form, it was selected for further development. Together, 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 clastogencity 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.

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.

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

Body Weight: Exposure of R-138727 increased with decreasing body weight. Major bleeding (Thrombolysis in Myocardial Infarction [TIMI] major bleeding) 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.

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

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

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.

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.

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.

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

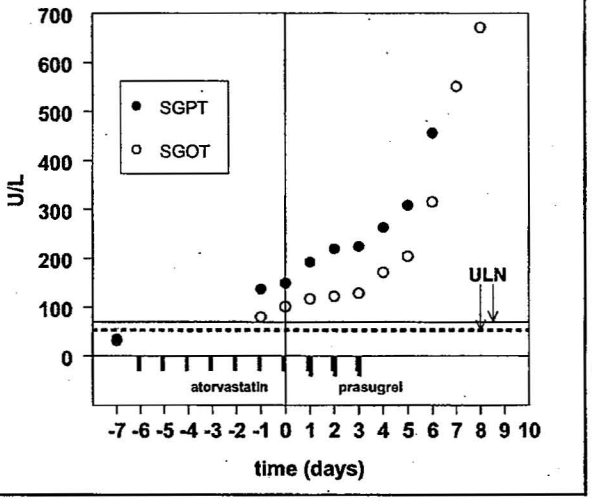
Food Effects: In a study of healthy subjects, the AUC of the active metabolite was unaffected by a high fat, high calorie meal; however, C_{max} was decreased by 49%, and the time to reach C_{max} (T_{max}) was increased from 0.5 to 1.5 hours. Because AUC is considered to be more important than C_{max}, and because T_{max} has little meaning, Prasugrel can be administered without regard to food.

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 2). 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 2: 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 digoxin needs no dose adjustment 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 6.1.1., below.

6. Clinical/Statistical

6.1.1. 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 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.

6.1.2. 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."

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]).

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 CK-MB or troponin were not 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)

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.

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.

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.

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