

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.

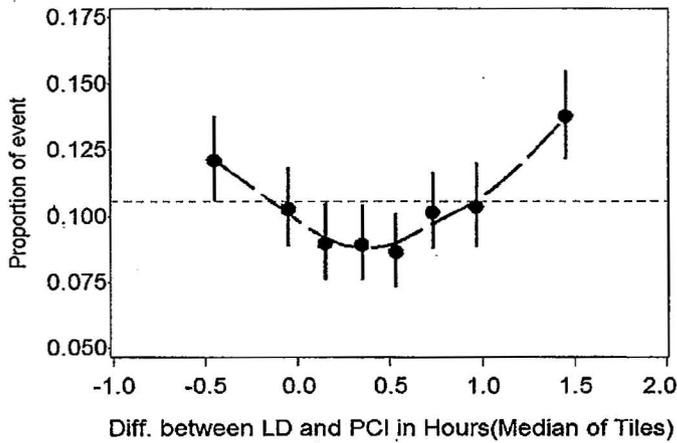


Figure 5: Maximum effectiveness is achieved when the loading dose is administered at the start or within 30 min of start of PCI (Red dots – represent proportion of events corresponding to the midpoints of the octiles; Blue bars – 95% Confidence interval; Black line – Smooth trend line; Green line – is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

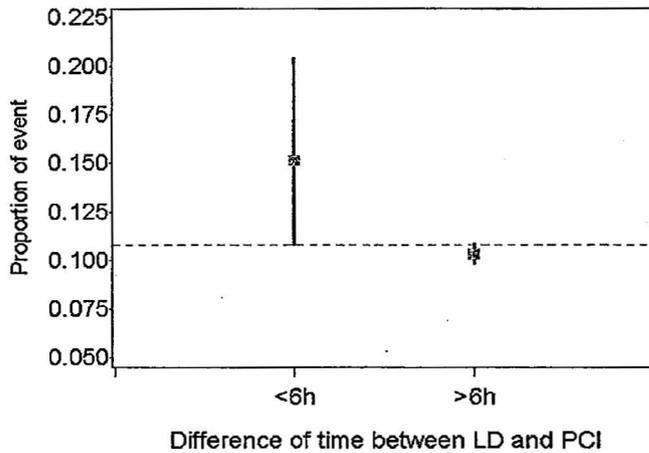


Figure 6 Pre-treatment with clopidogrel/prasugrel 6 hrs before the start of PCI results in decreased effectiveness compared to no pre-treatment (Orange squares – represent proportion of events; Black bars – 95% Confidence interval)

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

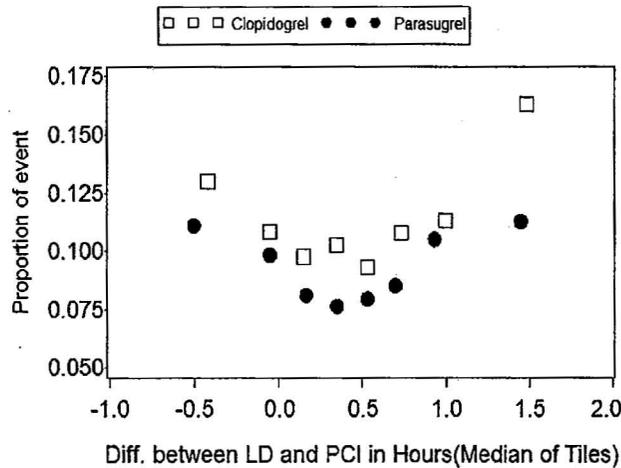


Figure 7 The effect of the timing of loading dose relative to the start of PCI is similar across prasugrel and clopidogrel

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.

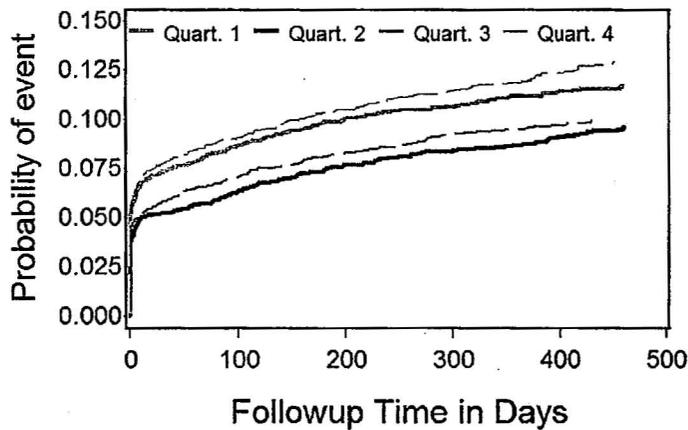


Figure 8: The cumulative event rate of the efficacy endpoint is lower when the loading dose is administered at the start of PCI or within 30 minutes of the start of the PCI irrespective

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.

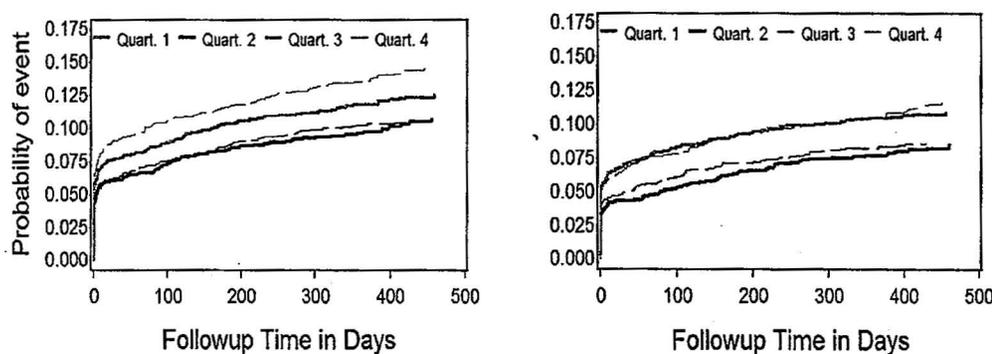


Figure 9 Cumulative event rate of the efficacy endpoint across quartiles of difference in time of loading dose and start of PCI is similar between clopidogrel (left) and prasugrel (right)

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.

In the phase 1b study TAAD, 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 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.

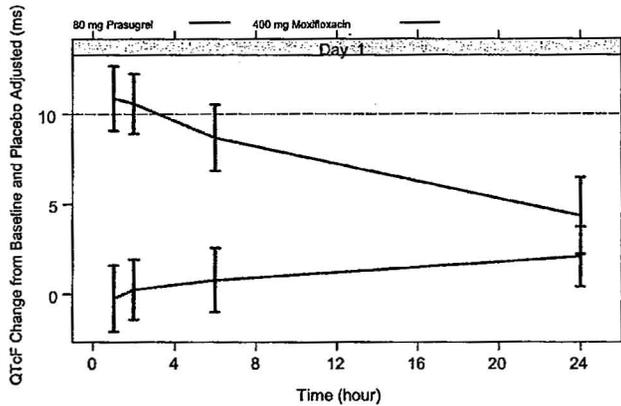


Figure 10 Time course of mean $\Delta\Delta\text{QTcF}$

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.

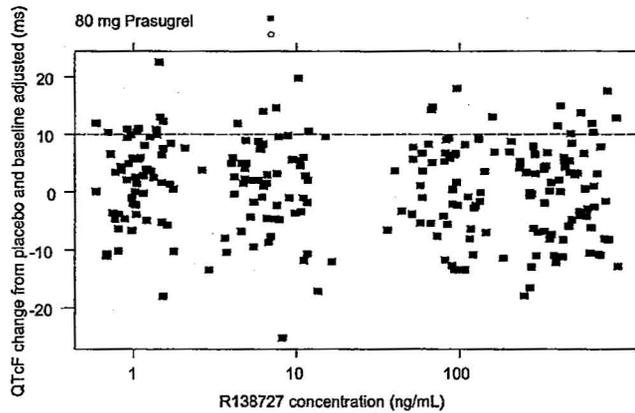


Figure 11 Log concentration- $\Delta\Delta\text{QTcF}$ relationship for R-138727

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.

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.

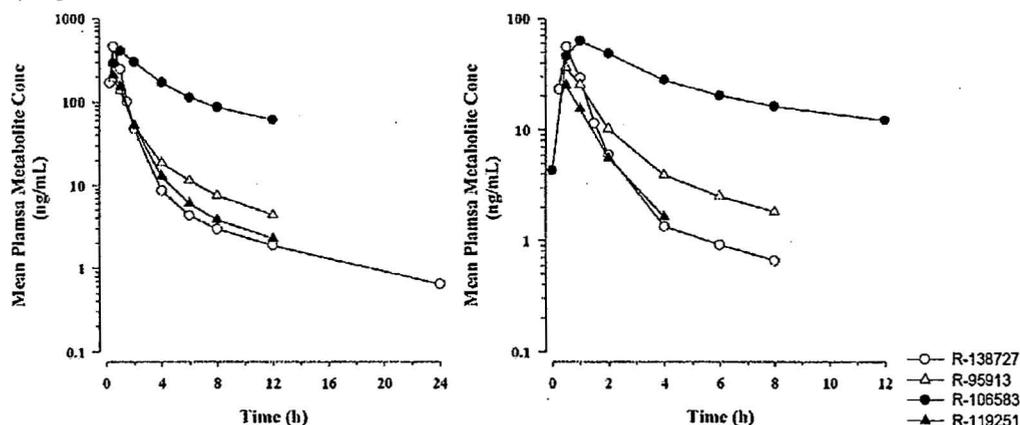


Figure 12. The mean concentration vs. time profiles of R-138727, R-95913, R-119251, and R-106583 following a single prasugrel 60-mg LD (left panel) and during 10-mg MD (right panel), Study TAAV.

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
	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}

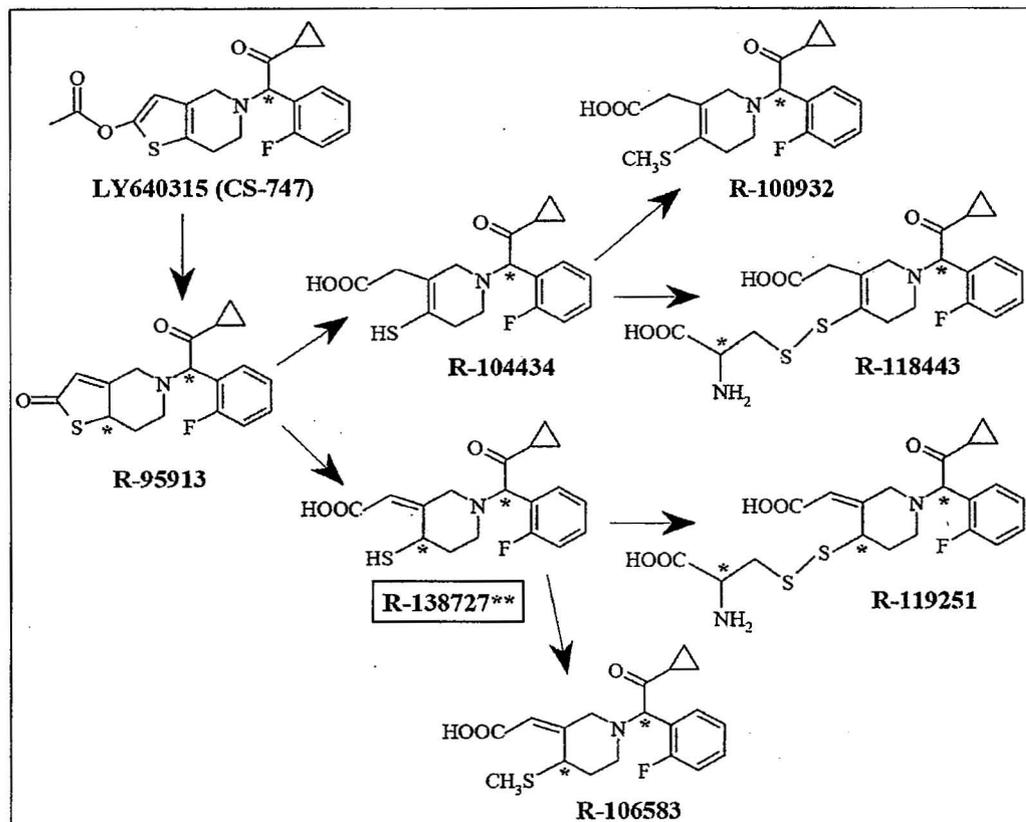
values of the active metabolite decreased by 30% with no changes in AUC values. This indicates that the rate but not the extent of prasugrel dissolution decreased in the conditions of high pH in the stomach. This may delay the onset of effect after a LD but would not be relevant during MD. When prasugrel 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 form 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.