

control group, and 16, 15, and 21 in the prasugrel 50, 100, and 300 mg/kg/day groups, respectively (per 110 animals in each group).

The Pharmacology/Toxicology Team and the Executive Carcinogenicity Advisory Committee concluded that the 2-year rat and mouse studies were reassuring, and found no evidence of a prasugrel-associated increase in malignant tumors in either species. Overall, although inconclusive, they regarded the hepatic findings to be consistent with induction of hepatic drug metabolizing enzymes.

No genetic toxicity was observed for prasugrel in standard tests that included an *in vitro* bacterial mutation test, Chinese hamster lung chromosomal aberration assay, and *in vivo* mouse micronucleus test.

Prasugrel did not cause any significant effects on fertility, early embryonic development, embryo-fetal development, or pre-/postnatal development in the rat or rabbit (approximately 30 times human exposure). At doses high enough to cause effects on maternal body weight and/or food consumption, there was a slight decrease in offspring body weight relative to controls. Placental transfer of prasugrel metabolites to the fetus of pregnant rats was low. ¹⁴C-prasugrel was excreted in the milk of lactating rats.

4.7. Pharmacology Toxicology Reviewer's Recommendations

"The extent and scope of the pharmacological and toxicological documentation provided are appropriate to support the clinical use of prasugrel at daily oral dose of 10 mg.

Adequate exposure was obtained in the toxicology studies, and all circulating metabolites in humans occurred in the circulation of species used in the non-clinical toxicity studies. The non-clinical studies adequately address the safety of prasugrel.

The proposed prescribing information includes an appropriate description of the genotoxicity, animal carcinogenicity studies, developmental and reproductive studies, and appropriate advice on breast feeding."

5. Clinical Pharmacology/Biopharmaceutics

5.1. Absorption, Distribution, Metabolism, Excretion

More than 79% of an oral dose of prasugrel is absorbed. The pro-drug is rapidly hydrolyzed by intestinal hydroxysterases to a thiolactone, which is then converted to the active metabolite by a single step, primarily by CYP3A4 and CYP2B6, and to a lesser extent by CYP2C9 and CYP2C19. The parent drug cannot be detected in plasma. Absorption and metabolism are both rapid; peak plasma concentrations of the active metabolite are reached approximately 30 minutes after administration. Exposure to the active metabolites increases slightly more than proportionally over the therapeutic dose range. The administration of repeated doses of 10 mg does not lead to the accumulation of the active metabolite.

In subjects with stable atherosclerosis, estimates of the apparent volume of distribution of prasugrel's active metabolite ranged from 30-84 L, and estimates of apparent clearance ranged from 73-266 L/hr.

Binding of the active metabolite to plasma proteins was not determined *in vivo*, but was highly bound *in vitro*. The inactive metabolites are also highly bound to human plasma proteins.

Prasugrel is cleared both by the liver and the kidney: about 68% of the prasugrel dose is excreted in the urine and 27% in the feces, as inactive metabolites. The active metabolite R-138727 has an elimination half life of about 7.4 hours (range 2 to 15 hours).

The active metabolite contains 2 chiral centers; therefore, there are 4 enantiomers: (R,S), (R,R), (S,R), and (S,S). The R- and S-configurations at the 1' position interconvert *in vivo*. Thus, the 4 enantiomers of R-138727 can be considered to be 2 pairs: (R,S)/(R,R) and (S,R)/(S,S). Each possesses different activity towards the platelet P2Y₁₂ ADP receptor; however, the ratio of enantiomers was consistent across subjects. Thus, variation in enantiomeric ratios is not important in interpreting the clinical data. The (R,R)/(R,S) pair comprises about 84% of the total active metabolite, and is the most potent.

5.2. Demographic Interactions/Special Populations

5.2.1. Body Weight

Exposure of R-138727 increased with decreasing body weight. Major bleeding (Thrombolysis in Myocardial Infarction [TIMI] major bleeding - any intracranial hemorrhage, or bleeding requiring intervention associated with a decrease in hemoglobin [Hgb] \geq 5 g/dL) was 2-fold higher in subjects weighing less than 60 kg, but efficacy was similar across body weight groups. The sponsor proposes a reduction in the maintenance dose from 10 mg to 5 mg in subjects weighing less than 60 kg, and the Clinical Pharmacology team concurs with this recommendation.

5.2.2. Gender

The data do not support a rationale for dose adjustment based on sex, and none is recommended.

5.2.3. Pediatric Patients

The pharmacokinetics of prasugrel were not studied in pediatric subjects, and no recommendations are supported.

5.2.4. Advanced Age

Advanced age is an important predictor of morbidity and mortality in the ACS patient population. Likewise, age is an important predictor of bleeding in this patient population. The sponsor proposed prasugrel dose reduction in patients over the age of 75. The Clinical Pharmacology review team does not agree with this plan.

Whereas the hazard ratio (HR) was 0.78 in favor of prasugrel (versus clopidogrel) in preventing the primary triple endpoint in subjects less than 75 years of age, efficacy of the two drugs was similar (HR statistically indistinguishable from 1) for subjects over 75. For TIMI Major bleeding, the HR favored clopidogrel, and was similar for subjects less than and greater than age 75 years (hazard ratios of 1.47 and 1.23, respectively). Thus, a reduction in dose might lessen bleeding in patients over 75 years of age, the impact of dose reduction on efficacy is unknown, and could be unfavorable. Therefore, the Clinical Pharmacology team opined against a dose reduction for patients over the age of 75.

5.2.5. Race

Exposure to prasugrel's active metabolite in Caucasian, African, and Hispanic subjects was similar; however, exposure was approximately 40-45% higher in Asian versus Caucasian subjects. After adjusting for body weight and other covariates, C_{max} and $AUC(0-t_{last})$ were still

20% higher in Asians than in Caucasians. Although there was considerable variability in the IPA response, IPA was generally higher in Asian subjects than in Caucasians. Consistent with these disparities in pharmacokinetics and pharmacodynamics, the highest incidence of bleeding-related adverse events was reported for Korean subjects. In light of the above, the Clinical Pharmacology team recommended advice in labeling to the effect that prasugrel should be administered with caution in patients of Asian descent.

5.2.6. Renal Impairment

There were too few subjects in the development program with end-stage renal disease (ESRD) to draw firm conclusions regarding pharmacokinetics or pharmacodynamics in this patient population. After 60 and 10 mg doses of prasugrel, the exposure to R-138727 (both C_{max} and $AUC[0-t_{last}]$) 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 platelet aggregation between subjects with renal impairment and healthy matched subjects at each time point were not statistically significant. However, given the limited sample size, it is difficult to draw conclusions regarding platelet aggregation in patients with ESRD. Bleeding events were not assessed in these studies. The Clinical Pharmacology Review team recommended a contraindication for prasugrel in patients with ESRD. Of note, a contraindication in this patient population would be unusual. More typically, the package insert would note that experience is limited in this patient population.

5.2.7. Hepatic Impairment

The PK parameters estimated for the active metabolite were similar in healthy subjects and subjects with moderate hepatic impairment. The pharmacodynamic response measured as maximum platelet aggregation to 20 μ M ADP was similar as well.

A dose adjustment is not required for the patients with mild and moderate hepatic impairment.

The Clinical Pharmacology/Biopharmaceutics review team opined that prasugrel should be contraindicated in patients with severe hepatic impairment due to the potential risk of bleeding.

5.3. *Extrinsic Factors*

5.3.1. Food Effects

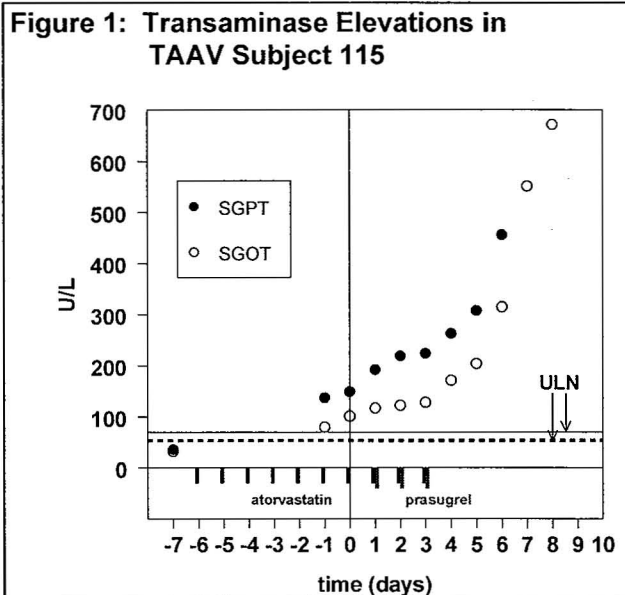
In Study TAAF, when a single 15-mg prasugrel dose was co-administered with a high-fat high-calorie meal, C_{max} of the active metabolite was reduced by nearly half (49%), and T_{max} was delayed from 0.5 to 1.5 hours. The extent of absorption (AUC) was unaffected. Because patients undergoing PCI are generally fasting, the review team opined that prasugrel can be administered without regard to food. More properly, the label should state that the drug should be administered in the fasting state.

5.3.2. Drug-Drug Interaction Information

There were no clinically important drug-drug interactions with a CYP3A4 inhibitor (ketoconazole), a CYP3A4 inducer (rifampicin), or a CYP2B6 substrate (bupropion). Conversely, a clinically significant pharmacodynamic drug-drug interaction, prolongation of the bleeding time, was observed when prasugrel was co-administered with aspirin, heparin, and warfarin. Caution should be exercised when these drugs are co-administered with prasugrel.

Although the pharmacokinetic interactions between atorvastatin and prasugrel are limited, acute liver failure was reported in one subject who received prasugrel and atorvastatin in a PK study.

Subject 115, a 59 year-old male in the 2-period PK study TAAV, received prasugrel alone in a Period 1 without untoward effects. In Period 2, he received atorvastatin 80 mg QD, day -6 to 3, per protocol. Hepatic transaminases were elevated to 2-3X ULN on Day -1, after receipt of 5 doses of atorvastatin, and prior to receiving his initial dose of prasugrel (Figure 1). A 60-mg LD of prasugrel was administered on Day 1, and MDs of 10-mg were administered on Days 2 and 3. Upon receipt of the serum biochemistry results on Day 3, a further increase in the subject's liver enzymes was evident and both drugs were discontinued. The increases in liver enzymes resolved after approximately 56 days (not shown).



In this subject, the transaminases were moderately elevated on Days -1 and 0. The additional increase observed on Days 1, 2, and 3 occurred before administration of prasugrel (the Day 1 sample was obtained in the early morning hours, and so could not have been affected by the initial prasugrel LD, administered that day). The more striking increases in transaminases (Day 4 and beyond) might have occurred as a result of atorvastatin alone, even in the absence of prasugrel. Thus, given this uncertainty, and given that this occurred in only a single subject, this secondary reviewer does not believe that any specific advice is appropriate or necessary for labeling.

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. Digoxin clearance was not affected by prasugrel co-administration, and no dose adjustment is needed for digoxin when co-administered with prasugrel.

5.4. Exposure-Response Relationships

The sponsor based dose selection for the pivotal trial 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 TAAD, 4 prasugrel regimens were compared with the approved clopidogrel regimen: prasugrel 40-mg loading dose (LD)/5-mg maintenance dose (MD); 40-mg LD/7.5-mg MD; 60-mg LD/10-mg MD; 60-mg LD/15-mg MD; clopidogrel 300-mg LD/75-mg MD. Both the 40-mg and 60-mg prasugrel LDs resulted in more rapid onset with significantly greater IPA than the 300-mg LD of clopidogrel. The 60-mg prasugrel LD consistently achieved the highest IPA. 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 was associated with more bleeding.

The phase 2 Study TAAH assessed bleeding events associated with three regimens of prasugrel (40 mg LD + 7.5 mg daily MD, 60 mg LD + 10 mg daily MD, or 60 mg LD + 15 mg daily MD), versus a standard regimen of clopidogrel (300 mg LD + 75 mg daily MD) in subjects undergoing urgent or elective PCI. The results of the study are described in Section 6, below.

5.5. Form Conversion from Salt to Base

5.5.1. Bioequivalence of Prasugrel – Low, Medium, and High Salt-to-Base Conversion

The sponsor conducted two bioequivalence studies wherein they compared the bioavailability of lots with low (5%), intermediate (58%), and high (70%) degrees of conversion to base, with and without co-administration of a PPI (lansoprazole) to raise gastric pH. The sponsor concluded that up to 70% conversion from salt to free base was clinically acceptable in patients, both with and without concomitant PPI use; however, the agency's clinical pharmacology reviewer did not concur.

- When prasugrel 60-mg was administered without a PPI:
Prasugrel lots with low, intermediate, and high salt to base conversion were bioequivalent with respect to R-138727, prasugrel's active moiety. This was true with respect to both C_{max} and area under the curve (AUC).
- When prasugrel 60-mg was administered on a background of lansoprazole:
Prasugrel lots with low, intermediate, and high salt to base conversion were still bioequivalent for R-138727 with respect to AUC, but *were not bio-equivalent with respect to C_{max}* (Table 1). The mean difference in C_{max} between the low and the high conversion lots was 29% (90% confidence interval [C.I.] 17%, 38%), and there was a 20% difference in C_{max} between the medium and high conversion lots (90% C.I. 8%, 31%). There was no statistically significant difference in C_{max} for the low and medium conversion lots.

Table 1: Relative Bioavailability of R-138727, the Active Moiety of Prasugrel – Comparison of Low, Medium, and High Extents of Conversion with Background 30-mg Lansoprazole (sponsor's table TACS 7.2)

Geometric least square means (90% CI)			Ratio of means (90% CI)		
prasugrel-LC	prasugrel-MC	prasugrel-HC	M-C/LC	H-C/L-C	H-C/M-C
AUC(0-t_{last}) (ng•h/mL)					
470 (424, 522)	467 (421, 518)	409 (368, 454)	0.99 (0.93, 1.06)	0.87 (0.82, 0.93)	0.88 (0.82, 0.93)
C_{max} (ng/mL)					
331 (285, 384)	297 (257, 344)	236 (204, 274)	0.90 (0.77, 1.04)	0.71 (0.62, 0.83)	0.80 (0.69, 0.92)

LC ≡ low conversion; MC ≡ medium conversion; HC ≡ high conversion

5.5.2. Pharmacodynamics of Prasugrel – Low, Medium, and High Salt-to-Base Conversion

Analysis of the pharmacodynamics of prasugrel in the presence and absence of PPI provides insight into the potential consequences of these differences in C_{max} . The effects of thienopyridines on platelet aggregation last for the life of a platelet and are concentration-dependent. A delay in reaching C_{max} , i.e., a lengthened T_{max} or a lower C_{max} , could delay the full effect of the drug on platelet aggregation. For the 60-mg prasugrel loading dose, these differences translated into absolute disparities in inhibition of platelet aggregation (IPA) of

approximately 20% at 0.5 hours post-dose (high versus low- or medium-salt-to-base conversion) and 12% at 1 hour post-dose, when prasugrel is given on a background of lansoprazole (Figure 2). Thus, at the time points that bracket T_{max} , the high salt-to-base conversion lots are not bio-equivalent to lots with medium or low conversion. However, at subsequent time points (2, 4, and 24 hours post-dose), inhibition of platelet aggregation continued to increase, such that IPA was virtually identical with lots of all degrees of conversion by two hours (Figure 2). In essence, therefore, the bioinequivalence results in a delay of perhaps 20 minutes in achieving maximal inhibition of platelet aggregation. This is manifested only with the high salt-to-base conversion product, and only in the presence of PPI or H2 receptor antagonists.

5.5.3. Relevance of Altered Pharmacodynamics of High Salt-to-Base Conversion

Because PCI may precipitate periprocedural myocardial infarction, a considerable number of events occur very soon after PCI. As a case in point, in TAAL, of all the non-fatal myocardial infarctions recorded during the course of the 15-month study, *30% of them occurred within the first hour of the study!* Clearly, therefore, rapid inhibition of platelet aggregation may be important in preventing periprocedural MIs, and the delay in achieving inhibition of platelet aggregation resulting from use of the high salt-to-base conversion product in the presence of PPIs or H2 receptor blockers has at least the potential to be clinically meaningful.

However, to understand fully the significance of the delay, it is important to contrast the prasugrel's overall IPA activity to that of clopidogrel. Figure 3 shows the IPA in response to 20 μ M ADP for subjects who received prasugrel versus clopidogrel from Study TAAJ (loading and daily maintenance doses). Although prasugrel lots with high salt-to-base conversion exhibit delayed inhibition of platelet aggregation in the presence of high gastric pH, the difference seems negligible when placed into context with the effect of clopidogrel, at least on a population basis. Prasugrel has a markedly higher IPA than clopidogrel at all time points following administration.

Figure 2: Inhibition of Platelet Aggregation (IPA) to 20 μ M ADP, Following 60-mg Prasugrel: Lots with Low, Medium, and High Extents of Salt-to-Base Conversion on Background of Lansoprazole 30-mg (* $p < 0.01$, high conversion versus low or medium conversion, mean \pm SD; calculated by CDER, Study TACS)

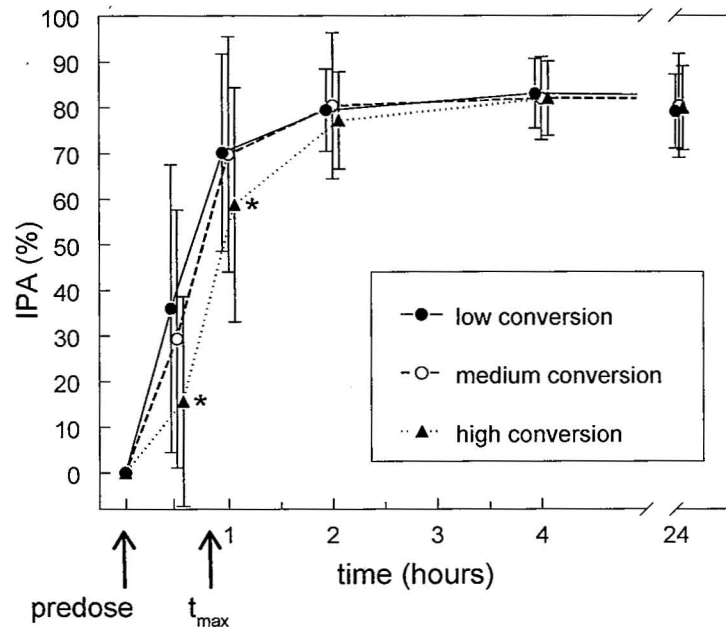
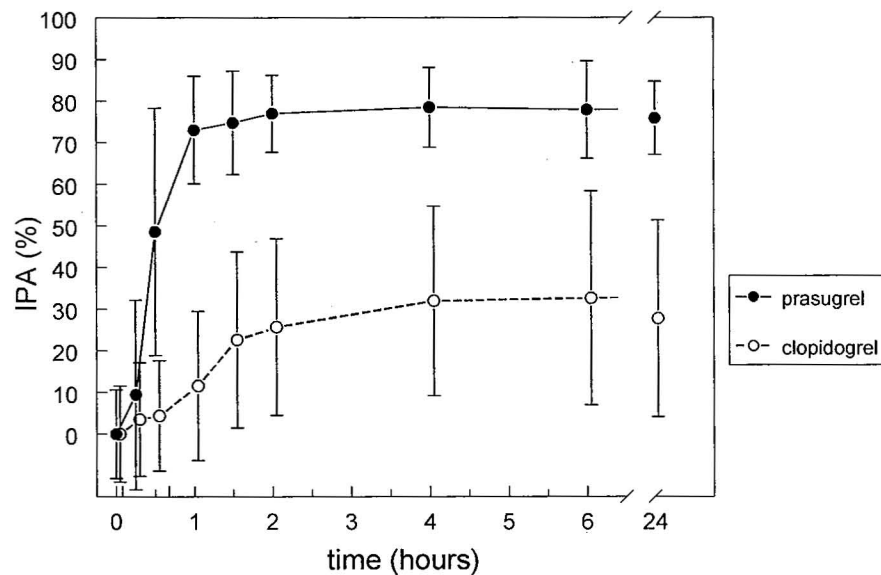


Figure 3: Inhibition of Platelet Aggregation (IPA) to 20 μ M ADP, Following Loading Doses of Prasugrel 60 mg or Clopidogrel 300 mg (from Study TAAJ, mean \pm SD)



6. Dose Identification/Selection and Limitations

In retrospect, the rationale for dose selection for the phase 3 study seems only questionably adequate. Although the tested prasugrel regimen proved superior to clopidogrel in terms of endpoint events in the phase 3 study, it is unknown whether a lower dose would have achieved a more favorable risk-benefit profile, with similar efficacy but lower rates of bleeding.

The identification for dose selection for the phase 3 study was largely accomplished through a small study of IPA (Study TAAD, see 5.4, described above), and a medium-sized phase 2 study (TAAH).

Study TAAH, "A Double-Blind, Randomized, Multicenter, Dose-Ranging Trial of CS-747 (LY640315) Compared With Clopidogrel in Subjects Undergoing Percutaneous Coronary Intervention" assessed the bleeding events associated with three regimens of prasugrel. Subjects undergoing urgent or elective PCI were randomized to receive prasugrel 40 mg LD + 7.5 mg daily MD, prasugrel 60 mg LD + 10 mg daily MD, prasugrel 60 mg LD + 15 mg daily MD, or a standard regimen of clopidogrel (300 mg LD + 75 mg daily MD). Subjects were treated for one month, and the study was powered to detect two-fold increases in the risk of bleeding, assuming that the bleeding rate in the clopidogrel group would be >5%.

Rates of significant (TIMI major + TIMI minor) bleeding were much lower than anticipated, and statistically indistinguishable between the treatment groups. The rates at Day 30 were 1.5%, 2.0%, 1.6%, and 1.2% in the prasugrel 40/7.5, 60/10, 60/15, and clopidogrel 300/75 groups, respectively. (These percentages reflect only 3 or 4 events in each group). In terms of effect, rates of major adverse cardiac events (MACE) were similar in all prasugrel groups: 7.5% in the 40/75 and 60/10 groups; 6.8% in the 60/15 group. The rate of MACE was 9.4% in the clopidogrel group (P=NS versus pooled prasugrel). In short, neither bleeding rates nor MACE rates provided a firm foundation for dose selection.

The sponsor's rationale behind dose selection for the phase 3 study is paraphrased from the TAAL study protocol:

- In TAAH, prasugrel 60/10 or 60/15 resulted in a consistent trend towards reduced 30-day MACE compared with clopidogrel.
- In TAAH, the prasugrel 60/10 or 60/15 regimens were not associated with significant increases in 30-day bleeding rates compared with clopidogrel.
- Based on dose-ranging studies in subjects with stable coronary disease and subjects undergoing elective or urgent PCI, the 10-mg MD of prasugrel did not result in higher rates of TIMI Minimal bleeding and/or non-TIMI bleeding episodes (for example, no increase in epistaxis or oral bleeding) compared with the 75-mg MD of clopidogrel.

Thus, a 60-mg LD followed by a 10-mg once-daily MD was selected for the registrational trial (TAAL) based on the results of TAAH and TAAD. Importantly, however, the sponsor's decision was based on weak trends in the data and a handful of events, rather than statistical certainty. It is possible that a lower prasugrel dose would have resulted in similar efficacy with less risk of bleeding, but the development program does not assess this possibility.