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.

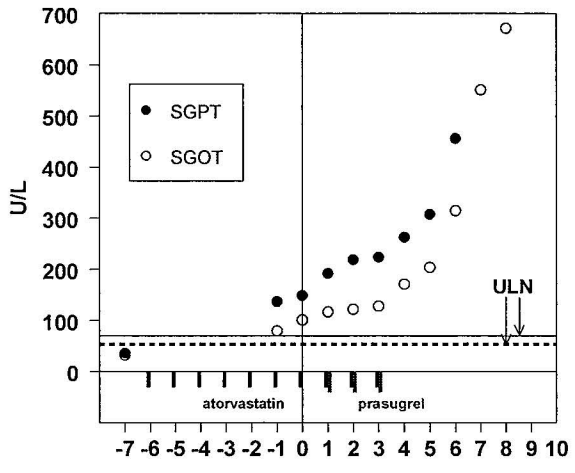
5.3.2. Drug-Drug Interaction Information

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)

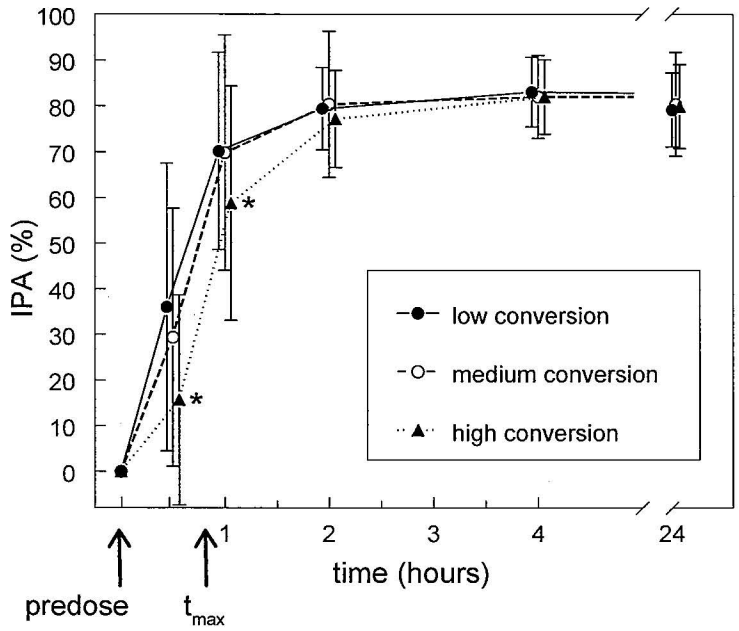
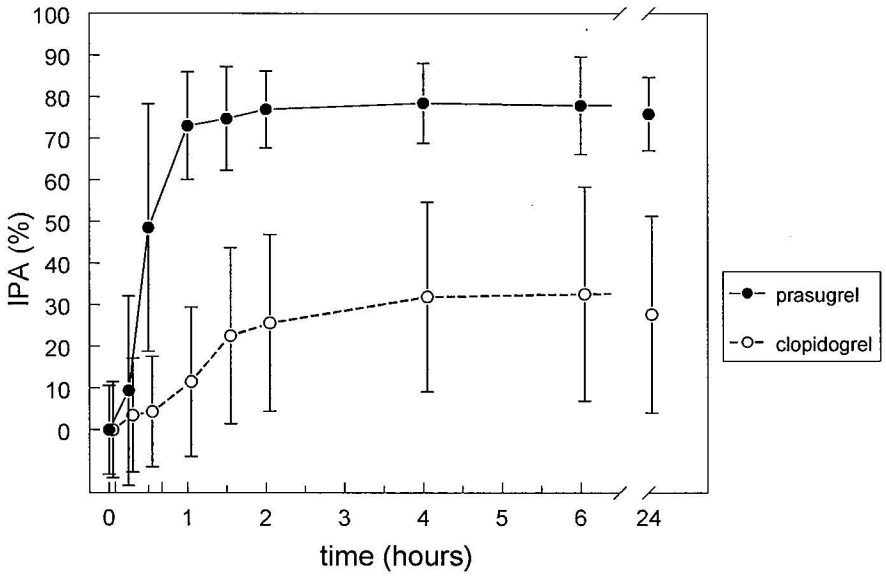


Figure 3: Inhibition of Platelet Aggregation (IPA) to 20 μM ADP, Following Loading Doses of Prasugrel 60 mg or Clopidogrel 300 mg (from Study TAAJ, mean ± SD)



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