

1.3 Summary of OCPB Findings

1.3.1 Background

Eli Lilly and Co is seeking the approval of prasugrel for the reduction of atherothrombotic events and the reduction of the stent thrombosis in acute coronary syndromes (ACS).

1.3.2 Current Submission

The investigation of prasugrel was performed under the IND 63449. The clinical pharmacology program for the NDA 22-307 includes 48 clinical pharmacology and biopharmaceutics studies. The assessment of the prasugrel PK and PD in healthy subjects included a single and a multiple dose PK, a dose ascending, a mass-balance and a food-effect, and 10 drug-drug interaction PK and PD studies. The influence of race, age, hepatic and renal impairment on prasugrel PK and PD were evaluated in 13 studies. The PK and PD in subjects with atherosclerotic vascular disease were evaluated in 4 studies. The efficacy of prasugrel as an anti-thrombotic therapy in the treatment of patients with ACS managed by Percutaneous Coronary Intervention (PCI) was supported by one large Phase 3 clinical study (TAAL).

Also, protein binding, metabolism, and formation of the isomer sets (RS/RR and SR/SS) of R-138727, the active metabolites were studied in 7 in vitro studies. A population PK/PD data analysis was performed for the pivotal study TAAL. A thorough QT study was also done.

In total, 36 studies submitted under the NDA 22-307 were reviewed.

Pharmacokinetics

Absorption, Distribution, Metabolism, Excretion

Following oral administration, more than 79% of the dose is absorbed. The absorption and metabolism are rapid, with peak plasma concentrations (C_{max}) of the active metabolite occurring approximately 30 minutes after dosing. The active metabolite's exposure (AUC) increases slightly higher than proportionally over the therapeutic dose range. The administration of repeated doses of 10 mg does not lead to the accumulation of the active metabolite.

The parent drug is not detected in plasma following oral administration. It is rapidly hydrolyzed by hydroxysterases in the intestine to a thiolactone, which is then converted to the active metabolite by a single step primarily by CYP3A4 and CYP2B6 and to a lesser extent by CYP2C9 and CYP2C19.

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

The binding of the active metabolite to plasma proteins was not determined in vivo, and in vitro, it was 98% in a 4% human serum albumin solution in phosphate buffer, pH 7.4. All the inactive metabolites are highly bound to human plasma proteins.

Although the plasma-to-whole blood ratio measured by total radioactivity was generally greater than one, it does not prove that the penetration into red blood cell was limited to a specific molecular entity.

The active metabolite R-138727 contains 2 chiral centers, and thus is comprised of 4 enantiomers which possess different activities towards the platelet P2Y₁₂ ADP receptor, with the (R,R)/(R,S) pair being the most potent. In humans, the (R,R)/(R,S) pair comprised about 84% of the total active metabolite in plasma. The ratios of R-138727 enantiomers were consistent among all subjects.

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

Pediatric Patients

The pharmacokinetics of prasugrel in children has not been studied in this NDA.

Intrinsic Factors

Body Weight

Dose adjustment to 5 mg QD in patients with body weight below 60 kg is acceptable. Trends of increased bleeding related adverse events were associated with increased exposures of R-138727. Exposure of R-138727 increased with decreasing body weight and the Thrombolysis in Myocardial Infarction (TIMI) Major bleeding risk was 2 fold higher in patients with body weight less than 60 Kg. Efficacy was similar across the body weight groups. Reducing the maintenance dose of prasugrel to 5 mg shifts more than 50% of patients with body weight less than 60 Kg to lower quartiles of exposure seen with 10 mg in patients with body weight greater than 60 kg.

Gender

No dose adjustment based on gender is recommended

Age

There is no need for the dose adjustment for the patients older than 75 years of age. Age ≥ 75 y was an independent predictor for increased risk of primary composite efficacy endpoint (Cardiovascular death, non-fatal myocardial infarction and non-fatal stroke CVD/ Non-fatal MI/Non-fatal Stroke) and TIMI Major bleeding. Even with 10 mg QD regimen, the risk of observing efficacy endpoint was ~ 2 fold higher in patients with age ≥ 75 y compared to patients below 75 y. Further the relative risk for TIMI major bleeding was 65% higher. However, prasugrel is shown to be better than clopidogrel in patients above 75 years age group. The impact of further dose reduction on the efficacy is not known. Hence dose reduction is not justified.

Race

The exposure to the prasugrel active metabolite in African, Hispanic, and Caucasian subjects were similar; however, the exposure were about 40-45% higher in Asian compared to Caucasian subjects. After adjusting for the population body weight and the effect of other covariates, C_{max} and AUC_{0-tlast} were still 20% higher in Asians than in Caucasians. The IPA response in the Asian subjects was stronger than in Caucasians. The highest incidence of bleeding-related adverse events was reported for Korean subjects.

The administration of prasugrel to subjects of Asian origin should be performed with caution.

Renal Impairment

After 60 and 10 mg doses of prasugrel, the exposure to R-138727 (both C_{max} and AUC_{0-tlast}) decreased by half in subjects with ESRD compared to that in healthy controls and subjects with moderate renal impairment. A conclusion about the MPA response in patients with ESRD is difficult to make due to the small sample size. The bleeding events were not assessed in these studies. The label should contraindicate prasugrel administration to ESRD patients.

Hepatic Impairment

The PK parameters estimated for the active metabolite R-138727 in healthy subjects and in subjects with moderate hepatic impairment were similar. The PD response measured as MPA to

20 mcM ADP was similar in the groups of healthy subjects, and subjects with mild and moderate hepatic impairment.

A dose adjustment is not required for the patients with mild and moderate hepatic impairment. Prasugrel should be contraindicated in patients with severe hepatic impairment due to the potential risk of bleeding.

Extrinsic Factors

Food Effect

In a study of healthy subjects, AUC of the active metabolite was unaffected by a high fat, high calorie meal, but C_{max} was decreased by 49% and the time to reach C_{max} (T_{max}) was increased from 0.5 to 1.5 hours. Prasugrel can be administered without regard to food.

Drug-drug interaction information

The *in vivo* DDI studies with a CYP3A4 inhibitor (ketoconazole), a CYP3A4 inducer (rifampicin), and a CYP2B6 substrate (bupropion) did not reveal any clinically important interactions. A clinically significant pharmacodynamic drug-drug interaction: prolongation of the bleeding time was observed when prasugrel was co-administered with aspirin, warfarin and heparin. Caution should be exercised when these drugs are coadministered with prasugrel. Due to an increased incidence of liver enzyme elevation observed following coadministration of prasugrel and atorvastatin, this combination should be prescribed under close physician monitoring.

The potential role of prasugrel as a Pgp substrate was not evaluated in this NDA. Co-administration of prasugrel with digoxin reveals that prasugrel is not an inhibitor of Pgp, as digoxin clearance was not affected by prasugrel coadministration.

Exposure-Response Relationships

Effectiveness

Prasugrel showed a concentration dependent inhibition of the platelet aggregation (IPA). The exposures achieved with the proposed loading dose of prasugrel result in maximum inhibition of the platelet aggregation. However, the relationship between the inhibition of platelet aggregation and the clinical outcome (CVD/Non-fatal MI/Non-fatal Stroke) is not clearly understood. Further, in a double blind, randomized dose-ranging trial in patients undergoing percutaneous coronary intervention (PCI), no consistent relationship between the dose of prasugrel and the endpoint (major adverse cardiovascular event [MACE] at 30-day visit) was observed. However, it should be noted that this study was not designed to characterize dose-response and the sample size was small.

Lowest incidence of the primary efficacy endpoint was seen when the loading dose was administered within 30 minutes of the start of Percutaneous Coronary Intervention (PCI). The increased incidence of the primary efficacy endpoint when the loading dose was administered at least 6 hrs prior to the start of PCI was confounded with Prior Coronary Bypass Graft Surgery. The effect of timing of loading dose on the efficacy was seen independently for prasugrel and clopidogrel, suggesting that pre-treatment 6 hrs before the start of PCI may not be necessary.

Safety

A meta analysis of the pharmacokinetic data from 6 clinical pharmacology studies found that among subjects treated with prasugrel 10-mg MD, a trend towards a higher rate of bleeding-related adverse events in the highest quartile of exposure to the active metabolites. Further in a

phase 1b study TAAD, the rate of epistaxis was higher in subjects treated with 15 mg prasugrel. Similar results indicating increased Thrombolysis in Myocardial Infarction (TIMI)/Major/Minor/Minimal bleeding rates were observed in the phase II study TAAH indicating exposure bleeding relationship. In the phase II study TAAH in ACS patients, increasing doses of prasugrel resulted in increased Thrombolysis in Myocardial Infarction (TIMI)/Major/Minor/Minimal bleeding (5.2% with 60/15-mg MD versus 3.5% with 40/7.5-mg and 60/10-mg doses respectively). However, this difference was primarily in TIMI minimal bleeding. All these studies indicate towards a relationship between the exposure of R-138727 and bleeding.

Prasugrel was found not to prolong the QT interval.

Biopharmaceutics

Prasugrel particle size does not seem to affect the bioavailability of the active metabolite after coadministration with 30 mg lansoprazole.

Lots with differing amounts of prasugrel salt (78, 50 and 5%) were found to be bioequivalent. However, when these lots were coadministered with 30 mg lansoprazole, these lots were bioequivalent in terms of AUC but not CMAX. (30 % differences in means between the high and low conversion lots). This difference in CMAX translated into a greater than 10% difference in IPA at 0.5 and 1 hour postdose.

2 QUESTION BASED REVIEW

2.1 General Attributes

History of Regulatory Development

EFFIENT[®] (prasugrel hydrochloride), an adenosine diphosphate (ADP) receptor antagonist of the thienopyridine class, is an inhibitor of platelet activation and aggregation mediated by the P2Y₁₂ ADP receptor. Prasugrel (also known as CS-747 and LY640315) was discovered by Sankyo Company, Ltd. (now Daiichi Sankyo), which sponsored the initial preclinical and clinical studies. Prasugrel is currently a co-development project between Daiichi Sankyo and Eli Lilly and Company.

In the present submission, the sponsor is seeking the approval of prasugrel for the reduction of atherothrombotic events and the reduction of the stent thrombosis in acute coronary syndromes (ACS).

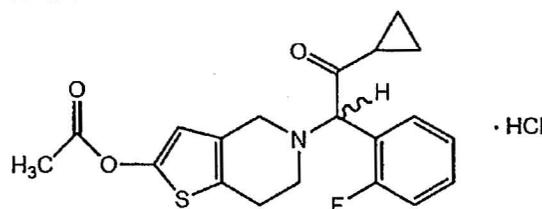
Highlights of chemistry and physical-chemical properties of the drug substance and product

Prasugrel is available as a hydrochloride salt. The Chemical Name (USAN): (±)-2-[2-Acetyloxy-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl]-1-cyclopropyl-2-(2-fluorophenyl)ethanone hydrochloride. Other Chemical Name: 2-Acetoxy-5-(a-cyclopropyl carbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride.

Molecular Formula: C₂₀H₂₀FNO₃S•HCl

Molecular Weight: 409.90

Structural Formula:



Prasugrel is administered as a racemic prodrug that is metabolized in vivo to the active moiety, R-138727 which contains 2 asymmetric centers, therefore, has 4 diastereomers.

Prasugrel hydrochloride is a white to light brown solid.

Solubility: It was not feasible to conduct equilibrium solubility determination of this molecule due to the rapid solution hydrolysis of prasugrel hydrochloride prodrug.

What are the proposed mechanisms of action and therapeutic indication?

Prasugrel's pharmacological action results from a covalent and irreversible binding of R-138727 to the P2Y₁₂ platelet adenosine diphosphate (ADP) receptor. Once bound, a platelet is rendered ineffective for its remaining lifespan. After prasugrel dosing is stopped, return to baseline platelet aggregation occurs only as new platelets are formed.

What are the proposed dosages and route of administration?

The sponsor recommends that prasugrel be initiated with a single oral 60 mg loading dose and then continued at a 10 mg once daily dose. All patients taking prasugrel should also take aspirin (75 mg to 325 mg) daily. Prasugrel may be taken with or without food. Patients weighing less than 60 kg should be given a single 60 mg loading dose and then continued at a 5 mg once daily dose. Patients 75 years of age and older should be given a single 60 mg loading dose and consideration may be given to a 5 mg once daily dose as an alternative to 10 mg once daily dose.

2.2 General Clinical Pharmacology

What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The investigation of prasugrel was performed under IND 63449. The clinical pharmacology program for NDA 22-307 includes 48 studies.

An assessment of prasugrel PK and PD in healthy subjects was performed in 8 clinical studies. The early studies investigated the base-formulation of the drug. A single and a multiple dose PK, a dose ascending, a mass-balance and a food-effect study were also performed. The influence of race, age, hepatic and renal impairment on prasugrel PK and PD were evaluated in 13 studies.

The PK and PD in subjects with atherosclerotic vascular disease were evaluated in 4 studies including the pivotal trial TAAL.

Drug-drug interaction PK and PD studies of prasugrel and aspirin, proton pump inhibitors, ketoconazole, rifampicin, atorvastatin, warfarin, bupropion, heparin, and digoxin were performed.

Also, protein binding, metabolism, and formation of the isomer sets (RS/RR and SR/SS) of R-138727, the active metabolites were studied in 7 in vitro studies.

Several studies describing the base formulation and also studies performed under the other investigation program in Japan were not reviewed.

In total, 36 studies submitted under the NDA 22-307 were reviewed.

Were the correct moieties identified and properly measured to assess clinical pharmacology?

Yes. The sponsor measured the concentrations of prasugrel metabolites since prasugrel is a prodrug and cannot be measured in plasma. In the majority of the clinical pharmacology studies, the active metabolite of prasugrel R138727 was measured as well as the inactive metabolites R-95913, R119251, and R106583. In the early studies, the other inactive metabolite R100932 was measured (instead of R119251). In order to measure the plasma concentrations of the active metabolite R-138787 of prasugrel, the sample should be derivatized immediately after the sample is taken. Due to the difficulties with the handling of blood samples, in the pivotal clinical study only inactive metabolites were measured in plasma, and the active metabolite characteristics were estimated based on the proposed population PK model.

For the assessment of pharmacodynamics, the inhibition of platelet aggregation (IPA) by 5 and 20 mcM of ADP was measured. Also, a few other methods were used, as VASP phosphorylation (flow cytometry), platelet reactivity index (PRI), bleeding time.

All assay methods were properly validated and are acceptable, chromatograms were shown.

EXPOSURE-RESPONSE RELATIONSHIP: EFFICACY

What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

The pharmacological response to clopidogrel or prasugrel is inhibition of platelet aggregation. A semi-mechanistic model was developed to describe relationship between the active metabolite concentrations of prasugrel or clopidogrel and inhibition of platelet aggregation. The active metabolites for both prasugrel and clopidogrel are reported to have similar affinities for binding to the P2Y₁₂ receptor of the platelets. Concentration dependent inhibition of platelet aggregation was seen as shown in Figure 1 below. Similarly a dose dependent increase in platelet aggregation was observed in Study TAAD.

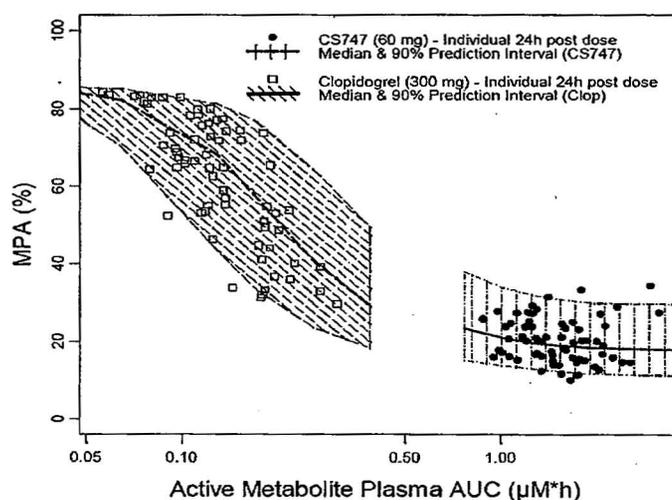


Figure 1 The inhibition of the platelet aggregation is dependent on the concentration of the active metabolites of prasugrel and clopidogrel

The clinical endpoint for measuring the efficacy is a composite of Cardiovascular death (CVD), Non-fatal Myocardial Infarction and Non-fatal Stroke. Till date there is no established relationship between inhibition of platelet aggregation and the clinical endpoint. Since only one dose level of prasugrel (60 mg LD/10 mg MD) was studied in the pivotal trial, dose-response analysis could not be performed. However, in a double blind, randomized dose-ranging trial in patients undergoing percutaneous coronary intervention, no consistent relationship between the dose of prasugrel and the endpoint (major adverse cardiovascular event [MACE] at 30-day visit) was observed as shown in Figure below. However, it should be noted that this study was not designed to characterize dose-response and the sample size was small (N=200 for 40/7.5 mg (LD/MD) and 60/10 mg groups and N=251 for 60/15 mg group).

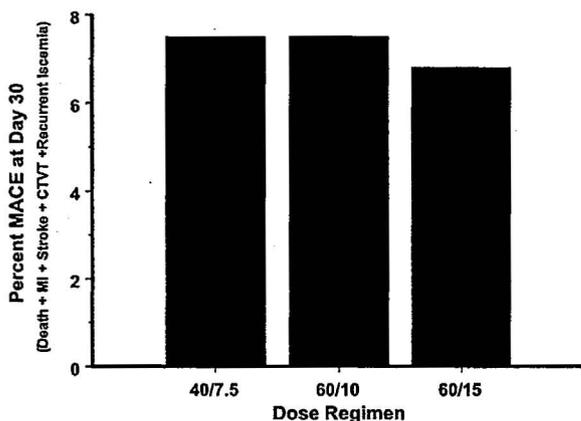


Figure 2 No relationship between dose and major cardiovascular events (MACE - Death+MI+Stroke+CTVT+Recurrent Ischemia at 30-day visit)

What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

A meta analysis of the pharmacokinetic data from 6 clinical pharmacology studies (TAAS, TAAZ, TABS, TABV and TACG) found that among subjects treated with prasugrel 10-mg MD, a trend towards a higher rate of bleeding-related adverse events in the highest quartile of exposure to the active metabolites as shown in Figure below.

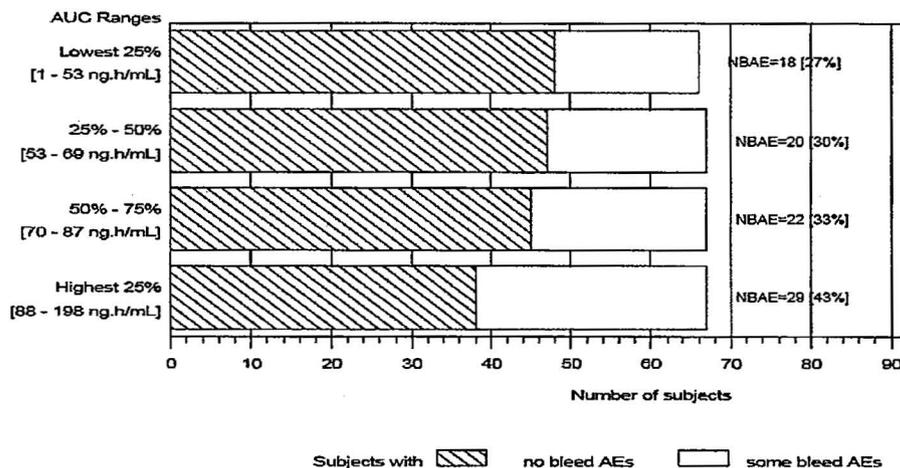


Figure 3 Increase in the active metabolite exposures trends to increase in number of bleeding adverse events (NBAE).

In the phase 1b study TAAAD, in subjects with stable atherosclerosis, the rate of epistaxis was higher in subjects treated with prasugrel 15-mg MD (5%) than in subjects treated with prasugrel MD of 10 mg (1%), 7.5 mg (1%) or 5 mg (1%).

In the phase II study TAAH in ACS patients, increasing doses of prasugrel resulted in increased TIMI/Major/Minor/Minimal bleeding (5.2% with 60/15-mg MD versus 3.5% with 40/7.5-mg and 60/10-mg doses respectively). However, this difference was primarily in TIMI minimal bleeding.

All these studies indicate a relationship between the exposure of R-138727 and bleeding.

Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Dose selection for the pivotal trial was based primarily on the effect of prasugrel on the inhibition of platelet aggregation (IPA) and bleeding compared to clopidogrel in subjects with stable atherosclerosis.

In Study TAAAD, 4 prasugrel LD/MD regimens were compared with the approved clopidogrel LD/MD regimen. As seen in Figure, both the 40-mg and 60-mg prasugrel LDs resulted in more rapid onset with significantly greater IPA to 20 μ M ADP from 2 to 6 hours after administration than the 300-mg LD of clopidogrel.

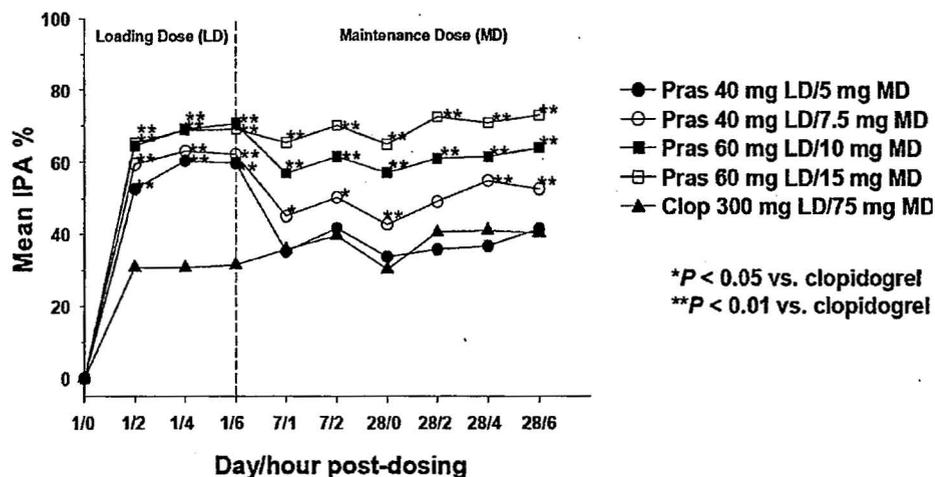


Figure 4 Prasugrel LD of 60 mg achieves highest IPA. Maintenance doses of 10 mg and 15 mg achieve significantly greater IPA compared to clopidogrel MD of 75 mg.

The 60-mg prasugrel LD consistently achieved the highest level of platelet inhibition. Both the 10- and 15-mg prasugrel MDs achieved consistent and significantly greater IPA than the 75-mg clopidogrel MD. However, the 15-mg MD of prasugrel was associated with higher bleeding adverse events (AEs) hence 10-mg prasugrel MD was selected. This effect of increased trend for bleeding with 15-mg prasugrel MD compared to 10-mg prasugrel MD was also observed in Study TAAH. Further, 10-mg prasugrel MD had 0% poor PD responders (as defined by IPA <20% to 20 μ M ADP) compared to about 20% with 7.5-mg prasugrel MD.

Hence, the dose regimen of a single 60-mg loading dose (LD), followed by a 10-mg once-daily maintenance dose (MD) was selected to be studied in the registration trial TAAL.

However, given the lack of consistent relationship between the inhibition of platelet aggregation and the risk for cardiovascular events, it is not known whether a mean 10% increased effect (prasugrel LD 60 mg Vs 40 mg) on platelet inhibition would translate into a meaningful incremental reduction of cardiovascular risk. Hence it is not known whether a lower dose would have provided similar benefit with decreased risk for bleeding. The current submission does not have enough data to explore the value of lower doses.

FDA PHARMACOMETRIC DATA ANALYSES

The relationship between the efficacy endpoint/TIMI major bleeding and body weight/age were performed using the intent-to-treat (ITT) set, consisting of all randomized subjects except where otherwise specified in Study TAAL. Kaplan-Meier and Cox regression analysis were employed to explore the relationships. Age and body weight were tested either as continuous or categorical covariates. Multivariate analyses utilized a Cox proportional hazard model with entry and exit criteria of $\alpha=0.05$ in a stepwise selection method. The following factors were included in the multivariate analyses: weight (<60 Kg, ≥ 60 kg), age (<75 years, ≥ 75 years) and sex. The qualifying event (UA/NSTEMI or STEMI) was used as the stratification factor.

The relationship between body weight/age and clearance of the active metabolite of prasugrel was derived based on the population pharmacokinetic analysis. The analysis was performed for studies TAAD and TABR.

Pretreatment with clopidogrel prior to PCI has been accepted to potentially provide increased benefit. This is based on the observation that pretreatment at 6 hours or longer prior to PCI is needed with a 300 mg or larger loading dose to achieve maximal effects on the platelet aggregation more rapidly^{1,2,3}. Among patients in whom clopidogrel was initiated at least 6 hours prior to PCI in the CREDO trial, a 38% reduction in the relative risk of the cardiovascular endpoint (death, MI or stroke) was observed⁴ compared to those who received loading dose later. Further, the ACC/AHA 2007 guidelines for the management of patients with UA/NSTEMI recommend administration of clopidogrel 300 mg at least 6 hours earlier than planned catheterization or PCI⁵. However, it should be noted that this is a Class IIa/Level B evidence, indicating conflicting evidence from single randomized trial or non-randomized studies⁵.

Hence the relationship between the time of loading dose with respect to the start of PCI and the incidence of the efficacy endpoint was graphically explored. The difference between the times of the loading dose and the start of PCI were divided into octiles (8 equal parts) and the proportions of the events were plotted against the midpoints of the octiles. Kaplan-Meier and Cox regression analysis were employed to further explore the relationships between the quartiles of loading dose and PCI time difference and the time-to- efficacy endpoint. Further exploratory analyses of the difference in the time of loading dose and the start of PCI were performed to identify correlated risk factors.

¹ Seyfarth et al. Am Heart J. 2002;143:118-123

² Muller et al. Heart. 2001;85:92-93

³ Helft et al. Arterioscler Thromb Vasc Biol. 2000;20:2316-2321

⁴ Steinhubl et al. JAMA. 2002;288,19:2411-2420

⁵ ACC/AHA Guidelines Revision. Circulation. 2007;116:803-877