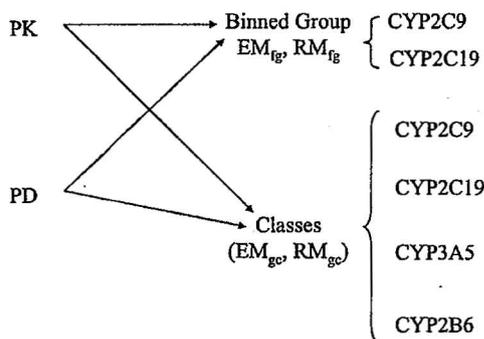


Figure 3: Statistical Analysis Strategy for IGA Study

Statistical Analysis Strategy for IGA Study



Linear Mixed-effects Models

TAAL (Efficacy)

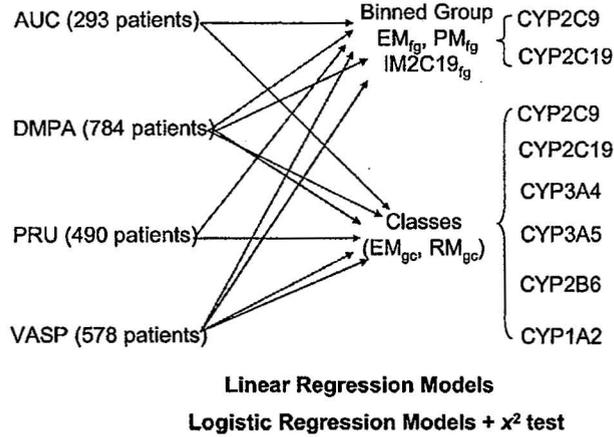
The primary clinical endpoint was a composite of CV death, nonfatal MI, or nonfatal stroke as adjudicated by CEC with reaching any component; patients received aspirin and were randomized to receive either a 300 mg LD/75 mg MD of Clopidogrel or a 60 mg LD/10 mg MD of Prasugrel. Endpoints from randomization through a patient's termination visit or 464 days whichever was earlier. The primary genetic endpoints were the combined CYP2C19 and CYP2C9 functional group: EM_{fg} and RM_{fg}. Variations in CYP2C19 and CYP2C9 were associated with lower exposure to active metabolite and decreased inhibition of platelet aggregation following administration of Clopidogrel. The effect of CYP genetic variations on cardiac event rate was completed in all patients with ACS and also in the subgroup of patients with UA/NSTEMI.

TABR

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.

Figure 4: Statistical Analysis Strategy for TABR Study

Statistical Analysis Strategy for TABR Study



4.5 Confirmation of Analysis and Results

We were able to confirm the analysis and results submitted by the sponsor after modifying the computational code submitted by the sponsor. Important results reproduced by this work are shown below:

Figure 5: IGA Study. Analyses with Pharmacokinetic Measurements

Baseline Characteristics (Pg 67, TB 8.10)			Pharmacokinetic Parameters						CONFIRMATION: Effects between AUC0-4(last) and CYP Genetic Classifications					
	Prasugrel	Clopidogrel	Drug	Dose	N	G-Mean	Median	SA	95%	Gene	Prasugrel w/ eth	Prasugrel w/o eth	Clopidogrel w/eth	Clopidogrel w/o eth
N	32	19	Prasugrel	60mg	268	1508.4	1676.6	853.7	2858.8	3A5	0.947	0.398	0.502	0.651
Age	35.64 ± 11.40	33.09 ± 11.56	Prasugrel	30mg	189	233.5	207.2	135.9	860.7	2B6	0.542	0.413	0.029	0.040
Mass ± SD			Clopidogrel	300mg	539	178.5	169.8	88.8	277.9	2C9	0.344	0.188	0.586	0.627
Body Weight	72.10 ± 12.75	71.98 ± 11.44	Clopidogrel	60mg	47	805.6	686.6	282.7	1450.8	2C19	0.0038	0.311	0.0000011	0.0000034
Mass ± SD			78mg	78	106.6	103.7	36.2	288.1	2C19	(0.062)*	(0.679)*			
Ethnicity	n (%)	n (%)	Mean Cmax by Treatment						2C19	0.00043	0.0277	0.00002	0.000033	
CA	200 (60.15)	151 (77.39)	Drug	Dose	N	G-Mean	Median	SA	95%	+2C9				
AS	94 (29.82)	38 (19.99)	Prasugrel	60mg	268	1508.4	1563.7	853.3	2730.3					
AF	18 (5.62)	7 (3.67)	Prasugrel	30mg	189	233.9	223.9	97.3	854.8					
Gender	n (%)	n (%)	Clopidogrel	300mg	539	182.8	134.9	66.4	401.3					
Male	227 (70.94)	143 (75.79)	Clopidogrel	60mg	47	322.3	319.1	136	818.4					
Female	93 (29.06)	36 (18.99)	78mg	78	106.2	108.8	39.2	324.8						
Smoking Status (PK)	33 (10.31)	20 (10.52)												

Conclusion: no correlation of genotype with Prasugrel pharmacokinetics if ethnicity effects are excluded.

Figure 6: IGA Study. Analyses with Pharmacodynamic Measurements

Baseline Characteristics (Pg 44, TB 8.4)		Pharmacodynamic Parameter (Δ MPA)		CONFIRMATION: Effects between Δ MPA and CYP Genetic Classifications				
N	777	Change from Baseline in Maximal Platelet Aggregation in Response to 20 μ M ADP, by Treatment and Time		Gene	Prasugrel w/ eth	Prasugrel w/o eth	Clopidogrel w/eth	Clopidogrel w/o eth
Age	33.91 \pm 13.29			3A5	0.437	0.779	0.089	0.463
Body Weight	72.43 \pm 12.97			2B6	0.906	0.889	0.019	0.021
Body Weight	76.97 \pm 11.99			2C9	0.755	0.598	0.863	0.698
Female	41 (5.28%)			2C19	0.724	0.887	0.00032	0.005
Female	49 (6.31%)			2C19 +2C9	0.408	0.834	0.0002	0.0013
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4.6 Conclusions

No correlation of genotype with Prasugrel pharmacokinetics if ethnicity effects are excluded. (IGA study) No correlation of genotype with Prasugrel pharmacodynamics independently of ethnicity. (IGA study) No significant correlation of genotype with Prasugrel pharmacokinetics or with clinical endpoints. (TAAL study) No consistent correlation of genotype for individual cytochrome genes with Prasugrel pharmacodynamics measured by three different methods.

5 Labeling

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."

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Yaning Wang
6/23/2008 02:08:02 PM
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Patrick Marroum
6/27/2008 04:31:19 PM
BIOPHARMACEUTICS

Recommendation:

The Office of Clinical Pharmacology reviewed the CMC amendment in response to the FDA requests. The clinical pharmacology reviewer agrees with Lilly's conclusion that the Cmax difference observed for the current formulation with PPI is probably of no clinical significance.

Elena Mishina, Ph. D.
Clinical Pharmacology Reviewer

Date _____

Patrick Marroum, Ph. D.
Cardio-Renal Team Leader

cc list: NDA 63,449, MehulM, UppoorR, MarroumP, MishinaE, SrinivasacharK, Ge,
Zhengfang HFD 110 BIOPHARM

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