

How does the plasma concentration of the inactive prasugrel metabolites correlate with QT?

Based on concentration-QT modeling, prasugrel metabolites do not exhibit any significant slope. The inactive metabolites (R119521 and R106583) exposures achieved in a large Phase III clinical study TAAL were analyzed. After a 60-mg loading dose the exposures were much lower for R-106583 and similar for R-119521. In the population PK study of TAAL (1159 subjects) fewer than 2% of the subject had exposures of R-119521 higher than that observed in the QT study. With this information it could be said that the exposures of R-119521 were good enough in the present QT study to rule out any exposure-response relationship for R-119521 in spite of predicting the scenarios which might have higher exposure than in the present QT study. Furthermore, considering, that the 60-mg loading dose will be given in patient under clinical supervision, it would be reasonable to compare exposures of metabolites in this TQT study (80-mg prasugrel) to that following a 10-mg maintenance dose. In this case, the 80-mg dose would comfortably cover the exposures expected after a 10-mg maintenance dose. Moreover, no relationship was observed between concentration- $\Delta\Delta QTcF$ for any of the metabolites in the observed concentration ranges. Thus it can be said that prasugrel is unlikely to prolong QT interval after clinically relevant exposures.

PK CHARACTERISTICS OF THE DRUG AND ITS MAJOR METABOLITE(S)

What are the single dose and multiple dose PK parameters? How do the PK parameters change with time following chronic dosing?

The proposed dose regimen is associated with chronic administration after the loading dose. The comparison of the mean concentration vs. time profiles of R-138727 (active metabolite), and inactive metabolites following a single prasugrel 60-mg LD and during 10-mg MD is shown in the figure below.

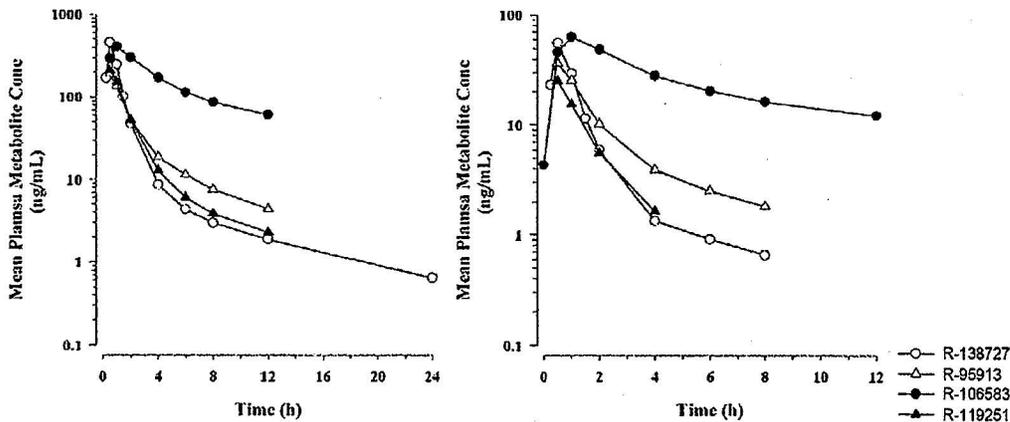


Figure 12. The mean concentration vs. time profiles of R-138727, R-95913, R-119251, and R-106583 following a single prasugrel 60-mg LD (left panel) and during 10-mg MD (right panel), Study TAAV.

The PK parameters of the prasugrel active metabolite after the LD and MD were calculated in healthy subjects (sponsor's meta-analysis) are listed in the table below.

Table 3 Pharmacokinetic Parameter Estimates for R-138727

| Parameters | LS Geometric Mean (90% CI) | | Variability (CV) | | |
|--|--------------------------------|---------------------|--------------------|---------------------|-------------------|
| | 60-mg LD (N=437) | 10-mg MD (N=284) | Within- Subject | Between- Subject | Between- Study |
| C _{max} (ng/mL) | 475 (439, 514) | 69.9 (64.3, 76.0) | 38.1% | 30.1% | 14.9% |
| t _{max} ^a (h) | 0.5 (0.25, 2.07) | 0.5 (0.25, 2.25) | NC | NC | NC |
| AUC(0-t _{last}) (ng•h/mL) | 514 (478, 552) | 67.5 (62.6, 72.7) | 19.3% | 27.6% | 14.9% |
| t _{1/2} ^b (h) | 7.36 (1.97, 14.6) ^c | NA | NC | 24.4% | 7.25% |

LD = loading dose; MD = maintenance dose; N = number of subjects; NA = not available; NC = not calculated; a Median (minimum, maximum). b Geometric mean (minimum, maximum). c Number of subjects=230.

How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The sponsor's meta-analysis of noncompartmental PK estimates from 16 Phase 1 studies compared the exposure estimates from 506 healthy male and female subjects and evaluated the effect of specific subject factors on exposure to the active metabolite. Noncompartmental analyses and the population PK analysis have produced results consistent across studies and between the 2 methods of analysis. The PK of R-138727 in subjects with stable atherosclerosis and subjects with ACS undergoing PCI also have been assessed by conventional noncompartmental methods and/or population PK methods in Studies TAAD, TABR, and TAAL. The exposures to the active metabolite in patients are very similar to those in healthy subjects (Table below).

Table 4. AUC values of R-138727 in Healthy Subjects and in Patients.

| | R-138727 AUC (ng•h/mL) | | | | |
|------------------------|------------------------------|-----------------------------|---------------------------|---------------------------|-----------------------|
| | Noncompartmental Analysis | Model-Predicted Analysis | | | |
| | PK meta-analysis | TAAJ | TAAD | TABR | TAAL ^a |
| | Healthy subjects | Healthy subjects | Stable atherosclerosis | Stable atherosclerosis | ACS undergoing PCI |
| 60-mg LD | | | | | |
| N | 437 | 66 | 40 | 55 | 1159 |
| Median | 528 | 526 | 530 | 394 | 478 |
| 5th-95th percentile | 297-980 | 348-846 | 341-810 | 253-527 | 275-1021 |
| 10-mg MD | | | | | |
| N | 284 | — | 19 | 55 | 1159 |
| Median | 70.5 | — | 88.7 | 59 | 79.6 |
| 5th-95th percentile | 41.1-128 | — | 56.0-119 | 37.9-78.9 | 45.8-170 |

What are the characteristics of drug absorption (possible transporters and pH impact)?

Prasugrel is a prodrug, it is metabolized in vivo to the active metabolite which appears rapidly in plasma after oral dosing, reaching a peak concentration in about 30 minutes and then declining biphasically with a terminal half-life of about 7.4 hours. When prasugrel was coadministered with a proton pump inhibitor lansoprazole, and therefore, the gastric pH was elevated, the C_{max}

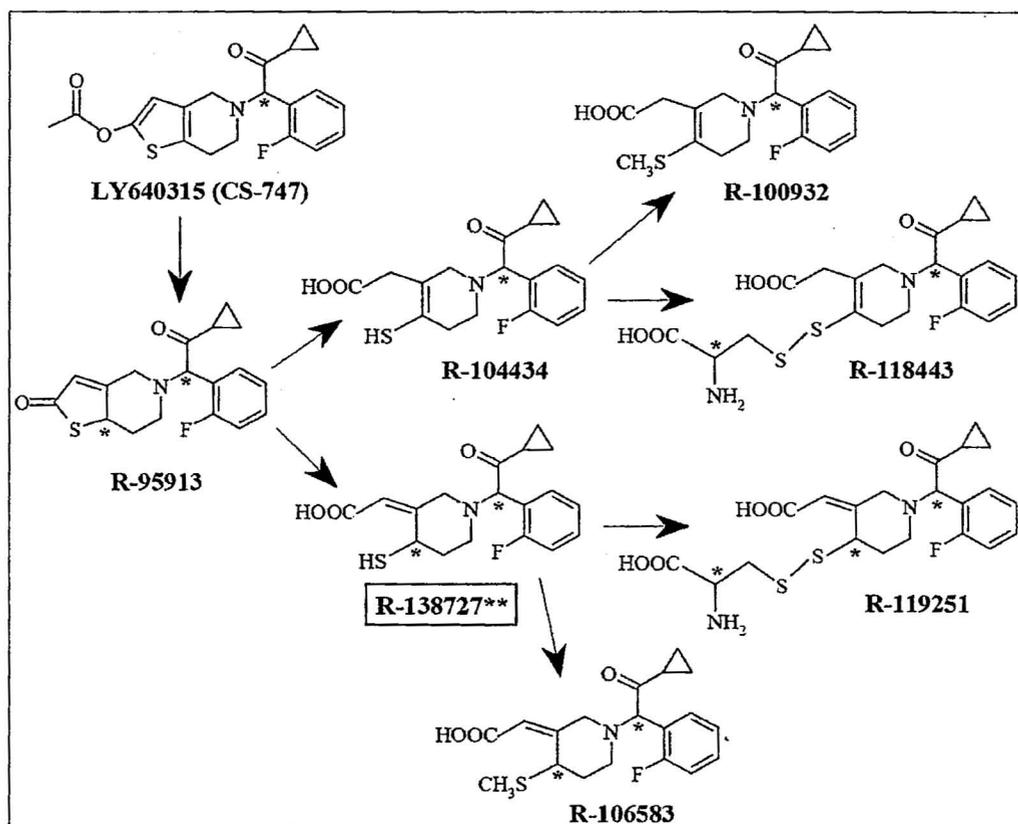
values of the active metabolite decreased by 30% with no changes in AUC values. This indicates that the rate but not the extent of prasugrel dissolution decreased in the conditions of high pH in the stomach. This may delay the onset of effect after a LD but would not be relevant during MD. When prasugrel was coadministered with an H₂-receptor antagonist ranitidine, which also elevates gastric pH, the active metabolite's C_{max} and AUC decreased by about 20% after the LD with no changes occurring after the MD (see DDI section). After oral administration to healthy subjects at least 79% of the prasugrel dose was absorbed.

What are the characteristics of drug distribution (including plasma protein binding?)

Prasugrel's active metabolite is extensively distributed into the tissues. The estimates of apparent volume of distribution of R-138727 ranged from 30 L to 84 L in healthy subjects and subjects with stable atherosclerosis (Studies TAAD, TAAJ, and TABR). The binding of the active metabolite to plasma proteins was not determined in vivo, and in vitro, it was 98% in 4% human serum albumin solution in phosphate buffer, pH 7.4. The inactive metabolites are highly bound to human plasma proteins. The fraction bound to plasma proteins at various concentrations, determined by ultracentrifugation, was 94.6% for R-95913 (50, 100, and 500 ng/mL), 95.1% for R-106583 (100 and 500 ng/mL), and 76.4% for R-119251 (100, 500, and 1000 ng/mL). Although in the mass-balance study in 5 subjects, 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.

Does the mass balance study suggest renal or hepatic as the major route of elimination?

Prasugrel (prodrug) was metabolized rapidly in vivo and was not detected in plasma collected from the 5 subjects following the [¹⁴C] prasugrel dose (mass-balance study TAAB). The radiochemical profiles and mass spectral data confirmed the presence of 16 metabolites in plasma collected over the first 12 hours. R-106583 is the major metabolite in human plasma, followed by R-95913 and R-138727 which is a pharmacologically active metabolite. About 90% of the total radioactivity was excreted in the urine over 240 hours, accounting 68% of the dose. A total of thirteen metabolites were identified in urine. The major metabolites observed in the urine were four diastereomers of M1 (m/z 336). The metabolites M1-A and M1-B and M1-C and M1-D were inter-convertible. Approximately 27% of the ¹⁴C dose was eliminated in feces, 91% of which was recovered within the first 72 hours post-dose. Six metabolites were detected in feces, which were also observed in plasma. The simplified scheme of prasugrel metabolism is shown below.



The estimates of apparent clearance of prasugrel's active metabolite ranged from 73 L/hr to 266 L/hr in healthy subjects and subjects with stable atherosclerosis (population PK analysis, Studies TAAD, TAAJ, and TABR).

What are the characteristics of drug metabolism?

Prasugrel is rapidly hydrolyzed in vivo and is not detected in plasma. In vitro studies showed that human carboxylesterases (hCE) 1 and 2, the dominant forms in the liver and intestinal tract, respectively, are capable of hydrolyzing prasugrel to R-95913, the precursor to prasugrel's active metabolite, and that hCE2 had a maximal hydrolysis rate approximately 26 times higher than that of hCE1. The results suggest that the hydrolysis of prasugrel to R-95913 is mediated efficiently by hCE2 prior to reaching the portal vein. The metabolism of R-95913 to the active metabolite R-138727 is catalyzed by several isoforms of CYP, with CYP3A and CYP2B6 being the main contributors to this oxidative step. Since CYP3A constitutes approximately 80% of the intestinal CYP enzymes, most of R-138727 formed during first pass metabolism is probably formed by intestinal CYP3A during absorption. The active metabolite is further metabolized to 2 inactive compounds by S-methylation or conjugation with cysteine.

The active metabolite R-138727 contains 2 chiral centers, and thus is comprised of 4 enantiomers, (R,S), (R,R), (S,R), and (S,S). The R- and S-configurations at the 1' position interconvert in vivo, and therefore the 4 enantiomers of R-138727 can be considered to be 2 pairs, (R,S)/(R,R) and (S,R)/(S,S). The enantiomers 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 subjects, regardless of dose, time of sample collection, or whether the blood was sampled after the first prasugrel dose or after 4 weeks of treatment. Therefore, the variation in enantiomeric ratios is not important in interpreting the clinical data.

The active metabolite's half-life is 7.4 hours. It further converts to the inactive metabolites. The comparison of the pharmacokinetic parameters of prasugrel metabolites in healthy subjects is shown in the Table below.

Table 5. Comparison of the Pharmacokinetic Parameters of Prasugrel Metabolites

| Parameter | Geometric Mean (%CV) | | | | | | | |
|--|----------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| | Active Metabolite | | R-95913 | | R-119251 | | R-106583 | |
| | LD (N=34) | MD (N=32) | LD (N=34) | MD (N=32) | LD (N=4) | MD (N=32) | LD (N=34) | MD (N=32) |
| C _{max} (ng/mL) | 453 (35) | 56.5 (48) | 190 (46) | 36.2 (54) | 216 (38) | 24.0 (49) | 399 (27) | 63.5 (29) |
| t _{max} ^a (h) | 0.50 (0.25-1.00) | 0.50 (0.25-1.00) | 0.50 (0.50-1.00) | 0.50 (0.50-1.00) | 0.50 (0.50-1.00) | 0.50 (0.50-1.00) | 1.00 (0.50-2.00) | 1.00 (0.50-4.00) |
| AUC(0-t _{last}) (ng•h/mL) | 460 (21) | 54.5 (26) | 324 (42) | 59.6 (52) | 317 (28) | 30.6 (34) | 1760 (30) | 299 (30) |
| t _{1/2} ^c (h) | 6.88 (26.4) | -- ^b | 6.81 (25.7) | -- ^b | 5.33 (50.4) | -- ^b | 8.41 (25.2) | -- ^b |

The concentration vs. time profiles of R-95913 (the precursor to the active metabolite) and of R-119251 (the cysteine conjugate of the active metabolite) parallel those of the active metabolite. These metabolites reach the peak plasma concentrations at the same time as the active metabolite. Their profiles decline in parallel with each other and with the active metabolite. This suggests that the elimination of the active metabolite and R-119251 are formation-rate limited and depend on the elimination rate of R-95913. The most abundant metabolite, the S-methyl conjugate R-106583, reach the peak of plasma concentration later, and decline slower than those of the active metabolite and 2 other major inactive metabolites. These metabolites at concentrations of 100 μM and 300 μM did not significantly affect ADP-induced aggregation of human platelets in platelet-rich plasma. These metabolites do not accumulate during multiple dosing and have adequate margins of safety.

Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Prasugrel dose-proportionality was assessed in the studies S001, S004, TAAW and during the population PK data analyses. The first 2 studies used a base formulation and did not measure the plasma concentrations of the active metabolite. In the study TAAW, the measurements of the prasugrel metabolites R138727, R95913, R106583, and R119251 after low prasugrel doses (5-10 mg) were performed only up to 4 hours post-dose. Only metabolite R106583 was measurable through 24 hours post-dose. Therefore, a comparison of the AUC₀₋₄ was performed for this study. AUC₀₋₄ hours for all metabolites of prasugrel related to the absorption-early distribution state, hence, it is not appropriate to evaluate the dose proportionality based on this parameter. In this study the active metabolite's C_{max} was dose proportional over the 5-60 mg dose range and the AUC_{inf} and AUC₀₋₄ increased more (26% and 18%) than dose proportional. The relationship between dose and the PK parameters of R138727 is shown in the figure below.

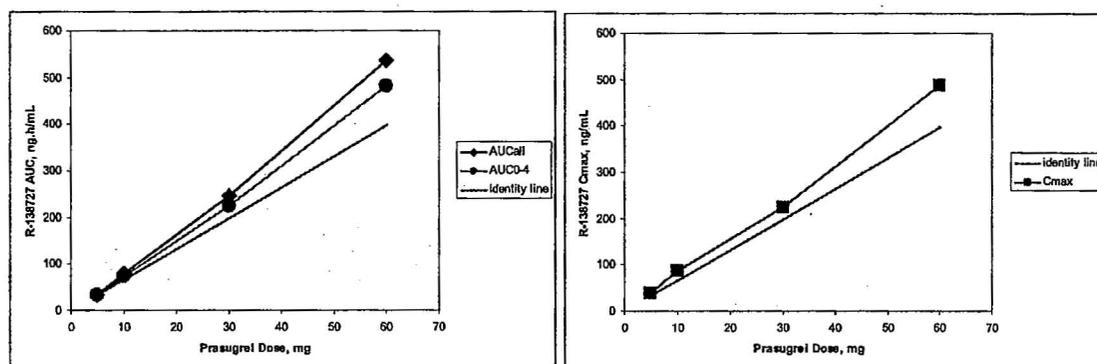


Figure 13. PK Parameters of R138727 vs. Prasugrel Dose, Study TAAW.

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 drug.

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-∞ 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 C_{max} 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).

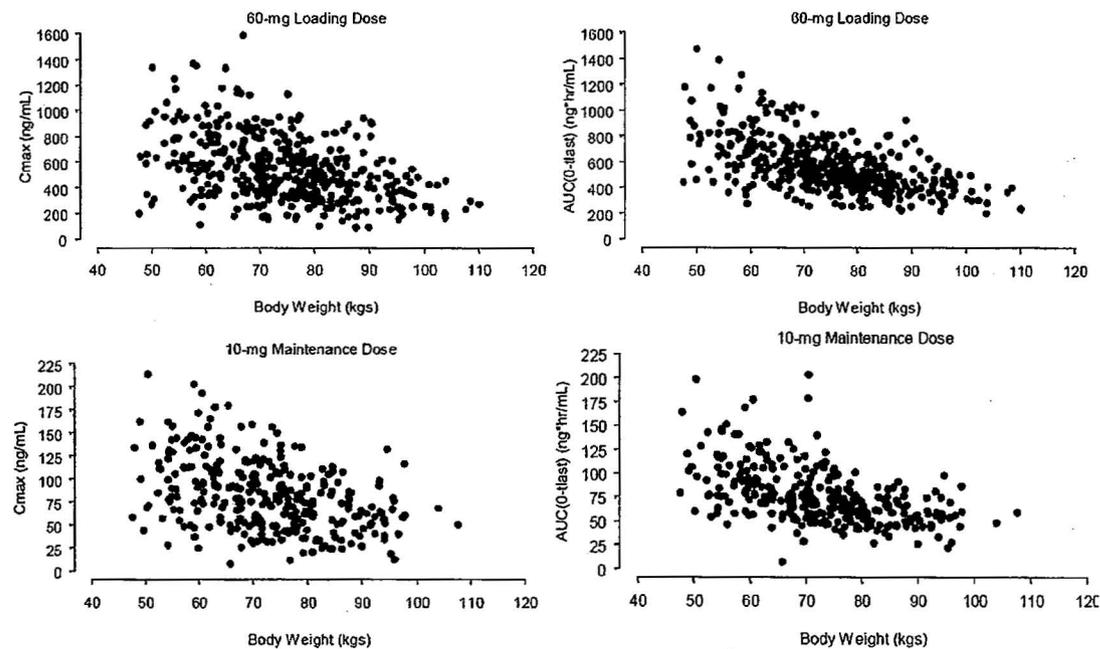


Figure 14. Observed AUC_{0-tlast} and C_{max} of R-138727 vs. body weight following a 60-mg LD or during 10-mg MD of prasugrel

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.

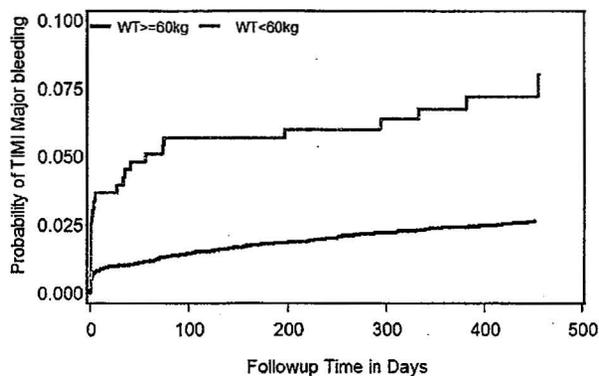


Figure 15 Risk for TIMI Major bleeding is higher in patients with body weight less than 60 Kg.

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.

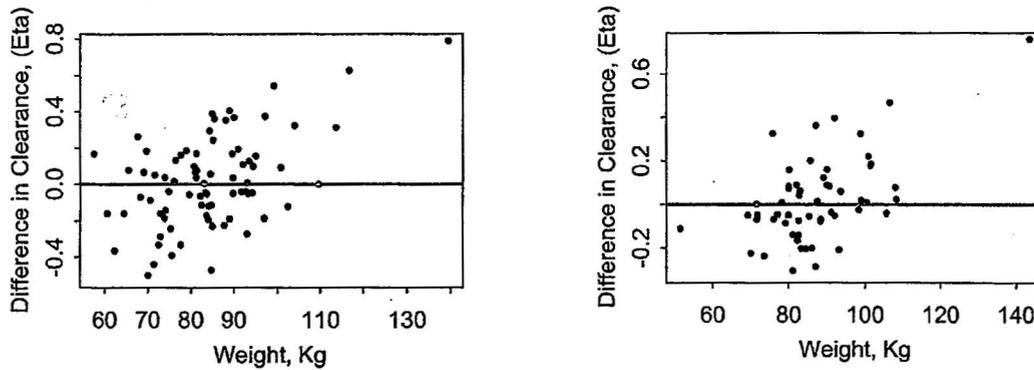


Figure 16 Clearance of R-138727 increases with increase in body weight (Left: Study TAAD; Right: Study TABR)

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

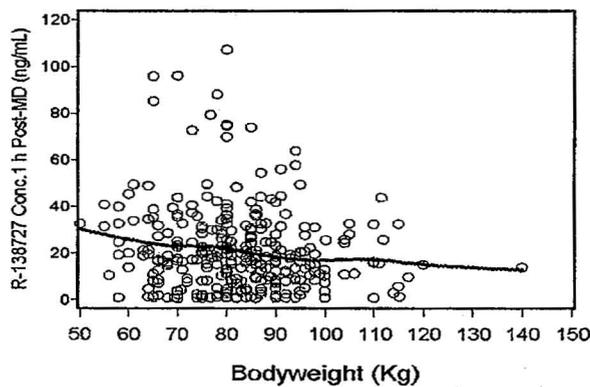


Figure 17 Decreased Exposures of R-138727 with increased body weight in Study TAAL. (Circles represent plasma concentrations 0.75-1.25 h post MD; Blue line is a smooth trend line)

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.

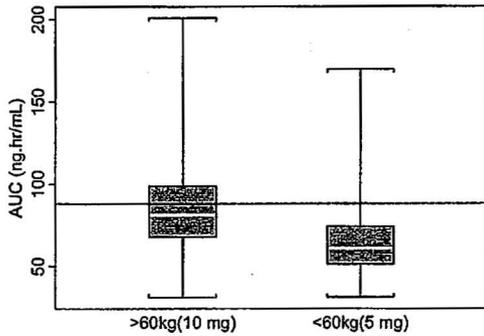


Figure 18 Simulation (N=2000) of the proposed dose of 5 mg in patients with body weight < 60kg will result in exposures predominantly corresponding to lower two quartiles of those expected with 10 mg MD in patients with body weight >60 kg. (The red dashed line represent the concentration range beyond which the bleeding related adverse events were highest from Figure 3). ($CL = 123 \times (WT/85)^{0.798}$; 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.

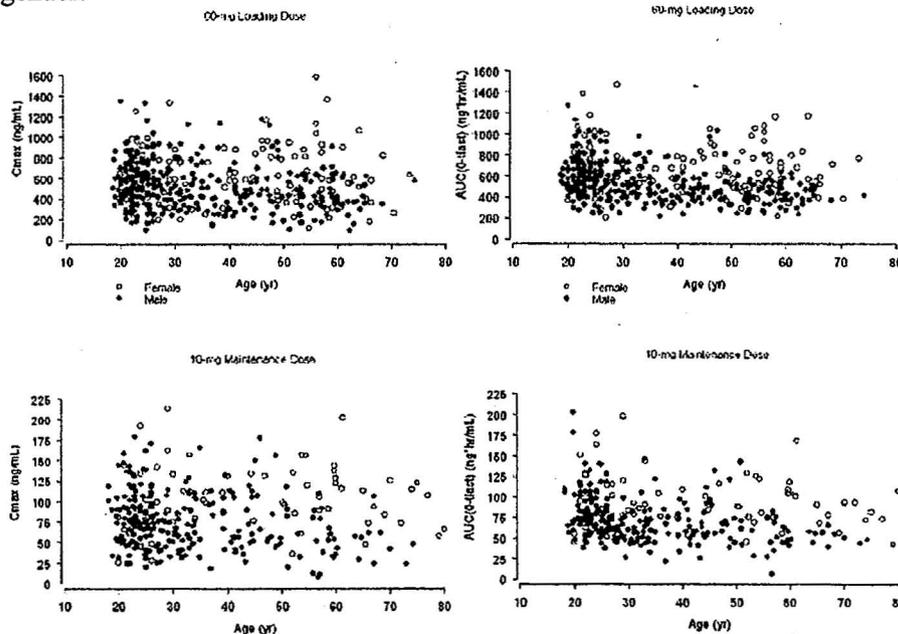


Figure 19 Effect of age by gender on observed R-138727 Cmax and AUC0-tlast following a 60-mg LD and daily 10-mg MD of prasugrel

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 AUC_{0-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 \geq 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.

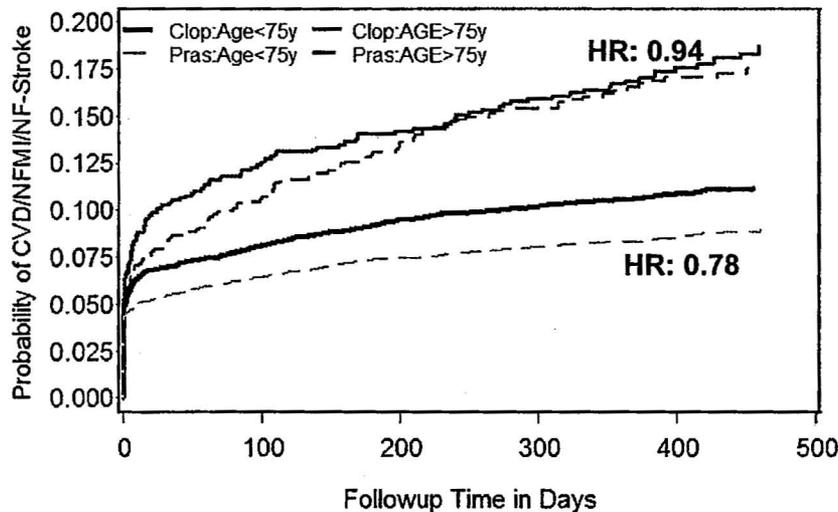


Figure 20: Risk for CVD/Non-fatal MI/ Non-fatal Stroke is high in patients above 75 years of age compared to patients below 75 years. (The Hazard Ratios are for Prasugrel compared to Clopidogrel in each of the age groups)

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-Meier 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.