Known versus unknown function of genotypes of interest

To assess the impact of the predicted metabolic phenotypes on the clinical outcome, the sponsor classified patients with an IM2C9 genotype and a normal CYP2C19 as missing due to their potential confounding effect for clinical outcome. The sponsor excluded these patients from the clinical outcome analysis. Thus, the reduced metabolizers include those patients who either are homozygous null CYP2C19 or have combination genotypes with heterozygous CYP2C19 (IM2C19) and the presence of a reduced-function CYP2C9 allele (IM2C9). This subset is called "GVC Evaluable (GVCE) patients".

References:

Wilkison GR. 2005. Drug metabolism and variability among patients in drug response. New England Journal of Medicine 352(21):2211-2221.

Lynch T, Price A. 2007. The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects. American Family Physician 76(3):391-396.

Table 2. Demographic and Baseline Characteristics between ITT patients and GVCE patients

	UA/NSTEMI				STEMI				ALL ACS			
	Prasugrel		**Clopidogrel**		**Prasugrel**		**Clopidogrel**		**Prasugrel**		**Clopidogrel**	
	ITT	GVC	ITT	GVC	ITT	GVC	ITT	GVC	ITT	GVC	ITT	GVC
N	5044	880	5030	914	1769	374	1765	366	6813	1254	6795	1280
GVC%		17.4%		18.2%		21.1%		20.7%		18.4%		18.8%
Age (yr)												
≥65 N	2057	344	2030	337	568	107	631	118	2625	451	2661	455
%	40.8	39.1	40.4	36.9	32.1	28.6	35.8	32.2	38.5	36.0	39.2	35.6
≥75 N	716	114	686	104	185	24	222	33	901	138	908	137
%	14.2	12.95	13.6	11.38	10.5	6.42	12.6	9.02	13.2	11.00	13.4	10.70
Sex (Female Y/N)												
Female N	1325	249	1399	290	380	94	419	93	1705	343	1818	383
%	26.3	28.30	27.8	31.73	21.5	25.13	23.7	25.41	25.0	27.35	26.8	29.92
Ethnicity (Caucasian Y/N)												
Caucasian	2575	852	4569	885	1688	372	1705	365	6263	1224	6274	1250
N %	90.7	96.82	90.8	96.83	95.4	99.47	96.6	99.73	91.9	97.61	92.3	97.66
TIMI Risk Score (high risk category)												
5-14 N	1304	213	1282	211	193	33**	230	46**	1497	246	1512	257
%	26.3	24.37	26.0	23.30	17.2	11,15	19.9	16.08	22.0	19.6	22.3	20.1
TIMI Risk Index (highest risk (fifth quartile) category)												
>27.4-94 N	1029	165	979	154	341	67	361	66	1373	232	1338	220
%	20.4	18.75	19.5	16.87	19.4	17.96	20.5	18.03	20.2	18.52	19.7	17.20
History of CHF (Y/N)												
Yes N	217	32	211	22	5	5	5	5	265	37	247	27
%	4.3	3.64	4.5	2.41	1.3	1.34	1.4	1.37	3.9	2.95	3.6	2.11
Metabolic Syndrome (Y/N)												
Yes N	2257	392	2254	433	709	146	684	152	2966	538	2938	585
%	44.8	44.55	44.8	47.37	40.1	39.04	38.8	41.53	43.5	42.9	43.2	45.7
Troponin over ULN at baseline												

Yes	N	3538	575	3561	611	864	171	879	176	4402	746	4440	787
	%	79.8	74.29	80.9	76.95	64.3	59.17	64.6	61.97	76.2	70.18	77.0	73.01
Prior TIA/Stroke (Y/N)													
Yes	N	213	35	192	36	49	6	64	9	262	41	256	45
	%	4.2	3.98	3.8	3.94	2.8	1.6	3.6	2.46	3.9	3.27	3.8	3.52
Diabetes (Y/N)													
Yes	N	1246	205	1226	225	330	61	344	59	1576	266	1570	284
	%	24.7	23.3	24.4	24.62	18.7	16.31	19.5	16.12	23.1	21.21	23.1	22.19
Prior MI (Y/N)													
Yes	N	1051	183	1024	171	175	35	184	28	1226	218	1208	199
	%	20.8	20.8	20.4	18.71	9.9	9.36	10.4	7.65	18.0	17.38	17.8	15.55
Prior PCI (Y/N)													
Yes	N	790	113	807	113	114	16	119	20	904	129	926	133
	%	15.7	12.84	16.0	12.36	6.4	4.28	6.7	5.46	13.3	10.29	13.6	10.39

(Source: GVCE sample: extracted from statistical reviewer Ms. Liu's analysis results Table 1 and Table 2
(Source: ITT sample: Sponsor's Table 11.1)

Table 3. Results of primary efficacy (composite of CV death, nonfatal MI, or nonfatal Stroke) between ITT patients and GVC patients

Subject population	Prasugrel	Clopidogrel	Cox PH model Hazard Ratio (95%CI)	Gehen-Wilcoxon p-value	Log-rank p-value
***UA/NSTEMI* (74% of all ACS)**					
ITT	9.30%	11.23%	0.82 (0.73, 0.93)	0.002*	
GVCE (17% of ITT)	8.64%	9.08%	0.95 (0.69, 1.29)	0.694	
EM (68%)	9.73%	7.54%	1.30 (0.88, 1.91)	0.213	0.185
RM (32%)	6.34%	12.37%	0.50 (0.28, 0.88)	0.018	0.014
UA/NSTEMI					
ITT < 75 yrs (86% of ITT)	8.23%	10.45%	0.78 (0.68, 0.90)	<0.001	
GVCE < 75 yrs (88% of GVCE)	7.3%	8.8%	0.83 (0.59, 1.18)	0.304	
EM (67%)	8.49%	6.75%	1.26 (0.79, 2.02)	0.374	
RM (33%)	5.33%	10.86%	0.48 (0.24, 0.96)	0.047	
UA/NSTEMI					
ITT w/ Diabetes (24% of ITT)	10.83%	15.01%	0.70 (0.56, 0.88)	0.002	
GVCE w/ Diabetes (24% of GVCE)	10.7%	10.2%	1.05 (0.59, 1.88)	0.843	
EM (70%)	11.51%	9.43%	1.22 (0.60, 2.46)	0.619	
RM (30%)	9.09%	12.12%	0.76 (0.26, 2.19)	0.716	
***STEMI* (26% of all ACS)**					
ITT	9.84%	12.24%	0.79 (0.65, 0.97)	0.019	
GVCE (21% of ITT)	9.36%	8.74%	1.08 (0.67, 1.74)	0.769	
EM (67%)	7.41%	8.70%	0.84 (0.45, 1.57)	0.578	0.593
RM (33%)	12.98%	8.85%	1.54 (0.69, 3.31)	0.282	0.292
STEMI					
ITT < 75 yrs (88.5% of ITT)	9.03%	11.21%	0.80 (0.64, 0.99)	0.037	
GVCE < 75 yrs (92.3% of GVCE)	8.9%	8.1%	1.10 (0.65, 1.84)	0.739	
EM (67%)	7.69%	8.96%	0.84 (0.43, 1.66)	0.590	
RM (33%)	9.52%	8.33%	1.17 (0.46, 2.96)	0.724	
STEMI					
ITT w/ Diabetes (19% of ITT)	13.64%	18.60%	0.71 (0.49, 1.04)	0.061	

GVCE w/ Diabetes (16.2% of GVC)	6.6%	11.9%	0.53 (0.16, 1.81)	0.287	
EM (66%)	5.00%	15.39%	0.30 (0.06, 1.50)	0.111	
RM (34%)	9.52%	5.00%	-		
***All ACS* (ITT)**					
ITT	9.44%	11.49%	0.81 (0.73, 0.90)	<0.001**	
GVCE (18.6% of GVCE)	8.85%	8.98%	0.98 (0.76, 1.28)	0.871	
EM (67%)	9.06%	7.88%	1.15 (0.83, 1.59)	0.453	0.398
RM (33%)	8.43%	11.39%	0.74 (0.45, 1.14)	0.195	0.168
All ACS					
ITT < 75 yrs (86.7% of ITT)	8.44%	10.65%	0.78 (0.70, 0.88)	<0.0001	
GVCE < 75 yrs (89.1% of GVCE)	7.8%	8.6%	0.91 (0.68, 1.21)	0.527	
EM (67%)	8.23%	7.39%	1.11 (0.76, 1.63)	0.658	
RM (33%)	6.67%	10.10%	0.66 (0.38, 1.13)	0.164	
All ACS					
ITT w/ Diabetes (23.1% of ITT)	12.18%	16.75%	0.71 (0.59, 0.85)	<0.001	
GVCE w/ Diabetes (21.7% of GVCE)	9.8%	10.56%	0.92 (0.54, 1.55)	0.743	
EM (69%)	10.60%	10.61%	0.93 (0.50, 1.75)	0.762	
RM (31%)	9.20%	10.47%	0.90 (0.35, 2.32)	0.912	

* primary analysis, reported by the sponsor and replicated by the statistical reviewer Ququan Liu.

** if primary analysis is significant, then, perform the test in ACS ITT patient population, reported by the sponsor and replicated by the statistical reviewer Ququan Liu.

The analysis results are extracted from Reviewer Tables 5-10, and sponsor's Tables TAAL 11.15, 11.34, and sponsor's Figure 11.a.

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/s/

Sue Jane Wang
5/7/2008 07:42:57 AM
BIOMETRICS
Secondary statistics genomic review and evaluation

Addendum

NDA #: 22,307 **Sn #:** 000 **Date:** 05/30/2008
Drug Name: EFFIENT™ (prasugrel hydrochloride) Tablets
Indication: Treatment of subjects with acute coronary syndromes (ACS)
Reviewer: Ququan Liu

Background:

A question was raised recently from the review team on how benefit/risk of the test drug should be evaluated (benefit: reduction of clinical events, risk: bleeding).

Statistical Analysis:

Assessment of benefit/risk is a clinical judgment and it is very subjective. A statistical approach using hazard function is used to assess whether risk is increasing or decreasing over time for the clinical endpoint or bleeding.

1. Clinical Endpoint: The hazard function plot indicates that the hazard's patterns appear to be similar in both treatment groups. The hazard is high at the early time where most events occurred. The hazard is decreasing over time: declines dramatically at the early time and then slowly (Figure 1, Table 1).

Figure 1 Hazard Function of Clinical Endpoint

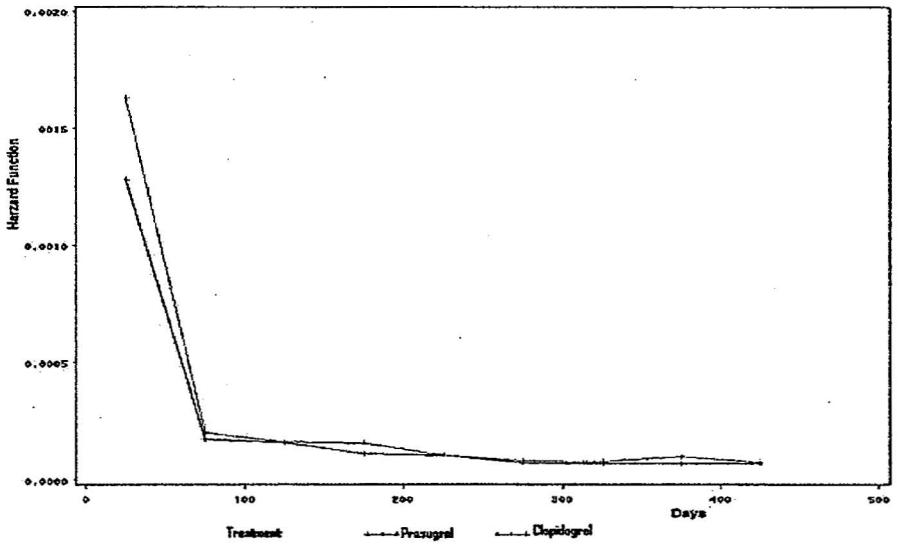

Table 1 Hazard in Clinical Endpoint

	Prasugrel			Clopidogrel		
Interval Day [Lower, Upper)	Number Failed	Number Censored	Hazard	Number Failed	Number Censored	Hazard
0 50	418	152	0.001281	526	159	0.00163
50 100	53	41	0.000171	61	43	0.000201
100 150	48	29	0.000157	48	27	0.000161
150 200	32	549	0.000111	44	513	0.000156
200 250	28	104	0.000103	28	75	0.000105
250 300	18	548	0.000071	20	562	0.00008
300 350	16	158	0.000068	18	137	0.000078
350 400	15	595	0.00007	21	556	0.000099
400 450	12	913	0.000068	13	928	0.000075
450 .	3	3081	.	2	3014	.

2. Bleeding Events: The bleeding events were classified into three groups: TIMI Major, TIMI Minor, or TIMI Major/ Minor. The hazard function plots indicate that the hazard is high at the early time where most bleeding events occurred. The hazard is generally decreasing over time, but appears to fluctuate after the early time (Figures 2-4, Tables 2-4).

Figure 2 Hazard function of TIMI Bleeding (Major)

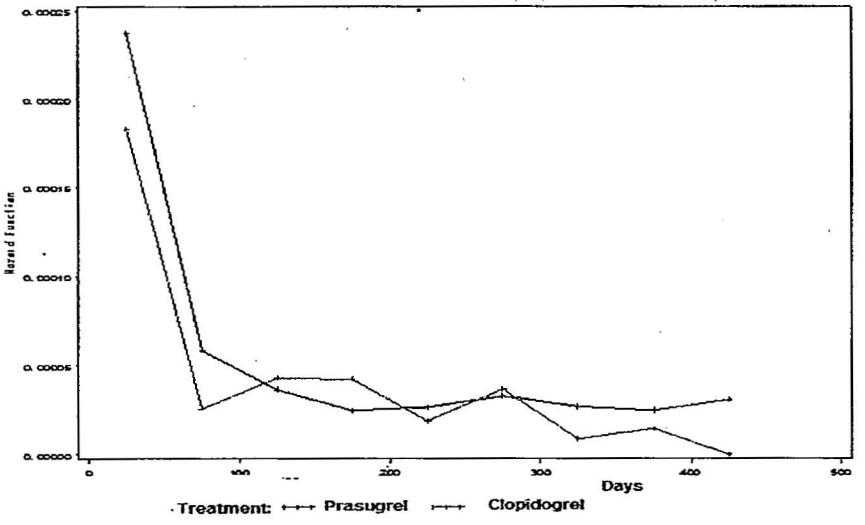

Table 2 Hazard in TIMI Bleeding (Major)

	Prasugrel			Clopidogrel		
Interval Day [Lower, Upper)	Number Failed	Number Censored	Hazard	Number Failed	Number Censored	Hazard
0 50	77	429	0.000237	59	479	0.000183
50 100	18	140	0.000058	8	107	0.000026
100 150	11	122	0.000037	13	104	0.000043
150 200	7	630	0.000025	12	600	0.000043
200 250	7	155	0.000027	5	135	0.000019
250 300	8	604	0.000033	9	634	0.000037
300 350	6	196	0.000027	2	175	8.964E-6
350 400	5	641	0.000025	3	614	0.000015
400 450	5	889	0.000031	0	921	0
450 .	2	2789	.	0	2836	.

Figure 3 Hazard function of TIMI Bleeding (Minor)

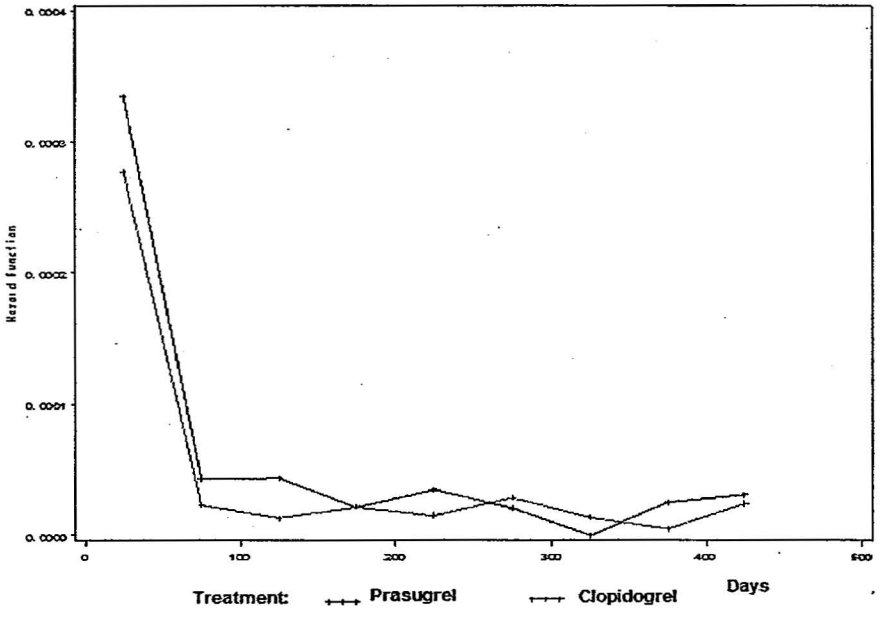

Table 3 Hazard in TIMI Bleeding (Minor)

	Prasugrel			Clopidogrel		
Interval Day [Lower, Upper)	Number Failed	Number Censored	Hazard	Number Failed	Number Censored	Hazard
0 50	108	435	0.000334	89	481	0.000277
50 100	13	148	0.000043	7	107	0.000023
100 150	13	119	0.000044	4	108	0.000013
150 200	6	631	0.000021	6	595	0.000021
200 250	9	150	0.000035	4	138	0.000015
250 300	5	599	0.000021	7	640	0.000029
300 350	0	193	0	3	174	0.000014

Figure 4 Hazard function of TIMI Bleeding (Major/Minor)

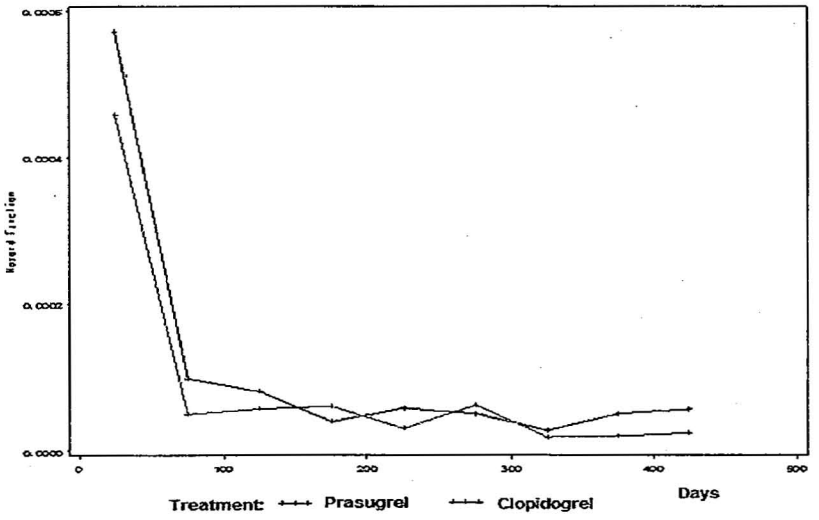

Table 4 Hazard in TIMI Bleeding (Major/Minor)

	Prasugrel			Clopidogrel		
Interval Day [Lower, Upper)	Number Failed	Number Censored	Hazard	Number Failed	Number Censored	Hazard
0 50	184	409	0.000571	147	462	0.000459
50 100	30	133	0.000099	15	102	0.00005
100 150	24	112	0.000081	17	101	0.000057
150 200	11	620	0.00004	17	588	0.000061
200 250	15	147	0.000058	8	134	0.000031
250 300	12	593	0.00005	15	627	0.000062
300 350	6	189	0.000028	4	172	0.000018
350 400	10	627	0.000051	4	605	0.00002
400 450	9	863	0.000057	4	902	0.000025
450 .	2	2745	.	0	2792	.

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/s/

Ququan Liu
6/4/2008 04:44:35 PM
BIOMETRICS

James Hung
6/7/2008 10:00:16 AM
BIOMETRICS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

Addendum

NDA/Serial Number:	22-307 / S_000
Drug Name:	EFFIENT™ (prasugrel hydrochloride) Tablets
Indication(s):	Treatment of subjects with acute coronary syndromes (ACS)
Applicant:	Eli Lilly
Date(s):	Date of Document: December, 26 2007
	PDUFA Due Date: June 26, 2008
Review Priority:	Priority
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Ququan Liu, M.D., M.S.
Concurring Reviewers:	James Hung, Ph.D.
Medical Division:	Division of Cardio-Renal Drug Products, HFD-110
Clinical Team:	Karen Hicks, M.D, Norman Stockbridge, M.D., Ph.D.
Project Manager:	Meg Pease-Fye, M.S.
Keywords:	EFFIENT™ , Prasugrel, ACS

Background:

The medical reviewer, Dr. Karen Hicks requested to look into whether heterogeneity of treatment effects is present in the following subgroups: GPIIb/IIIa inhibitors use; troponin level at baseline; and GPIIb/IIIa inhibitors use and troponin level at baseline in different genders.

Statistical Analysis:

Both test for interaction and subgroup analysis are conducted. All these analyses are exploratory.

There was no evidence suggesting large heterogeneity in the prasugrel effect relative to clopidogrel, regardless of GPIIb/IIIa inhibitors use, troponin level at baseline and genders. The results are summarized in the following tables.

Table 1 Interaction Test (ITT)

Interaction Effect	P-value
Treatment*GPIIb/IIa inhibitors prior to and during PCI	0.6291
Treatment*GPIIb/IIa inhibitors prior to and during PCI* Troponin	0.5349
Treatment*GPIIb/IIa inhibitors up to cath lab	0.9290
Treatment*GPIIb/IIa inhibitors up to cath lab * Troponin	0.5244

Table 2 Subgroup Analysis:
Use of GPIIb/IIIa Inhibitors prior to and during PCI

		UA/NSTEMI			STEMI			All ACS		
		Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI
Yes	N	1764	1768	0.82	924	953	0.73	2688	2721	0.79
	n	172	208	0.67, 1.01	91	125	0.56, 0.96	263	333	0.67, 0.93
	%	9.75	11.77		9.85	13.12		9.78	12.24	
No	N	3280	3262	0.82	845	812	0.87	4125	4074	0.83
	n	297	357	0.70, 0.96	83	91	0.65, 1.18	380	448	0.72, 0.95
	%	9.06	10.94		9.82	11.21		9.21	11.00	
Female										
Yes	N	433	486	0.88	198	205	0.68	631	691	0.80
	n	41	52	0.58, 1.32	22	32	0.39, 1.17	63	84	0.58, 1.12
	%	9.47	10.70		11.11	15.61		9.98	12.16	
No	N	892	913	0.92	182	214	0.94	1074	1127	0.92
	n	96	107	0.70, 1.21	19	24	0.52, 1.72	115	131	0.72, 1.18
	%	10.76	11.72		10.44	11.21		10.71	11.62	
Male										
Yes	N	1331	1282	0.80	726	748	0.75	2057	2030	0.78
	n	131	156	0.64, 1.01	69	93	0.55, 1.03	200	249	0.65, 0.94
	%	9.84	12.17		9.50	12.43		9.72	12.27	
No	N	2388	2349	0.78	663	598	0.86	3051	2947	0.80