Hispanic n	242	237	27	19	269	256
%	4.80	4.71	1.53	1.08	3.95	3.77
Asian n	37	42	23	22	60	64
%	0.73	0.83	1.30	1.25	0.88	0.94
Other n	13	14	3	0	16	14
%	0.26	0.28	0.17	0	0.23	0.21
Prior TIA/stroke						
yes n	213	192	49	64	262	256
%	4.22	3.82	2.77	3.63	3.85	3.77
no n	4831	4834	1720	1701	6551	6539
%	95.78	96.18	97.23	96.37	96.15	96.23
Diabetes						
yes n	1246	1226	330	344	1576	1570
%	24.70	24.37	18.65	19.49	23.13	23.11
no n	3798	3804	1439	1421	5237	5225
%	75.30	75.63	81.35	80.51	76.87	76.89
Timi Risk Score						
0-2 n	613	605	592	601	-	-
%	12.35	12.27	52.67	51.94		
3-4 n	3045	3044	339	326	-	-
%	61.37	61.73	30.16	28.18		
5-7 n	1304	1282	-	-	-	-
%	26.28	26.00				
5-14 n	-	-	193	230	-	-
%			17.17	19.88		
Mean	3.8	3.8	2.7	2.8	-	-
SD	1.2	1.2	1.9	2.0		
Timi Risk Index						
Q1: 3.90 - 13.60	1015	1039	362	354	1356	1387
n	20.15	20.68	20.56	20.09	19.95	20.44
%						
Q2: > 13.60 - 17.50	1005	998	347	354	1400	1365
n	19.95	19.86	19.70	20.09	20.59	20.11
%						
Q3: > 17.50 - 21.70	972	1031	364	338	1310	1369
n	19.30	0.52	20.67	19.18	19.27	20.17
%						
Q4: > 21.70 - 27.40	1016	977	347	355	1359	1327
n	20.17	19.45	19.70	20.15	19.99	19.55
%						
Q5: > 27.40 - 94.00	1029	979	341	361	1373	1338
n	20.43	19.49	19.36	20.49	20.20	19.72
%						
Mean	21.12	20.86	20.63	20.98	20.99	20.89
SD	8.96	8.71	9.11	9.60	9.00	8.95
Prior MI						
yes n	1051	1024	175	184	1226	1208
%	20.84	20.36	9.89	10.42	18.00	17.78
no n	3993	4006	1594	1581	5587	5587
%	79.16	79.64	90.11	89.58	82.00	82.22
Prior PCI						

yes n %	790 15.66	807 16.04	114 6.44	119 6.74	904 13.27	926 13.63
no n %	4254 84.34	4223 83.96	1655 93.56	1646 93.26	5909 86.73	5869 86.37
History of CHF						
yes n %	217 4.30	211 4.49	5 1.34	5 1.37	265 3.89	247 3.64
no n %	4827 95.70	4819 95.81	369 98.66	361 98.63	6548 96.11	6548 96.36
Metabolic Syndrome						
yes n %	2257 44.75	2254 44.81	709 40.08	684 38.75	2966 43.53	2938 43.24
no n %	2787 55.25	2776 55.19	1060 59.92	1081 61.25	3847 56.47	3857 56.76
Troponin over ULN at Baseline						
yes n %	3538 79.76	3561 80.86	864 64.29	879 64.63	4402 76.16	4440 77.03
no n %	898 20.24	843 19.14	480 35.71	481 35.37	1378 23.84	1324 22.97

(Source: Sponsor's Table 11.1)

3.1.2 Sponsor's Analysis Results

1. Prasugrel

When prasugrel was examined, the relationship between functional groupings (EMfg/RMfg comparison) and composite event rate was not significant, reaching a 1-sided p-value of 0.812 in the comprehensive model for All ACS patients over all time points, at 30 days, or at 90 days. This was consistent in the UA/NSTEMI population. See Table 3, Figures 1 and 2 below.

Table 3 Number and Percentage of Subjects Reaching the Composite Endpoint of CV Death, Nonfatal MI, or Nonfatal Stroke from Randomization through Study End: Prasugrel 2C19/2C9 EMfgs versus RMfgs

Subject Population	Pras. 2C19/2C9 EM N	n	(%[1])	Pras. 2C19/2C9 RM N	n	(%[1])	Total N	n	(%[1])	Cox Proportional HR (95% CI)[2]	Gehan-Wilcoxon p-value[3]
UA/NSTEMI	596	52	(9.73)	284	18	(6.34)	880	76	(8.64)	1.535 (0.904, 2.604)	0.928
All ACS	839	76	(9.06)	415	35	(8.43)	1254	111	(8.85)	1.065 (0.713, 1.589)	0.812

Abbreviation: CI = confidence interval, HR = hazard ratio, N = number randomized, n = number of subjects reaching the endpoint, NE = not evaluated due to insufficient data.
[1] % is percentage of randomized subjects reaching the endpoint.
[2] HR and two-sided 95% CI derived using COX proportional hazards model.
[3] One-sided p-values are based on Gehan-Wilcoxon test comparing event free survival distributions over the course of the study.
Clinical presentation, UA/NSTEMI vs. STEMI, was used as a stratification factor in analysis involving All ACS subjects.

Source: [T_CDNMS_ALL_PEHsvPRHs.txt, \\SPREEPRD\GENESIS\SPREE\RMP\Clinical\Primary Care\CS747\Acute Coronary Syndrome\Genomic\H77-MC-TAAL\Programs\Analysis\TAAL Genomic Efficacy.sas]
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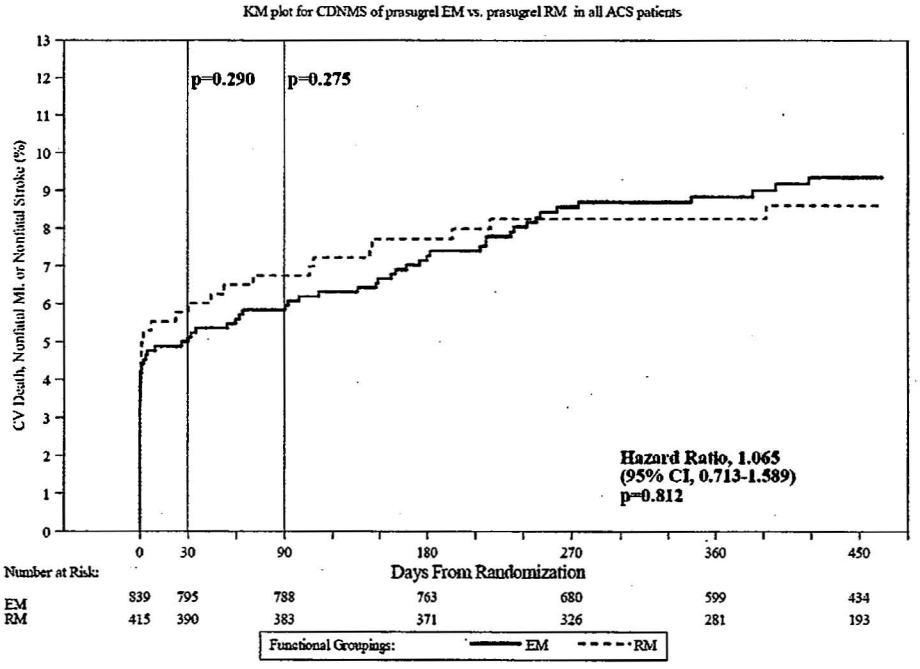
(Source: Sponsor's Table 14)

Figure 1 Hazard ratio comparing the primary efficacy endpoint (composite of CV death, nonfatal MI, or nonfatal stroke) for those patients in the All ACS population of the genetic subgroup receiving prasugrel: 2-bin functional grouping.



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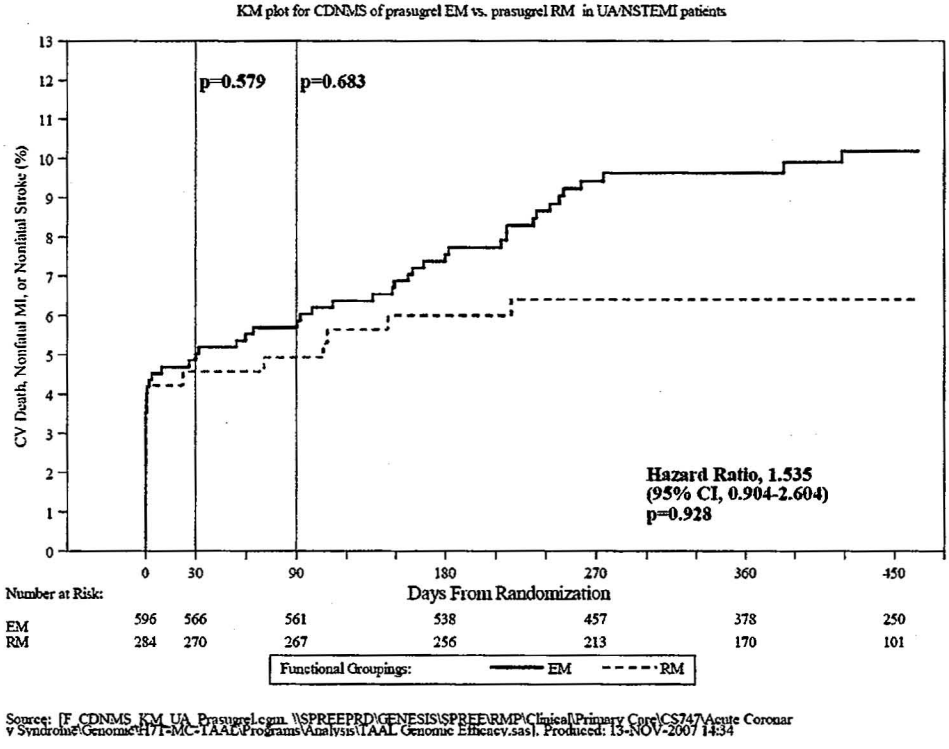
Abbreviations: EM = extensive metabolizer functional group (EM_{fg}), RM = reduced metabolizer functional group (RM_{fg}).
Overall, 30-day, and 90-day p-values.

(Source: Sponsor's Figure 11.1)

Figure 2 Hazard ratio comparing the primary efficacy endpoint (composite of CV death, nonfatal MI, or nonfatal stroke) for those patients in the UA/NSTEMI population of the genetic subgroup receiving prasugrel: 2-bin functional grouping.



Abbreviations: EM = extensive metabolizer functional group (EM_{fg}), RM = reduced metabolizer functional group (RM_{fg}).

Overall, 30-day and 90-day p-values.

(Source: Sponsor's Figure 11.2)

2. Clopidogrel

When clopidogrel was examined the relationship between the composite efficacy endpoint and reduced-metabolizer status was statistically significant for the All ACS population (1-sided p-value of 0.010) and was consistent in the UA/NSTEMI subpopulation (1-sided p-value of 0.008). See Table 4, Figures 3 and 4 below.

Table 4 Number and Percentage of Subjects Reaching the Composite Endpoint of CV Death, Nonfatal MI, or Nonfatal Stroke from Randomization through Study End: Clopidogrel 2C19/2C9 EMfgs versus RMfgs

	Clop. 2C19/2C9 EM			Clop. 2C19/2C9 RM			Total			Cox Proportional	Gehan-Wilcoxon
Subject Population	N	n	(%[1])	N	n	(%[1])	N	n	(%[1])	HR (95% CI)[2]	p-value[3]
UA/NSTEMI	623	47	(7.54)	291	36	(12.37)	914	83	(9.08)	0.590 (0.382, 0.911)	0.008
All ACS	876	69	(7.88)	404	46	(11.39)	1280	115	(8.98)	0.679 (0.467, 0.985)	0.010

Abbreviation: CI = confidence interval, HR = hazard ratio, N = number randomized, n = number of subjects reaching the endpoint, NE = not evaluated due to insufficient data.

[1] % is percentage of randomized subjects reaching the endpoint.

[2] HR and two-sided 95% CI derived using COX proportional hazards model.

[3] One-sided p-values are based on Gehan-Wilcoxon test comparing event free survival distributions over the course of the study.

Clinical presentation, UA/NSTEMI vs. STEMI, was used as a stratification factor in analysis involving All ACS subjects.

Source: [T_CDNMS_ALL_CEMsvCRMs.txt, \\SPREEPRD\GENESIS\SPREE\RMP\Clinical\Primary Care\CS747\Acute Coronary Syndrome\Genomic\H7T-MC-TAAL\Programs\Analysis\TAAL Genomic Efficacy.sas]

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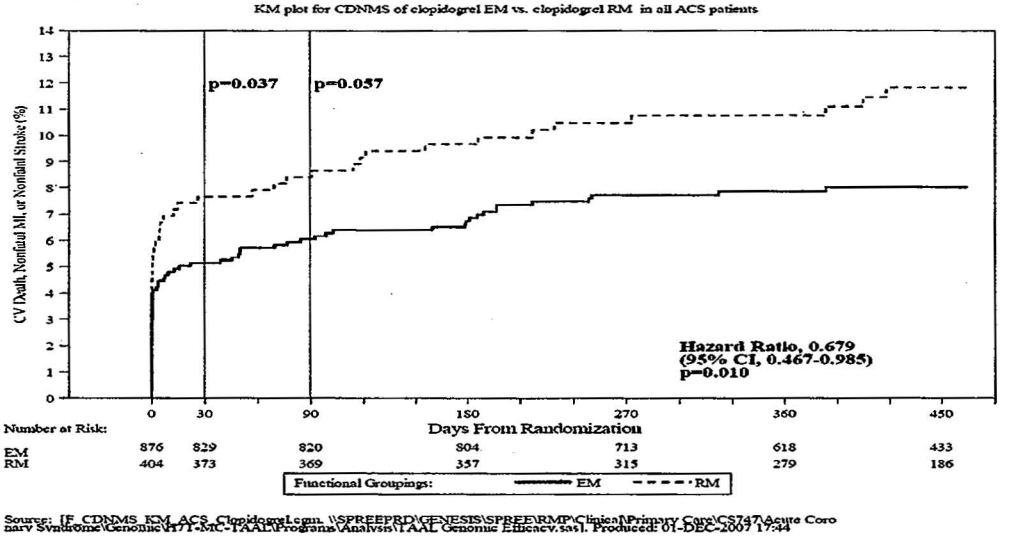
(Source: Sponsor's Table 15)

Figure 3 Hazard ratio comparing the primary efficacy endpoint (composite of CV death, nonfatal MI, or nonfatal stroke) for those patients in the All ACS population of the genetic subgroup receiving clopidogrel: 2-bin functional grouping.



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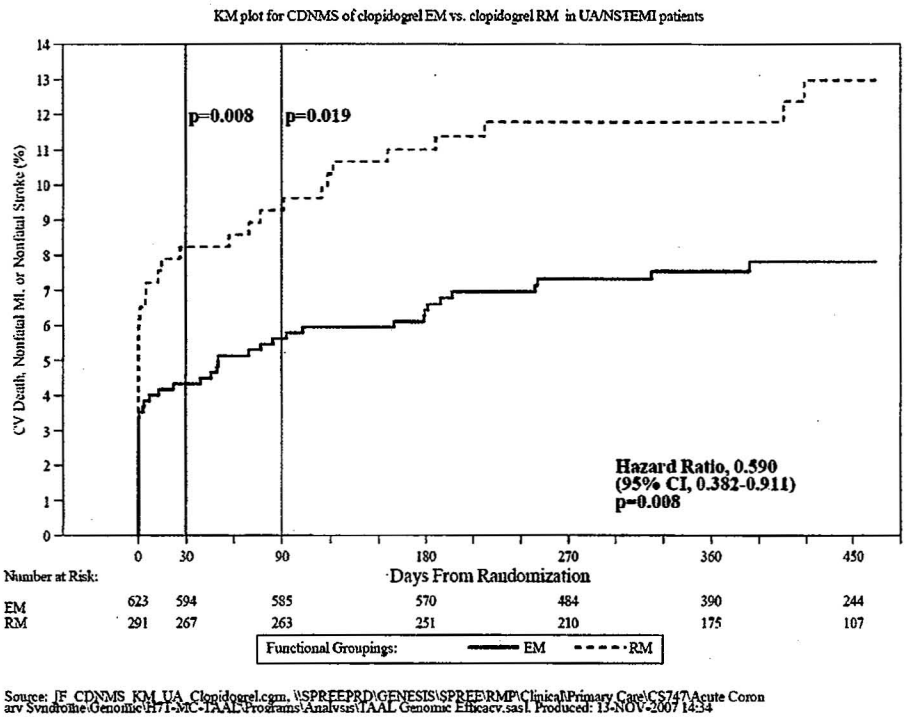
Abbreviations: EM = extensive metabolizer functional group (EM_{fg}). RM = reduced metabolizer functional group (RM_{fg}).[1]

Overall, 30-day and 90-day p-values.

(Source: Sponsor's Figure 11.3)

Figure 4 Hazard ratio comparing thy endpoint (composite of CV death, nonfatal MI, or nonfatal stroke) for those patients in the UA/NSTEMI population of the genetic subgroup receiving clopidogrel: 2-bin functional grouping.



Abbreviations: EM = extensive metabolizer functional group (EM_{fg}), RM = reduced metabolizer functional group (RM_{fg}).

Overall, 30-day and 90-day p-values.

(Source: Sponsor's Figure 11.4)

3.1.3 Reviewer's Analysis Results

1. Efficacy

1) The statistical reviewer conducted efficacy analysis on the genetics sample. There was very small difference in the incidence rate of the primary composite event between prasugrel (8.85%) and clopidegrel (8.98%) (hazard ratio = 0.98, p = 0.87, Table 5), whereas in the ITT population prasugrel had a statistically significant lower event rate than clopidogrel (9.44% vs. 11.49%, hazard ratio = 0.81, p < 0.0001, Table 6). The results of genetics sample are quite different from those of ITT sample; thus, in my view, genetics sample is not a representative of the ITT population and interpretability of the results of the genetics sample is highly questionable. At the very least, the interpretation of the results of the genetics sample is not applicable to the ITT patient population.

Table 5 Number and Percentage of Subjects Having Genetics Information and Reaching the Composite Endpoint from Randomization through Study End –CEC Adjudicated

Subject population	Prasugrel			Clopidogrel			Total			Cox Proportional HR (95% CI)	Gehan-Wilcoxon p-value
	N	n	%	N	n	%	N	n	%		
UA/NSTEMI	880	76	8.64	914	83	9.08	1794	159	8.86	0.95 (0.69, 1.29)	0.6943
STEMI	374	35	9.36	366	32	8.74	740	67	9.05	1.08 (0.67, 1.74)	0.7689
All ACS	1254	111	8.85	1280	115	8.98	2534	226	8.92	0.98 (0.76, 1.28)	0.8711

(Source: Reviewer's Analysis)

Table 6 Number and Percentage of Subjects Reaching the Composite Endpoint of CV Death, Nonfatal MI, or Nonfatal Stroke—CEC Adjudicated (ITT)

Subject population	Prasugrel			Clopidogrel			Total			Cox Proportional HR (95% CI)	Gehan-Wilcoxon p-value
	N	n	%	N	n	%	N	n	%		
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)

2) The statistical reviewer also conducted efficacy analyses comparing prasugrel to clopidogrel within each binned functional group (EM/RM). In the EM group, the results seemed to suggest that the event rates were higher in the prasugrel group compared to the clopidogrel group in all ACS patients under this study and the subgroup of patients with UA/NSTEMI. However, an opposite trend was suggested in the RM group; the event rates were higher in the clopidogrel group compared to the prasugrel group in all patients, and the subgroup of patients with UA/NSTEMI; see Tables 7 and 8, Figures 7, 8, 9 and 10.

Table 7 Number and Percentage of Subjects Reaching the Composite Endpoint from Randomization Through Study End - CEC Adjudicated – All Randomized Subjects with Extensive Metabolizer Functional Group (EM)

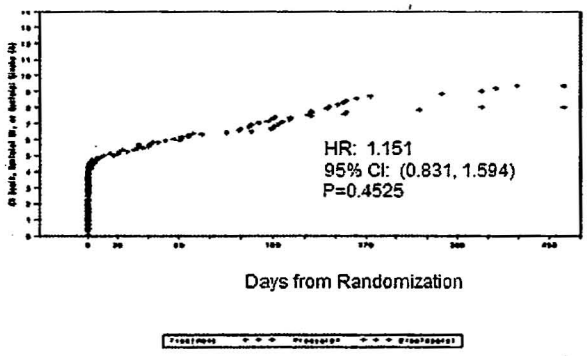
Subject population	Prasugrel	Clopidogrel	Total	Cox Proportional HR (95% CI)	Gehan-Wilcoxon p-value	Log-Rank p-value

	N	n	%	N	n	%	N	n	%			
UA/NSTEMI	596	58	9.73	623	47	7.54	1219	105	8.61	1.30 (0.88, 1.91)	0.2126	0.1847
STEMI	243	18	7.41	253	22	8.70	496	40	8.06	0.844 (0.453, 1.574)	0.5782	0.5930
All ACS	839	76	9.06	876	69	7.88	1715	145	8.45	1.15 (0.83, 1.59)	0.4525	0.3979

(Source: Reviewer's analysis)

Figure 5 Kaplan-Meier Estimates of the Incidence of the Composite Endpoint. All ACS (EM)

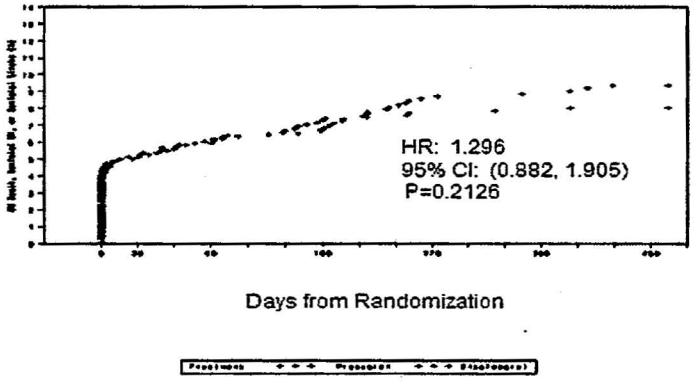
Kaplan-Meier estimates of the incidence of the composite endpoint of CV death, nonfatal MI, or nonfatal stroke. All ACS population of the genetic subgroup with extensive metabolizer group (EM)



(Source: Reviewer's analysis)

Figure 6 Kaplan-Meier Estimates of the Incidence of the Composite Endpoint. UA/NTEMI (EM)

Kaplan-Meier estimates of the incidence of the composite endpoint of CV death, nonfatal MI, or nonfatal stroke. All randomized UA/NSTEMI subjects of the genetic subgroup with extensive metabolizer function group (EM)



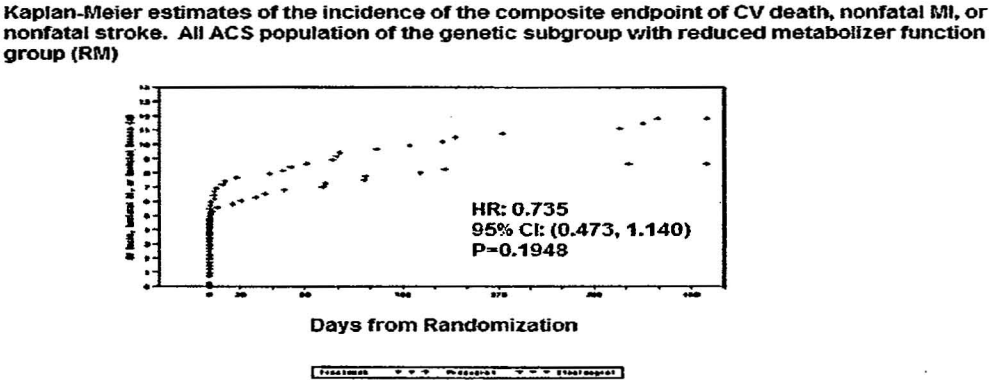
(Source: Reviewer's analysis)

Table 8 Number and Percentage of Subjects Reaching the Composite Endpoint from Randomization Through Study End - CEC Adjudicated – All Randomized Subjects with Reduced Metabolizer Functional Group (RM)

Subject population	Prasugrel			Clopidogrel			Total			Cox Proportional HR (95% CI)	Gehan-Wilcoxon p-value	Log-Rank p-value
	N	n	%	N	n	%	N	n	%			
UA/NSTEMI	284	18	6.34	291	36	12.37	575	54	9.39	0.50 (0.28, 0.88)	0.0176	0.0139
STEMI	131	17	12.98	113	10	8.85	244	27	11.07	1.52 (0.69, 3.31)	0.2822	0.2923
All ACS	415	35	8.43	404	46	11.39	819	81	9.89	0.74 (0.47, 1.14)	0.1948	0.1675

(Source: Reviewer's analysis)

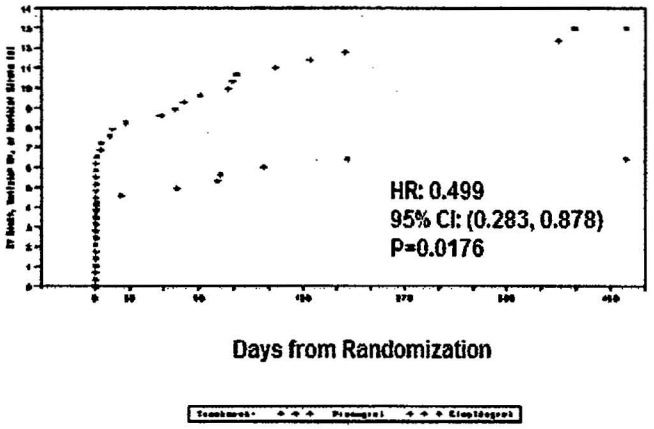
Figure 7 Kaplan-Meier Estimates of the Incidence of the Composite Endpoint. All ACS (RM)



(Source: Reviewer's analysis)

Figure 8 Kaplan-Meier Estimates of the Incidence of the Composite Endpoint.
UA/NTEMI (RM)

Kaplan-Meier estimates of the incidence of the composite endpoint of CV death, nonfatal MI, or nonfatal stroke. All randomized UA/NSTEMI subjects with reduced metabolizer function group (RM)



(Source: Reviewer's analysis)

2. Heterogeneity test: For the genetics sample, the results of the primary composite endpoint between the EM and RM appear to be heterogenesous, as suggested in Table 9. However, given the treatment difference is almost none, it is extremely difficult to know what to make out of this apparent heterogeneity.

Table 9 Heterogeneity Test

Population	Heterogeneity test p-value
UA/NSTEMI	0.0049*
STEMI	0.2585
ACS	0.0968*

*Statistically significant at α=0.1
(Source: Reviewer's Analysis)

3. Subgroup Analysis

1) Diabetes millitus status: The primary efficacy endpoint was analyzed by diabetes millitus status and by diabetes mellitus status within genetic function group. It appears that the efficacy varies from diabetes mellitus status and genetic function group across three populations and there is not a clear trend observed (Table 10).

2) Age (<75 or ≥75 years): The primary efficacy endpoint was analyzed by age (<75 or ≥75 years). It appears that prasugrel is effective only in patients <75 years old and patients <75 years old with RM in both UA and all ACS population (Table 10).

3) Interaction of treatment by prior transient ischemic attack (TIA/Stroke): The interaction of treatment by prior TIA/Stroke is tested and it appears that prior transient ischemic attack or stroke has no impact on the efficacy among the two treatment groups (p=0.4471).

Table 10 Subgroup Analysis, Genetics Population

	UA/NSTEMI			STEMI			ALL ACS		
	Prasugrel N n %	**Clopidogrel** N n %	HR 95% CI P-value	**Prasugrel** N n %	**Clopidogrel** N n %	HR 95% CI P-value	**Prasugrel** N n %	**Clopidogrel** N n %	HR 95% CI P-value (Gehen-Wilcoxon)
Diabetes									
Diabetes=yes	205 22 10.7	225 23 10.2	1.05 0.59, 1.88 0.8431	61 4 6.6	59 7 11.9	0.53 0.16, 1.81 0.2869	266 26 9.8	284 30 10.56	0.92 0.54, 1.55 0.7430
Diabetes=no	675 54 8.0	689 60 8.7	0.91 0.63, 1.32 0.5828	313 31 9.9	307 25 8.1	1.23 0.73, 2.09 0.4304	988 85 8.6	996 85 8.5	1.01 0.75, 1.36 0.9873
Diabetes=yes /EM	139 16 11.51	159 15 9.43	1.22 0.60, 2.46 0.6187	40 2 5.00	39 6 15.39	0.30 0.06, 1.50 0.1110	179 18 10.06	198 21 10.61	0.93 0.50, 1.75 0.7615
Diabetes=no /EM	457 42 9.19	464 32 6.90	1.34 0.85, 2.12 0.2329	203 16 7.88	214 16 7.48	1.06 0.53, 2.11 0.8864	660 58 8.79	678 48 7.08	1.25 0.85, 1.83 0.2858
Diabetes=yes /RM	66 6 9.09	66 8 12.12	0.76 0.26, 2.19 0.7162	21 2 9.52	20 1 5.00	-	87 8 9.20	86 9 10.47	0.90 0.35, 2.32 0.9117
Diabetes=no /RM	218 12 5.50	225 28 12.44	0.43 0.22, 0.84 0.0119	110 15 13.64	93 9 9.68	1.46 0.64, 3.34 0.3502	328 27 8.23	318 37 11.64	0.70 0.43, 1.15 0.1675
Age									
<75 yrs	766 56 7.3	810 71 8.8	0.83 0.59, 1.18 0.3036	350 31 8.9	333 27 8.1	1.10 0.65, 1.84 0.7378	1116 87 7.8	1143 98 8.6	0.91 0.68, 1.21 0.5265
≥75 yrs	114 20 17.5	104 12 11.5	1.53 0.75, 3.13 0.3053	24 4 16.7	33 5 15.2	1.12 0.30, 4.18 0.8581	138 24 17.4	137 17 12.4	1.41 0.76, 2.62 0.3798
<75 yrs/EM	509 42 66.45	554 42 68.40	1.09 0.71, 1.67 0.7404	229 17 65.43	231 19 69.37	0.89 0.46, 1.72 0.7050	738 59 66.13	785 61 68.68	1.03 0.72, 1.47 0.9432
≥75 yrs/EM	87 16 76.32	69 5 66.35	2.71 0.99, 7.40 0.0418	14 1 58.33	22 3 66.67	0.53 0.06, 5.15 0.6126	101 17 73.19	91 8 66.42	2.00 0.86, 4.63 0.1100
<75 yrs/RM	257 14 33.55	256 29 31.6	0.47 0.25, 0.89 0.0259	121 14 34.57	102 8 30.63	1.52 0.64, 3.63 0.3235	378 28 33.87	358 37 31.32	0.71 0.44, 1.17 0.2332
≥75 yrs/RM	27 4 23.68	35 7 33.65	0.68 0.20, 2.32 0.4445	10 3 41.67	11 2 33.33	1.71 0.29, 10.25 0.6012	377 26.81	46 9 33.58	0.92 0.34, 2.46 0.6934

(Source: Reviewer's Analysis)

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

The genetic sample is a convenient sample of the ITT population. Based on the large difference between the results of this sample and the ITT population (see Tables 5 and 6), I think the genetics sample is not a proper representative of the entire patient cohort under study. The efficacy results are very much inconsistent; the genetic subset showed

little difference in the incidence rate of the primary endpoint event between the two drug groups whereas the entire population clearly showed a statistically significant benefit with prasugrel. Therefore, whatever the genetics sample seems to suggest may not be applicable to the ITT population.

The apparent heterogeneity in the results between the EM and RM subgroups is very difficult to interpret in the context of the ITT patients, particularly given that there was little difference in the incidence of the primary composite event between the treatment groups in the genetics sample and the subgroup analysis does not seem to provide a robust result to support overall primary efficacy of the genetics sample.

4.2 Conclusions and Recommendations

Based on my evaluation, the genetic sample is not a proper representative of the ITT population. Thus, whatever the genetics sample seems to suggest may not be applicable to the entire population under the study. In addition, given that the genetics sample shows little treatment difference on the primary composite event, the apparent heterogeneity between the EM and RM subgroups in this sample is extremely difficult to interpret. The results of these exploratory analyses do not provide useful information for the drug labeling.

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