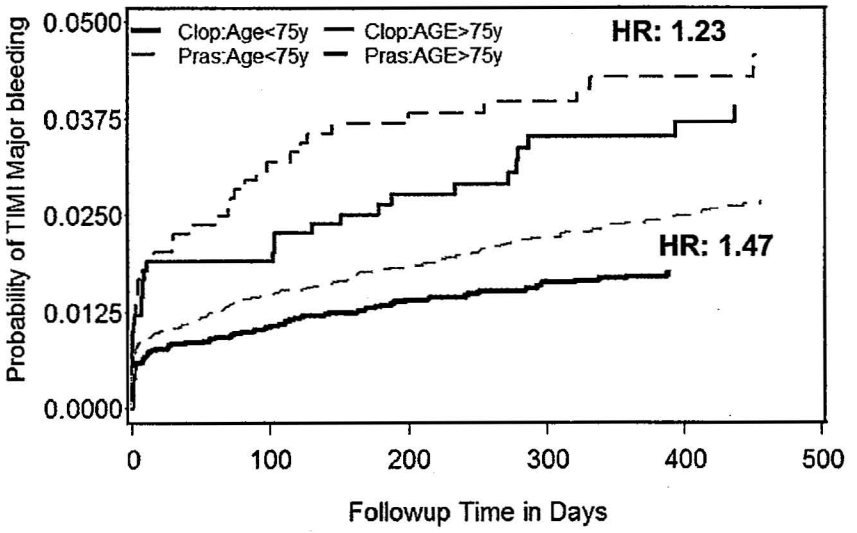

Figure 21 Risk for TIMI Major bleeding is high in patients above 75 years of age compared to patients below 75 years. *(The Hazard Ratios are for Prasugrel compared to Clopidogrel in each of the age groups)*

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 ≥ 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.

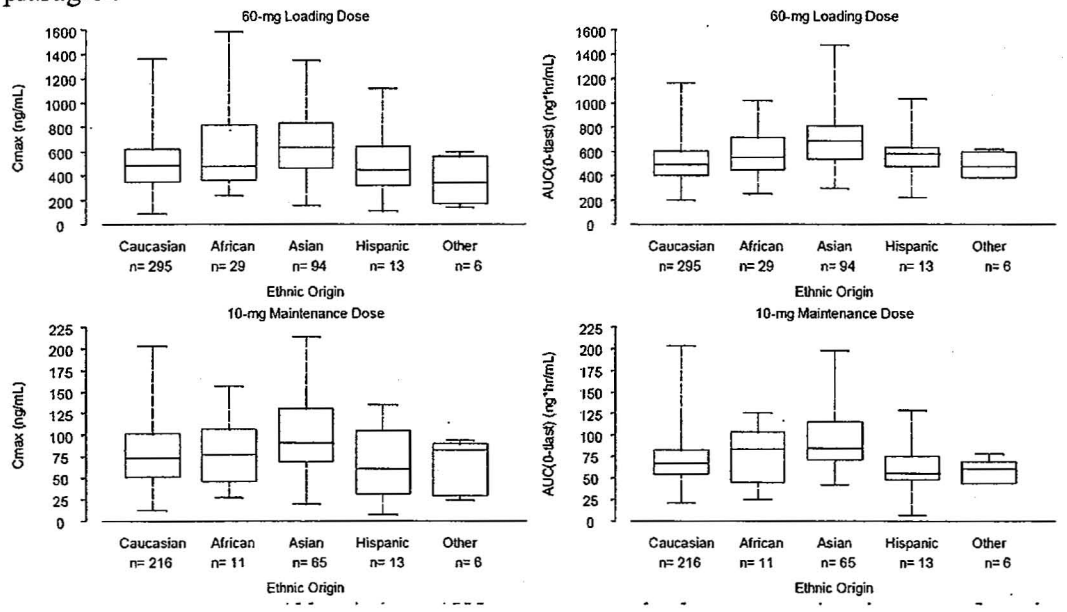

Figure 22 Box plots compare the observed AUC0-tlast and Cmax values of R-138727 by ethnic group following 60-mg LD or 10-mg MD of prasugrel

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). APPEARS THIS WAY ON ORIGINAL
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.

2.5 General Biopharmaceutics

The significant, unresolved issues related to in vitro dissolution or in vivo BA and BE

Is the HCL salt formulation of prasugrel bioequivalent to the prasugrel base formulation?

The sponsor investigated the extent of conversion of the salt to the base in 2 bioequivalence studies where lots with high extent of conversion (70%), intermediate extent of conversion (58%) and low extent of conversion (5 %) were compared with and without the coadministration of 30 mg lansoprazole. The low medium and high extent of conversion lots were found to be bioequivalent to each other. However, when given with lansoprazole, the low medium and high extent of conversion were found to be bioequivalent to each other with respect to AUC but not to CMAX. There was on average a 29% difference (90% confidence interval 0.62-083) in CMAX between the low conversion and the high conversion lot. The difference between the medium and high conversion lot was less pronounced (10% with a 90 % CI of 0.77-1.04). This difference between these lots translated into differences in mean IPA of greater than 10% at 0.5 and 1 hour post dose. These differences can be potentially clinically significant. This difference can be attributed to difference in dissolution characteristics at higher pH between the base and the salt form. At higher pH the dissolution of the HCL salt is faster than the prasugrel base resulting in faster absorption rates explaining the 30% difference in CMAX.
The sponsor was made aware of the Agency's concern with regards of not being able to control the amount of conversion from the salt form to the base resulting in highly variable peak plasma concentrations from lot to lot. In a teleconference held on April 23, 2008, the [redacted] b(4)

Does the particle size of prasugrel have an effect on bioavailability?

The effect of particle size on the bioavailability of prasugrel was tested in a bioequivalence study where [redacted] were b(4) compared after coadministration with 30 mg lansoprazole. The results show that the difference in surface area did not have any effect on the extent of absorption as measured by AUC but had a slight effect on the rate of absorption as measured by CMAX as the 90% CI were slightly outside the 80-125% limits on the lower side (79-114% for the low and high surface area ratio and 78-112% for the medium to high surface area ratio). This slight difference in CMAX is not expected to be clinically significant.

What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The to-be-marketed formulation of prasugrel was used in the pivotal Study TAAL. The table below lists the prasugrel formulations used in the clinical studies, including TAAL.

Table 7 Summary of Formulations Used in Clinical Studies

Formulation Used	Study Alias
Prasugrel base tablets	148-007, S001, S002, S003, S004, TAAA, TAAC, TAAD, TAAE, TAAF, TAAH
Commercial Tablet: Prasugrel.HCl tablets	TAAF, TAAI, TAAJ, TAAK, TAAL, TAAN, TAAO, TAAP, TAAQ, TAAR, TAAS, TAAT, TAAU, TAAV, TAAW, TAAX, TAAZ, TABF, TABL, TABM, TABN, TABR, TABS, TABV, TABW, TABX, TABZ, TACF, TACG, TACJ, TACK, TACR, TACS
Prasugrel.HCl tablets used in Japan studies	J101, J102, J103, J105, J106, J201
Radiolabeled Prasugrel base Solution	TAAB

What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Except for Studies S002 (pilot study, 6 subjects) and TAAF, clinical pharmacology and pivotal TAAL studies were conducted in fasted subjects. In Study TAAF, coadministration of a single 15-mg prasugrel dose with a high-fat high-calorie meal Cmax was reduced by nearly half, tmax was delayed from 0.5 to 1.5 hours but not the extend of absorption. The figure below shows the effect of food on the kinetics of R138727.

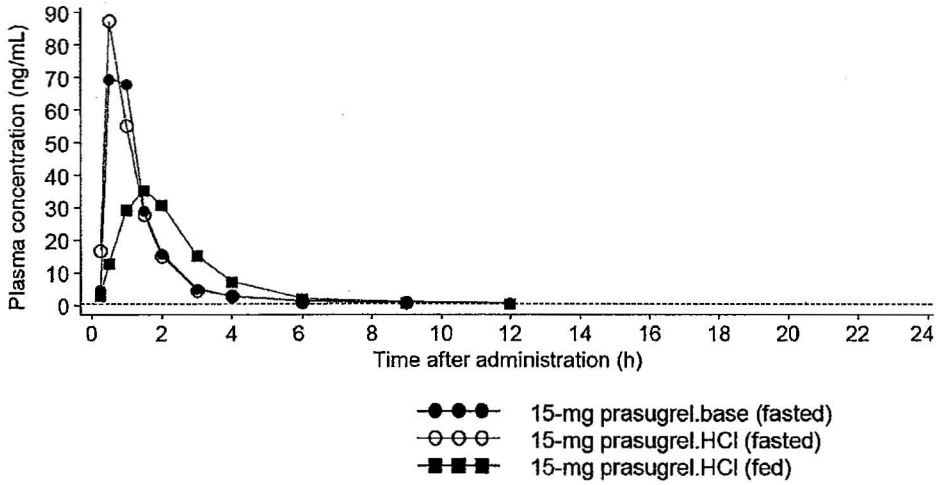

Figure 23. R138727 Plasma Concentrations vs Time. Food Effect

Table 8. Fed vs Fasted PK Parameters for Prasugrel Metabolites

Metabolites	PK Parameter (unit)	Geometric mean[a] (90% CI) [CS-747.HCl (Fed)]	Geometric mean[a] (90% CI) [CS-747.HCl (Fasted)]	Ratio of Geometric mean[a] (90% CI) [CS-747.HCl (fed) vs CS-747.HCl (fasted)]
R-138727	AUC (0-∞)·(ng·h/ml)	122 (108. 138)	129 (114, 146)	0.949 (0.893, 1.01)
	AUC (0-t_{last}) (ng·h/ml)	118 (105, 134)	124 (110, 141)	0.952 (0.890, 1.02)
	C_{max} (ng/ml)	63.6 (53.7, 75.4)	124 (105, 147)	**0.512 (0.428, 0.612)[b]**
R-95913	AUC (0-∞) (ng·h/ml)	144 (127, 163)	117 (103, 133)	**1.23 (1.13, 1.34)[b]**
	AUC (0-t_{last}) (ng·h/ml)	133 (117, 151)	107 (93.8, 121)	**1.25 (1.14, 1.36)[b]**
	C_{max} (ng/ml)	50.4 (43.8, 58.1)	62.8 (54.5, 72.4)	**0.803 (0.680, 0.948)[b]**
R-119251	AUC (0-∞) (ng·h/ml)	69.0 (59.9, 79.4)	75.1 (65.4, 86.3)	0.918 (0.849, 0.993)
	AUC (0-t_{last}) (ng·h/ml)	63.4 (54.9, 73.1)	70.8 (61.3, 81.7)	0.896 (0.827, 0.970)
	C_{max} (ng/ml)	27.3 (23.1, 32.3)	53.6 (45.3, 63.4)	**0.510 (0.427, 0.609)[b]**
R-106583	AUC (0-∞) (ng·h/ml)	789 (686. 907)	741 (645. 852)	1.06 (1.02, 1.11)
	AUC (0-t_{last}) (ng·h/ml)	691 (604, 791)	660 (577, 755)	1.05 (0.998, 1.10)
	C_{max} (ng/ml)	98.2 (86.0, 112)	121 (106, 139)	**0.810 (0.741, 0.885)[b]**

When prasugrel was administered with a high fat food breakfast, the disposition of all prasugrel metabolites changed (Table above).
For the inactive metabolite R-95913, food intake increased AUC(0-∞) between 13% and 34% (90% CI) and similarly for AUC(0-tlast). For the active and other inactive metabolites measured (R-119251 and R-106583), both AUC(0-∞) and AUC(0-tlast) are bioequivalent in the fed and fasted conditions. For all metabolites, food intake decreased the Cmax values, and increased median tmax from 0.5 to 1.5 hours.
Because PCI is usually performed in the fasted state, the food effect may be not clinically relevant and therefore, prasugrel can be administered with or without food.

How the elevated gastric pH affect the prasugrel bioavailability?

Prasugrel's dissolution in vitro is faster at pH 1 than at pH 6.8 and is intermediate at pHs in between. Therefore, treatment with drugs that increase gastric pH could slow the rate and/or extent of dissolution and absorption of a prasugrel dose. Treatment with such gastric pH modifiers is common in patients with ACS. In Study TAAL, 41% of subjects took a PPI and 15% took a H2-receptor antagonist through 3 days after the LD. Therefore, any effect occurring when given with prasugrel could be clinically relevant.
The different classes of gastric pH modifiers had different magnitudes of effect on the rate of prasugrel absorption.

Effect of PPIs: Lansoprazole given with a prasugrel LD or MD reduced the Cmax of prasugrel's active metabolite by nearly 30%, did not change tmax and did not affect the AUC(0-8) of prasugrel's active metabolite (Study TAAI).
It is likely that the lower Cmax with PPIs will delay the onset of platelet inhibition when prasugrel is given to a patient taking a PPI, but will not affect the level of platelet inhibition during MD.

Since a 30% differences in Cmax for the active metabolite of prasugrel did not change the PD response, this differences probably would not of clinical significance, and no dose adjustment of prasugrel is required when administered with lansoprazole.

Effect of H2 Antagonists: Oral ranitidine was studied with a prasugrel LD or MD (Study TABS). Ranitidine reduced the rate of absorption, the Cmax of prasugrel's active metabolite decreased by 14%, although it did not change tmax and did not affect the AUC(0-tlast) of prasugrel's active metabolite. This effect on active metabolite Cmax was less than that measured during treatment with lansoprazole. The platelet aggregation assessments included early time points that were lacking in the PPI Study TAAI. The assessment of ranitidine interaction in Study TABS showed no statistically significant difference in IPA at any time point except for 0.5 hours after the prasugrel LD + ranitidine. The reduction in IPA at 0.5 hours was 12 percentage points, which was associated with a 9 percentage point increase in MPA to 20 μM ADP. Prasugrel can be coadministered with or without a H2-receptor antagonist.

2.6 Analytical section

How the active moieties are identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Plasma samples collected in clinical studies were analyzed for prasugrel active (R-138727) and/or inactive (R-119251, R-106583, and R-95913) metabolites using validated liquid chromatography with tandem mass spectrometric detection (LC/MS/MS) methods. The methods for quantifying prasugrel metabolites in human plasma were first developed at Lilly Laboratory for Bioanalytical Research (LLBR). The methods were transferred to Advion BioServices, and the LLBR and Advion methods were successfully cross-validated.
In the drug-drug interaction studies, the assay validations for all measured moieties were provided.

What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The lower limit of quantitation was 0.5 ng/mL for R-138727 and 1 ng/mL for R-119251, R-106583, and R-95913. The upper limit of quantitation was 250 ng/mL for R-138727 and 500 ng/mL for R-119251, R-106583, and R-95913. Samples above the limit of quantitation were diluted and reanalyzed to yield results within the calibrated range.
The sponsor described each method used in the clinical studies, their cross-validation methods, as well as the validated standard curve range, intra/inter-assay precision, and intra/inter-assay accuracy for each method. Storage conditions and freeze/thaw stability data for prasugrel are also summarized in this appendix.
Derivatization of R-138727 in blood with 2-bromo-3-methoxyacetophenone within 30 seconds after collection was required to ensure the stability of the active metabolite during sample processing and storage.
The LC/MS/MS method used R138727-MP-d4 (3'-methoxyphenacyl derivative of deuterated R138727) as an internal standard for R-138727. Due to these difficulties, it was not possible to determine the plasma concentrations of the prasugrel active metabolite in the pivotal study TAAL which was performed at the multiple centers. The sponsor instead determined the inactive

metabolites plasma concentrations and used plausible pharmacokinetic modeling to predict the concentrations of the active metabolite.

What analytical methodologies were used to assess pharmacodynamic action?

Many of the studies that evaluated the PK of prasugrel's metabolites also evaluated the effect of prasugrel on platelet function. The primary method used to determine the PD response to prasugrel was light transmittance aggregometry (LTA) using 20 μM ADP as the agonist; 5 μM ADP was also used. Prasugrel administration results in inhibition of the platelet aggregation response to ADP, a result that may be reported as either a change in MPA, which decreases with increasing PD response, or inhibition of platelet aggregation (IPA), which increases with increasing PD response. Duplicate determinations of MPA were included in Studies TAAD, TAAJ, and TACJ, permitting the reproducibility of the LTA assay to be assessed. In addition to LTA, the PD response to prasugrel was also explored with additional assays as described in the sponsor's Table APP.2.7.1.5. They were VASP (platelet reactivity index) phosphorylation, serum thromboxane B2, activated partial thromboplastin time, factor Xa inhibition and activated clotting time values of anti-Xa.

The bleeding time assessment using a modified Ivy technique is a standard test. A pressure of 40 mmHg was applied using a blood pressure meter cuff inflated around the subject's arm. Three punctures were made on the subject's forearm at 5 second intervals using an Accu-check Softclix lancing device (Roche). A single sheet of filter paper was used to dab the outer perimeter of the three puncture wounds every 15 seconds. Bleeding time was recorded as the time from puncture to when a small clot formed.

Were the validation characteristics of the assays acceptable?

Yes. In all studies the assays have their validation reports, they are acceptable. See individual study reviews.

What is the overall conclusion regarding NDA 22-307?

Overall the Clinical Pharmacology and Biopharmaceutics section is acceptable.