Plasma samples for the determination of concentrations of prasugrel's inactive metabolites (R-106583, and R-119251) were collected after administration of the 60-mg LD and/or following 10-mg MD administration. Collection and measurement of prasugrel active metabolite (R-138727) could not be achieved in Study TAAL due to the complexities of handling samples at the study sites, including complicated and labor intensive blood collection, difficult processing procedures, and reagent requirements. Therefore, a multilinear regression correlation model was used to quantitatively predict R-138727 concentrations from its 2 downstream inactive metabolites (R-119251 and R-106583). The predicted R-138727 concentration versus time data combined with dosing information and pre-specified subject factors of clinical and demographic interest were analyzed, using population techniques, to characterize R-138727 pharmacokinetics.

Methods

Multi-Linear Regression Correlation Model:

A structural multi-linear regression correlation model for the prediction of prasugrel's active metabolite, R-138727, was developed using concentration-time data from the two downstream inactive metabolites of R-138727, R-119251 and R-106583. Log transformed concentrations were used in the assessment of correlation.

Estimates of the model parameters and error terms were obtained by fitting the concentration-time data by means of the nonlinear mixed-effects modeling program, NONMEM (version V) with PRED.

Patient factors were examined for a reduction in variability or bias in the prediction of R- 138727 and included: dose, age, Cockcroft-Gault creatinine clearance, serum creatinine, sex, smoking status, body weight, and co-administration with food or ketoconazole.

The correlation model was qualified by predicting the concentrations of R-138727 from the concentrations of R-119251 and R-106583 for studies TAAD and TABR. The predictive performance of the model was further tested with data from studies TABW, TACG, TAAN and TABZ.

Population Pharmacokinetics:

A three-compartment model with zero-order absorption, proportional between-patient variability on apparent clearance of active metabolite and proportional residual error was selected as the structural model for prasugrel active metabolite. As the R-138727 concentrations utilized in the pharmacokinetic model themselves reflected predicted values from the multi-linear regression correlation model, the potential influence of subject-specific factors using pharmacostatistical methods for covariate screening and selection were not applied. Rather, any influence on the posthoc derived R-138727 systemic exposures was assessed descriptively.

Details of the methods can be found in the sponsor report H7T-MC-TAAI Population Pharmacokinetics Report (\\Cdsesub1\evsprod\NDA022307\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\h7t-mc-taal-pop-pk)

Results

- The correlation model for predicting the active metabolite concentrations is represented by the equation below. Log-transformed concentration of R-11925 and R-106583 were used to perform the analysis.

$$R\text{-}138727 = A^* R\text{-}119251 + B^*R\text{-}106583^*EXP(-C^*TIME)+D$$

- The model showed good correlation with only a minor deviation ~6% from the line of unity and described the variability within ~4.5%.
- Age, dose, co-administration of ketoconazole and food were identified as significant factors relating to the differences between R-138727 and R-106853. Final parameter estimates of the correlation model are shown in the table.

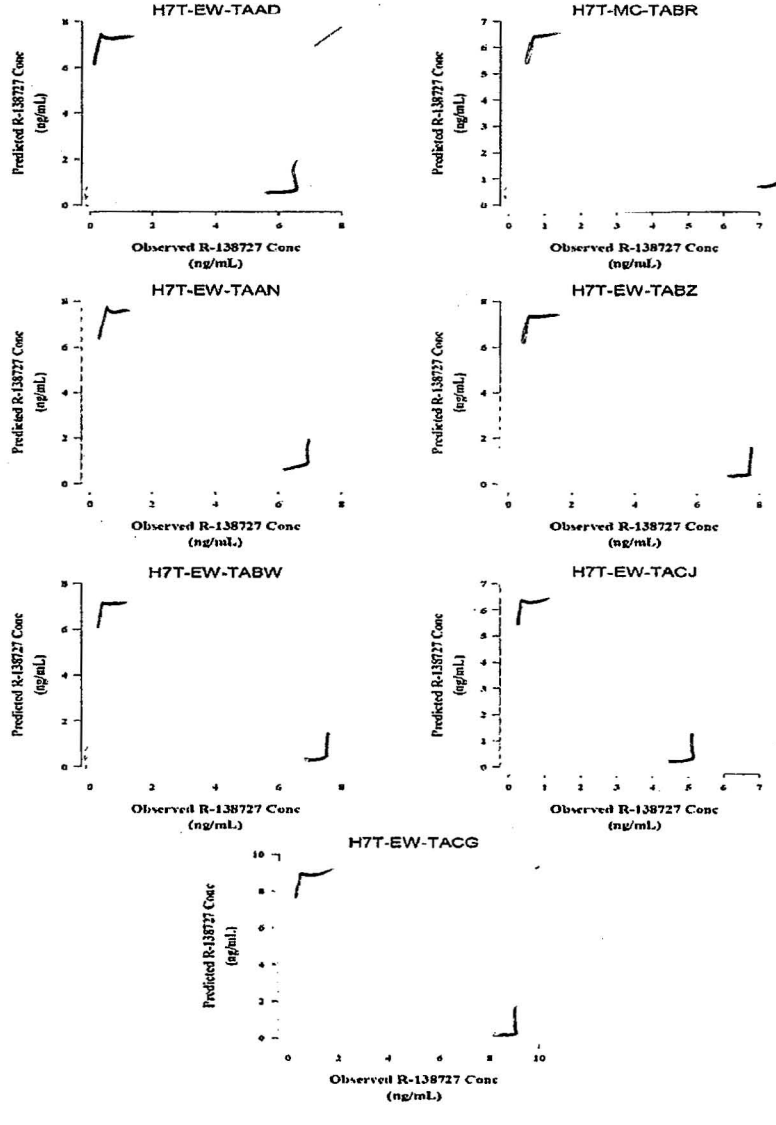
Table 7: Final correlation analysis model
(per sponsor report H7T-MC-TAAI; Table 2, page 116)

Parameter	Estimate	%Standard Error of Estimate
Correlation of R-119251 to R-138727 (A)	0.896	1.70
Correlation of R-106583 to R-138727 (B)	0.354	6.98
Correction of Correlation of R-106583 to R-138727 over Time (C)	0.807	5.34
Intercept to Correct between Loading and Maintenance Doses (D)	-0.305	9.34
Effect of Ketoconazole on the Correction of Correlation of R-106583 to R-138727 over Time (Effect on C)	-0.586	4.81
Effect of Food on the Correction of Correlation of R-106583 to R-138727 over Time (Effect on C)	-0.477	8.53
Effect of Dose on the Correlation of R-106583 to R-138727 (Effect on B)	-0.218	16.2
Effect of Age on the Correction of Correlation of R-106583 to R-138727 over Time(Effect on C)	0.0103	23.0
Proportional Residual Error	34.8%	10.0

Proportional residual error represented as %CV: calculated as %CV = SQRT(SIGMA(N))*100%.

- The prediction was within 6% of the observed data across different studies thus establishing the predictive ability of the model as shown in **Figure 18**. The details of the multilinear correlation regression analysis can be found in the sponsor report H7T-MC-TAAL; Appendix TAAL.4 (\\Cdsesub1\evsprod\NDA022307\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\h7t-mc-taal-pop-pk)

Figure 18: The correlation model performs reasonably well across different studies.
(per sponsor report H7T-MC-TAAL; Figure 5, page 119)



b(4)

- The pharmacokinetics of R-138727 was adequately described by a three compartment model with zero-order absorption. The final population pharmacokinetic parameter estimates are shown in the table

Table 8: Final population pharmacokinetic parameter estimates for Study TAAI.

(per sponsor report H7T-MC-TAAL; Table TAAL.9.2)

Parameter Description	Population Estimate (%SEE)	Between-Subject Variability[a] (%SEE)
Duration of Absorption	0.0865	--
D1 (hr)	(94.9)	
Rate Constant for First-Pass Formation of R-138727	5.77	--
K12 (hr^{-1})	(57.2)	
Fraction of First Pass Formation of R-138727	55.0 FIXED	--
FFP (%)		
Apparent Clearance of R-138727	120	52.7
CL20/F (L/hr)	(2.47)	(10.2)
Apparent Volume of Distribution for R-138727	74.3	--
V2/F (L)	(6.82)	
Rate of R-138727 Formation from R-95913	0.0517	--
K32 (hr^{-1})	(5.51)	
Proportional Residual Error for R-138727[b]	65.9% (2.81)	

Abbreviations: CV = coefficient of variation; SEE = standard error of the estimate.

[a] %CV = (SQRT(EXP(OMEGA(variance estimate))-1))*100%

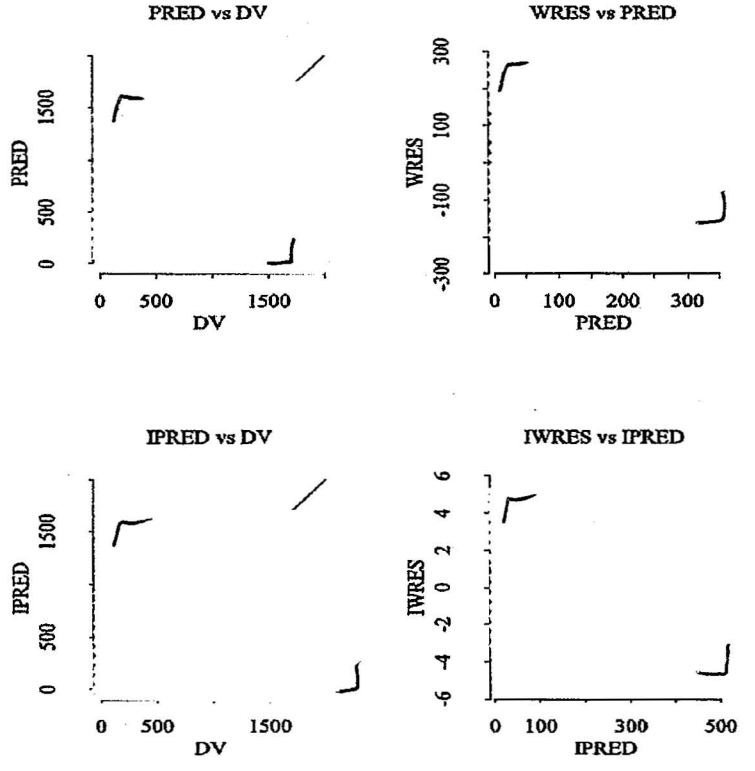
[b] %CV = SQRT(SIGMA(variance estimate))*100%

- The systemic exposure increased with decreasing body weight; whereby median exposure in subjects weighing <60 kg were approximately 35% higher compared to subjects having a mean body weight of 84 kg.
- The systemic exposure of R-138727 was not appreciably affected by age, body mass index, gender, diabetes, smoking, and renal impairment.
- The exposure of prasugel active metabolite is comparable between healthy subjects, subjects with stable atherosclerosis and the target population; therefore, properties observed in healthy subjects are applicable to subjects with acute coronary syndromes and stable atherosclerosis.

Reviewer's Comments

- The population pharmacokinetic and the PK/PD analyses for studies TAAD and TABR are acceptable. The sponsor has done a commendable job of characterizing the concentration-IPA relationship for both prasugrel and clopidogrel.
- The sponsor chose an exponential function to describe the relationship between the clearance of R-138727 and body weight in studies TAAD and TABR based on the data. This relationship was predominantly driven by a single extremely high body weight (>140 Kg). Such a relationship is not physiologically representative as unusually high clearances will be achieved at the higher body weights.
- The multilinear correlation model developed for the prediction of the R-138727 concentration of the downstream inactive metabolites is acceptable and the predictive performance of the model is reasonable.
- Given the systematic under prediction of individual predictions (IPRED) and large weighted residuals associated with high concentration (see **Figure 19**), the population pharmacokinetic model for study TAAL is not acceptable.

Figure 19: Goodness-of-fit for final prasugrel PK model for Study TAAL.
(per sponsor report H7T-MC-TAAL; Appendix TAAL.3)



b(4)

OFFICE OF CLINICAL PHARMACOLOGY GENOMICS REVIEW

NDA: 22-307	Submission Date(s): 12/26/2007
Brand Name	Effient™
Generic Name	Prasugrel
Reviewer	Federico Goodsaid
Team Leader	Felix Frueh
OCPB Division	Genomics
ORM division	Division of Cardio-Renal Drug Products, HFD-110
Sponsor	Eli Lilly
Relevant IND(s)	63449
Submission Type; Code	Priority
Formulation; Strength(s)	Tablets, 5mg &10mg
Indication	Treatment of subjects with acute coronary syndromes (ACS)

1 Executive Summary

A label claim in this submission 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. The goals of this genomic review were to assess sponsor analyses plan for genomic data, analytical performance of genotype assays, and genotype association analysis, and to be able to confirm association claims from the sponsor between genotype and plasma drug levels. The thienopyridines are a class of prodrugs that are metabolized in vivo to generate an active metabolite that inhibits the platelet P2Y12 receptor. The thienopyridines include Clopidogrel (second generation thienopyridine) and Prasugrel (third generation thienopyridine; currently in clinical development).

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.

1.1 Recommendation

Concur with text in label section 12.3: "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."

1.2 Phase IV Commitments

None.

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3 Summary of Genomic Findings

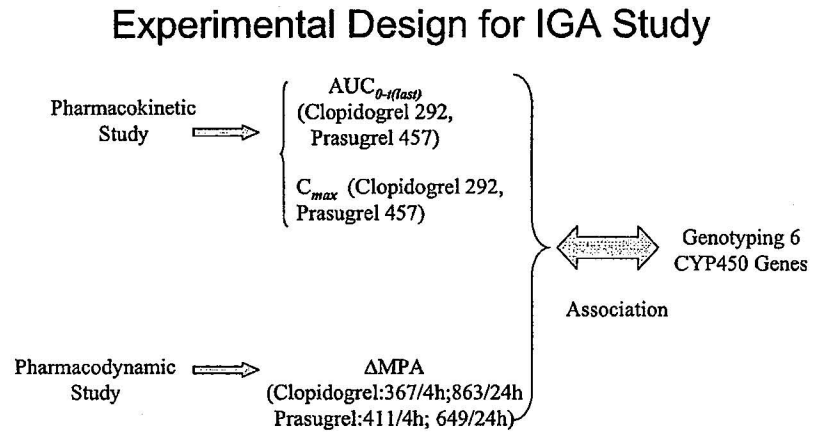
In healthy subjects, patients with stable atherosclerosis, and patients with acute coronary syndromes (ACS) receiving Prasugrel, there was no clinically significant effect of genetic variation: in CYP3A5, CYP2B6, CYP2C9, or CYP2C19 as defined by active metabolite exposure levels; in healthy subjects and patients with stable atherosclerosis receiving prasugrel, no effect of genetic variation on PD measures of platelet function was observed; in patients with ACS receiving Prasugrel, these evaluations suggest there is no effect of genetic variation on the primary or secondary efficacy measures in Prasugrel treated patients for any individual CYP enzyme.

4 Review of Genomics Data

4.1 Clinical Studies

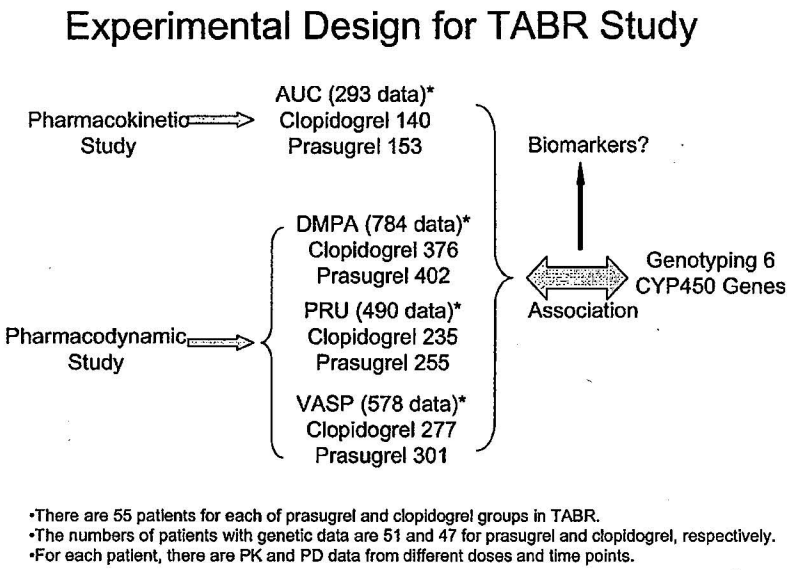
Genomic data for this submission were reported in three clinical study datasets. The **Integrated Genetic Analysis (IGA)** dataset was a study of the effects of variation in genes encoding CYP enzymes involved in thienopyridine metabolism on PK and PD in response to LD or MD of Prasugrel or Clopidogrel in healthy subjects.

Figure 1: Experimental Design for IGA Study



The **TAAL** (PK) study investigated 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 **TAAL** (Efficacy) study investigated the relationship between variation in the genes encoding CYP enzymes that are involved in Prasugrel or Clopidogrel metabolism and clinical efficacy outcomes in the subset of patients. Finally, the **TABR** study investigated 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.

Figure 2: Experimental Design for TABR Study



4.2 Genes

CYP2C19, CYP2C9, CYP3A4, CYP2B6, CYP1A2 and CYP3A5.

4.3 Genotyping Method

DMET Chip: 98.3% overall success rate.

4.4 Genomic Data Analysis Strategy

Analysis strategies for each of the studies are outlined below.

IGA

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 genotypes for the genes listed above. Independent analyses with binning for CYP2C9 and CYP2C19 were also reported.