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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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:	Ruquan 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

Table of Contents

1. EXECUTIVE SUMMARY ..... - 4 -

1.1 CONCLUSIONS AND RECOMMENDATIONS ..... - 4 -
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES ..... - 4 -

2. INTRODUCTION ..... - 4 -

2.1 OVERVIEW ..... - 4 -
2.2 DATA SOURCES ..... - 5 -

3. STATISTICAL EVALUATION ..... - 5 -

3.1 EVALUATION OF EFFICACY ..... - 5 -
3.1.1 STUDY: TAAL ..... - 5 -
3.1.1.1 Study Objectives ..... - 5 -
3.1.1.2 Study Design ..... - 5 -
3.1.1.3 Efficacy Measures ..... - 6 -
3.1.1.4 Patient Disposition, Demographic and Baseline Characteristics ..... - 8 -
3.1.1.5 Sponsor's Primary Efficacy Results ..... - 11 -
3.1.1.6 Sponsor's Component Analysis of the Composite Endpoint Results ..... - 13 -
3.1.1.7 Sponsor's Secondary Efficacy Results ..... - 14 -
3.1.1.8 Reviewer's Results ..... - 16 -
3.1.1.9 Conclusions ..... - 19 -
3.2 EVALUATION OF SAFETY ..... - 19 -

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS ..... - 19 -

5. SUMMARY AND CONCLUSIONS ..... - 22 -

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE ..... - 22 -
5.2 CONCLUSIONS AND RECOMMENDATIONS ..... - 22 -

List of Tables

Table 1 Patient disposition, demographic and baseline characteristics ..... - 8 -
Table 2 Number and Percentage of Subjects Reaching the Composite Endpoint of CV Death, Nonfatal MI, or Nonfatal Stroke—CEC Adjudicated, ITT ..... - 12 -
Table 3 Number and Percentage of Subjects Reaching Components of the Composite Endpoint—CEC Adjudicated, All Randomized Subjects ..... - 14 -
Table 4 Number and Percentage of Subjects Reaching the Secondary Composite Endpoints—CEC Adjudicated, All Randomized Subjects ..... - 15 -
Table 5 Censoring Distribution for primary endpoint, All ACS Population ..... - 18 -
Table 6 Censoring Distribution for primary endpoint, UA/NSTEMI Population ..... - 18 -
Table 7 Censoring Distribution for primary endpoint, STEMI Population ..... - 19 -
Table 8 Subgroup Analysis of Primary endpoint ..... - 19 -
Table 9 Primary Endpoint Analysis, US vs. Non-US ..... - 21 -

List of Figures

Figure 1 Study Design ..... - 5 -
Figure 2 Plan for evaluating secondary endpoints in UA/NSTEMI. ..... - 8 -
Figure 3 Kaplan-Meier estimates of the incidence of the primary composite endpoint of CV death, nonfatal MI, or nonfatal stroke—CEC adjudicated All randomized UA/NSTEMI subjects. ..... - 12 -
Figure 4 Kaplan-Meier estimates of the incidence of the primary composite endpoint of CV death, nonfatal MI, or nonfatal stroke—CEC adjudicated All randomized STEMI subjects ..... - 12 -
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. ..... - 13 -
Figure 6 Log(-Log(Estimated Survivor Function)) – primary endpoint ..... - 16 -
Figure 7 Log(-Log(Estimated Survivor Function)) – primary endpoint ..... - 17 -
Figure 8 Log(-Log(Estimated Survivor Function)) – primary endpoint ..... - 17 -

1. EXECUTIVE SUMMARY

1.1 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.

1.2 Brief Overview of Clinical Studies

This sNDA includes one study (TAAL) to support the safety and efficacy of prasugrel in patients with acute coronary syndrome (ACS) who were to undergo PCI. The primary objective of this study (TAAL) was to test the hypothesis that prasugrel coadministered with aspirin was superior to clopidogrel co-administered with aspirin in the treatment of subjects with acute coronary syndrome (ACS) who were to undergo percutaneous coronary intervention (PCI), as measured by a reduction in the composite endpoint of cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal stroke at a median follow-up of at least 12 months.

1.3 Statistical Issues and Findings

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 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.

2. INTRODUCTION

2.1 Overview

Prasugrel (CS-747, LY640315), a member of the thienopyridine class of antiplatelet agents, is an orally administered pro-drug requiring in vivo metabolism to form the active metabolite (R-138727) that irreversibly inhibits platelet activation and

aggregation. Prasugrel's proposed therapeutic use is for the reduction of atherothrombotic events (CV death, nonfatal MI, or nonfatal stroke) and the reduction of stent thrombosis in patients with ACS (unstable angina [UA], non-ST-segment elevation myocardial infarction [NSTEMI], or ST-segment elevation myocardial infarction [STEMI]) who are managed with PCI. The proposed dose regimen of prasugrel is a single 60-mg loading dose (LD), followed by a 10-mg once-daily maintenance dose (MD) or, in some patients at higher risk of bleeding, a lower 5-mg once-daily MD.

2.2 Data Sources

The sponsor's SAS datasets were stored in the directory of \\Cdsesub1\evsprod\NDA022307\0000 of the Center's electronic document room.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 STUDY: TAAL

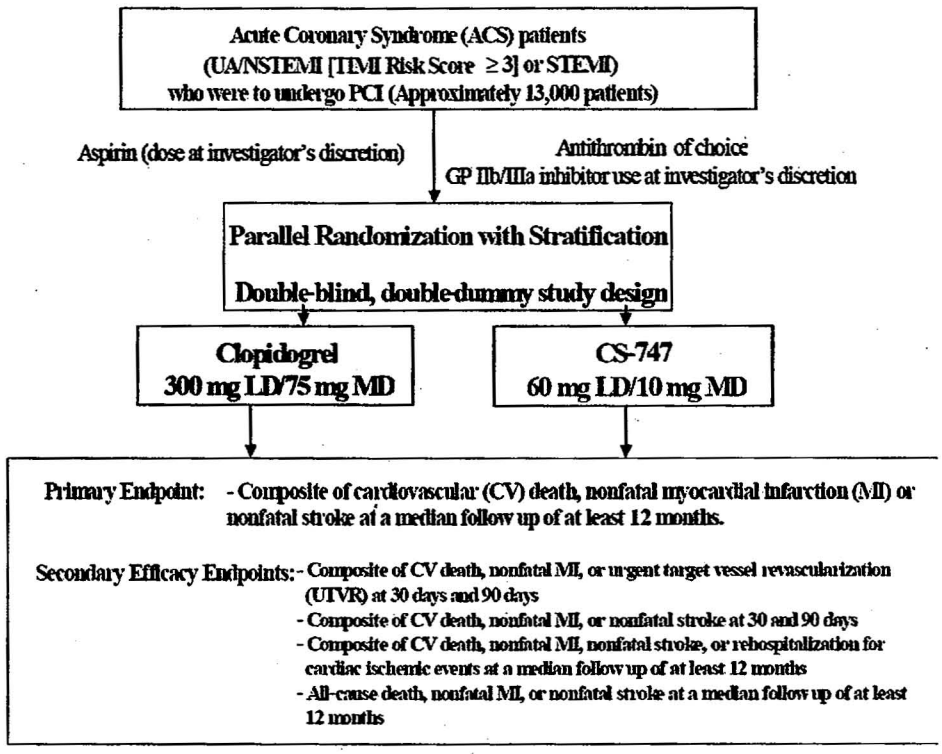
3.1.1.1 Study Objectives

The primary objective of this study (TAAL) was to test the hypothesis that prasugrel coadministered with aspirin was superior to clopidogrel co-administered with aspirin in the treatment of subjects with acute coronary syndromes (ACS) who were to undergo percutaneous coronary intervention (PCI), as measured by a reduction in the composite endpoint of cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal stroke.

3.1.1.2 Study Design

Study H7T-MC-TAAL (TAAL) was a Phase 3, multicenter, randomized, parallel-group, double-blind, double-dummy, active-controlled study. Clopidogrel was selected as the active comparator. A total of 13608 ACS subjects including 3534 subjects with STEMI were enrolled to the study. Subjects were randomly assigned in a 1:1 ratio to receive either prasugrel or clopidogrel. The study employed a double-dummy design: subjects received the active formulation of one drug and the placebo formulation of the other for the loading dose and maintenance doses. Subjects were randomized at the site level and stratified by clinical presentation: UA/NSTEMI versus STEMI. Subjects received aspirin during the 24 hours prior to PCI and continued throughout the study. Subjects received follow-up to a maximum of 15 months. The study design is described below (Figure 1).

Figure 1 Study Design



(Source: Sponsor's Figure 9.1)

3.1.1.3 Efficacy Measures

(1) Primary Efficacy Endpoint

The primary efficacy measure was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke at a median of 12 months follow-up.

(2) Secondary Efficacy Endpoints

Secondary efficacy measures included:

- The composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke through 30 days and 90 days post randomization.
- The composite of cardiovascular death, nonfatal myocardial infarction, or urgent target vessel revascularization through 30 days and 90 days post randomization.
- The composite of all-cause death, nonfatal myocardial infarction, or nonfatal stroke at study end. The composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or rehospitalization for cardiac ischemic events at study end.
- Definite or probable (Academic Research Consortium definition) stent thrombosis at study end.

(3) Statistical Analysis Methodology

1) Efficacy endpoints: An independent CEC adjudicated all efficacy endpoints that were reported by the investigator in a blinded fashion according to the procedures. Per protocol, the primary, secondary, and other efficacy endpoint analyses were based on the endpoints as adjudicated by the CEC.

2) Plan for evaluating primary endpoint: The primary efficacy endpoint analysis will be based on the time from randomization to the onset of the first primary outcome using the Gehan-Wilcoxon test due to a potentially varying hazard ratio. Primary analyses will be carried out in a hierarchical manner. At the first step, time-to-first primary outcome will be carried out at a one-sided significance level of 0.025 (equivalent to a two-sided test at 0.05) in the UA/NSTEMI subject population. If superiority of prasugrel treatment in the UA/NSTEMI subject population is successfully established, then time-to-first primary outcome will be carried out at a one-sided significance level of 0.025 in the all ACS subject population. In this analysis, ACS classification (UA/NSTEMI or STEMI) will be used as a stratification factor.

3) Plan for evaluating Secondary endpoints

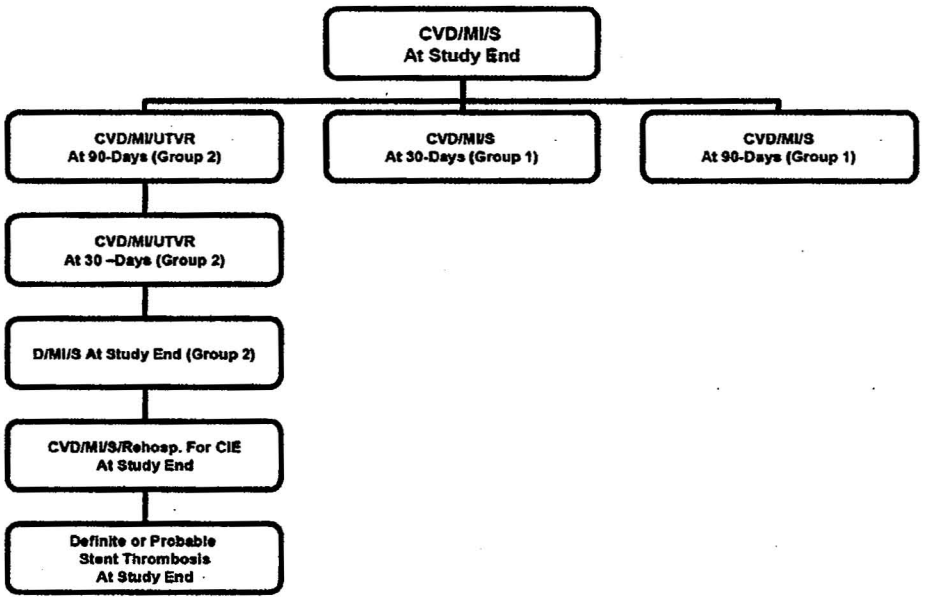
A. Plan for Evaluating Secondary Endpoints in UA/NSTEMI Subject Population

Following the establishment of the superiority of prasugrel over clopidogrel relative to the primary endpoint, additional analyses for secondary efficacy endpoints will be performed using the log-rank test. The secondary endpoints comprised two groups: the first group (Group 1) are those endpoints that do not need to be adjusted for multiplicity, and the second group (Group 2) are those that need to be predefined in a hierarchical manner (Figure 2).

Regardless of the order performed, each secondary endpoint listed in Group 1 will be eligible for inclusion in the label if statistically significant superiority of prasugrel versus clopidogrel is achieved.

To protect the overall type 1 error rate at a level of 0.05, the 5 remaining secondary endpoints (Group 2) were evaluated hierarchically each at a one-sided 0.025 alpha level.

Figure 2 Plan for evaluating secondary endpoints in UA/NSTEMI.



Endpoints are to be evaluated hierarchically contingent on successfully establishing superiority relative to preceding endpoints

(Source: Sponsor's Figure 9.4)

B. Plan for Evaluating Secondary Endpoints in All ACS Subject Population

Contingent on the superiority of prasugrel to be established relative to the primary endpoint in the All ACS population, with a view of assessing superiority of prasugrel in the STEMI population, each of the 7 secondary endpoints (endpoints from Groups 1 and 2) was evaluated in a hierarchical method described above in All ACS population. The log-rank test was used for each analyses at a one-sided 0.025 significance level. The clinical presentation, UA/NSTEMI or STEMI, was used as the stratification factor in these analyses.

3.1.1.4 Patient Disposition, Demographic and Baseline Characteristics

Table 1 summarizes patient disposition, demographic and baseline characteristics.

Table 1 Patient disposition, demographic and baseline characteristics

		UA/NSTEMI		STEMI		ALL ACS	
		Prasugrel	Clopidogrel	Prasugrel	Clopidogrel	Prasugrel	Clopidogrel
Randomized	n	5044	5030	1769	1765	6813	6795
	%	37.07	36.96	13.00	12.97	50.07	49.93
Completed	n	4766	4760	1637	1641	6403	6401
	%	94.49	94.63	92.54	92.97	93.98	94.20

Drop-out n	278	270	132	124	410	394
%	5.51	5.37	7.46	7.03	6.02	5.80
Age (yr)						
Mean	61.5	61.3	59	59.8	60.9	61.0
SD	11.19	11.35	11.21	11.65	11.25	11.45
<65 n	2987	3000	1201	1134	4188	4134
%	59.22	59.64	67.89	64.25	61.47	60.84
≥65 n	2057	2030	568	631	2625	2661
%	40.78	40.36	32.11	35.75	38.53	39.16
<70 n	3728	3730	1417	1366	5145	5096
%	73.91	74.16	80.10	77.39	75.52	75.00
≥70 n	1316	1300	352	399	1668	1699
%	26.09	25.84	19.00	22.61	24.48	25.00
<75 n	4328	4344	1584	1543	5912	5887
%	85.80	86.36	89.54	87.42	86.78	86.64
≥75 n	716	686	185	222	901	908
%	14.20	13.64	10.46	12.58	13.22	13.36
Sex (n, %)						
Female	1325	1399	380	419	1705	1818
	26.27	27.81	21.48	23.74	25.03	26.75
Male	3719	3631	1389	1346	5108	4977
	73.73	72.19	78.52	76.26	74.97	73.25
Ethnicity (n, %)						
Caucasian	4575	4569	1688	1705	6263	6274
	90.70	90.83	95.42	96.60	91.93	92.33
African	177	168	28	19	205	187
	3.51	3.34	1.58	1.08	3.01	2.75
Hispanic	242	237	27	19	269	256
	4.80	4.71	1.53	1.08	3.95	3.77
Asian	37	42	23	22	60	64
	0.73	0.83	1.30	1.25	0.88	0.94
Other	13	14	3	0	16	14
	0.26	0.28	0.17	0	0.23	0.21
Geographic Region (n, %)						
North America	1774	1764	390	382	2164	2146
	35.17	35.07	22.05	21.64	31.76	31.58
United States	1694	1688	345	332	2039	2020
	33.58	33.56	19.50	18.81	29.93	29.73
South America	270	264	0	0	270	264
	5.35	5.25	0	0	3.96	3.89
Western Europe	1262	1265	517	509	1779	1774
	25.02	25.15	29.23	28.84	26.11	26.11
Eastern Europe	1145	1155	512	510	1657	1665
	22.70	22.96	28.94	28.90	24.32	24.50
Rest of World	593	582	350	364	943	946
	11.76	11.57	19.79	20.62	13.84	13.92
Mid-East	366	354	240	259	606	613
	7.26	7.04	13.57	14.67	8.89	9.02
Africa	143	144	61	56	204	200
	2.84	2.86	3.45	3.17	2.99	2.94
Asia Pacific	84	84	49	49	133	133
	1.67	1.67	2.77	2.78	1.95	1.96

Weight (kg), (n, %)						
< 50	31 0.62	34 0.68	15 0.86	11 0.63	46 0.68	45 0.67
50 - < 70	844 16.94	910 28.28	298 17.14	333 19.17	1142 16.99	1243 18.51
70 - < 90	2451 49.19	2433 48.88	942 54.17	895 51.53	3393 50.48	3328 49.56
>= 90	1657 33.25	1601 32.16	484 27.83	498 28.67	2141 31.85	2099 31.26
TIMI Risk Score (n, %)						
0-2	613 12.35	605 12.27	592 52.67	601 51.94		
3-4	3045 61.37	3044 61.73	339 30.16	326 28.18		
5-7	1304 26.28	1282 26.00	193 17.17	230 19.88		
Mean SD	3.8 1.2	3.8 1.2	2.7 1.9	2.8 2.0		
Timi Risk Index (n, %)						
Q1: 3.90 - 13.60	1015 20.15	1039 20.68	362 20.56	354 20.09	1356 19.95	1387 20.44
Q2: > 13.60 - 17.50	1005 19.95	998 19.86	347 19.70	354 20.09	1400 20.59	1365 20.11
Q3: > 17.50 - 21.70	972 19.30	1031 20.52	364 20.67	338 19.18	1310 19.27	1369 20.17
Q4: > 21.70 - 27.40	1016 20.17	977 19.45	347 19.70	355 20.15	1359 19.99	1327 19.55
Q5: > 27.40 - 94.00	1029 20.43	979 19.49	341 19.36	361 20.49	1373 20.20	1338 19.72
Mean SD	21.12 8.96	20.86 8.71	20.63 9.11	20.98 9.60	20.99 9.00	20.89 8.95
ECG Abnormality (n, %)						
Yes	3644 72.24	3654 72.64	1747 98.76	1741 98.64	5391 79.13	5395 79.40
No	1400 27.76	1376 27.36	22 1.24	24 1.36	1422 20.87	1400 20.60
Cardiac Marker > ULN (n, %)						
Yes	4004 79.38	4011 79.74	1286 72.70	1265 71.67	5290 77.65	5276 77.65
No	1040 20.62	1019 20.26	483 27.30	500 28.33	1523 22.35	1519 22.35
History of Diabetes (n, %)						
Yes	1246 24.70	1226 24.37	330 18.65	344 19.49	1576 23.13	1570 23.11
No	3798 7530	3804 75.63	1439 81.35	1421 80.51	5237 76.87	5225 76.89

Prior TIA/stroke (n, %)						
Yes	213 4.22	192 3.82	49 2.77	64 3.63	262 3.85	256 3.77
No	4831 95.78	4834 96.18	1720 97.23	1701 96.37	6551 96.15	6539 96.23
Prior MI (n, %)						
Yes	1051 20.84	1024 20.3	175 9.89	184 10.42	1226 18.00	1208 17.78
No	3993 79.16	4006 79.64	1594 90.11	1581 89.58	5587 82.00	5587 82.22
Prior PCI (n, %)						
Yes	790 15.66	807 16.04	114 6.44	119 6.74	904 13.27	926 13.63
No	4254 84.34	4223 83.96	1655 93.56	1646 93.26	5909 86.73	5869 86.37
History of CHF(n, %)						
Yes	217 4.30	211 4.49	5 1.34	5 1.37	265 3.89	247 3.64
No	4827 95.70	4819 95.81	369 98.66	361 98.63	6548 96.11	6548 96.36
Metabolic Syndrome (n, %)						
Yes	2257 44.75	2254 44.81	709 40.08	684 38.75	2966 43.53	2938 43.24
No	2787 55.25	2776 55.19	1060 59.92	1081 61.25	3847 56.47	3857 56.76
Troponin over ULN at Baseline (n, %)						
Yes	3538 79.76	3561 80.86	864 64.29	879 64.63	4402 76.16	4440 77.03
No	898 20.24	843 19.14	480 35.71	481 35.37	1378 23.84	1324 22.97
Tobacco Use (n, %)						
Yes	3255 64.53	3292 65.45	1207 68.23	1198 67.88	4462 65.49	4490 66.08
No	1789 35.47	1738 34.55	562 31.77	567 32.12	2351 34.51	2305 33.92

(Source: Sponsor's Table 11.1, confirmed by the reviewer's analysis)

3.1.1.5 Sponsor's Primary Efficacy Results

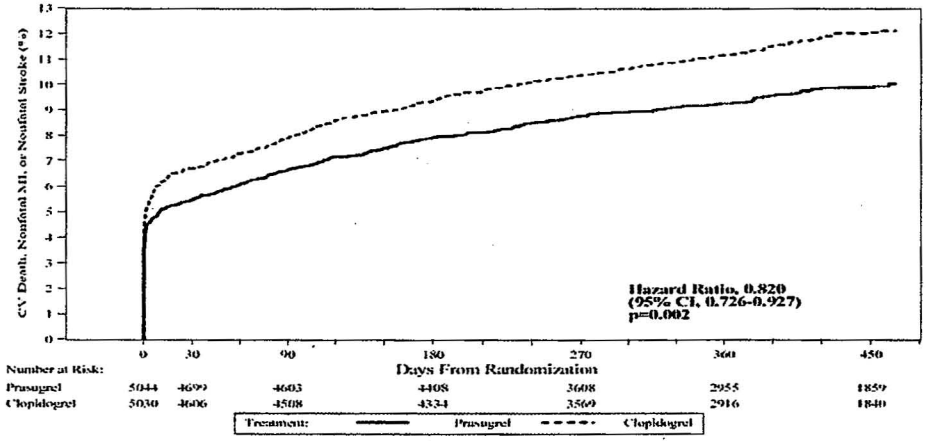
The incidence of the primary endpoint was statistically significantly lower in subjects randomized to prasugrel compared to clopidogrel in the UA/NSTEMI, STEMI, and All ACS populations (Table 2). In the UA/NSTEMI and All ACS populations there was an early separation and continued divergence of the Kaplan-Meier curves in favor of prasugrel (Figures 3 and 5). For subjects with STEMI, there was an early separation in favor of prasugrel that was sustained throughout the study (Figure 4).

Table 2 Number and Percentage of Subjects Reaching the Composite Endpoint of CV Death, Nonfatal MI, or Nonfatal Stroke—CEC Adjudicated, ITT

	Prasugrel			Clopidogrel			Total			Cox Proportional	Gehan-Wilcoxon
Subject Population	N	n	(%)	N	n	(%)	N	n	(%)	HR (95% CI)	p-value
UA/NSTEMI	5044	469	(9.30)	5030	565	(11.23)	10074	1034	(10.26)	0.820 (0.726, 0.927)	0.002
STEMI	1769	174	(9.84)	1765	216	(12.24)	3534	390	(11.04)	0.793 (0.649, 0.968)	0.019
All ACS	6813	643	(9.44)	6795	781	(11.49)	13608	1424	(10.46)	0.812 (0.732, 0.902)	<0.001

(Source: Sponsor's Table 11.5, confirmed by the reviewer's analysis)

Figure 3 Kaplan-Meier estimates of the incidence of the primary composite endpoint of CV death, nonfatal MI, or nonfatal stroke—CEC adjudicated All randomized UA/NSTEMI subjects.



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

Figure 4 Kaplan-Meier estimates of the incidence of the primary composite endpoint of CV death, nonfatal MI, or nonfatal stroke—CEC adjudicated All randomized STEMI subjects.