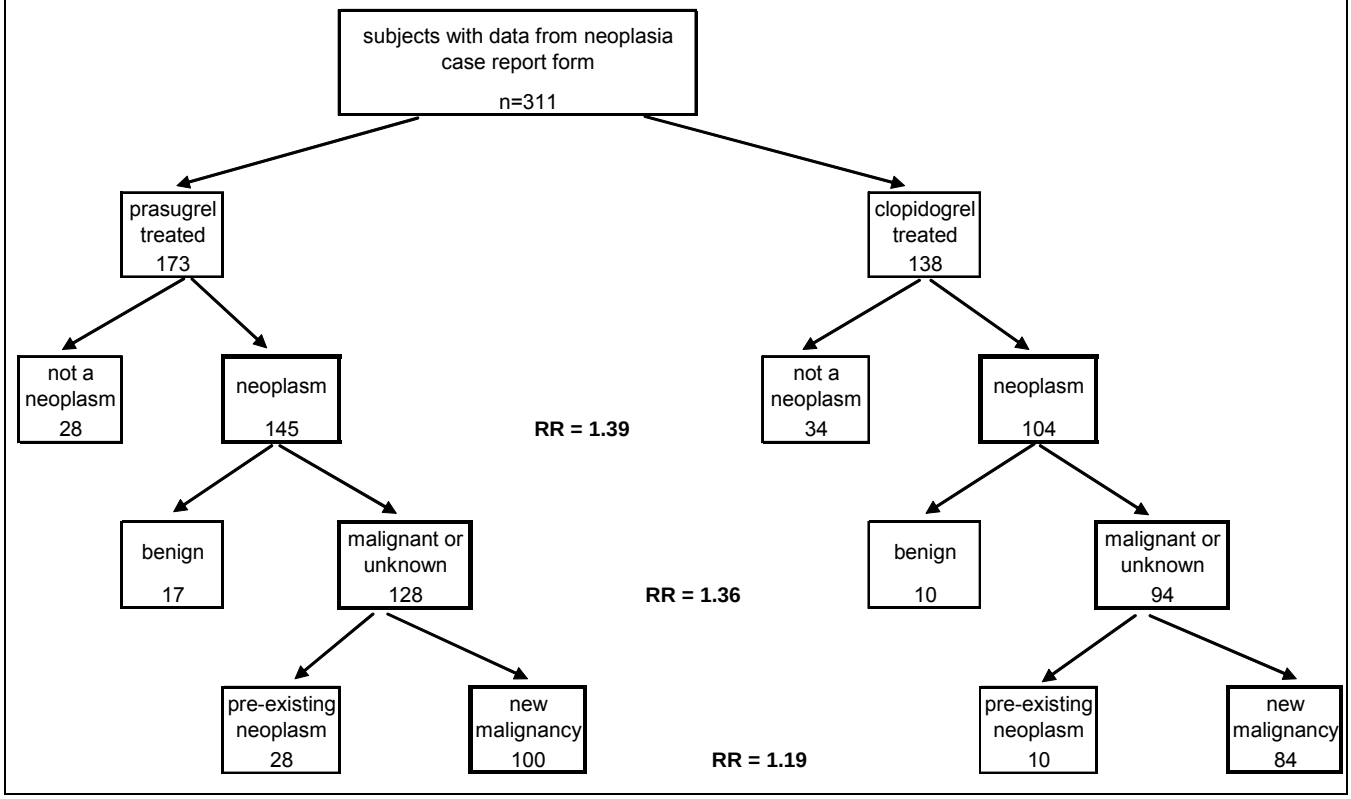


Table 18: Sponsor's May 9, 2008, Analysis of New, Non-Benign Neoplasms

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_fqvitj11_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_fqvitj11_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.

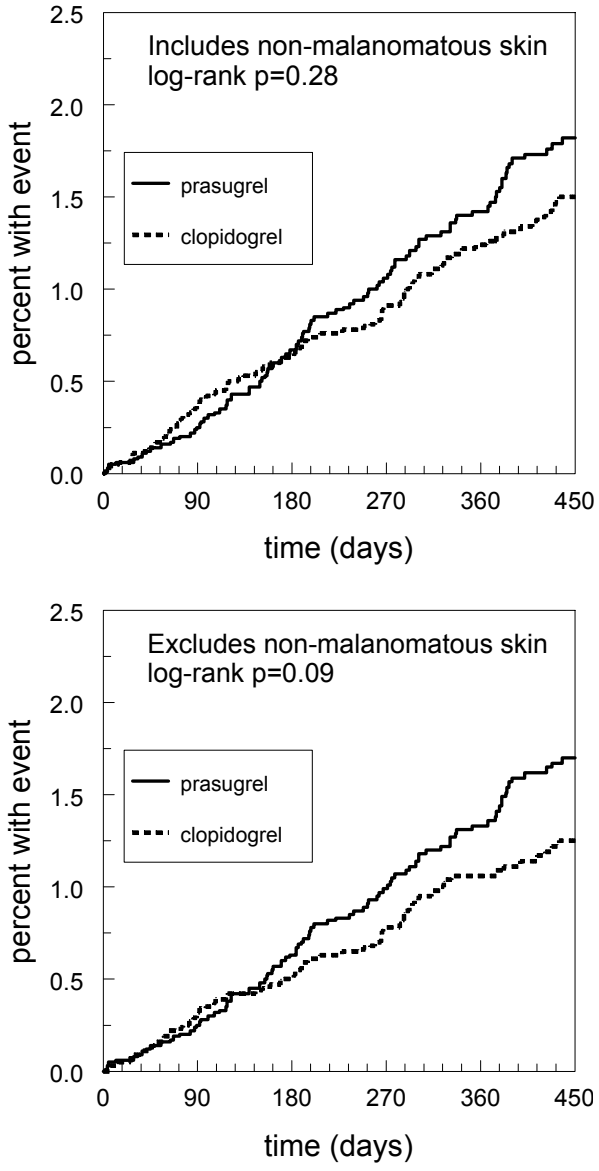
Dr. Marciniak also reviewed the data from the clopidogrel development program, and found no apparent effect of clopidogrel on cancer rates. CURE showed a doubling in the rate of colorectal cancer with clopidogrel compared to placebo (16 versus 8), but this was not observed in CAPRIE or CHARISMA. Clopidogrel 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.

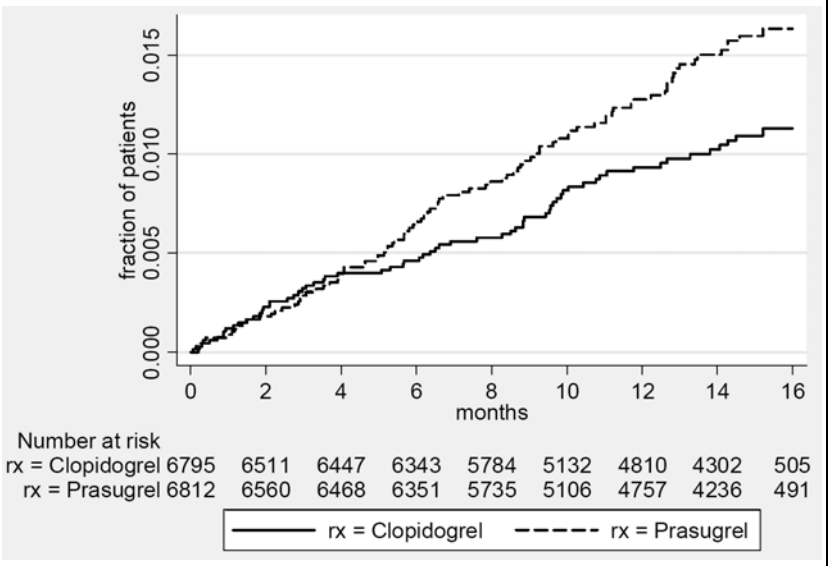
2. There are no data in TAAL to support a belief that prasugrel is a "promoter" in humans. Given the absence of a well defined cancer screening at study entry, short drug exposure to the study drugs (6 to 15 months), and no specified follow up to detect specific cancers, the cancers diagnosed on study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

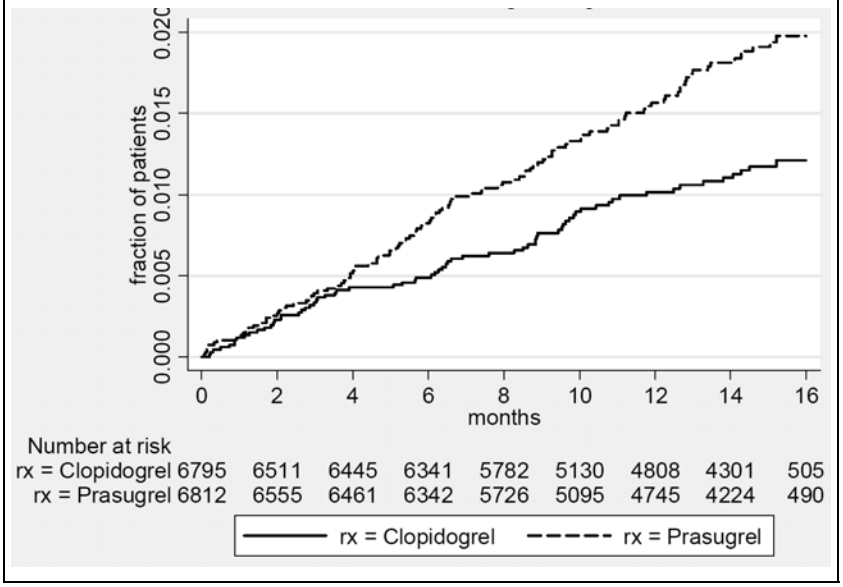
Figure 20: New, Non-Benign Neoplasms – Top: All; Bottom: Excluding Non-Melanomatous Skin



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





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.

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, ΔQTcF 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 ≥ age 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.

Two unanticipated issues came to light during the review process: 1) the imbalance in neoplasms between the prasugrel and clopidogrel groups; and 2) form conversion from salt to base, with bioinequivalence between the forms in the presence of a PPI. In addition, other individuals thought that a public discussion of the bleeding risk would be of value. Ultimately, the Office reached the conclusion that a public presentation of these issues to the Cardiovascular and Renal Drugs Advisory Committee would be advisable, and such is planned for February 3, 2009.

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 $\geq$3 to $\leq$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 and 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.

In light of the above considerations, and in light of the public health implications of a product that has been shown to be superior to established therapy on an important outcome measure, the Division does not wish to deny or delay approval of prasugrel on the basis of this product issue.

(b) (4)

[redacted]

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- The sponsor has already altered the manufacturing process to limit form conversion to some extent. The ramifications of this are two-fold:

  (b) (4)

  [redacted]

(b) (4)

[redacted] If fact, the "best case" scenario for bioavailability, i.e., no effect of form conversion, has already been studied. In Study TAAL, prasugrel's bioavailability would not have been diminished in subjects who were not taking gastric pH-altering medications. **(b) (4)**

[redacted]

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 stoke 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.

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/s/

Ellis Unger
1/9/2009 06:44:41 PM
MEDICAL OFFICER

DIVISION OF CARDIOVASCULAR and RENAL PRODUCTS

Date: July 7, 2009

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

Status: priority

Submitted: 26 December 2007

Goal Date: 26 September 2008

To: The File

Re: **Prasugrel's Association with Cancer**

This document is based, in part, on the reviews of:

- Chemistry (S. Chatterjee, Z. Ge, and K. Srinivasachar), May 14, 2008
- Preclinical Pharmacology and Toxicology (B. Tesfamariam and A. DeFelice), April 26, 2008
- Clinical Pharmacology and Biopharmaceutics (E. Mishina, S. Mada, P. Marroum, R. Madabushi, Y. Wang), May 23, 2008
- Clinical (K. Hicks), April 28, 2008
- Secondary (E. Unger), July 10, 2008
- Secondary (T. Marciniak), June 19, 2008
- Consult from Division of Epidemiology, Office of Surveillance and Epidemiology (D. Wysowski), June 12, 2008
- Consult from Division of Drug Oncology Products, Office of New Drugs (B. Mann, J. Johnson, P. Cortazar)

Study TAAL[1] was the pivotal, active-control, double-blind, double-dummy, registrational study of prasugrel for subjects with acute coronary syndrome (ACS) who were scheduled to undergo percutaneous coronary intervention (PCI). The primary hypothesis was that prasugrel plus aspirin was superior to clopidogrel plus aspirin in the treatment of these subjects, as measured by a reduction in the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, at a median follow-up of ≥12 months. Subjects were randomized 1:1 to either prasugrel (60-mg load; 10-mg daily maintenance) or a standard regimen of clopidogrel (300-mg load; 75 mg daily maintenance). All subjects received standard therapies, including aspirin.

The intent-to-treat population included 13,608 subjects: 6,813 subjects were randomized to prasugrel and 6,795 subjects were randomized to clopidogrel. Median length of follow-up was 450 days.

[1] "A Comparison of CS-747 and Clopidogrel in Acute Coronary Syndrome Subjects who are to Undergo Percutaneous Coronary Intervention/TIMI 38"

Prasugrel succeeded on the primary efficacy endpoint; however, its use was associated with proportionally greater numbers of cancers than clopidogrel. Depending on the particular criteria used to identify the cases, the relative risk (RR) of cancer could be as low as 1.19, or as high as 1.52.

Sponsor's Initial Analyses of Neoplasia:

The applicant highlighted the imbalance in neoplasia in their initial submission (H7T-MC-TAAL Study Report; section 12.4.4); however, their analyses were difficult to interpret. There was not always a clear distinction between neoplasms known at the time of randomization versus those discovered during the course of the study, there was little attempt to categorize neoplasms as malignant or non-malignant, and there was little emphasis on categorization of cancers by organ or organ system.

The distinction between "pre-existing" versus "new" neoplasms was particularly difficult. A "Pre-Existing Conditions" case report form (CRF) was used to record "…*all ongoing medical conditions at the time of study entry/screening*." There appeared to be inconsistencies as to whether investigators recorded, or did not record, histories of pre-existing neoplasms, presumably related to their interpretations of whether or not a cancer was an "ongoing medical condition." For example, some investigators might consider a bladder cancer, resected 7 years prior to admission without known recurrence, as an "ongoing medical condition," whereas others might not. Moreover, for patients in the throes of an acute coronary event, it is safe to presume that there was little emphasis on recording historical information relevant to prior cancers.

For treatment-emergent serious adverse events in the system organ class (SOC) "neoplasms benign, malignant and unspecified (including cysts and polyps)," the applicant found 87 cases in the prasugrel group, versus 60 in the clopidogrel group, for a relative risk (RR) of 1.44, 95% confidence interval (CI) 1.04 to 2.00. The applicant provided exculpatory interpretations of the data for specific cancers, as follows:

Colorectal Cancer: The applicant found 19 colonic and rectal neoplasms in the prasugrel group and 8 in the clopidogrel group, but found reassurance in the fact that half of cases in the prasugrel group were discovered as a result of an antecedent GI bleed. (Because GI bleeding was more common in prasugrel subjects, they reasoned that more GI cancers would be detected.)

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

Lung Cancer: There were 8 and 2 lung cancers reported as adverse events in the prasugrel and clopidogrel groups, respectively. However, when "lung neoplasms" were added to the cancers, the respective numbers were 12 and 10. The applicant 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. The applicant took reassurance from the fact that in half of the 16 cancers in the prasugrel group, the diagnosis was made within 6 months of starting the study drug; therefore, they considered these unlikely to represent new cancers.

The applicant's summary interpretation, as stated in the original submission, was (page 899, H7T-MC-TAAL Study Report):

> "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."

Further Analyses:

The applicant espoused the view that the observed difference between prasugrel and clopidogrel in the frequency of neoplasms was the result of ascertainment bias. They argued that prasugrel caused a 30-40% increase in bleeding rates relative to clopidogrel. A disproportionately greater frequency of bleeding events in the prasugrel group would lead to a disproportionately greater number of patient evaluations, which would uncover disproportionately more cancer cases.

Although the theory seemed plausible on its face, the Division undertook its own analysis of 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 cancers, gastrointestinal (GI) bleeds for GI cancers, and dysfunctional uterine bleeding for gynecologic cancers. The analysis showed that the between-group difference in neoplasms largely persisted.

The Division sought additional information from the applicant, to clarify diagnoses and malignancy status for all cases, to distinguish new from pre-existing cancers, to collect investigators' assessment of symptoms, signs, and laboratory studies that led to a diagnosis, and to collect information on vital status. The applicant developed "Neoplasia" case report forms to capture this information, and sent clinical monitors to the all sites with an affected subject to oversee collection of the data.

The applicant provided their new analyses in a May 9, 2008, submission, wherein they identified 313 subjects 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. There were 175 and 138 subjects treated with prasugrel and clopidogrel, respectively, who had one or more of these events during the study. Table 1 shows the applicant's tabulation of these neoplasms, and is identical to Table 10 from the applicant's May 9, 2008 submission (except for the addition of a final line that omits non-melanomatous skin cancers).

Their analysis considered "non-benign" neoplasms, which included neoplasms known to be malignant and those whose nature was undetermined. The RR for prasugrel vs. clopidogrel was 1.19 (95% CI: 0.89, 1.58). Because non-melanomatous skin cancers are readily curable by excision and generally not serious in nature, they are often considered separately from solid tumors. When such tumors were excluded from this analysis, there were 94 and 72 new, non-benign neoplasms in the prasugrel and clopidogrel groups, respectively, for a RR of 1.30 (95% CI: 0.96, 1.76).

Table 1: Sponsor's May 9, 2008, Analysis of New, Non-Benign Neoplasms

neoplasm location	prasugrel	clopidogrel
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
other		
all	100	84
all, excluding non-melanomatous skin	94	72

In terms of the applicant's original contention that excess cancers were detected in the prasugrel group because of a higher incidence of bleeding events (ascertainment bias), the numbers of new, non-benign neoplasms where bleeding or anemia led to a diagnosis were 37 and 33 in the prasugrel and clopidogrel groups, respectively. Thus, the data did not support the applicant's claim of ascertainment bias; RR was largely unchanged when such cases were eliminated from the totals.

Cancer Mortality: There were 27 and 19 cancer deaths in the prasugrel and clopidogrel groups, respectively, for a RR of 1.42 (95% CI: 0.79, 2.55). If cancer deaths in subjects with pre-existing cancers are included in the totals, the numbers of deaths are 33 and 21, respectively (RR=1.57, 95% CI: 0.91, 2.71). The imbalance in cancer deaths is concerning, because mortality would not be expected to be affected by ascertainment bias. The applicant 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)."

The applicant subsequently made the argument that cancer deaths were discovered as a result of the additional data collection that preceded the May 9, 2008 submission. Specifically, they noted that vital status was obtained for 175 subjects treated with prasugrel and 138 subjects treated with clopidogrel (ratio 1.27). Therefore, given similar cancer fatality rates in two groups of different sizes, the imbalance in cancer deaths was uninterpretable.

FDA Analyses:

The Division performed an independent analyses of the cancer cases, and found some differences with the applicant with respect to whether particular cases represented neoplasia, whether neoplasms were histologically malignant, benign, or undetermined, and whether or not they had been known at screening. Some of the disagreement was related to whether particular tumors were classified as "pre-existing" if no formal diagnosis had been established prior to the adverse event. The Division also identified a small number of cases that had not been previously reported as neoplasia by the applicant.

Dr. Marciniak found 100 and 66 non-benign tumor cases in the prasugrel and clopidogrel groups, respectively (excluding non-melanomatous skin cancers), for a RR of 1.51, 95% confidence interval (CI) 1.11-2.06. Figure 1 shows the Kaplan-Meier time-to-event analysis as presented in prasugrel's CDER Regulatory Briefing on 9/5/2008, where the log-rank p=0.009. The applicant found 6 and 12 cases of non-melanomatous skin cancer in the prasugrel and clopidogrel groups, respectively. If these cases had been included in the Marciniak analysis, the RR would have been 1.35 (95% CI 1.01-1.81).

Figure 1: New, Non-Benign Neoplasms – DCaRP Analysis

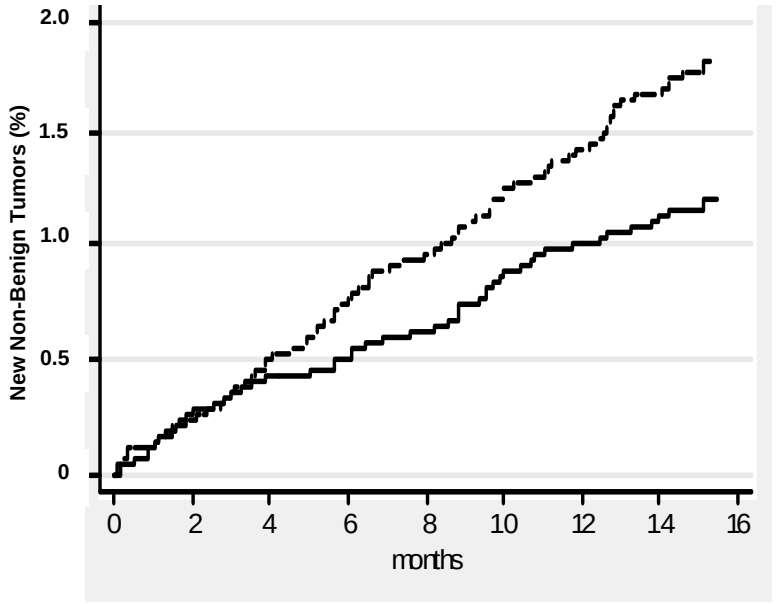

Table 2 summarizes the results of analyses conducted by the applicant and initial analyses by Dr. Marciniak.

Table 2: Relative and Absolute Risk of Non-Benign Neoplasia; Analyses by Sponsor and Marciniak

Analysis by:	Prasugrel n=6741		Clopidogrel n=6716		Relative Risk (95% CI)	Absolute Risk (%)
	n	%	n	%		
Sponsor (5/9/08)						
all non-benign	100	1.48	84	1.25	1.19 (0.89, 1.58)	0.23
exclude skin	94	1.39	72	1.07	1.30 (0.96, 1.76)	0.32
Marciniak						
all non-benign	106	1.57	78	1.16	1.35 (1.01, 1.81)	0.41
exclude skin	100	1.48	66	0.98	1.51 (1.11, 2.06)	0.50

Because of the disparity between the accounting of the cases by Dr. Marciniak and the applicant, much additional attention was given to obtaining agreement on the actual numbers of cases of new, non-benign neoplasms. Doctors Marciniak, Unger, Stockbridge, and Temple blindly adjudicated a subset of the cases, and conclusions were shared with the applicant. Agreement was reached that the numbers of cases of new, non-benign neoplasms were 94 and 80 in the prasugrel and clopidogrel groups, respectively. Subsequently, however, Dr. Marciniak argued successfully that two cases should be added to the prasugrel group, and two subtracted from the clopidogrel group, making the totals 96 and 78 in the prasugrel and clopidogrel groups, respectively. Still later, Dr. Marciniak indentified 7 additional subjects who had experienced adverse events that were unquestionably classified as skin carcinomas (basal cell or squamous cell), but had not been considered in any of the applicant's analyses because they had not been coded to the system organ class "neoplasms benign, malignant and unspecified (including cysts and polyps)" in the original submission. Six of these subjects were in the prasugrel group, and one was in the clopidogrel group. Thus, in the Division's final accounting, the numbers of new, non-benign neoplasms were 102/6741 (1.51%) in the prasugrel group and 79/6716 (1.18%) in the clopidogrel group, for a relative risk of 1.29 (95% C.I. 0.96-1.72).

Given that prasugrel and clopidogrel share a number of 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 promoter. There were a few differences in frequencies of particular tumor types in some of the studies, but the results were inconsistent. 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). Moreover, Dr. Marciniak suggested that the lack of a consistent trend indirectly undermines the applicant's assertion that excess bleeding led to ascertainment bias in TAAL, given that bleeding would have been expected to lead to ascertainment bias in the clopidogrel development program, yet no signal was found.

The Division sought the expertise of the Division of Drug Oncology Products, and their consult team 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.

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.

Non-Clinical Data:

In considering the plausibility of prasugrel-induced carcinogenesis or tumor promotion, there are few data in the literature to support a mechanism. Specifically, there is little evidence suggesting that prasugrel, clopidogrel, or modulation of the $P2Y_{12}$ receptor would have important effects on genotoxicity, tumorigenesis, tumor promotion, metastasis, or angiogenesis.

The 2-year rodent carcinogenicity studies were described fully in the Preclinical Pharmacology and Toxicology review. The rodent data do not show significantly increased rates of malignant neoplasms, although positive trends in some tumor types were highlighted by Dr. Marciniak. The two-year rat carcinogenicity study showed findings primarily consistent with hepatic enzyme induction. At doses in the mouse approximating 500 times the exposure in humans, 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). Prasugrel was not associated with greater numbers of malignant tumors in extra-hepatic tissues. The Pharmacology/Toxicology review team and the Executive Carcinogenicity Advisory Committee opined that they found no evidence of a prasugrel-associated increase in malignant tumors in either species, and interpreted the results as reassuring.

Considering the brevity of the clinical trial TAAL relative to the typical doubling time of common tumors, there was uniform agreement within the review team that if, in fact, prasugrel was causally related to the imbalance in neoplasms, the mechanism must have involved tumor promotion rather than carcinogenicity. On October 17, 2008, the Division asked the applicant to conduct tumor progression studies to evaluate the effects of prasugrel metabolites *in vitro*, using

human tumor cell lines, and *in vivo*, in congenitally immunodeficient 'nude' mice. In response to our request, the applicant conducted the following studies:

- *in vitro* effects of R-138727 and R-106583 on proliferation of human cell lines derived from lung, colon and prostate tumors; and
- *in vivo* effects of prasugrel on growth of human tumor xenografts derived from lung, colon and prostate in 'nude' mice.

The results are summarized in Dr. Belay Tesfamariam's review, dated 2/2/09:

- *In vitro:* Exposure of serum-starved human tumor cell lines (lung, colon and prostate) to prasugrel metabolites did not increase cell proliferation relative to starved cells stimulated to proliferate by addition of 10% fetal bovine serum.

- *In vivo:* In tumor-bearing 'nude' mice implanted with human lung, colon and prostate tumor cells, prasugrel did not enhance tumor growth rates.

Dr. Tesfamariam concluded: "In the context of the negative findings in the genotoxicity and the 2-year rodent carcinogenicity bioassays, these additional data on tumor progression assays add to the weight-of-evidence that prasugrel exhibits neither carcinogenic nor tumor progressing activity."

Analysis:

Prasugrel was associated with an excess number of new malignant tumors. Depending on whether risk is calculated from the analyses of the Division or those of the Sponsor, and depending on whether or not non-melanomatous skin cancers are included, the point estimate for relative risk is in the range of 1.2 - 1.5, with absolute risk in the range between 0.23% and 0.50% over the 12-month course of the study. The applicant's analyses do not show a statistically significant difference between treatment groups. Some of the Division's analyses demonstrate a nominally statistically significant difference between treatment groups, whereas others do not.

In deciding whether prasugrel plays a causal role in stimulating tumors, several factors merit consideration:

1. Mechanism

It is difficult to conceive of a mechanism through which prasugrel could cause or stimulate cancer development. One could posit that platelet aggregation and thrombosis (processes with which prasugrel interferes) provide natural defenses against tumor development and metastasis, that prasugrel is pro-angiogenic or mitogenic, or that it acts as a tumor cell growth factor; however, these concepts are purely speculative. There is a paucity of non-clinical data suggesting a role for prasugrel in tumor promotion.

2. Drug Class

It is noteworthy that prasugrel shares some similarities with clopidogrel, and there is no evidence that clopidogrel stimulated cancer development in its large development program. Therefore, if prasugrel were causing tumor stimulation, its effect is unique and not a class effect.

This would seem to make causality less likely. In the entire history of drug development, the only products thought to stimulate tumor development are the recombinant erythropoietins (Epoetin alfa; Darbepoetin alfa), and these are growth factors, whereas prasugrel is not.

3. Tumor Types

The distribution of tumor types was typical of a coronary artery disease patient population, and appeared 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 non-benign tumors in these categories for prasugrel and clopidogrel were prostate: 11 versus 9; breast: 5 versus 1; lung/bronchial: 17 versus 13; and colorectal: 23 versus 10, respectively. 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. Thus, if prasugrel is causally related to the excess tumors observed in TAAL, the stimulation appears to be fairly general in nature.

4. Carcinogenicity; Tumor Promotion

Considering the biology of the tumor types observed and the relatively brief (15-month) time frame of TAAL, it is simply not plausible for carcinogenicity to underlie these trends. Moreover, the results of prasugrel's carcinogenicity studies were not regarded to be positive (except by Dr. Marciniak, who held a minority view). Thus, if prasugrel *is* playing a role here, it is through enhancement of tumor progression and not carcinogenesis. The *in vitro* and *in vivo* data do not, however, support the hypothesis that prasugrel promotes tumor growth and/or progression.

5. Cancer Deaths

There were 27 and 19 cancer deaths in the prasugrel and clopidogrel groups, respectively, for a RR of 1.42 (95% CI: 0.79, 2.55). If cancer deaths in subjects with pre-existing cancers are included in the totals, the numbers of deaths are 33 and 21, respectively (RR=1.57, 95% CI: 0.91, 2.71). The applicant has argued that the imbalance is a byproduct of ascertainment bias. Because there were greater numbers of subjects with neoplasia-related adverse events in the prasugrel group (175) than the clopidogrel group (138), and because vital status was specifically sought for this subgroup of subjects, the imbalance in deaths would be expected to approximate 175/138 = 1.27. In fact, the RR for cancer deaths exceeds 1.27, although it is not strikingly different. Thus, the applicant's argument does provide some measure of reassurance. Nevertheless, deaths are always a reason for concern.

6. Multiplicity of Safety Analyses

Safety analyses are observational in nature and conducted without the benefit of pre-specified hypotheses or correction for multiplicity; therefore, there is always the possibility of a false positive finding. False positive results are, of course, *expected* under these circumstances. Beyond a mere association between prasugrel and excess cancers, therefore, biological plausibility, exposure-response, and other factors are helpful to support causality, and these factors seem to be missing here.

Conclusion:

In summary, by the Division's classification of non-benign tumors, there is a trend showing more adverse events of new, non-benign neoplasms in the prasugrel group than the clopidogrel group. The relative risk is 1.29, with 95% CI: 0.96, 1.72. The absolute risk is 0.33%, over a median follow-up of 12 months. However, given the lack of a plausible underlying mechanism of action, non-clinical data that fail to show tumor promotion, the multiplicity of safety analyses, the fact that fairly extensive data on a related drug (clopidogrel) show no signal, and the reality that only the erythropoietins have been shown to promote tumors, there is a good chance that these observations are spurious.

There is unanimous agreement within the Division that these findings should not stand in the way of prasugrel's approval, and the Office concurs with this position. However, there are differing opinions in the Division as to how labeling should be handled. There are some who argue that if there is a risk of tumor stimulation, it should be related to exposure. These individuals advocate placing a limit on the duration of prasugrel use to perhaps 30 days, with patients switching to clopidogrel at that point. Counter-arguments have been raised to this proposal: 1) Any proposed duration of treatment is necessarily arbitrary; 2) Switching involves logistical issues. Some patients will simply discontinue their thienopyridine, which could lead to stent thrombosis; 3) The strategy of switching from prasugrel to clopidogrel has not been tested. The pharmacodynamic effects of the change are not likely to be important, but the issues of logistics, as well as physician and patient acceptance, are key. For the majority of the review staff who believe more strongly that the imbalance is spurious, the exposure issue is moot, and they would not place any limitation on duration of use. I agree with the majority view on this issue.

Some have suggested a postmarketing requirement to study the tumor issue more carefully in a randomized controlled trial. This is consistent with the advice the Division received from the Division of Drug Oncology Products, Office of Oncology Drug Products, OND. The Division received advice from the Division of Epidemiology, OSE, that registry data are not likely to answer the question of cancer causality.

The Division has been in discussions with the applicant on a large outcome study (TABY), that could be used to assess the role of prasugrel in stimulating cancer. Specific areas under discussion include screening for cancer, identification of pre-existing tumors, and definitions and classification of tumors. This reviewer suggests that the completion of this study should be a post-marketing requirement under the Food and Drug Administration Amendments Act (FDAAA) of 2007, and that is the plan at this juncture.

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/s/

Ellis Unger
7/7/2009 07:06:08 PM
MEDICAL OFFICER

DIVISION OF CARDIOVASCULAR and RENAL PRODUCTS

Date: September 29, 2008

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

Status: priority

Submitted: 26 December 2007

Goal Date: 26 September 2008

From: Ellis F. Unger, M.D., Deputy Director, DCaRP

To: The File

Re: **Importance of Bleeding to Prasugrel's Risk Benefit Relation**

This document is based, in part, on the reviews of:

- Clinical Pharmacology and Biopharmaceutics (Elena V. Mishina, Sripal Mada, Patrick Marroum, Raj Madabushi, Yaning Wang), May 23, 2008
- Clinical (Karen A. Hicks), April 28, 2008
- Secondary (Ellis F. Unger), July 10, 2008

Overview of the Pivotal Efficacy Study, TAAL:

Study TAAL was the pivotal, active-control, double-blind, double-dummy, registrational study of prasugrel for subjects with acute coronary syndrome (ACS) who were scheduled to undergo percutaneous coronary intervention (PCI). The primary hypothesis was that prasugrel plus aspirin was 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 (referred to as the "triple endpoint" in this document), at a median follow-up of ≥12 months.

Briefly, subjects were randomized 1:1 to either prasugrel (60-mg load; 10-mg daily maintenance) or a standard regimen of clopidogrel (300-mg load; 75 mg daily maintenance). Randomization was stratified by clinical presentation: unstable angina (UA)/ non-ST-segment elevation myocardial infarction (NSTEMI) versus ST-segment elevation myocardial infarction (STEMI). Aspirin (75-325 mg PO or 250-500-mg IV) was to be administered within 24 hours prior to the index PCI.

The intent-to-treat population included 13,608 subjects: 6,813 subjects were randomized to prasugrel and 6,795 subjects were randomized to clopidogrel. Median length of follow-up was 450 days.

In total, 643 subjects (9.4%) in the prasugrel group and 781 subjects (11.5%) in the clopidogrel group experienced a 1° triple endpoint event of CV death, nonfatal MI, or nonfatal stroke (Table 1). Prasugrel caused a statistically significant reduction in the triple composite endpoint in both the UA/NSTEMI and STEMI populations.

Table 1: Number and Percentage of Subjects Reaching Composite Endpoint

	Prasugrel			Clopidogrel			Cox Proportional HR (95% C.I.)	p
subject population	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

Table 2 displays the individual components of the 1° endpoint, as well as all-cause mortality, and intracranial hemorrhage [ICH]. The incidence of nonfatal MI is statistically significantly lower in the prasugrel group (hazard ratio [HR]=0.76; p<0.001), and this component of the composite endpoint drives the overall study results. The CV death component shows a weak trend in favor of prasugrel (HR=0.89; p=0.31). There was no effect of prasugrel on nonfatal stroke (which includes non-fatal ICH), all-cause mortality, or ICH.

Table 2: Components of 1° Efficacy Endpoint, All-Cause Death, Fatal Bleeds, and ICH

	endpoint	Prasugrel n=6813		Clopidogrel n=6795		Cox Proportional HR (95% C.I.)	p	delta events per 1000 patients treated (positive = favorable for prasugrel)
		n	%	n	%			
primary endpoint	CV Death	133	2.0	150	2.2	0.89 (0.70,1.12)	0.31	2.6
	Nonfatal MI	475	7.0	620	9.1	0.76 (0.67,0.85)	<0.001	21.5
	Nonfatal Stroke	61	0.9	60	0.9	1.02 (0.71,1.45)	0.93	-0.1
	All-Cause Death	188	2.76	197	2.90	0.95 (0.78,1.16)	0.64	1.4
	Hemorrhagic	22	0.32	5	0.07	4.39 (1.66, 11.6)	<0.002	-2.49
	Non-hemorrhagic	166	2.44	192	2.83	0.86 (0.70, 1.06)	NS	3.9
	ICH	20	0.29	19	0.28	1.05 (0.56, 1.97)	NS	-0.1

Bleeding in the Pivotal Efficacy Study, TAAL:

The risk of bleeding was well considered in the primary and secondary clinical reviewers. Prior to considering the bleeding risk associated with prasugrel in TAAL, it is useful to consider the standard Thrombosis in Myocardial Infarction (TIMI) bleeding definitions used in the study:

- TIMI Major bleeding ≡ any intracranial hemorrhage, or bleeding requiring intervention associated with a decrease in hemoglobin (Hgb) >5 g/dL;

- TIMI Minor bleeding ≡ bleeding requiring intervention that does not meet the requirements for TIMI Major bleed, and is associated with a decrease in Hgb ≥3 g/dL to ≤5 g/dL.

Table 3 summarizes the bleeding events in TAAL. Bleeding was categorized as related or unrelated to coronary artery bypass graft (CABG) surgery. Prasugrel was associated with more bleeding than clopidogrel, irrespective of the bleeding definition, seriousness, or location, and across most subgroups. (Subjects who experienced events in more than one category are represented more than once.)

Table 3: 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

There were 21 and 5 fatal non-CABG-related bleeding events in the prasugrel and clopidogrel groups, respectively (RR = 4.19, p=0.002; Table 3). All 5 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, 2 were 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. It is noteworthy, however, that for ICH, the bleeding event least amenable to treatment, there was no difference between the two drugs. The frequencies of ICH were 19/6741 (0.28%) and 17/6716 (0.25%) in the prasugrel and clopidogrel groups, respectively.

The excess in fatal bleeding events did not lead to greater overall mortality on prasugrel; all-cause mortality slightly favored prasugrel (HR=0.95; p=0.64, Table 2). Considering actual event

rates rather than risk reduction, per 1000 patients treated with prasugrel rather than clopidogrel there are 2 additional fatal bleeding events, 3 additional non-fatal TIMI Major bleeds, 5 additional TIMI Minor bleeds, and 21 additional TIMI Minimal bleeds.

To put the bleeding into context with efficacy, compared to clopidogrel, prasugrel treatment was associated with 24 fewer endpoint events per 1000 patients treated: 21 non-fatal myocardial infarctions, 3 cardiovascular deaths, and 0 strokes. In terms of deaths therefore, prasugrel treatment (compared to clopidogrel) was associated overall with 3 fewer cardiovascular deaths per 1000 subjects treated, despite 2 additional deaths due to fatal hemorrhage. (Overall mortality favored prasugrel by 1.4 events/1000 patients treated.) Thus, prasugrel had, overall a slightly favorable effect on overall mortality or even overall mortality plus ICH, accompanied by a substantial reduction in non-fatal MIs.

Subgroups at Particular Risk of Bleeding:

There were no significant treatment-by-demographic characteristic interactions with respect to TIMI Major or Minor bleeding. None of the subgroups was associated with a particularly high HR for prasugrel, although the HR tended to be higher in females and those of lower body weight (Table 4). A few factors deserve special consideration, and they are listed below.

Table 4: Non-CABG-Related TIMI Major or Minor Bleeding Events by Subgroup

	Subject population	Prasugrel			Clopidogrel			Cox Proportional HR (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	<50	45	2	4.4	45	6	13.3		
	50 - <70	1133	78	6.884	1232	61	4.951	1.41 (1.01, 1.96)	0.046
	70 - <90	3378	151	4.47	3297	107	3.245	1.39 (1.08, 1.78)	0.009
	>=90	2125	68	3.2	2081	55	2.643	1.22 (0.85, 1.74)	0.275

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 all age strata. Specifically, the overall HR for bleeding was 1.31 (worse for prasugrel). Similarly, the HR was 1.35 for subjects over 70 years of age, and also 1.35 for subjects over 75 years of age. Thus, based on hazard

ratio alone, use of prasugrel, versus clopidogrel, in older patients seems to carry the same risk as in any patient, including younger patients.

However, the *outcomes* secondary to bleeding in prasugrel-treated subjects ≥ 75 years of age were of particular concern. Specifically, the frequency of fatal hemorrhage was 9/891 (1.01%) for prasugrel-treated subjects, versus 1/894 (0.11%) for clopidogrel-treated subjects. For symptomatic intracranial hemorrhage (ICH), there were 7 (0.79%) versus 3 (0.34%) 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.

If the ≥75 year-old population is removed from TAAL, the prasugrel's bleeding risk is somewhat diminished relative to the population as a whole (Table 5). In particular, fatal bleeding events are then 12 for prasugrel vs. 4 for clopidogrel (RR=2.99); for fatal ICH and symptomatic ICH, the numbers of cases in the two treatment groups are approximately equal.

Table 5: Non-CABG-Related Bleeding in Subjects Less Than 75 Years of Age

endpoint	Prasugrel			Clopidogrel			RR (95% C.I.)
	N	n	%	N	n	%	
TIMI Fatal	5850	12	0.2	5822	4	0.1	2.99 (0.96,9.3)
TIMI Life-Threatening	5850	67	1.1	5822	45	0.8	1.48 (1.02,2.16)
TIMI Major	5850	119	2.0	5822	88	1.5	1.35 (1.02,1.77)
TIMI Minor	5850	119	2.0	5822	95	1.6	1.25 (0.95,1.63)
Fatal ICH	5850	5	0.1	5822	4	0.1	1.24 (0.33,4.63)
Symptomatic ICH	5850	12	0.2	5822	14	0.2	0.85 (0.39,1.84)

Patients 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 latter >3 months prior to screening), a subgroup comprising 3.8% of the total study population, the HR for the composite efficacy endpoint was unfavorable for prasugrel, going against the grain of the study as a whole. The HR was 1.44 in favor of *clopidogrel*: 50 of 262 prasugrel treated subjects (19.1%) experienced an endpoint event, compared to 36 of 256 clopidogrel-treated subjects (14.4%). 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 (95% C.I.: 1.65, 19.3). If stokes are subtracted from the composite endpoint, the frequencies of events are similar in the prasugrel and clopidogrel groups (12.6% and 13.2%, respectively). 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 stokes 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 review team recommended a contraindication in the labeling for prasugrel in patients with a prior history of TIA or stroke (hemorrhagic, non-hemorrhagic, or unknown).

Patients Undergoing Coronary Artery Bypass Graft (CABG) Surgery:

The frequency of CABG-related TIMI major bleeding was higher in subjects treated with prasugrel compared to clopidogrel. For both drugs, but especially 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.

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 is reasonable to discontinue prasugrel 7 or more days prior to surgery.

Summary and Conclusions:

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

Nonetheless, even in the unmodified population studies in TAAL, overall survival was not impaired by prasugrel, and ICH was similar in both groups.

Although the excess of fatal and non-fatal bleeding in prasugrel patients is obviously unwelcome, it dose not outweigh the benefit of prasugrel; both of these are related to greater inhibition of platelet aggregation. Bleeding events are graded in severity from fatal, to severely debilitating (ICH in many cases), to alarming but ultimately transient. We believe outcomes favor prasugrel (and will do so more when patients over 75 and patients with prior stroke or TIA are excluded).

1. Overall mortality slightly favored prasugrel; HR 0.95; 95% CI 0.78-1.16, p=0.64
2. Reduction in non-fatal MI: HR=0.76; 95% CI 0.67–0.85, p<0.001
3. Non-fatal strokes (ICH and thrombotic): no difference in overall population; but favored prasugrel if patients with prior TIA/stroke or age >75 are excluded: HR=0.64; 95% CI 0.42–1.00, p<0.05

In sum, patients receive a 25% reduction in non-fatal MI without survival or ICH cost. There is a great deal of 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.

The benefit-risk relation of prasugrel can be assessed in quantitative terms, as follows (see Tables 2 and 3):

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 attributable 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 additional TIMI Minimal bleeds.

The tradeoff between efficacy and bleeding is largely between prevention of non-fatal myocardial infarction versus causation of transient morbidity. The Division believes that this is a worthwhile trade for patients who might receive prasugrel.

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/s/

Ellis Unger
7/6/2009 12:14:08 PM
MEDICAL OFFICER

DIVISION OF CARDIOVASCULAR and RENAL PRODUCTS

Date: September 25, 2008

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

Status: priority

Submitted: 26 December 2007

Goal Date: 26 September 2008

From: Ellis F. Unger, M.D., Deputy Director, DCaRP

To: The File

Re: **Importance of Prasugrel's Conversion from a Salt to the Base Form**

This document is based, in part, on the reviews of:

- Chemistry (Sharmista Chatterjee, Zhengfang Ge, and Kasturi Srinivasachar), May 14, 2008
- Clinical Pharmacology and Biopharmaceutics (Elena V. Mishina, Sripal Mada, Patrick Marroum, Raj Madabushi, Yaning Wang), May 23, 2008
- Clinical (Karen A. Hicks), April 28, 2008
- Secondary (Ellis F. Unger), July 10, 2008

Background:

The prasugrel NDA was one of the applications included in the Quality by Design (QbD) pilot program. The sponsor initiated the development program using the free base of the drug substance, but became aware that the hydrochloride (HCl) salt had better bioavailability at higher gastric pH. Gastric pH is an important issue in patients who use anti-platelet medications, because a substantial fraction of these patients take proton pump inhibitors [PPI] of H2 receptor antagonists to reduce gastric acidity. Thus, with the concurrence of the Division, the sponsor decided to switch the manufacturing process to the HCl salt form of the drug substance.

Late in development, at the time that the pivotal efficacy study was nearly completed, the sponsor discovered that an acid-base reaction (b) (4) , was converting up to 86% of the salt form to the free base. Using x-ray powder diffraction, the sponsor determined that conversion from salt to base was beginning at the initial (b) (4) . Conversion continued during storage to some extent, reaching a plateau after approximately (b) (4). Relative humidity and storage temperature were key factors affecting conversion. Of note, the conversion of a drug product from salt-to-base is a heretofore-unknown phenomenon. For prasugrel, the conversion may have been discovered as a result of following a science-based drug development approach

encouraged under the Quality by Design paradigm of drug development, and might not have been detected otherwise. The degree to which conversion of this nature occurs with other products is unknown.

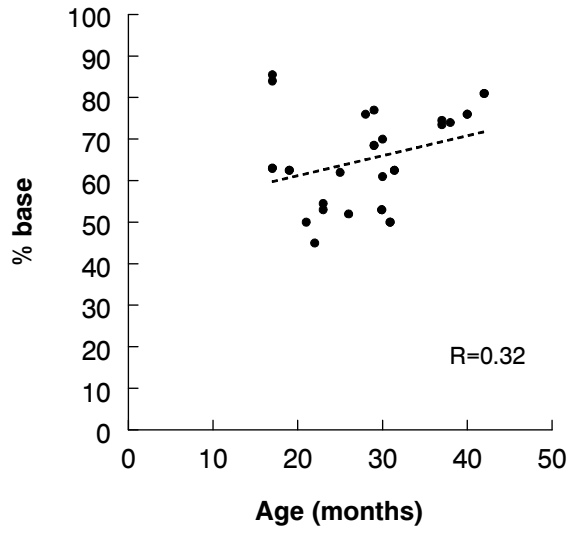
Extent of Conversion:

The sponsor assayed several lots for salt to base conversion, performing batch analyses of the lots at various times post-manufacture; the extent of conversion ranged from 45 to 86%. They did not report serial data on single lots. When percent conversion of the individual lots is plotted as a function of time since manufacture, it is clear that the degree of conversion is not linear with lot age (Figure 1, from secondary review). The sponsor has added several in-process controls as well as a desiccant to packaging to limit form conversion of the to-be-marketed product to Not More Than (NMT) (b) (4). Importantly, because there are no serial data on conversion of the lots, it is not possible to identify a specific lot administered to a particular subject, and back-calculate the extent of salt to base conversion at the time of administration.

(b) (4)

(b) (4)

Figure 1: Base Content of Prasugrel as a Function of Time



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

The sponsor conducted two bioequivalence studies in which the bioavailability of lots with low (5%), intermediate (58%), and high (70%) degrees of conversion to base were compared, with and without co-administration of a PPI (lansoprazole) to raise gastric pH. The sponsor concluded that even lots with a high degree of conversion from salt to free base (70%) were

clinically acceptable, both with and without concomitant PPI use. The lots were not, however, bioequivalent.

The prasugrel lots with low, intermediate, and high salt to base conversion were bio-equivalent with respect to R-138727, prasugrel's active moiety, when the drug was administered alone. 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, however, the three lots were still bio-equivalent for R-138727 with respect to AUC, but *the lots 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	467	409	0.99	0.87	0.88
	(424, 522)	(421, 518)	(368, 454)	(0.93, 1.06)	(0.82, 0.93)	(0.82, 0.93)
C_{max} (ng/mL)						
	331	297	236	0.90	0.71	0.80
	(285, 384)	(257, 344)	(204, 274)	(0.77, 1.04)	(0.62, 0.83)	(0.69, 0.92)

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

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

What are the consequences of these differences in C_{max} for PPI or H2 receptor antagonist users? 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 disparities in inhibition of platelet aggregation (IPA) of approximately 50% at 0.5 hours post-dose (high versus low- or medium-salt-to-base conversion) and 16% 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). Thus, the high salt-to-base conversion lots are technically bio-inequivalent from the low- and medium-conversion lots in the presence of a PPI. Inequivalence in platelet aggregation is greatest at 0.5 hours (50%), there is little difference at one hour, and there is no detectable difference at 2 hours and beyond. In essence, the bioinequivalence results in a delay of perhaps 20 minutes in achieving maximal inhibition of platelet inhibition.

This is manifested only with the high salt-to-base conversion product, and only in the presence of PPI or H2 receptor antagonists.

Relevance of Altered Pharmacodynamics of High Salt-to-Base Conversion:

Because percutaneous coronary interventions (PCI) may precipitate periprocedural myocardial infarction, a considerable number of events occur very soon after PCI. Specifically, in TAAL, of the 1095 non-fatal myocardial infarctions recorded during the course of the 15-month study, 332 events, or 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 μM 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 is 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 3).

Figure 2: Inhibition of Platelet Aggregation (IPA) to 20 μM 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 ± SD; calculated by CDER, Study TACS)

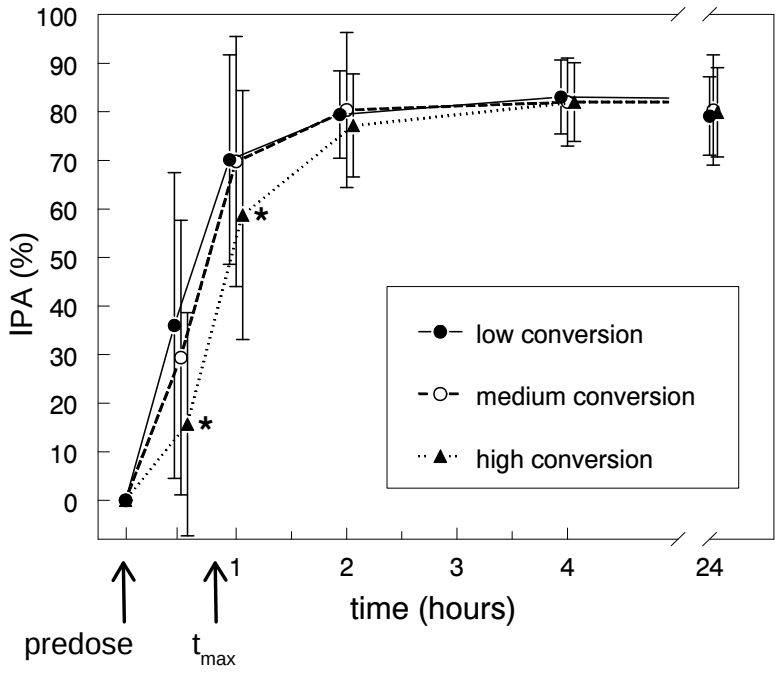
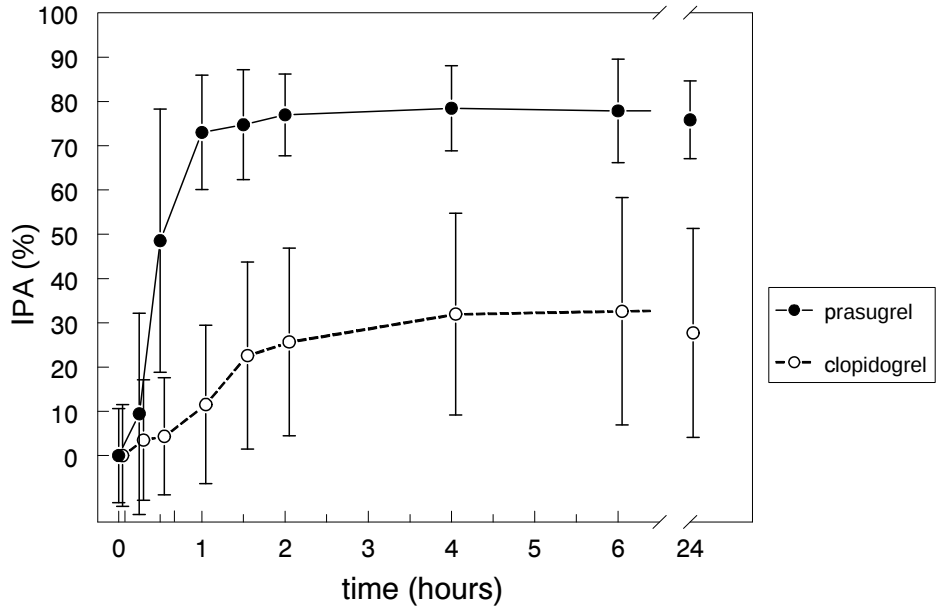


Figure 3: Inhibition of Platelet Aggregation (IPA) to 20 μM ADP, Following Loading Doses of Prasugrel 60 mg or Clopidogrel 300 mg (from Study TAAJ, mean ± SD)



Clinical Relevance of Salt-to-Base Conversion:

Study TAAL was the pivotal, active-control, double-blind, double-dummy, registrational study of prasugrel for subjects with acute coronary syndrome (ACS) who were scheduled to undergo PCI. The primary hypothesis was that prasugrel plus aspirin was 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 (referred to as the "triple endpoint" in this document), at a median follow-up of ≥12 months.

Briefly, subjects were randomized 1:1 to either prasugrel (60-mg load; 10-mg daily maintenance) or a standard regimen of clopidogrel (300-mg load; 75 mg daily maintenance). Randomization was stratified by clinical presentation:

- unstable angina (UA)/ non-ST-segment elevation myocardial infarction (NSTEMI)
- ST-segment elevation myocardial infarction (STEMI).

Aspirin (75-325 mg PO or 250-500-mg IV) was administered within 24 hours prior to the index PCI. Proton pump inhibitors were permitted at the discretion of the treating physician.
The intent-to-treat population included 13,608 subjects: 6,813 subjects were randomized to prasugrel and 6,795 subjects were randomized to clopidogrel. Median length of follow-up was approximately 15 months.

In total, 643 subjects (9.4%) in the prasugrel group and 781 subjects (11.5%) in the clopidogrel group experienced a primary composite endpoint event of cardiovascular death, nonfatal MI, or nonfatal stroke (Table 2). Treatment with prasugrel was associated with a statistically significant reduction in the composite endpoint in both the UA/NSTEMI and STEMI populations, (Table 2 and Figure 4, top and bottoms panels, respectively).

Table 2: Number and Percentage of Subjects Reaching Composite Endpoint

	Prasugrel			Clopidogrel			Cox Proportional HR (95% C.I.)	p
subject population	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

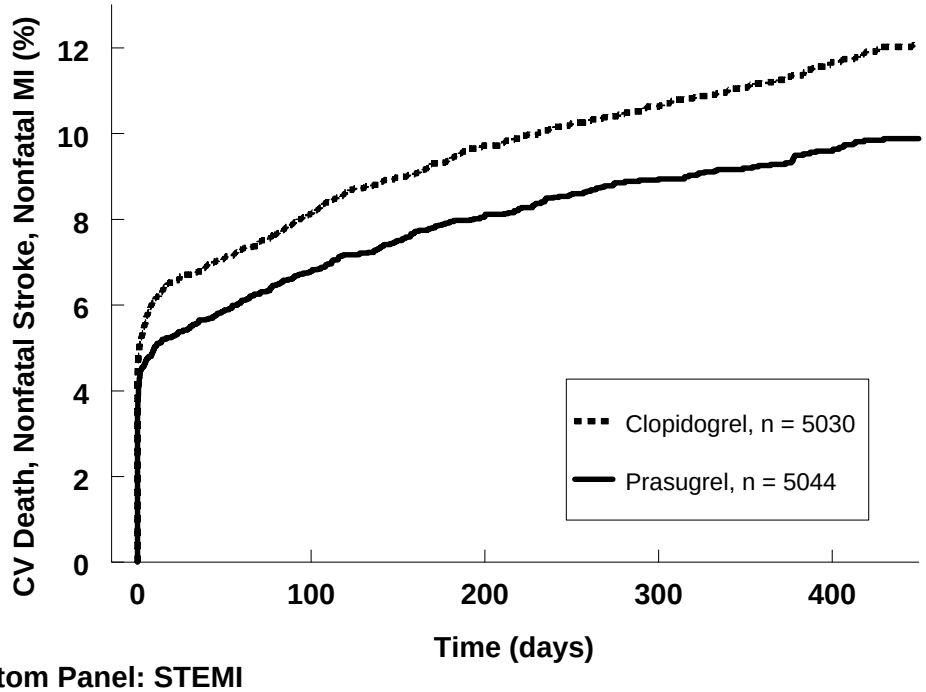
Table 3 displays the individual components of the 1° endpoint for the UA/NSTEMI and STEMI populations. The incidence of nonfatal MI is statistically significantly lower in the prasugrel group in both the UA/NSTEMI and STEMI populations; this component of the composite endpoint drove the overall study 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.

Table 3: Components of 1° Efficacy Endpoint (from table 11.7 in TAAL Study Report)

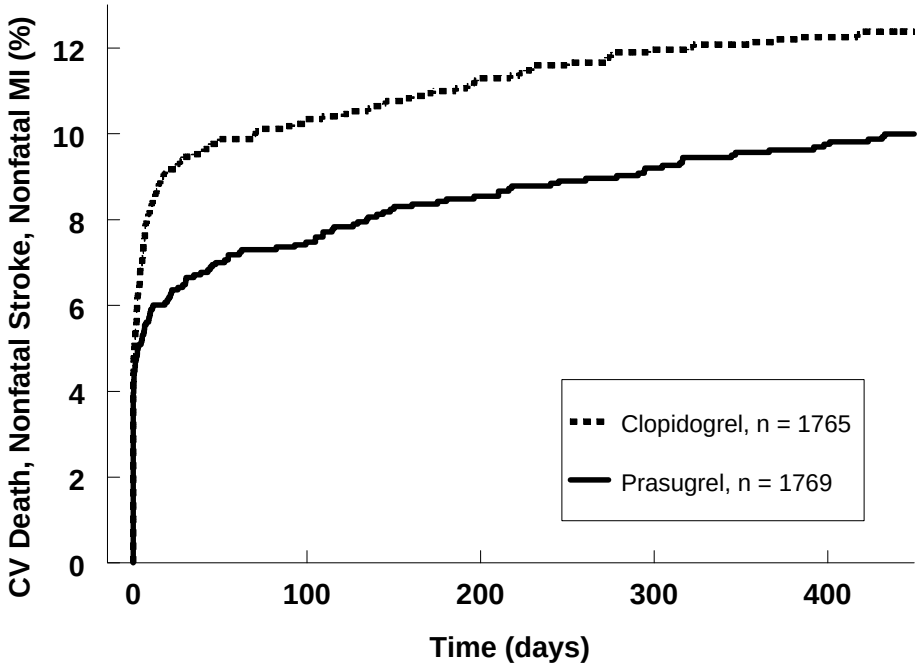
endpoint	Patient population	Prasugrel			Clopidogrel			Cox Proportional HR (95% C.I.)	p
		N	n	%	N	n	%		
CV Death	UA/NSTEMI	5044	90	1.8	5030	92	1.8	0.98 (0.73,1.31)	0.885
	STEMI	1769	43	2.4	1765	58	3.3	0.74 (0.50,1.09)	0.129
Nonfatal MI	UA/NSTEMI	5044	357	7.1	5030	464	9.2	0.76 (0.66,0.87)	<0.001
	STEMI	1769	118	6.7	1765	156	8.8	0.75 (0.59,0.95)	0.016
Nonfatal Stroke	UA/NSTEMI	5044	40	0.8	5030	41	0.8	0.98 (0.63,1.51)	0.922
	STEMI	1769	21	1.2	1765	19	1.1	1.10 (0.59,2.04)	0.77

Figure 4: Kaplan-Meier Estimates of the 1° Efficacy Endpoint CV Death, Nonfatal MI, Nonfatal Stroke

Top Panel: NSTEMI/UA



Bottom Panel: STEMI



Impact of Salt-to-Base Conversion on Efficacy:

Some estimate of the clinical importance of salt-to-base conversion can be gleaned by considering efficacy as a function of prasugrel lot. 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 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, the review team analyzed efficacy on the triple composite endpoint as a function of prasugrel lot used for the loading dose (Figure 5, top) and the lot administered Day 2 to 30 (Figure 5, 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 5: 1° Efficacy Endpoint by Prasugrel Lot Administered for Loading Dose (Through Day 1, Top) and Maintenance Dose (Through Day 30, Bottom)

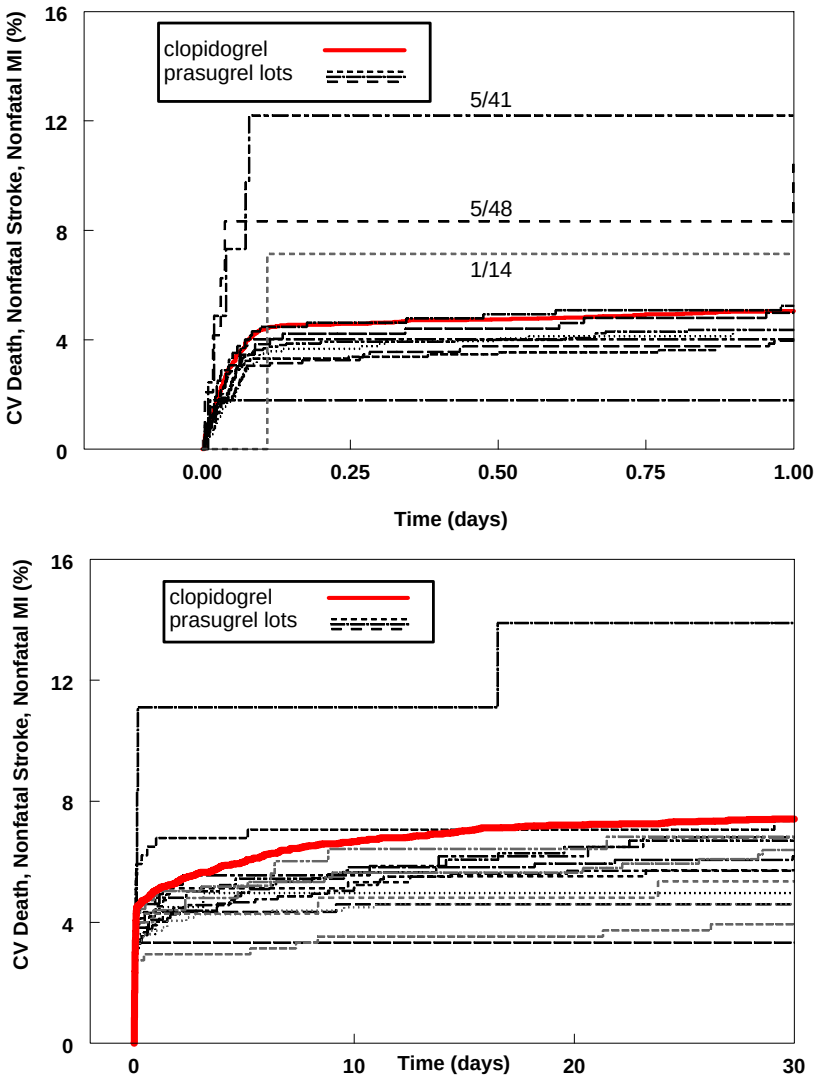
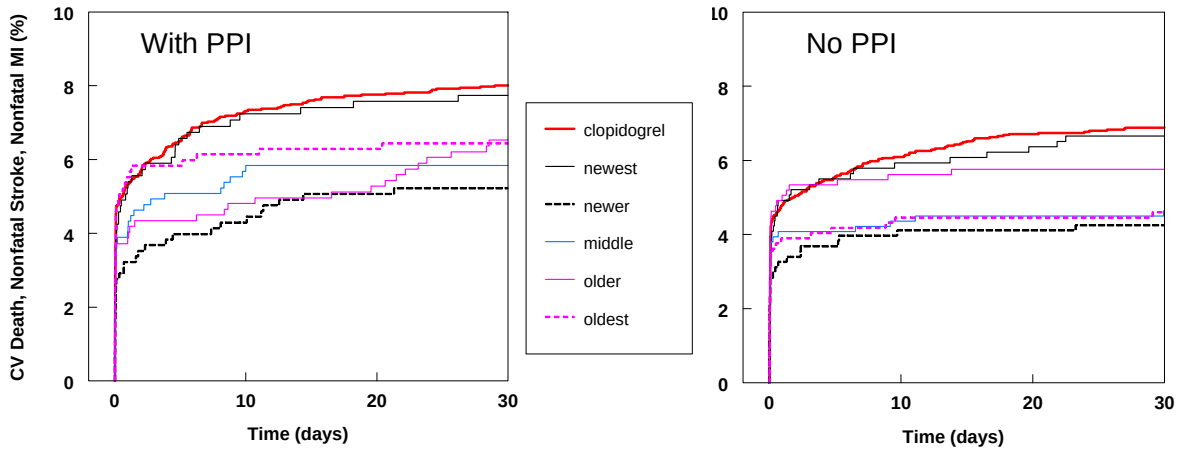


Figure 6: 1° Efficacy Endpoint by Age of Prasugrel Lot Administered Through Day 30



Because the sponsor asserts that there was at least some conversion of salt to base during storage, the review team 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 6, from secondary review).

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.)

Association between Use of Proton Pump Inhibitors and Efficacy

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.

Impact of Salt-to-Base Conversion on Safety

The principal risk of prasugrel is bleeding. In essence, salt-to-base conversion has the potential to lead to lower bioavailability in the presence of PPI or H2 antagonists, which would tend to cause less bleeding. Thus, potentially lower bioavailability does not pose a safety risk, per se.

Table 4: Non-CABG-Related TIMI Major or Minor Bleeding Events Through 3 Days by PPI Medication Use and H2 Receptor Blocker Use

Study Population	Prasugrel			Clopidogrel			Cox Proportional HR (95% C.I.)
	N	n	%	N	n	%	
Overall	6741	138	4.5	6716	113	3.4	
PPI Yes	2760	70	2.5	2719	62	2.3	1.11 (0.79, 1.56)
PPI No	3981	68	1.7	3997	51	1.3	1.35 (0.94, 1.94)
H2 Antagonist Yes	1027	30	2.9	1017	25	2.5	1.19 (0.70, 2.02)
H2 Antagonist No	5714	108	1.9	5699	88	1.5	1.23 (0.93, 1.63)

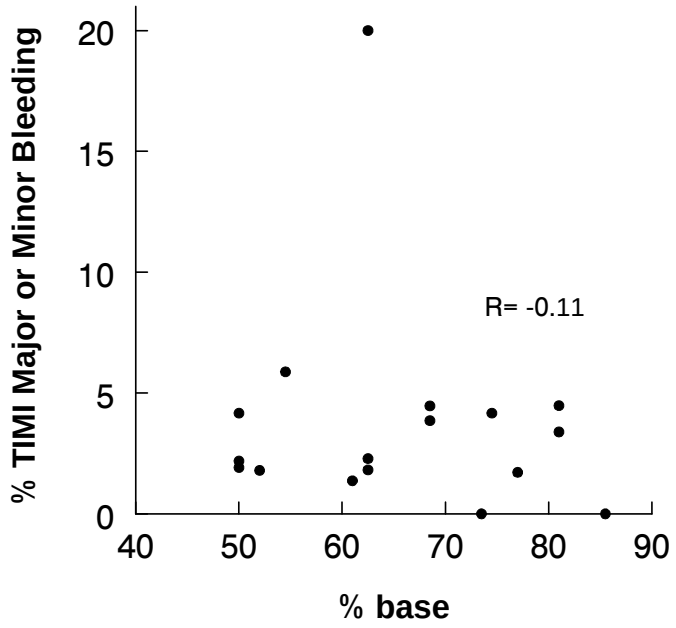
Table 4 shows the incidence of TIMI Major and Minor bleeding events through 3 days, dichotomized by PPI use or non-use (top) or H2 receptor antagonists use or non-use (bottom) through 3 days. If higher gastric pH decreased the bioavailability of prasugrel, one would expect to observe fewer bleeding events in patients who received PPI or H2 antagonists in the prasugrel group, relative to the clopidogrel group.

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 antagonists were discretionary, and physicians may have been more willing to prescribe them for patients perceived to be at higher risk of bleeding events.

Given to the limited numbers of bleeding events, due in part to considering events through only Day 3, the analysis is not robust. Whereas the data do not suggest a bioavailability issue, neither do they provide much reassurance to refute one. They do suggest that prasugrel's bleeding risk, with or without PPIs or H2 receptor antagonists, is consistent with the study as a whole.

When the review team analyzed TIMI Major or Minor bleeding rates by lot administered during the first 30 days, there was no relation between salt-to-base conversion and bleeding (Figure 7).

Figure 7: TIMI Major or Minor Bleeding Versus Base Content of Lot Administered Through Day 30



Importance of Dose to Safety and Efficacy:

Finally, when considering the potential influence of salt-to-base conversion on safety and efficacy, it is useful to place the potential differences in bioavailability into perspective. If we assume a worst-case scenario, that is, that salt-to-base conversion cannot be controlled, that this phenomenon results in a 38% difference in C_{max} between the low- and high-conversion lots at the 30 minute time point, and that the impact on platelet aggregation, although transient, is important, it should be recognized that the variability is only moderate when compared to the variability in weight-adjusted dose between patients of higher and lower weight (all patients receive the same dose of prasugrel). Of course the critical issue is whether higher weight patients taking gastric pH raising medications could receive lots with higher salt-to-base conversion and experience reduced efficacy. Fortunately, the clinical data provide a fair measure of reassurance in this regard.

Conclusions:

The conversion of the drug product from salt to base is a heretofore-unknown phenomenon that could have been discovered as a result of following the Quality by Design paradigm of drug development. Conversion affects the pharmacokinetics of the product when it is co-administered with a PPI or H2 receptor antagonist; the high-conversion drug substance is technically bio-inequivalent to the low- and medium-conversion lots. The difference in bioavailability is evident in C_{max}, but not AUC, and translates into less biological activity than the low- and medium-conversion products at the 0.5- and 1-hour time points. However, at 2 hours and beyond, the difference disappears. This can be conceptualized as a delay of approximately 20 minutes in achieving maximal inhibition of platelet aggregation. On the other hand, inhibition

of platelet aggregation resulting from prasugrel 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 clopidogrel.

The clinical data are also reassuring with regard to salt-to-base conversion. In terms of efficacy, the results for essentially all prasugrel lots administered during the first 30 days trended favorably relative to clopidogrel (Figure 5). Moreover, the use of PPI had no discernable effect on the efficacy of prasugrel in relation to clopidogrel. From the standpoint of safety, the importance of salt-to-base conversion is more difficult to assess, because the analyses are based on bleeding events, which were relatively uncommon. In any case, a product with high salt-to-base conversion administered in the presence of a PPI or H2 receptor antagonist has reduced bioavailability, which would lead to *less* bleeding. In actual use, the relation between PPI use and bleeding for subjects who received prasugrel was similar to that of clopidogrel, and there was no apparent relation between the salt/base content of the lots used during the first 30 days and bleeding events.

(b) (4)

In conclusion, although the conversion of the product from the salt to base form is counter to product purity, it could have been detected as a result of the QbD initiative. Such conversion may be an issue for marketed products, although this is purely conjecture. More importantly, approval of a product with significant conversion sets a poor precedent. On the other hand, the biological activity of prasugrel on inhibition of platelet aggregation exceeds clopidogrel at all time points, and the clinical data argue strongly that the salt-to-base conversion has no clinically important effect on the performance of prasugrel. Its performance exceeds that of clopidogrel, and therefore salt-to-base conversion should not be a reason to deny approval of this NDA.