

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.

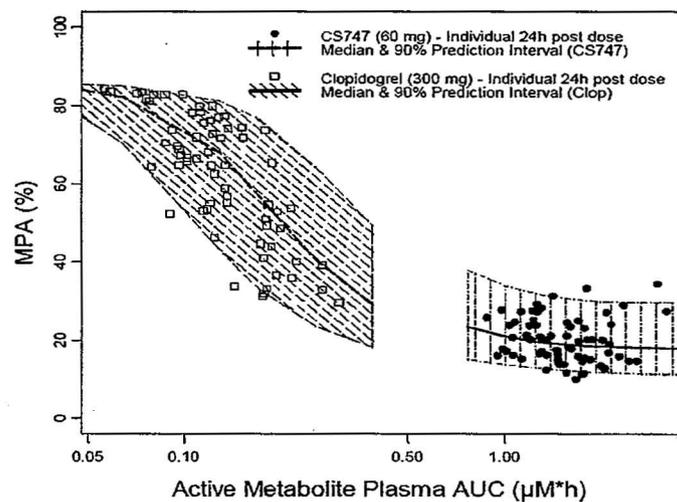


Figure 1 The inhibition of the platelet aggregation is dependent on the concentration of the active metabolites of prasugrel and clopidogrel

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).

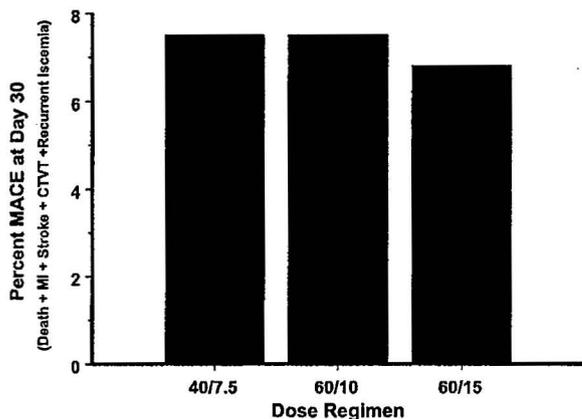


Figure 2 No relationship between dose and major cardiovascular events (MACE - Death+MI+Stroke+CTVT+Recurrent Ischemia at 30-day visit)

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.

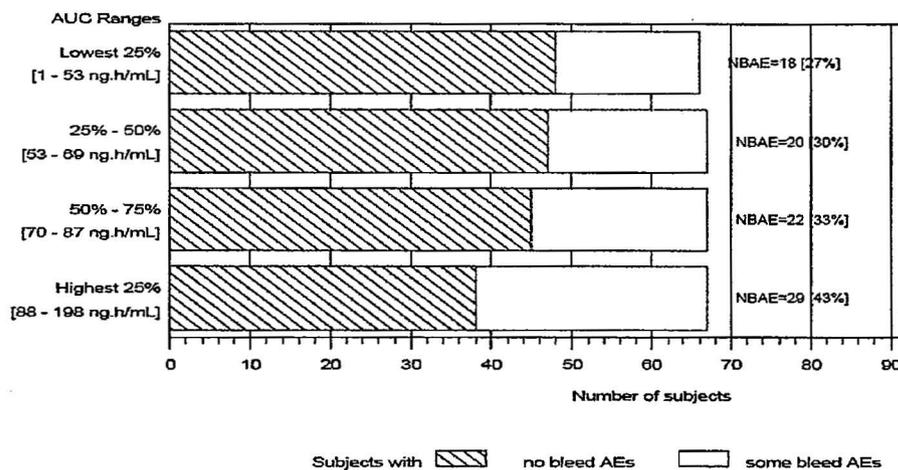


Figure 3 Increase in the active metabolite exposures trends to increase in number of bleeding adverse events (NBAE).

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.

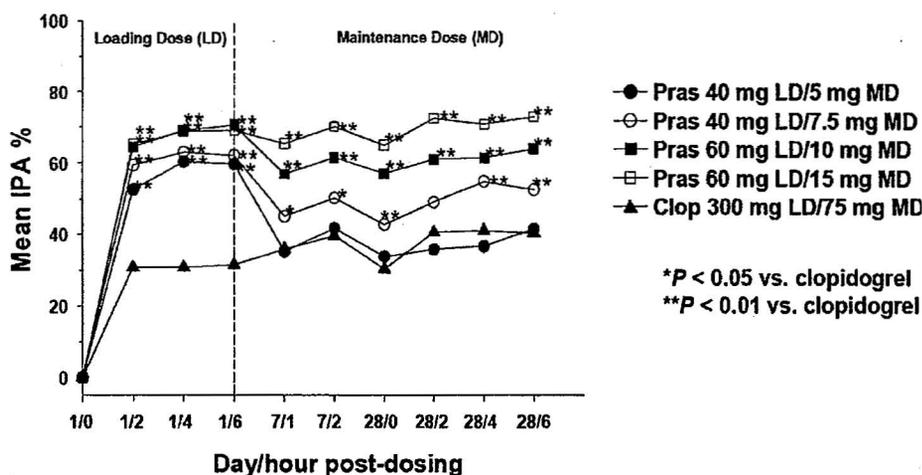


Figure 4 Prasugrel LD of 60 mg achieves highest IPA. Maintenance doses of 10 mg and 15 mg achieve significantly greater IPA compared to clopidogrel MD of 75 mg.

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

What is the impact of early loading dose (6 hours prior to the start of PCI) on the incidence of efficacy events?

The range for the time difference between loading dose and start of PCI across the octiles are shown in the table below:

Table 1 The range for the time difference between loading dose and start of PCI

Group	N	Range of Loading Dose Time – PCI Start Time (hrs)	Median (hrs)
1	1667	-234.83 - -0.12	-0.45
2	1703	-0.10 – 0.00	-0.05
3	1616	0.02 – 0.25	0.15
4	1658	0.27 – 0.43	0.35
5	1665	0.45 – 0.62	0.53
6	1773	0.63 – 0.83	0.73
7	1487	0.85 – 1.15	0.96
8	1699	1.17 – 530.00	1.45
<6 h*	231	-234.83 - -6.00	-19.82
>6 h*	13037	-5.9 0 – 530.00	0.45

* For comparing the range of differences in the loading dose time and the start of PCI in patients who were early pre-treated (<6 hrs Vs >6 hrs)

Irrespective of the treatment arms, the lowest incidence of CVD/Non-fatal MI/Non-fatal Stroke was observed when the loading dose was administered at the start of PCI or within 30 minutes of the start of the procedure as shown in Table 1.

The difference in the timing of the loading dose relative to the start of the PCI was not correlated with the risk factors associated with UA/NSTEMI or STEMI, such as prior history of CHF or MI or TIA/Stroke or Carotid/Vertebral Arterial disease or cerebrovascular accident. No correlation was observed with prior PCI. A weak but statistically significant correlation was observed with the use of GPIIb/IIIa antagonist, prior CABG and Stent use up to PCI or hospital discharge. However, it is not clear as to why the incidence of the events was higher when pre-treated, an observation that is not consistent with the current ACC/AHA 2007 guidelines for clopidogrel.

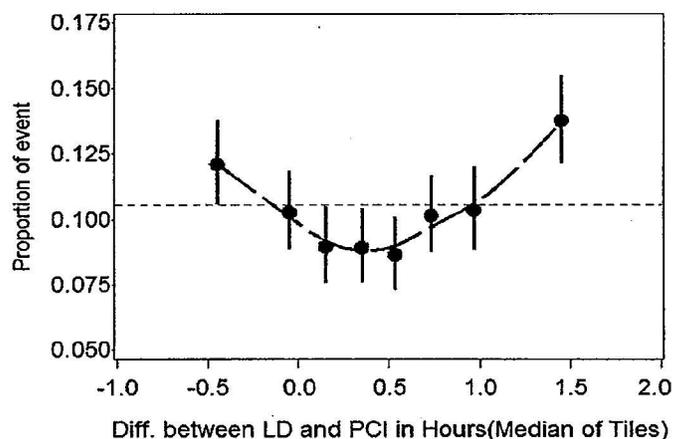


Figure 5: Maximum effectiveness is achieved when the loading dose is administered at the start or within 30 min of start of PCI (Red dots – represent proportion of events corresponding to the midpoints of the octiles; Blue bars – 95% Confidence interval; Black line – Smooth trend line; Green line – is the lowest confidence limit of the extremes)

Further the proportion of events were consistently higher when the time difference between the loading dose and the start of pci were divided into groups based on whether the patient received the loading dose at least 6 hours or before as shown in the figure below.

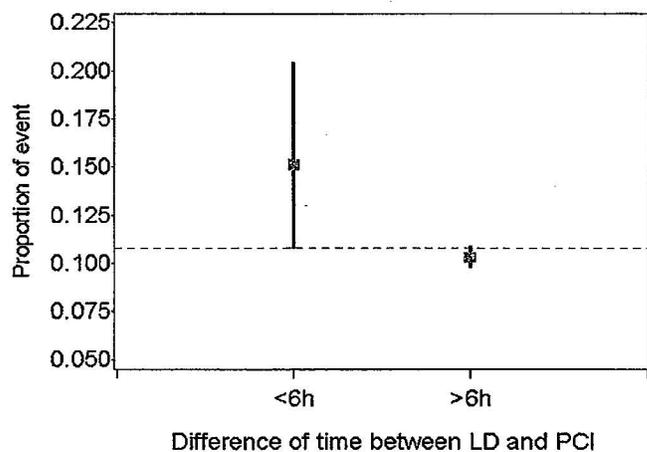


Figure 6 Pre-treatment with clopidogrel/prasugrel 6 hrs before the start of PCI results in decreased effectiveness compared to no pre-treatment (Orange squares – represent proportion of events; Black bars – 95% Confidence interval)

Similar relationship was seen across both the treatment arms as shown in the figure above.

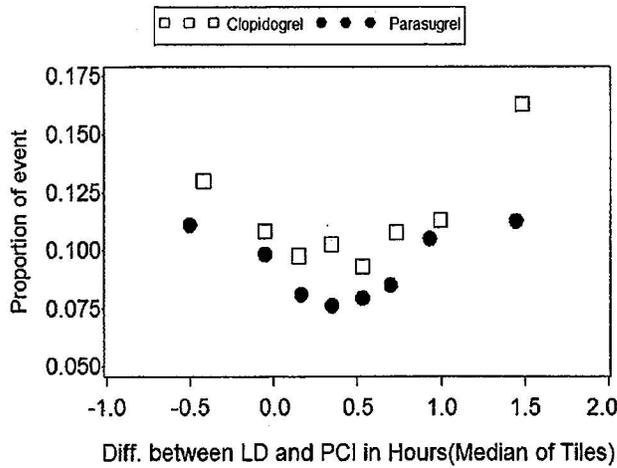


Figure 7 The effect of the timing of loading dose relative to the start of PCI is similar across prasugrel and clopidogrel

The value of administering the loading dose at the start of PCI is also evident from the Kaplan-Meier curves across the quartiles of difference between the loading dose and start of PCI as shown in Figure 8: The cumulative event rate of the efficacy endpoint is lower when the loading dose is administered at the start of PCI or within 30 minutes of the start of the PCI irrespective. Similar relationship was also seen when the data was divided into octiles instead of quartiles.

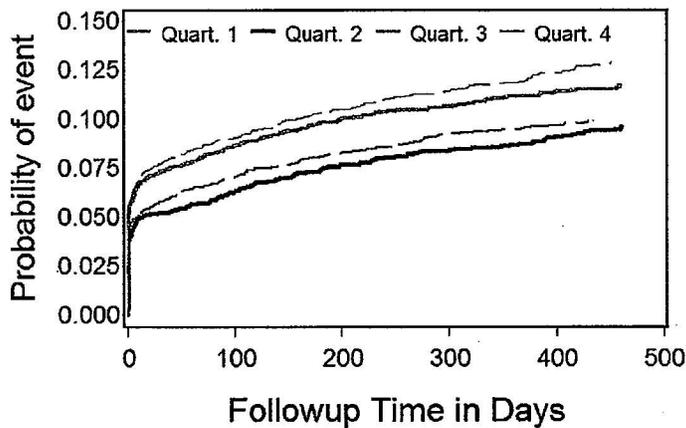


Figure 8: The cumulative event rate of the efficacy endpoint is lower when the loading dose is administered at the start of PCI or within 30 minutes of the start of the PCI irrespective

Cox Proportional regression shows that the relative risk for CVD/Non-fatal MI/Non-fatal Stroke is 28% and 24% lower for Quartiles 2 and 3 compared to Quartile 4. The details are presented in the table below:

Table 2 Comparison of Hazard Ratios for Quartiles

Quartile	N	Range of Loading Dose Time – PCI Start Time (hrs)	Hazard Ratio (95% Confidence Limit)	p-value
4*	3186	0.85 – 530.13	-	-
1	3370	-234.83 - 0	0.91 (0.79 – 1.05)	0.1858
2	3274	0.02 – 0.43	0.72 (0.62 – 0.84)	<0.0001
3	3438	0.45 – 0.83	0.76 (0.66 – 0.89)	0.0004

* Quartile – 4 was used as reference to compute the relative risk for rest of the quartiles.

This relationship was consistent between prasugrel and clopidogrel as shown in the figure above.

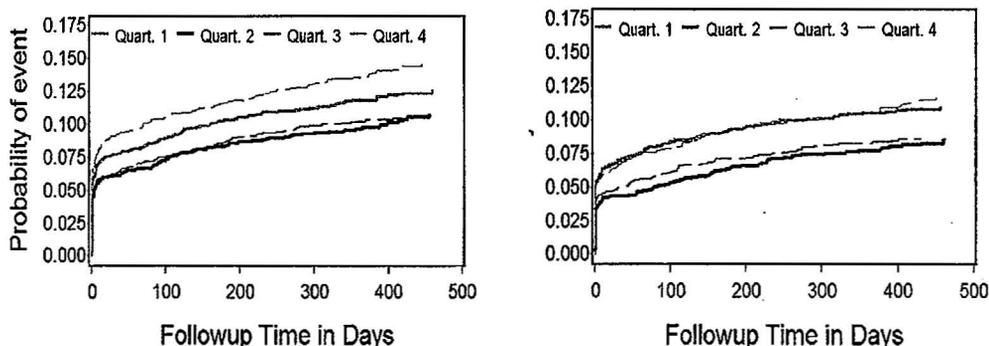


Figure 9 Cumulative event rate of the efficacy endpoint across quartiles of difference in time of loading dose and start of PCI is similar between clopidogrel (left) and prasugrel (right)

Exploratory analyses revealed a weak but statistically significant correlation was observed with the use of GPIIb/IIIa antagonist, prior CABG and Stent use upto PCI or hospital discharge.

Further, prior CABG was found to be a statistically significant predictor (χ^2 statistic $p < 0.0001$) of the timing of loading dose when a 2x2 contingency table was constructed between prior CABG and the timing of the loading dose (dichotomized by at least 6 hrs before PCI or not) in only those patients who received the loading dose before the start of PCI. After controlling for the prior CABG, no statistically significant association (CMH Statistics: General association $p = 0.1146$) was seen between timing of loading dose (at least 6hrs before PCI or not) and observing the efficacy endpoint. This could likely explain the reason for higher incidence of the primary endpoint when prasugrel or clopidogrel is dosed at least 6 hrs or before.

Hence with potent rapidly acting agents such as clopidogrel and prasugrel pre-treatment may not be necessary for achieving maximum effectiveness. However, the Loading Dose for either Prasugrel or Clopidogrel should be administered at least within 30 minutes of the start of the PCI.

EXPOSURE-RESPONSE RELATIONSHIP: SAFETY

Relationship between exposure and bleeding

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.

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

Does prasugrel prolong the QT or QTc interval?

No. The sponsor performed a thorough QT study (TAAP) to assess the effect of prasugrel on QT and QTc prolongation. The questions below were posted to the Interdisciplinary Review Team for QT Studies Consultation.

Is the design of TQT study TAAP acceptable?

Yes. Although there are several limitations with respect to study design:

- The 80 mg single dose was not sufficient to cover worst case scenarios after a 60- mg loading dose.
- ECG sampling times were not adequate to capture T_{max} for three of the metabolites
- Time-matched baseline (1, 2 and 6 h only) was captured only prior to period 1 and was used for all periods in double- delta analysis. Therefore the present double- delta analysis (change from placebo adjusted for baseline) was equivalent to a single-delta analysis (change from placebo).

Was the TQT study performed adequately?

Yes. The largest lower bound of the two sided 90% CI for Δ QTcF for moxifloxacin was greater than 5 ms indicating that the study was adequately designed to detect an effect on the QT interval. The complete information regarding ECG acquisition and interpretation is not available (See QT review).

Is the study TAAP a negative QT study?

Yes, even though the study design had several limitations, the lack of a positive signal from the concentration-QT modeling together with comparable levels of at least two metabolites in TAAP and Phase III trial (TAAL) suggest that prasugrel may not prolong QT at clinically relevant exposures. Moreover, since a 60-mg loading dose would be given once only at the start of treatment and will be administered in a controlled and monitored inpatient setting followed by the 10-mg maintenance dose (See Page 15, H7T-EW-TAAP), it would be reasonable to compare the exposures achieved by an 80-mg single dose of prasugrel to a 10-mg maintenance dose to interpret the effect of prasugrel on QT interval. In that case the 80-mg dose (8-fold higher than the maintenance dose) covers the exposures achieved by a 10-mg maintenance dose.

The time course of mean $\Delta\Delta\text{QTcF}$ for R-138727 following 80-mg prasugrel and moxifloxacin (400 mg) is illustrated below in the figure below.

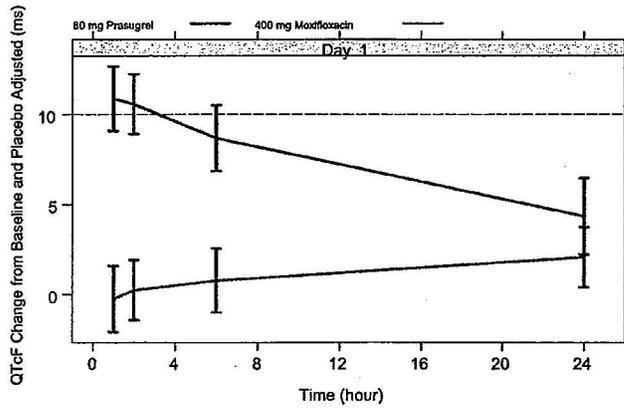


Figure 10 Time course of mean $\Delta\Delta\text{QTcF}$

There seems to be no significant relationship between R-138727 exposure and $\Delta\Delta\text{QTcF}$ from the figure below. The similar pattern for concentration- $\Delta\Delta\text{QTcF}$ was observed for other metabolites as well.

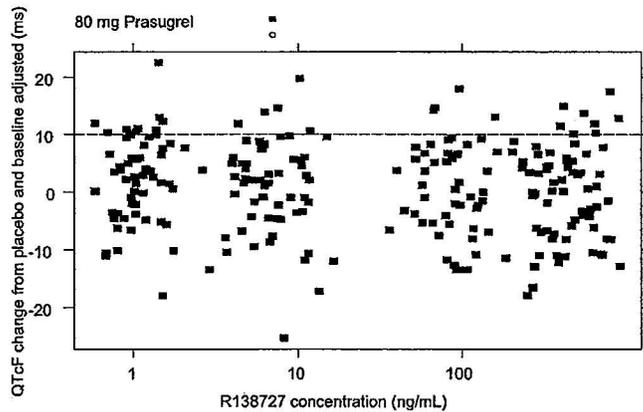


Figure 11 Log concentration- $\Delta\Delta\text{QTcF}$ relationship for R-138727

The sponsor used a single 80-mg prasugrel dose as their only active treatment in the present TQT study TAAP. Use of single oral dose is justified with respect to accumulation as there is no accumulation expected and also because the maintenance dose is 10-mg (1/8th of the current TQT studied dose) in the clinical setting. The sponsor compares the exposures achieved by the four metabolites in the present study to that possible in the worst-case scenarios after a 10-mg maintenance dose in the clinical setting, and concludes that the latter are obviously much lower. However, as the dosing regimen proposed is a 60-mg loading dose followed by a 10-mg maintenance dose, it would also be relevant to compare the worst case scenarios of the metabolites with the clinical 60-mg loading dose.