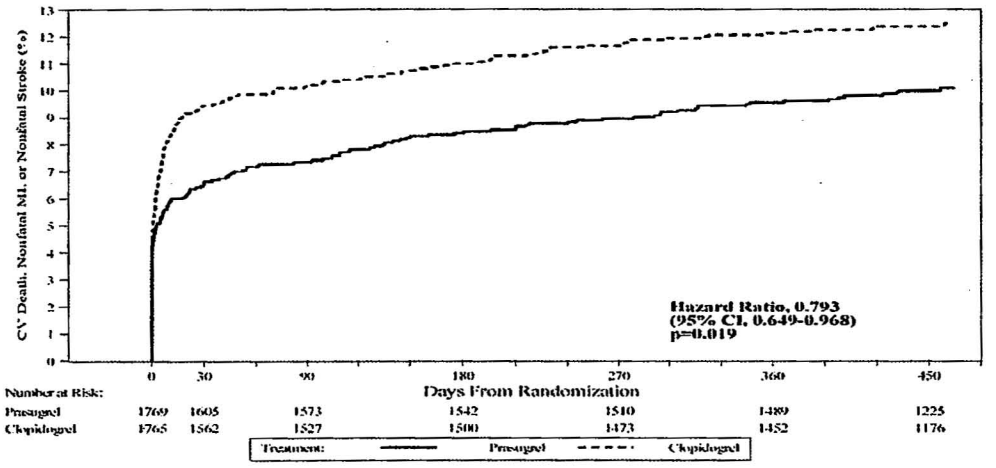
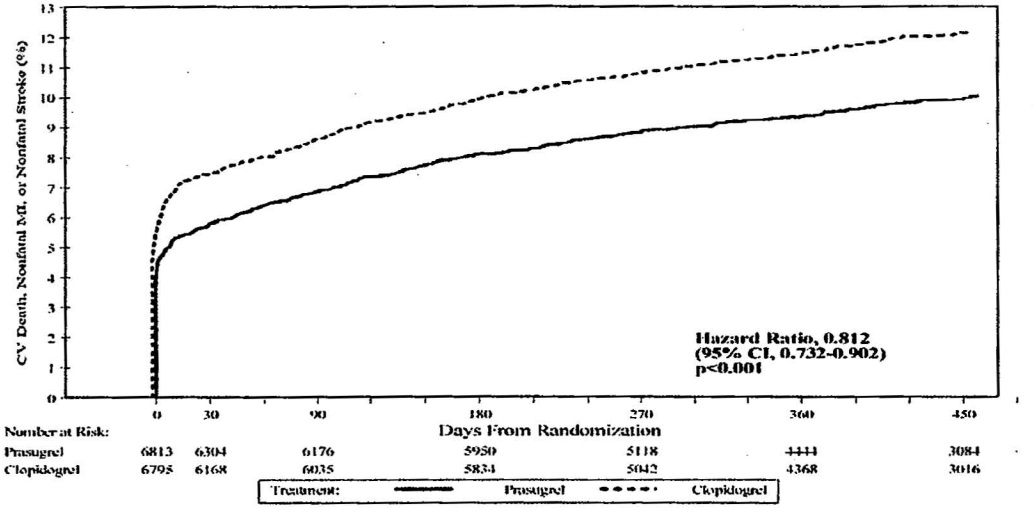


(Source: Sponsor's Figure 11.2b, confirmed by the reviewer's analysis)

Figure 5 Kaplan-Meier estimates of the incidence of the primary composite endpoint of CV death, nonfatal MI, or nonfatal stroke—CEC adjudicated All randomized All ACS subjects.



(Source: Sponsor's Figure 11.2c, confirmed by the reviewer's analysis)

3.1.1.6 Sponsor's Component Analysis of the Composite Endpoint Results

For the three components of the composite endpoint, only the incidence of nonfatal MI is statistically significantly lower in the prasugrel group compared to the clopidogrel group. Non-fatal stroke seems to be neutral between the two treatment groups and appears to

show a higher incidence with prasugrel in all ACS population and STEMI population. There does not appear to be little effect on CV death in the UA/NSTEMI population (Table 3).

Table 3 Number and Percentage of Subjects Reaching Components of the Composite Endpoint—CEC Adjudicated, All Randomized Subjects

Endpoints	Subject Population	Prasugrel N	Prasugrel n (%[a])	Clopidogrel N	Clopidogrel n (%[a])	Total N	Total n (%[a])	HR (95% CI)[b]	p-value[c]
CV Death	UA/NSTEMI	5044	90 (1.78)	5030	92 (1.83)	10074	182 (1.81)	0.979(0.732,1.309)	0.885
	STEMI	1769	43 (2.43)	1765	58 (3.29)	3534	101 (2.86)	0.738(0.497,1.094)	0.129
	All ACS	6813	133 (1.95)	6795	150 (2.21)	13608	283 (2.08)	0.886(0.701,1.118)	0.307
Nonfatal MI	UA/NSTEMI	5044	357 (7.08)	5030	464 (9.22)	10074	821 (8.15)	0.761(0.663,0.873)	<0.001
	STEMI	1769	118 (6.67)	1765	156 (8.84)	3534	274 (7.75)	0.746(0.588,0.948)	0.016
	All ACS	6813	475 (6.97)	6795	620 (9.12)	13608	1095 (8.05)	0.757(0.672,0.853)	<0.001
Nonfatal Stroke	UA/NSTEMI	5044	40 (0.79)	5030	41 (0.82)	10074	81 (0.80)	0.979(0.633,1.513)	0.922
	STEMI	1769	21 (1.19)	1765	19 (1.08)	3534	40 (1.13)	1.097(0.590,2.040)	0.770
	All ACS	6813	61 (0.90)	6795	60 (0.88)	13608	121 (0.89)	1.016(0.712,1.451)	0.930

(Source: Sponsor's Table 11.7, confirmed by the reviewer's analysis)

3.1.1.7 Sponsor's Secondary Efficacy Results

A statistically significantly lower incidence of each of the pre-specified secondary efficacy endpoints was shown in subjects with prasugrel compared to subjects with clopidogrel (Table 4).

Table 4 Number and Percentage of Subjects Reaching the Secondary Composite Endpoints—CEC Adjudicated, All Randomized Subjects

Analyzed Endpoint	Subject Population	Prasugrel N	Prasugrel n	Prasugrel (%[a])	Clopidogrel N	Clopidogrel n	Clopidogrel (%[a])	Total N	Total n	Total (%[a])	HR	(95% CI)[b]	p-value[c]
CV Death, Nonfatal MI or Nonfatal Stroke Through 90 Days	UA/NSTEMI	5044	333	(6.60)	5030	395	(7.85)	10074	728	(7.23)	0.835	(0.721, 0.966)	0.015
	STEMI	1769	129	(7.29)	1765	178	(10.08)	3534	307	(8.69)	0.715	(0.570, 0.897)	0.004
	All ACS	6813	462	(6.78)	6795	573	(8.43)	13608	1035	(7.61)	0.797	(0.705, 0.901)	<0.001
CV Death, Nonfatal MI or Nonfatal Stroke Through 30 Days	UA/NSTEMI	5044	274	(5.43)	5030	336	(6.68)	10074	610	(6.06)	0.808	(0.689, 0.948)	0.009
	STEMI	1769	115	(6.50)	1765	166	(9.41)	3534	281	(7.95)	0.684	(0.540, 0.868)	0.002
	All ACS	6813	389	(5.71)	6795	502	(7.39)	13608	891	(6.55)	0.767	(0.672, 0.876)	<0.001
CV Death, Nonfatal MI or UTVR Through 90 Days	UA/NSTEMI	5044	345	(6.84)	5030	420	(8.35)	10074	765	(7.59)	0.812	(0.704, 0.937)	0.004
	STEMI	1769	127	(7.18)	1765	168	(9.52)	3534	295	(8.35)	0.748	(0.594, 0.942)	0.013
	All ACS	6813	472	(6.93)	6795	588	(8.65)	13608	1060	(7.79)	0.794	(0.703, 0.896)	<0.001
CV Death, Nonfatal MI or UTVR Through 30 Days	UA/NSTEMI	5044	281	(5.57)	5030	349	(6.94)	10074	630	(6.25)	0.798	(0.682, 0.933)	0.005
	STEMI	1769	118	(6.67)	1765	155	(8.78)	3534	273	(7.72)	0.754	(0.594, 0.958)	0.020
	All ACS	6813	399	(5.86)	6795	504	(7.42)	13608	903	(6.64)	0.784	(0.688, 0.894)	<0.001

Analyzed Endpoint	Subject Population	Prasugrel N	Prasugrel n	Prasugrel (%[a])	Clopidogrel N	Clopidogrel n	Clopidogrel (%[a])	Total N	Total n	Total (%[a])	HR	(95% CI)[b]	p-value[c]
All Cause Death, Nonfatal MI or Nonfatal Stroke Through Study End	UA/NSTEMI	5044	504	(9.99)	5030	590	(11.73)	10074	1094	(10.86)	0.844	(0.749, 0.950)	0.005
	STEMI	1769	188	(10.63)	1765	232	(13.14)	3534	420	(11.88)	0.797	(0.657, 0.966)	0.020
	All ACS	6813	692	(10.16)	6795	822	(12.10)	13608	1514	(11.13)	0.831	(0.751, 0.919)	<0.001
CV Death, Nonfatal MI, Nonfatal Stroke or Rehospitalization for CIE Through Study End	UA/NSTEMI	5044	598	(11.86)	5030	688	(13.68)	10074	1286	(12.77)	0.858	(0.769, 0.958)	0.006
	STEMI	1769	199	(11.25)	1765	250	(14.16)	3534	449	(12.71)	0.781	(0.648, 0.941)	0.009
	All ACS	6813	797	(11.70)	6795	938	(13.80)	13608	1735	(12.75)	0.838	(0.762, 0.921)	<0.001
Definite or Probable Stent Thrombosis Through Study End[d]	UA/NSTEMI	4798	39	(0.81)	4789	80	(1.67)	9587	119	(1.24)	0.492	(0.335, 0.722)	<0.001
	STEMI	1624	19	(1.17)	1633	40	(2.45)	3257	59	(1.81)	0.498	(0.287, 0.865)	0.011
	All ACS	6422	58	(0.90)	6422	120	(1.87)	12844	178	(1.39)	0.494	(0.361, 0.677)	<0.001

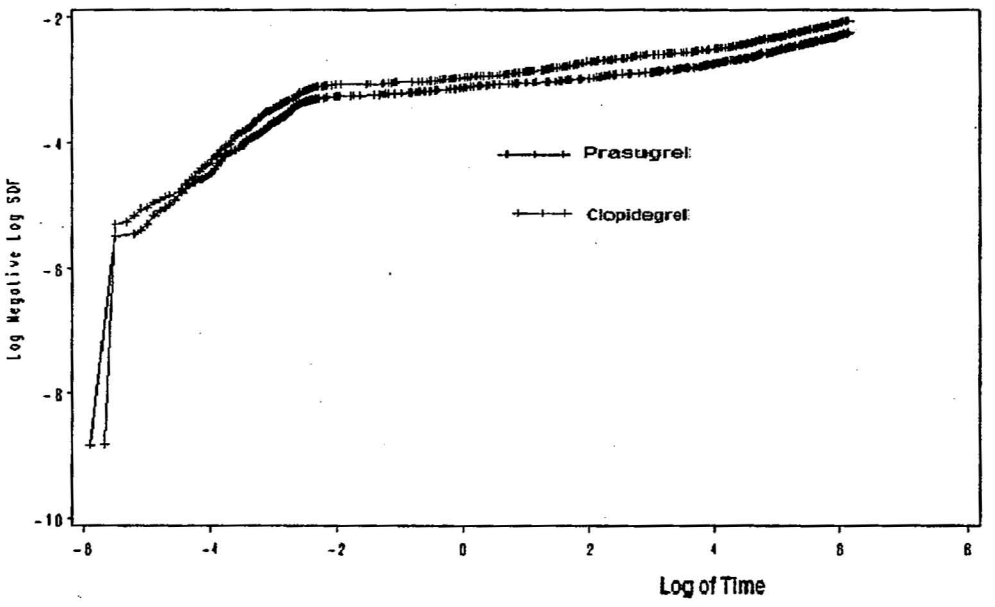
(Source: Sponsor's Table 11.6, confirmed by the reviewer's analysis)

3.1.1.8 Reviewer's Results

1. The reviewer verified the sponsor's primary and secondary efficacy analyses and concurred with their results.

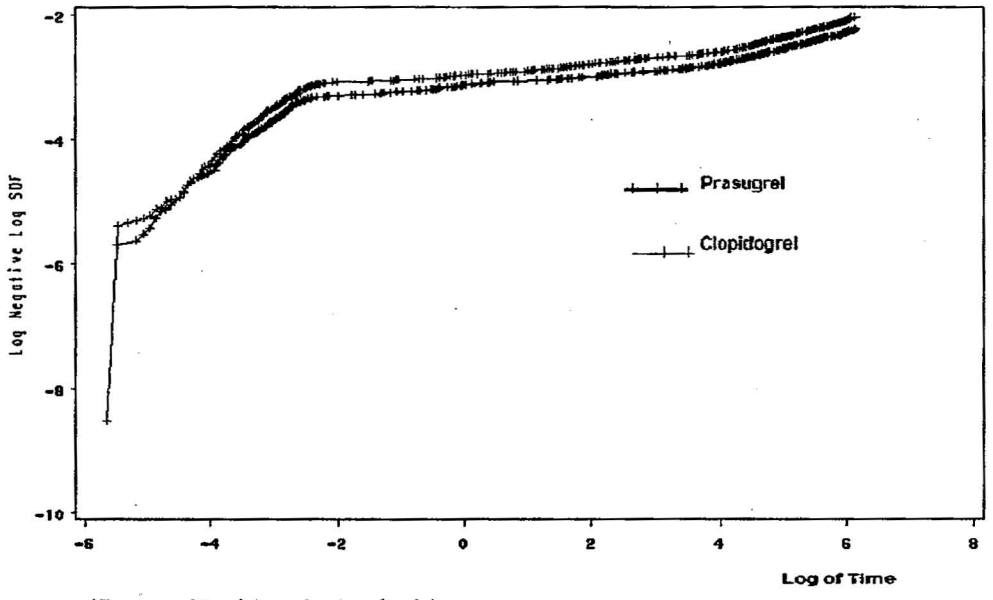
2. The reviewer investigated whether hazard ratios are approximately constant over time in the sponsor's Cox regression analyses. The log(-log survivor) plots (Figures 6-8) show that the two treatment lines are approximately parallel over time, except possibly crossing at a very early time. Thus, these plots suggest that the treatment effects measured by hazard ratio in favor of prasugrel are approximately constant over time.

Figure 6 Log(-Log(Estimated Survivor Function)) – primary endpoint (All ACS Population)



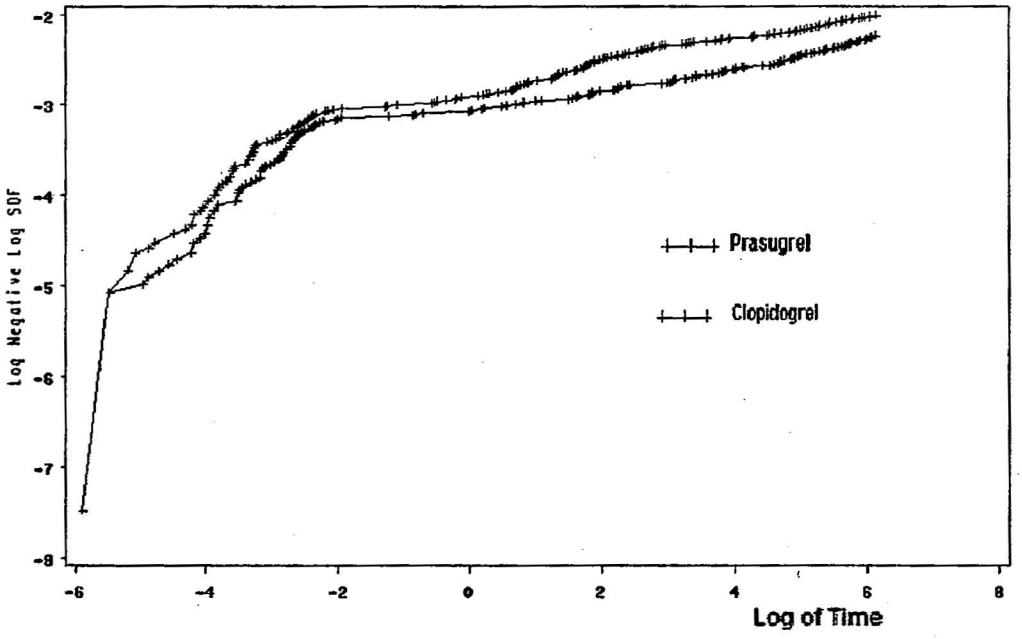
(Source: Reviewer's Analysis)

Figure 7 Log(-Log(Estimated Survivor Function)) – primary endpoint (UA/NSTEMI Population)



(Source: Reviewer's Analysis)

Figure 8 Log(-Log(Estimated Survivor Function)) – primary endpoint (STEMI Population)



(Source: Reviewer's Analysis)

3. The reviewer checked the censoring distributions for the primary endpoint to see whether the censoring pattern varies between the two treatment groups. The censoring distributions are similar between the two treatment groups in all three populations (Table 5-7).

Table 5 Censoring Distribution for primary endpoint, All ACS Population

Percentile of Censoring Time (%)	Censoring Time	
	Prasugrel N=6170	Clopidogrel N=6014
100	464	464
99	464	464
95	464	464
90	464	464
75	461.36	461.53
50	449.65	450.17
25	348.36	349.39
10	187.30	187.90
5	179.44	180.15
1	2.94	3.00
0	0.22	0.34

(Source: Reviewer's Analysis)

Table 6 Censoring Distribution for primary endpoint, UA/NSTEMI Population

Percentile of Censoring Time (%)	Censoring Time	
	Prasugrel N=6170	Clopidogrel N=4465
100	464	464
99	464	464
95	464	464
90	464	464
75	458.30	458.46
50	439.54	441.42
25	276.50	276.60
10	184.45	184.56
5	179.44	179.42
1	5.50	2.51
0	0.22	0.34

(Source: Reviewer's Analysis)

Table 7 Censoring Distribution for primary endpoint, STEMI Population

Percentile of Censoring Time (%)	Censoring Time	
	Prasugrel N=1595	Clopidogrel N=1549
100	464	464
99	464	464
95	464	464
90	464	464
75	464	464
50	458.38	458.11
25	450.47	450.32
10	437.56	437.41
5	179.37	205.37
1	1.67	3.56
0	0.28	0.51

(Source: Reviewer's Analysis)

3.1.1.9 Conclusions

The analysis of primary efficacy composite endpoint shows that prasugrel yields a statistically significantly lower incidence than clopidogrel in all three populations. It appears that the efficacy on the primary composite endpoint is driven by a statistically significant reduction of the incidence of nonfatal MI.

The analysis also shows a statistically significant reduction of the incidence in each of the pre-specified secondary efficacy endpoints with prasugrel compared to clopidogrel.

3.2 Evaluation of Safety

Please refer to Dr. Hick's review for safety assessment.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analysis was conducted for age, sex, ethnicity, body weight, prior TIA/stroke, use of GPIIb/IIIa inhibitors, history of diabetes mellitus, and region (Table 8). It appears that the benefit of pasugrel does not show in older patients, females, non-Caucasians, patients with prior TIA/stroke, patients with lighter body weight.

A consistent efficacy of prasugrel has been shown in both US and non-US regions (Table 9).

Table 8 Subgroup Analysis of Primary endpoint

	UA/NSTEMI			STEMI			All ACS		
	Prasugrel (N=5044)	Clopidogrel (N=5030)	HR 95% CI P-value	Prasugrel (N=1769)	Clopidogrel (N=1765)	HR 95% CI P-value	Prasugrel (N=6813)	Clopidogrel (N=6795)	HR 95% CI P-value
Age (yr)									

<65	N	2987	3000	0.75	1201	1134	0.76	4188	4134	0.75
	n	224	299	0.63, 0.89	98	121	0.58, 0.99	322	420	0.65, 0.87
	%	7.50	9.97	0.0008	6.16	10.67	0.0364	7.69	10.16	<.0001
≥65	N	2057	2030	0.90	568	631	0.88	2625	2661	0.90
	n	245	266	0.76, 1.07	76	95	0.65,1.18	321	361	0.77, 1.04
	%	11.91	13.10	0.3075	13.38	15.06	0.3445	12.23	13.57	0.1513
<70	N	3728	3730	0.75	1417	1366	0.79	5145	5096	0.76
	n	287	378	0.65, 0.88	121	146	0.62, 1.00	408	524	0.67, 0.87
	%	7.70	10.13	0.0002	8.54	10.69	0.0467	7.93	10.29	<.0001
≥70	N	1316	1300	0.96	352	399	0.85	1668	1699	0.93
	n	182	187	0.78, 1.17	53	70	0.59, 1.21	235	257	0.78, 1.11
	%	13.83	14.38	0.8126	15.06	17.54	0.3365	14.09	15.13	0.444
<75	N	4328	4344	0.78	1584	1543	0.80	5912	5887	0.78
	n	356	454	0.68, 0.90	143	173	0.64, 0.99	499	627	0.70, 0.88
	%	8.23	10.45	0.0006	9.02	11.21	0.0370	8.44	10.65	<.0001
≥75	N	716	686	0.97	185	222	0.85	901	908	0.94
	n	113	111	0.75, 1.26	31	43	0.54, 1.35	144	154	0.75, 1.18
	%	15.78	16.18	0.8539	16.76	19.37	0.4478	15.98	16.96	0.5329
Sex										
Female	N	1325	1399	0.91	380	419	0.79	1705	1818	0.88
	n	137	159	0.72, 1.14	41	56	0.53, 1.19	178	215	0.73,1.07
	%	10.34	11.37	0.5150	10.79	13.37	0.2107	10.44	11.83	0.1962
Male	N	3719	3631	0.79	1389	1346	0.80	5108	4977	0.79
	n	332	406	0.68, 0.91	133	160	0.63, 1.00	465	566	0.7, 0.9
	%	8.93	11.18	0.0014	9.58	11.89	0.0503	9.10	11.37	0.0002
Ethnicity										
Caucasian										
	N	4575	4569	0.80	1688	1705	0.80	6263	6274	0.80
	n	414	511	0.70, 0.91	167	209	0.65, 0.98	581	720	0.72, 0.89
	%	9.05	11.18	0.0011	9.89	12.26	0.0242	9.28	11.48	<.0001
African	N	177	168	1.03	28	19	0.66	205	187	0.98
	n	22	20	0.56, 1.89	3	3	0.13, 3.25	25	23	0.55, 1.72
	%	12.43	11.91	0.8896	10.71	15.79	0.5967	12.20	12.30	0.9647
Hispanic										
	N	242	237	1.08	27	19	0.70	269	256	1.04
	n	33	30	0.66, 1.77	3	3	0.14, 3.46	36	33	0.65, 1.67
	%	13.64	12.66	0.7287	11.11	15.79	0.6436	13.38	12.89	0.8737
Asian	N	37	42	-	23	22	-	60	64	-
	n	0	3	-	1	1	-	1	4	-
	%	-	7.14	-	4.35	4.55	-	1.67	6.25	-
Other	N	13	14	-	3	0	-	16	14	-
	n	0	1	-	0	0	-	0	1	-
	%	-	7.14	-			-	-	7.14	-
Prior TIA/ stroke										
yes	N	213	192	1.53	49	64	0.98	262	256	1.38
	n	39	24	0.92, 2.55	8	11	0.39, 2.42	47	35	0.89, 2.13
	%	18.31	12.50	0.0677	16.33	17.19	0.9127	17.94	13.67	0.1382
no	N	4831	4838	0.79	1720	1701	0.79	6551	6539	0.79
	n	430	541	0.69, 0.89	166	205	0.64, 0.97	596	746	0.71, 0.88

	%	8.90	11.18	0.0003	9.65	12.05	0.020	9.10	11.41	<.0001
Weight (kg)										
<60	N	289	327	0.90	113	110	0.88	402	437	0.70
	n	32	41	0.57, 1.44	18	20	0.47, 1.67	50	61	0.62, 1.30
	%			0.7987			0.8160			0.7560
>=60	N	4755	4703	0.82	1656	1655	0.78	6411	6358	0.81
	n	437	524	0.72, 0.93	156	196	0.64, 0.97	593	720	0.72, 0.90
	%			0.0019			0.0187			<0.0001
Use of GPIIb/IIIa inhibitors prior to and during PCI										
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	0.0939	9.85	13.12	0.018	9.78	12.24	0.0047
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	0.0089	9.82	11.21	0.3987	9.21	11.00	0.0058
Use of GPIIb/IIIa inhibitors up to cath lab										
Yes	N	366	353	0.85	171	199	0.69	537	552	0.80
	n	37	42	0.54, 1.31	14	23	0.36, 0.34	51	65	0.55, 1.15
	%	10.11	11.90	0.5441	8.19	11.56	0.2663	9.50	11.78	0.2769
No	N	4678	4677	0.82	1598	1566	0.80	6276	6243	0.81
	n	435	523	0.72, 0.93	160	193	0.65, 0.99	592	716	0.73, 0.91
	%	9.23	11.18	0.0023	10.01	12.32	0.0348	9.43	11.47	0.0002
Diabetes										
es	N	1246	1226	0.70	330	344	0.71	1576	1570	0.70
	n	135	184	0.56, 0.88	45	64	0.49, 1.04	180	248	0.58, 0.85
	%	10.84	15.01	0.0018	13.64	18.61	0.0610	11.42	15.80	0.0002
No	N	3798	3804	0.87	1439	1421	0.83	5237	5225	0.86
	n	334	381	0.76, 1.01	129	152	0.66, 1.05	463	533	0.76, 0.98
	%	8.79	10.02	0.0856	8.96	10.70	0.1174	8.84	10.20	0.0193

Table 9 Primary Endpoint Analysis, US vs. Non-US

		Prasugrel			Clopidegrol			HR	
		N	n	%	N	n	%	(95% CI)	
UA/NSTEMI	US	1694	164	9.68	1688	206	12.20	0.79	(0.64, 0.97)
	Non-US	3350	305	9.10	3342	359	10.74	0.84	(0.72, 0.98)
STEMI	US	345	27	7.83	332	38	11.45	0.67	(0.41, 1.10)
	Non-US	1424	147	10.32	1433	178	12.42	0.82	(0.66, 1.02)
All ACS	US	2039	191	9.37	2020	244	12.08	0.77	(0.64, 0.93)
	Non-US	4774	452	9.47	4775	537	11.25	0.83	(0.74, 0.94)

(Source: Reviewer's Analysis)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The major statistical analysis of the study is Cox's regression analysis. The interpretability of Cox's regression analysis relies on the assumption of proportionality of the hazard ratio. In this study, my analyses suggest that the proportional hazard assumption for Cox regression analysis seems to hold.

Multiplicity is a complicated issue due to the nature of the indication of the study. The pre-specified strategy for multiplicity adjustment seems to be efficient and practical, though several statistical reviewers had comments on this strategy in their reviews of the study protocol. However, the adjustment of multiplicity appears to be a moot issue, due to very small nominal p-values for both the primary composite endpoint and the pre-specified secondary endpoints.

5.2 Conclusions and Recommendations

Prasugrel is effective in reducing incidence of the primary composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in subjects with acute coronary syndrome who underwent percutaneous coronary intervention. The overall efficacy of the primary composite endpoint appeared to be driven by the reduction of incidence of nonfatal myocardial infarction.

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Ququan Liu
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James Hung
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MEMO

NDA/Serial Number:	22-307/S000
Drug Name:	EFFIENT (prasugrel hydrochloride) Tablets
Indication(s):	Treatment of subjects with acute coronary syndromes (ACS)

This ADDENDUM presents the statistical evidence observed regarding the disparity between the genetic voluntary convenience evaluable (GVCE) samples in the large adequate and well-controlled clinical trial – TAAL.

The GVCE sample, comprised of 17% to 21% of the ITT patients, is a biased sample of the ITT patients based on the baseline characteristics and the primary efficacy endpoint – the composite endpoint of cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal stroke at a medium of 12 months follow up.

Based on the baseline characteristics, both in UA/NSTEMI patients and in all ACS patients, it appears that the GVCE patients might be a slightly younger patient sample with less severe medical history (fewer patients with diabetes, less severe TIMI-risk score, less severe TIMI-risk-index, less prior MI, less PCI, less history of CHF, less troponin > ULN at baseline) in both the prasugrel and the clopidogrel treatment groups. The clopidogrel group appeared to have slightly more patients with metabolic syndrome (approximately 2.5% more) than in the prasugrel group. The detail of the apparent differences in the baseline characteristics can be found in Table 2 of the secondary genomics statistics review by Dr. Sue-Jane Wang signed on May 07, 2008.

In terms of the primary efficacy endpoint, Table 1 below summarizes the estimated odds ratio (and the 95% CI) of prasugrel over clopidogrel for the UA/NSTEMI, STEMI, and ACS between the voluntary GVCE sample, the non-consented (Non-GVCE) sample, and the ITT sample. The magnitudes of the odds ratio and their interval estimates are very similar between the ITT and the Non-GVCE (approximately 80% of ITT). That is, an approximate 19% to 27% risk reduction with prasugrel was observed. However, the odds ratio estimates for the GVCE sample are different in that there was essentially no risk reduction in those eligible patients who voluntarily consented to the pharmacogenetic study. In this voluntary subset, the risk ranges from 5% reduction in UA/NSTEMI subset to 8% increase in STEMI subset with overall reduction of 2% when both groups are combined, viz., ACS patients.

Sue-Jane Wang, Ph.D.
Associate Director for Pharmacogenomics and Adaptive Design
Office of Biostatistics, Office of Translational Sciences, CDER

Table 1. Results of primary efficacy (composite of CV death, nonfatal MI, or nonfatal Stroke) between ITT, GVCE, and non-GVCE patients in UA/NSTEMI subset, STEMI subset, and the all ACS patients

Subject population	Prasugrel	Clopidog	Odds Ratio (95%CI)	p-value chi-squar	p-value* Gehen-W
UA/NSTEMI **(74% of ACS)**					
ITT	9.30%	11.23%	0.81 (0.71, 0.92)	0.0014	0.002
GVCE (~17% ITT)	8.64%	9.08%	0.95 (0.68, 1.31)	0.7405	0.694
Non-GVCE	9.44%	11.71%	0.79 (0.68, 0.90)	0.0008	n/a
STEMI					
ITT	9.84%	12.24%	0.78 (0.63, 0.97)	0.0227	0.019
GVCE (~21% ITT)	9.36%	8.74%	1.08 (0.65, 1.78)	0.7706	0.769
Non-GVCE	9.96%	13.15%	0.73 (0.58, 0.92)	0.0084	n/a
ACS					
ITT	9.44%	11.49%	0.80 (0.72, 0.90)	<0.0001	<0.001
GVCE	8.85%	8.98%	0.98 (0.75, 1.29)	0.9067	0.871
Non-GVCE	9.57%	12.08%	0.77 (0.68, 0.87)	<0.0001	n/a

* extracted from Primary Statistical Reviewer Dr. Ruquan Liu.

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/s/

Sue Jane Wang
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BIOMETRICS

NDA 22,307
Prasugrel
Bleeding and Outcomes
February 2, 2009

Review

I asked Ququan Liu, M.D., M.S. to perform additional analyses looking at outcomes in patients who had survived a TIMI Major bleed or in patients who had survived a TIMI Major or Minor bleed. Dr. Liu's analyses are summarized below.

Had a Nonfatal TIMI Major Bleed				
Outcome	**Prasugrel (N=146)**	**Clopidogrel (N=111)**	**HR**	**95% CI HR**
Primary Endpoint	43 (29.5%)	36 (32.4%)	0.87	0.56, 1.36
CV Death	16 (11.0%)	9 (8.1%)	1.44	0.64, 3.27
Nonfatal MI	17 (11.6%)	21 (18.9%)	0.62	0.33, 1.18
Nonfatal Stroke	11 (7.5%)	11 (9.9%)	0.74	0.32, 1.72
CV Death and/or MI	33 (22.6)	26 (23.4%)	0.97	0.58, 1.63
ALL Death	28 (19.2)	13 (11.7)	1.73	0.90, 3.35
Did NOT Have a Nonfatal TIMI Major Bleed				
Outcome	**Prasugrel (N=6595)**	**Clopidogrel (N=6605)**	**HR**	**95% CI HR**
Primary Endpoint	588 (8.9%)	727 (11.0%)	0.80	0.72, 0.89
CV Death	110 (1.7%)	131 (2.0%)	0.84	0.65, 1.08
Nonfatal MI	454 (6.9%)	590 (8.9%)	0.76	0.68, 0.86
Nonfatal Stroke	49 (0.7%)	47 (0.7%)	1.05	0.7, 1.56
CV Death and/or MI	545 (8.3%)	686 (10.4%)	0.79	0.70, 0.88
ALL Death	153 (2.3)	173 (2.6)	0.89	0.71, 1.10
These analyses are descriptive only since the comparisons are not randomized. Analysis by Ququan Liu, M.D., M.S., Biometrics, FDA.				

Had a Nonfatal TIMI Major or Minor Bleed				
Outcome	**Prasugrel (N=303)**	**Clopidogrel (N=231)**	**HR**	**95% CI HR**
Primary Endpoint	73 (24.1%)	60 (26.0%)	0.92	0.65, 1.29
CV Death	24 (7.9%)	17 (7.4%)	1.13	0.61, 2.11
Nonfatal MI	42 (13.9%)	35 (15.2%)	0.91	0.58, 1.42
Nonfatal Stroke	13 (4.3%)	13 (5.6%)	0.74	0.34, 1.60
CV Death and/or MI	62 (20.5%)	48 (20.8%)	0.99	0.68, 1.44
ALL Death	40 (13.2)	23 (10.0)	1.37	0.82, 2.30
Did NOT Have a Nonfatal TIMI Major or Minor Bleed				
Outcome	**Prasugrel (N=6438)**	**Clopidogrel (N=6485)**	**HR**	**95% CI HR**
Primary Endpoint	558 (8.7%)	703 (10.8%)	0.79	0.71, 0.88
CV Death	102 (1.6%)	123 (1.9%)	0.84	0.64, 1.09
Nonfatal MI	429 (6.7%)	576 (8.9%)	0.74	0.66, 0.84
Nonfatal Stroke	47 (0.7%)	45 (0.7%)	1.05	0.70, 1.58
CV Death and/or MI	516 (8.0%)	664 (10.2%)	0.77	0.69, 0.87
ALL Death	141 (2.2)	163 (2.5)	0.87	0.70, 1.09
These analyses are descriptive only since the comparisons are not randomized. Analysis by Ququan Liu, M.D., M.S., Biometrics, FDA.				

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/s/

Karen Hicks
2/2/2009 03:39:40 PM
MEDICAL OFFICER

Ruquan Liu
2/2/2009 03:47:41 PM
BIOMETRICS

James Hung
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