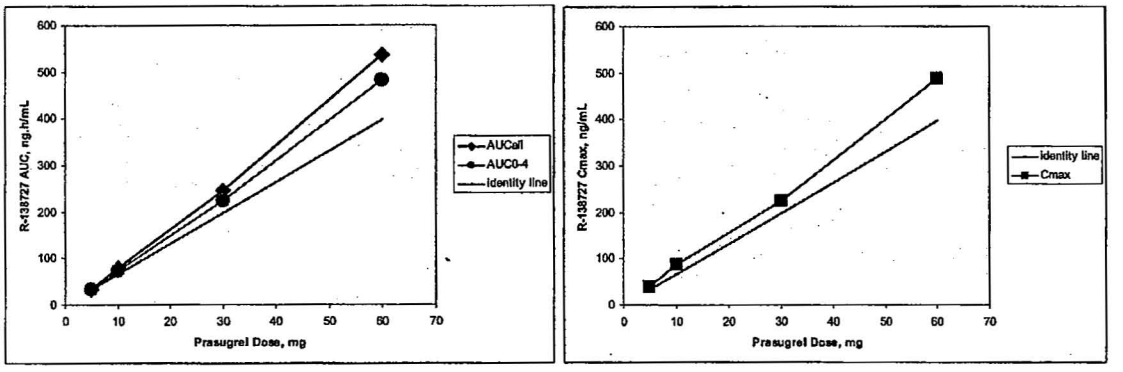

Figure 13. PK Parameters of R138727 vs. Prasugrel Dose, Study TAAW.

The assessment of dose-proportionality in the population PK did not find any disproportionality between doses (Appendix IV). The sponsor also performed a meta-analysis of the PK data which were reasonably combined from the different studies. Since for the general population the proposed dosing regimen includes only one dose of 60 mg followed by repeated 10 mg dose, slight disproportionality in AUC would not be of clinical significance. The administration of repeated doses of 10 mg does not lead to any accumulation of the active metabolite.

What is the inter- and intra-subject variability of the PK parameters, and what are the major causes of variability?

Prasugrel is a moderately variable dug.
The estimates of between-patient variability in apparent clearance in these studies have been moderate, ranging from 25% to 30%. Between-patient variability in apparent volume of distribution (Vd/F) was moderate at 28.5% in Study TAAD and 34.3% in Study TAAJ. The variability was explained by body weight, age, dose, co-administration of ketoconazole and food as significant factors relating to the differences between R-138727 and R-106853. (See PM review for details).

2.3 Intrinsic Factors

What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses? Based on what is known about exposure-response relationships, what dosage regimen adjustments, if any, are recommended for each subgroup listed below?

The effects of age, gender, race, and body weight was prospectively studied in the NDA.

Body Weight

In the sponsor's meta-analysis, body weight was found to significantly influence both Cmax and AUC0-tlast of R-138727.

Table 6. Effect of Body Weight on AUC and Cmax of R-138727

Parameters (units)	Change of Body Weight (kg)	Ratio of LS Geometric Mean (90% CI) Compare to 85 kg
C_{max} (ng/mL)	From 85 to 60	1.49 (1.39, 1.59)
AUC(0-t_{last}) (ng•h/mL)	From 85 to 60	1.45 (1.38, 1.52)

The individuals with lower body weight have higher R-138727 exposures. Relative to a population mean of 85 kg in the target patient population (Studies TABR, TAAD, and TAAL), an approximately 25 kg decrease in body weight is predicted to result in an increase of 49% and 45% in R-138727 Cmax and AUC, respectively, following LD or MD doses.

The apparent clearance of R-138727 decreased with decreasing body weight, which would produce increasing exposure as body weight decreases. Specifically, a 31% decrease in body weight from 84 kg to 58 kg produced an approximately 22% decrease in R-138727 CL/F and an increase of ≤10 percentage points in MPA.

The effect of body weight on the pharmacodynamic response was evaluated in the PM review (see Appendix V).

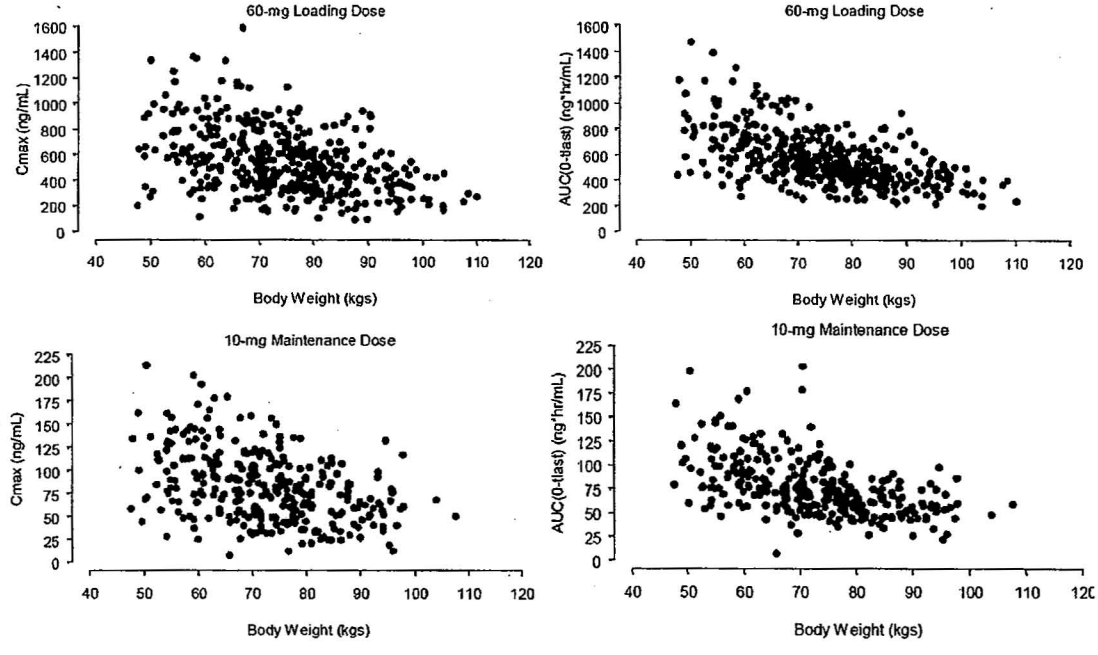

Figure 14. Observed AUC0-tlast and Cmax of R-138727 vs. body weight following a 60-mg LD or during 10-mg MD of prasugrel

Should the maintenance dose be reduced to 5 mg QD in patients with body weight below 60 Kg?

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

Relationship between body weight and efficacy

The exploratory univariate Cox model showed inconsistent results for the impact of body weight on efficacy depending on whether it is used as a continuous or categorical variable. Further, multivariate analysis did not reveal body weight as a significant predictor of risk for efficacy event in multivariate analyses.

Relationship between body weight and TIMI major bleeding

The risk for TIMI major bleeding with prasugrel was found to be higher in the lower body weight group as shown below in the Kaplan-Meier plot. The univariate Cox regression showed that the relative risk for TIMI major bleeding on prasugrel for patients with body weight less than 60 Kg was 4 fold higher (HR: 3.051 (2.013 – 4.623), p <0.0001) compared to patients with higher body weight. Body weight was retained as the significant predictor of TIMI major bleeding risk in multivariate analyses too (HR: 2.826; p<0.0001). Similar relationship was observed for the NCABG TIMI major bleeding.

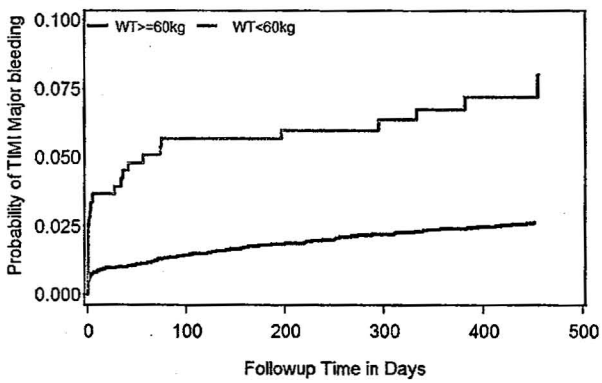

Figure 15 Risk for TIMI Major bleeding is higher in patients with body weight less than 60 Kg.

Relationship between body weight and exposure

The population pharmacokinetic analyses of studies TAAD and TABR reveal that the clearance of the active metabolite R-138727 increases with increase in the body weight as shown in the figure below. This indicates a decrease in exposures with increase in body weight.

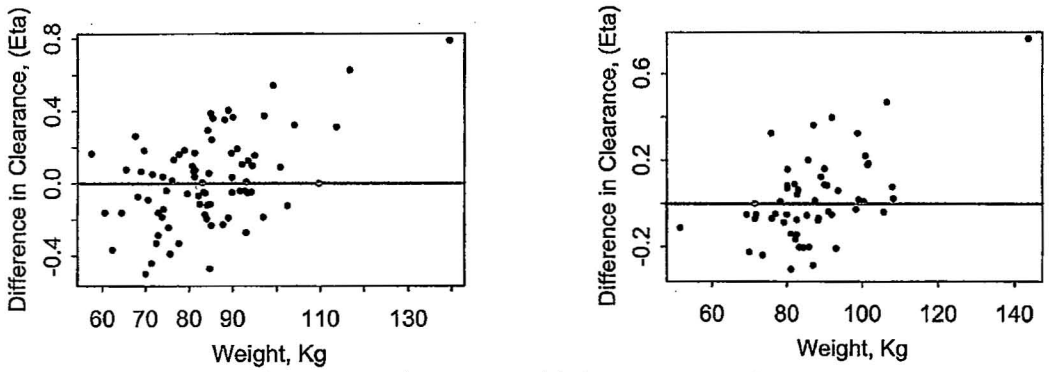

Figure 16 Clearance of R-138727 increases with increase in body weight (Left: Study TAAD; Right: Study TABR)

This decreased exposure with increase in bodyweight is also evident in the pivotal trial (Study TAAL) as shown in the figure below.

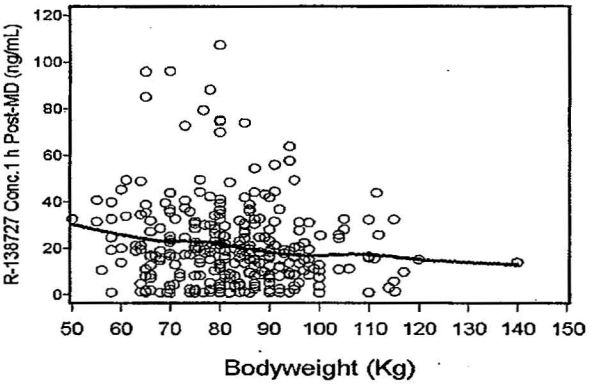

Figure 17 **Decreased Exposures of R-138727 with increased body weight in Study TAAL.** *(Circles represent plasma concentrations 0.75-1.25 h post MD; Blue line is a smooth trend lin)e*

Simulation of R-138727 exposure (model based AUC for the maintenance dose) show that the proposed dose adjustment of 5 mg MD by the sponsor is able to shift the exposure of the majority of subjects with body weight less than 60 Kg from the upper quartile to the lower quartile of those seen in patients with body weight greater than 60 Kg.

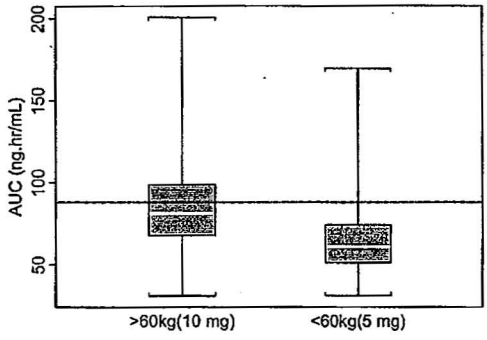

Figure 18 **Simulation (N=2000) of the proposed dose of 5 mg in patients with body weight < 60kg will result in exposures predominantly corresponding to lower two quartiles of those expected with 10 mg MD in patients with body weight >60 kg.** *(The red dashed line represent the concentration range beyond which the bleeding related adverse events were highest from Figure 3). (CL = 123 x (WT/85)$^{0.798}$; Between-subject variability (%CV) = 24% - Obtained from Reviewer's POPPK analysis of TABR for Simulation)*

Age and Gender

A gender effect was not detected in the population PK data analysis performed for the pivotal study TAAL. The sponsor's meta-analysis concluded that R-138727 PK is not clinically significantly affected by age with a range of 18 to 80 years, nor is R-138727 PK affected by gender.

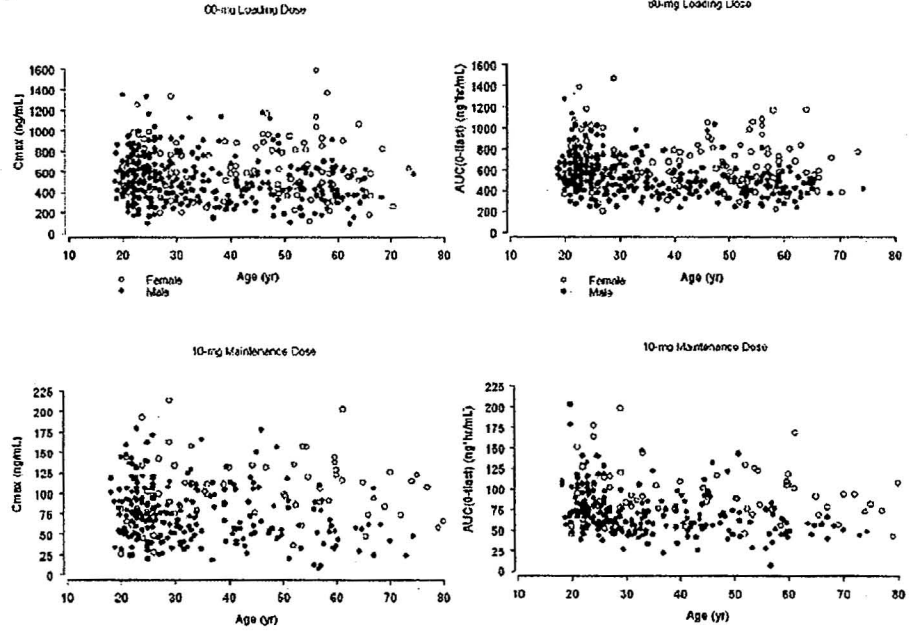

Figure 19 Effect of age by gender on observed R-138727 Cmax and AUC0-tlast following a 60-mg LD and daily 10-mg MD of prasugrel

No dose adjustment should be made based on gender.
In the sponsor's analysis, the older male subjects had lower exposure, specifically a 20% lower AUC0-tlast compare to men 65 years old.
The data from the studies in patients were reanalyzed, and the results are shown below:

Should the maintenance dose be reduced to 5 mg QD in patients with age ≥ 75 years?

Relationship between age and efficacy
Age was found to be a significant predictor of the CVD/Non-fatal MI/Non-fatal stroke (HR: 1.031, p<0.0001). When age was tested as a categorical covariate, the risk for CVD/Non-fatal MI/Non-fatal Stroke on prasugrel for patients with age greater than 75 years was 98%% higher (HR: 1.982 (1.647 – 2.386), p < 0.0001) compared to patients with age less than 75 years. The Kaplan-Meier curve depicting the effect of age is shown in Figure 20. This effect of age was also evident in the multivariate Cox proportional model (HR: 1.98; p<0.0001). Similar relationship was observed for the clopidogrel treatment arm.

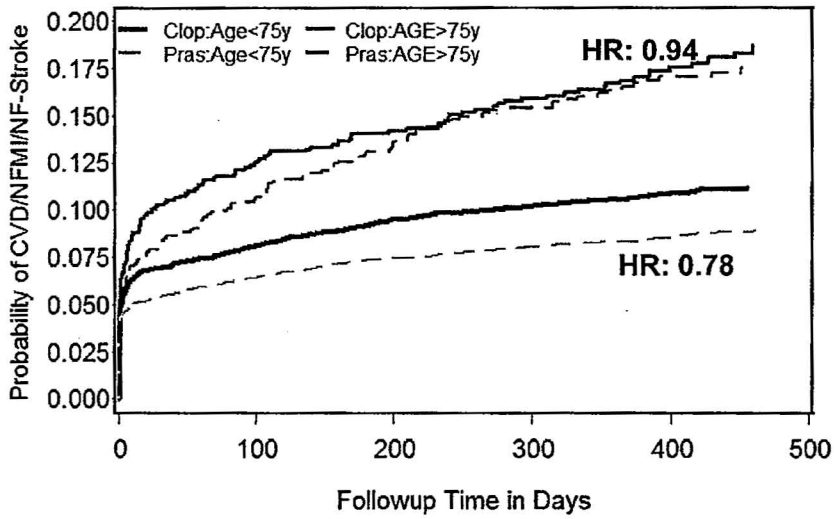

Figure 20: Risk for CVD/Non-fatal MI/ Non-fatal Stroke is high in patients above 75 years of age compared to patients below 75 years. *(The Hazard Ratios are for Prasugrel compared to Clopidogrel in each of the age groups)*

Relationship between age and TIMI major bleeding
Univariate analysis with age as a continuous measure was found to be a significant predictor of TIMI Major bleeding risk with 3.2% increase in risk per year (HR:1.032; p<0.0001) . When tested as a categorical covariate (cutoff 75 years) the relative risk for TIMI major bleeding with prasugrel was significant (HR: 1.818 (1.265 – 2.612); p=0.00120). The Kaplan-Meir curves showing the effect of age on bleeding risk is shown in Figure 21. Age was found to be an independent predictor of TIMI major bleeding risk in multivariate analyses too (HR: 1.650; p=0.0069). Similar relationship was observed for the NCABG TIMI major bleeding in a multivariate analysis.

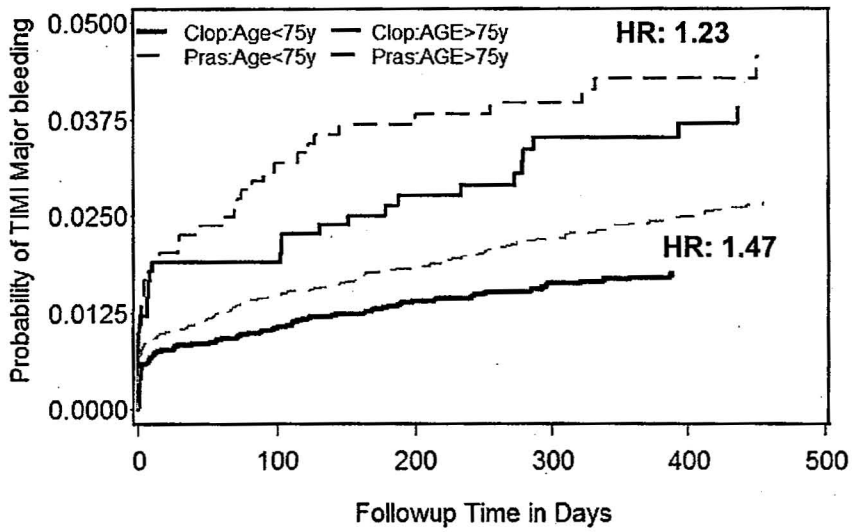

Figure 21 Risk for TIMI Major bleeding is high in patients above 75 years of age compared to patients below 75 years. *(The Hazard Ratios are for Prasugrel compared to Clopidogrel in each of the age groups)*

Since the risk of decrease of efficacy is higher with the existing dosing regimen in patients above 75 years of age, any further reduction in dose aimed at reducing the risk for bleeding might result in reduced efficacy. Based on the reviewer's analysis, prasugrel does not appear to provide safe and effective therapy to patients above 75 years compared to those below 75 years. Hence, prasugrel should not be the treatment of choice in patients above 75 years. Similar results were observed with clopidogrel. Hence P2Y12 antagonists such as clopidogrel and prasugrel should be avoided in elderly patients (age $\geq$ 75 years).

Race, in particular differences in exposure and/or response in Caucasians, African Americans, and/or Asians

There were 96% Caucasian subjects in the pivotal study TAAL. The sponsor performed 2 studies to assess the effect of Asian ethnicity on the pharmacokinetics and pharmacodynamics of prasugrel. The effect of other ethnic background was evaluated by means of meta-analysis performed by the sponsor.

The Cmax and AUC0-tlast values in subjects of African and Hispanic descent were similar to Caucasian subjects, and the Asian subjects had higher exposures than Caucasians. In every dose group, there was a 40-45% increase of Cmax and AUC values in Asian compared to Caucasian subjects. As a population, Asians have lower average body weight; therefore, a 65-kg Asian subject is predicted to have an exposure that is approximately 40% higher compared to a 77-kg Caucasian subject. After adjusting for body weight and effect of other covariates, Cmax and AUC0-tlast values were approximately 20% higher in Asians than in Caucasians. Within Asian populations (Study TABZ), the exposures to prasugrel were similar among Chinese, Japanese, and Korean subjects.

The figure below shows the comparison of the exposure parameters per population per dose of prasugrel.

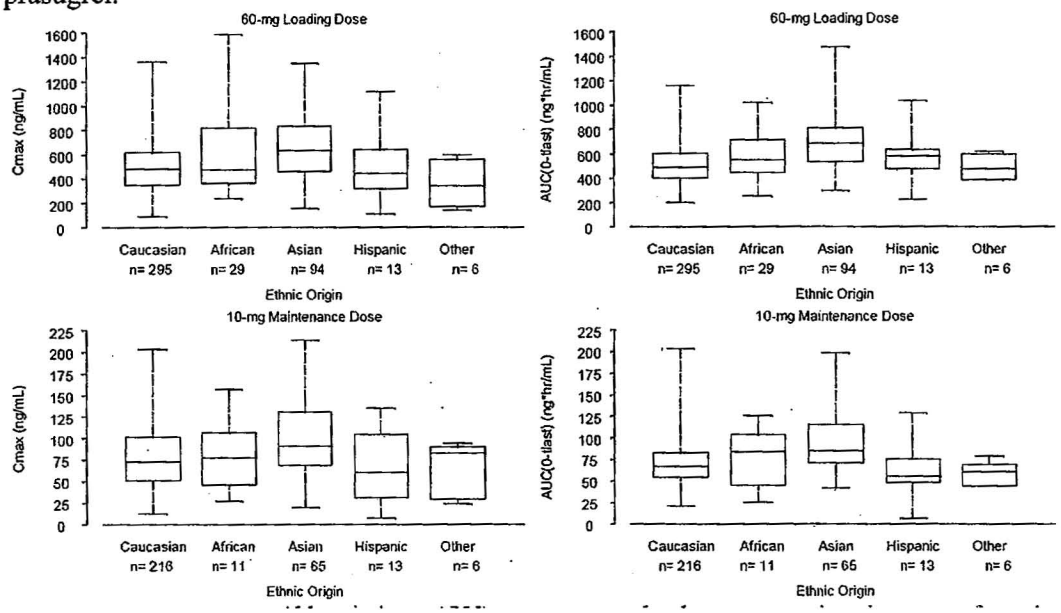

Figure 22 Box plots compare the observed AUC0-tlast and Cmax values of R-138727 by ethnic group following 60-mg LD or 10-mg MD of prasugrel

The IPA response in the Asian subjects was stronger than in Caucasians although the differences between all groups were not significant. The high variability of the method could mask the differences. The highest incidence of bleeding-related adverse events was reported for Korean subjects 20 out of 33, and the lowest incidence reported for Japanese subjects, 9 out of 10. For each ethnic group, the bleeding-related events were most frequently reported following the 10-mg MDs. The bleeding events analyses are performed in the clinical review.

The information related to the development of prasugrel in Japan under the other indication and IND was submitted with NDA 22,307. There were 8 PK and PD studies of prasugrel which were not reviewed except for their synopses. The excessive bleeding was associated with a administration lower dose (30 mg) administered to the Japanese subjects than it is proposed in this NDA.

Similar differences were observed after the multiple 10mg/day and 5mg/day doses of prasugrel

In the Package Insert, it should be mentioned that the administration of prasugrel to subjects of Asian origin should be performed with caution.

Renal Impairment

The impact of renal impairment on the PK of prasugrel was assessed in 3 studies. The two studies used 4 and 5 subjects in the ESRD group and were stopped early. After the 60 and 10 mg doses of prasugrel, the exposure to R-138727 (both Cmax and AUC(0-tlast)) decreased by half in subjects with ESRD compared to that in healthy controls and subjects with moderate renal impairment. The sponsor concluded that the differences in mean MPA values at each time point between subjects with moderate renal impairment and healthy matched subjects and between subjects with ESRD and healthy matched subjects were not statistically significant. However, at

each time point, including the baseline, ESRD subjects had less than maximal platelet aggregation (vs. healthy) with differences between 3 and 19%. It is not clear if this is an indication of increased IPA due to the low baseline MPA values in ESRD group. The statistical conclusion about the MPA response in patients with ESRD is difficult to make due to the small sample size, and the sponsor did not provide any recommendations regarding their dose adjustment.
The label should contraindicate prasugrel administration to ESRD patients.

Hepatic Impairment

The PK parameters estimated for the active metabolite R-138727 in healthy subjects and in subjects with moderate hepatic impairment were very similar (Studies TAAN and TABV). Only 4 subjects with mild hepatic impairment were studied. The PD response measure as MPA to 20 mcM ADP was similar in the groups of healthy subjects, and subjects with mild and moderate hepatic impairment. The effect of hepatic impairment on the prolongation of bleeding time and the frequency of the bleeding events was not evaluated in the two studies performed in subjects with hepatic impairment.
A dose adjustment for the hepatically impaired subjects is not required.

Does the pharmacogenomic data support the label claim: "In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving EFFIENT, there was no relevant effect of genetic variation in CYP3A5, CYP2B6, CYP2C9, or CYP2C19 on the pharmacokinetics of EFFIENT or its inhibition of platelet aggregation."?

This claim is linked to an accurate assessment of the link between patient genotype and the pharmacokinetics of EFFIENT. This claim was tested through the *de novo* analysis of the anonymized genotyping data reported by the sponsor.
Genotyping data were reported from three clinical studies. In the IGA study, the effects of variation in genes encoding CYP enzymes involved in thienopyridine metabolism on PK and PD in response to LD or MD of Prasugrel or Clopidogrel were studied in healthy subjects. The TAAL PK study examined the relationship between variation in the genes encoding CYP2C19 and CYP2C9 and Prasugrel AUC estimates of active metabolite derived from a subset of patients. The TABR study covered the relationship between variation in the genes encoding CYP2C19 and CYP2C9 and Prasugrel AUC estimates of active metabolite derived from aspirin-treated patients with stable atherosclerosis.
The genomic data analysis strategy for the IGA study focused on application of linear mixed-effects models for the analyses of PK and PD as a function of genotype for mutations in CYP3A5, CYP2B6, CYP2C9 and CYP2C19. Results for independent analyses with binning for CYP2C9 and CYP2C19 were also confirmed. In the TAAL study, a multi-linear regression correlation model was used to estimate AUC from the predicted R-138727 Prasugrel active metabolite concentrations during loading and maintenance dosing. The genomic data analysis strategy for the TABR study was analogous to that for IGA, but it included results for measurement of platelet aggregation by several methods, and selective application of linear regression and logistic regression models. The results of this review for data from these studies confirm the conclusion reported by the sponsor that there was no relevant effect of genetic variation on the pharmacokinetics of Prasugrel.

In healthy subjects, patients with stable atherosclerosis and patients with ACS receiving Prasugrel, there was no clinically significant effect of genetic variation in CYP3A5, CYP2B6, CYP2C9, or CYP2C19 as defined by active metabolite exposure levels. In healthy subjects, no effect of genetic variation in CYP3A5, CYP2B6, CYP2C9, or CYP2C19 genes on PD measures of platelet function was observed. In patients with ACS, these evaluations suggest there is no effect of genetic variation on the primary efficacy measures in prasugrel treated patients for any individual CYP enzyme.

2.4 Extrinsic Factors

What extrinsic factors (herbal products, smoking, and alcohol use) influence dose-exposure and/or- response and what is the impact of any differences in exposure on response?

The sponsor addressed the effects of smoking and alcohol use in the meta-analysis. About 20% of subjects were identified as smokers and 70% as consuming alcohol, based on self-reported information. While a statistically significant effect of smoking on the AUC(0-tlast) of R-138727 was detected, the magnitude of the difference between smokers and non-smokers was not clinically relevant. The ratio of LS geometric mean was 0.918 and 90% CI (0.871, 0.967) for R-138727 AUC(0-tlast) and the range of exposure values in smokers and non-smokers overlaps. Smoking status had no significant effect on Cmax. Alcohol consumption did not significantly affect R-138727 PK.

Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes.
Prasugrel is a pro-drug which is hydrolyzed in vivo and is not detected in plasma. In vitro studies showed that the hydrolysis of prasugrel to R-95913 (precursor of the active metabolite) is mediated efficiently by human carboxylesterase hCE2 prior to reaching the portal vein. The metabolism of R-95913 to the active metabolite R-138727 is catalyzed by the 4 cytochromes most capable of forming R-138727, in rank order: CYP3A4 > CYP2B6 > CYP2C9 ~ CYP2C19. The values of the apparent Michaelis-Menten constant (Km) for CYP2B6 (2.3 μM, 761 ng/mL) and CYP2C19 (3.8 μM, 1258 ng/mL) suggest that these enzymes have higher affinities for R-95913 conversion to R-138727 than does CYP2C9 (11 μM, 3641 ng/mL) and CYP3A4 (21 μM, 6951 ng/mL). Considering the abundance of CYP3A, the sponsor hypothesized that the most of R-138727 forms during first pass metabolism intestinal CYP3A during absorption. Inhibition of CYP2B6 (by a monoclonal antibody) and CYP3A (by ketoconazole), in incubations with human liver microsomes, substantially inhibited R-138727 formation, while inhibition of CYP2C9 (by sulfaphenazole) and CYP2C19 (by omeprazole) produced minor and more variable inhibition of R-138727 formation. Additionally, in vitro data showed that CYP3A4 and CYP3A5 may be similarly efficient in converting R-95913 to R-138727.

What drug-drug interaction studies were performed based on the in vitro information?

Prasugrel is metabolized in vitro by CYP3A4 and CYP2B6. The sponsor evaluated the interaction of prasugrel with the following drugs:

1. CYP3A4 inhibitor (ketoconazole),
2. CYP3A4 inducer (rifampicin), and

3. CYP2B6 substrate (bupropion).
4.

Although C_{max} of the prasugrel active metabolite was reduced by 34% when coadministered with ketoconazole, there was no change in AUC; therefore, the clinical drug interactions of prasugrel with other CYP3A4 inhibitors will not be of major concern and no dose adjustment is recommended. There was no significant interaction found between prasugrel and rifampicin. Prasugrel coadministration with a single dose of bupropion decreased its hydroxylation (Cmax by 32% and AUC by 24%). Dose adjustment of bupropion is not needed after coadministration with prasugrel.

Is prasugrel a substrate and/or inhibitor of P-glycoprotein transport processes?

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

In vivo studies with medications that are likely to be administered for the treatment of ACS

Aspirin, warfarin, heparin and atorvastatin are the drugs which may be administered to patients for the treatment of the reduction of atherothrombotic events, stent thrombosis in ACS (acute coronary syndrome), and patients with stable angina.
A significant pharmacodynamic drug-drug interaction, prolongation of the bleeding time was observed when prasugrel was co-administered with aspirin, warfarin and heparin.
At 24 hours post-dose, bleeding time ratio (BTR) increased by 41% in patients who received the 60/10 mg of prasugrel and 150 mg aspirin (compared to the prasugrel arm). An additional administration of 900 mg of aspirin has not changed BTR in this study. At 48 hours post-dose, BTR increased by 73% in patients who received 60/10mg prasugrel and a single 15 mg dose of warfarin (compared to the warfarin arm). At 4 and 6 hours post-dose BTR increased by 36% in the warfarin/prasugrel (compared to the prasugrel arm). The BTR at 4 and 6 hours post-dose was increased by 28% and 16% respectively in the prasugrel + UFH arm compared to the prasugrel alone arm. The increase in BTR was even higher when the prasugrel +UFH arm was compared with the UFH alone arm: 167% and 154% at 4 and 6 hours post-dose.
Based on the serious adverse effects observed following atorvastatin administration in subjects on prasugrel, the combination should be prescribed under close physician monitoring.

Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

Please see the interaction with the Proton Pump inhibitor and H2 antagonist (Section 2.5)

Are there other metabolic/transporter pathways that may be important?

No.