CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-839/SE1-019

Statistical Review(s)

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

STATISTICAL REVIEW AND EVALUATION

NDA #: 20-839

SERIAL #: SE1-S019

DRUG NAME: Plavix (clopidogrel bisulfate)

INDICATION: Acute Coronary Syndrome

SPONSOR: Sanofi-Synthelabo Inc.

DOCUMENT REVIEWED:

1. NEJM article "Effects of Clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation" (Vol. 345, No.7, 494-502, August 16, 2001)
2. Cover letter (CDER REC'D Date: August 21, 2001) including CD-ROM and reviewer's aids, SAS data base

STATISTICAL REVIEWER: H.M. James Hung, Ph.D. (HFD-710)

MEDICAL REVIEWER: Douglas Throckmorton, M.D. (HFD-110)

PROJECT MANAGER: Colleen LoCicero (HFD-110)

STATISTICAL KEY WORDS: Interim analysis, DSMB, sample size change, co-primary endpoint, log rank test, Haybittle-Peto boundary, conditional power, stochastic curtailment

Distribution: NDA 20-839, SE1-S019
HFD-110/Dr. Lipicky
HFD-110/Dr. Throckmorton
HFD-110/Ms. LoCicero
HFD-700/Dr. Anello
HFD-710/Dr. Chi
HFD-710/Dr. Mahjoob
HFD-710/Dr. Hung
HFD-710/chron

JHung/301-594-5436/DB1/plavix.doc/11-08-2001

TABLE OF CONTENTS

0. SUMMARY

This submission contains only one study. The conclusions in Section 4 constitute the summary.

1. INTRODUCTION

This statistical review pertains to the results of the CURE trial published in New England Journal of Medicine (NEJM) referenced above. Most of the numbers reported in this article have been confirmed by this reviewer's analyses. **Only the results of the reviewer's analyses will be presented in this review unless stated otherwise.**

2. OVERVIEW OF CURE STUDY RESULTS

The CURE study is a multi-center, randomized, parallel group, double-blind trial of clopidogrel versus placebo in patients with unstable angina or MI without ST segment elevation (acute coronary syndrome [ACS]) who are receiving aspirin (ASA) therapy. Patients would be given a loading dose of clopidogrel 300 mg or placebo, and the ASA dosage would be determined by the investigator. ASA therapy (75-325 mg once daily) should be started simultaneously with the study drug or the patient should continue with pre-admission ASA therapy, as applicable. Inclusion and exclusion criteria are summarized in the medical reviewer's review.

The duration of treatment and follow-up would be a minimum of 3 months (i.e., 90 days) and a maximum of 12 months (i.e., 365 days). Follow-up would end on a fixed date, which would be equivalent to 90 days after the randomization of the last patient (Study End Date). A patient is considered to have a complete follow-up if:
- the final visit is at least 365 days after randomization, or
- the final visit is on or after the fixed Study End Date
Any patient who does not meet these criteria is considered to be lost-to-follow-up. If the patient cannot be physically present at the final visit (+14 days allowed after 365 days or after Study End Date), a specific procedure will be followed, using a special form to document the contact.

The primary efficacy endpoint was the first occurrence of any component of cardiovascular death, myocardial infarction, or stroke (ischemic,hemorrhagic or of uncertain type). The secondary endpoint was the first occurrence of any component of cardiovascular death, myocardial infarction, stroke (ischemic,hemorrhagic or of uncertain type), or refractory ischemia. Other endpoints include the component endpoints of the above, severe ischemia during hospitalization, and mechanical or pharmacological coronary revascularization - PTCA, CABG or thrombolytic therapy. The definition of each endpoint was given in detail in the protocol (see Medical Reviewer's review).

<u>Sample Size Planning</u>

Sample size estimation was based on the event rates of an average of 8 to 9 months follow-up of patients from the OASIS registry of 8,000 patients. A total of 4,500 patients per arm was thought to be able to detect a 14-15% reduction in relative risk with power of 80% and 16-18% reduction with power of 90%, in the primary endpoint at two-sided significance level of 0.05, assuming the placebo event rate is 12-14%. This size enables one to detect a 12.5-15% reduction in relative risk of the secondary endpoint at $\alpha = 0.01$. Partitioning the alpha was believed to maintain an overall alpha level of 0.05, after adjustment for the overlap between the two sets of outcomes.

Interim Analysis Plan

The primary endpoint would be monitored using a modified Haybittle-Peto boundary of four standard deviations in the first half of the study and three standard deviations in the second half. The boundary would have to be exceeded on at least two consecutive time points, three months apart. There would be two interim monitoring looks performed by the DSMB Associated Statistician to assess efficacy scheduled at approximately 1/3 and 2/3 of expected events. Accordingly, the corresponding nominal alpha levels are 0.00006 and 0.0027, respectively. For the final analysis, the nominal alpha to be used is 0.049. Conditional power analyses and stochastic curtailment as described by Lan and Wittes would be employed to determine if the trial should stop for futility. If the upper limit of the 95% CI for the conditional power for the primary outcome falls below 25%, then, all other things being equal, the DSMB may recommend early termination.

Analysis methods

Statistical analysis is based on intent-to-treat principle. The time to event would be presented using Kaplan-Meier estimator. The hazard ratio would be estimated using Cox regression method. The treatment difference on the incidence rate of the endpoint would be tested using log rank test. Statistical significance would be claimed if the computed p-value is ≤ 0.05. The same strategy of analysis would be followed for the secondary outcome. The interpretation of the secondary and primary outcomes would depend on their coherence and consistency. If the primary outcome is of borderline statistical significance, the secondary outcome would be examined for consistency and similarity of effects.

Protocol Amendments

The protocol amendment (7/25/2000) was made to designate the secondary endpoint, CV death, MI, stroke or refractory ischemia, as a co-primary endpoint. The statistical criterion for alpha adjustment was given. The originally first primary endpoint (CV death, MI or stroke) would be tested at $\alpha = 0.045$ and the new co-primary endpoint would tested at $\alpha = 0.01$. These levels were determined through simulation studies taking into account the correlation between the two composite endpoints. The interim analysis boundary was adjusted accordingly.

Efficacy results

Initially, the study was designed to include 9000 patients. However, because the rate of primary events appeared to be lower than had originally been expected, the size of the study was increased to 12,500 patients. The new sample size is calculated assuming a rate of 10% in the placebo group, so that the study would have 90% power to detect a 16.9% reduction in risk of the primary events at two-sided alpha level of 0.045. For the second primary outcome, assuming a 14% rate of events in the placebo group, the study with this new size would have 90% power to detect a reduction of 16.4% in risk at the alpha level of 0.01.

Patients were recruited between December 1998 and September 2000 at 482 centers in 28 countries. The study end date is December 6, 2000. A total of 12,562 patients at 482 centers in 28 countries were randomized. According to the NEJM article, vital status was ascertained for 12,549 patients (99.9%), with 6 patients in the clopidogrel group and 7 in the placebo group lost to follow-up.

Baseline

Two treatment groups were comparable with respect to baseline demographic characteristics, medical history, electrocardiographic changes, and drug therapy, as shown in Table 1 of the NEJM article (the numbers in this table have been confirmed by this reviewer) and also in Table A.1 (in Appendix) for additional baseline variables.

Primary outcome

As shown in Table 1, the rate of the composite endpoint of CV death, nonfatal MI, or stroke was significantly lower in the clopidogrel group than in the placebo group (hazard ratio of 0.80 with 95% CI of 0.72 to 0.90, $p < 0.0001$). The rate of the composite endpoint of CV death, nonfatal MI, stroke, or refractory ischemia was also significantly lower in the clopidogrel group (hazard ratio of 0.86 with 95% CI of 0.79 to 0.94, $p = 0.0005$). The censoring distributions with respect to these two primary endpoints were comparable between the two treatment groups (Table A.2 in the Appendix). These treatment differences seemed to be largely attributed to the difference in nonfatal MI. The hazard ratio of CV death was 0.93, not statistically significant. The hazard ratio of refractory ischemia and the hazard ratio of all cause death was also around 0.93, not statistically significant.

This reviewer also analyzed investigators' reported events. The results of the investigators' reported events were similar to those of the EC adjudicated events (see Table 2).

Table 1. Incidence of adjudicated clinical events

	Clopidogrel (N=6259)	Placebo (N=6303)	Hazard ratio (95% CI)	p-value[5]
Primary Endpoints				
CV death, MI, stroke	582 (9.3%)	719 (11.4%)	0.80 (0.72, 0.90)	< 0.0001
CV death, MI, stroke, refractory ischemia	1035 (16.5%)	1187 (18.8%)	0.86 (0.79, 0.94)	0.0005
Secondary Endpoints				
CV death	318 (5.1%)	345 (5.5%)	0.93 (0.79, 1.08)	0.32
MI	324 (5.2%)	419 (6.7%)	0.77 (0.67, 0.89)	0.0004
Stroke	75 (1.2%)	87 (1.4%)	0.86 (0.63, 1.18)	0.35
Refractory ischemia	544 (8.7%)	587 (9.3%)	0.93 (0.82, 1.04)	0.20
During initial hosp.	85 (1.4%)	126 (2.0%)	0.68 (0.52, 0.90)	
After discharge	459 (7.6%)	461 (7.6%)	0.99 (0.87, 1.13)	
Others				
Death	359 (5.7%)	390 (6.2%)	0.92 (0.80, 1.07)	0.28
CV death	318 (5.1%)	345 (5.5%)	0.93 (0.79, 1.08)	
Non-CV death	41 (0.6%)	45 (0.7%)		

Reviewer's analysis $ nominal p-value from log rank test

Table 2. Incidence of investigators' reported clinical events

	Clopidogrel (N=6259)	Placebo (N=6303)	Hazard ratio (95% CI)	p-value[5]
Primary Endpoints				
CV death, MI, stroke	575 (9.1%)	723 (11.5%)	0.79 (0.71, 0.88)	< 0.0001
CV death, MI, stroke, Refractory ischemia	1009 (16.2%)	1171 (18.6%)	0.85 (0.78, 0.93)	0.0002
Secondary Endpoints				
CV death	311 (5.0%)	345 (5.5%)	0.91 (0.78, 1.06)	0.20
MI	319 (5.1%)	416 (6.6%)	0.76 (0.66, 0.88)	0.0003
Stroke	78 (1.2%)	94 (1.5%)	0.83 (0.62, 1.12)	0.23
Refractory ischemia	525 (8.4%)	560 (8.9%)	0.94 (0.83, 1.06)	0.28
During initial hosp.	87 (1.4%)	127 (2.0%)	0.68 (0.52, 0.90)	
After discharge	438 (7.0%)	433 (6.9%)	1.01 (0.88, 1.15)	
Others				
Death	359 (5.7%)	390 (6.2%)	0.92 (0.80, 1.07)	0.28
CV death	311 (5.0%)	345 (5.5%)	0.93 (0.79, 1.08)	
Non-CV death	48 (0.7%)	45 (0.7%)		

Reviewer's analysis $ nominal p-value from log rank test

Clopidogrel effect over time

The effect of clopidogrel relative to placebo in terms of hazard ratio or relative risk for the two primary endpoints appeared to be constant over the duration of the trial (see Figures 1 and 2, in the Appendix and Table 3).

Table 3. Incidence of adjudicated primary events over time

	Clopidogrel (N=6259)	Placebo (N=6303)	Relative risk (95% CI)	p-value[$]
CV death, MI, stroke				
24 hours	38 (0.6%)	53 (0.8%)	0.72 (0.48, 1.09)	0.12
30 days	272 (4.3%)	349 (5.5%)	0.78 (0.67, 0.92)	0.002
365 days	582 (9.3%)	719 (11.4%)	0.82 (0.73, 0.90)	0.001
CV death, MI, stroke, refractory ischemia				
24 hours	67 (1.1%)	102 (1.6%)	0.66 (0.49, 0.90)	0.008
30 days	487 (7.8%)	594 (9.4%)	0.83 (0.74, 0.93)	0.001
365 days	1035 (16.5%)	1187 (18.8%)	0.88 (0.81, 0.95)	0.001

Reviewer's analysis $ nominal p-value from Chi-square test

US vs. NON-US

The hazard ratios for the two primary endpoints were similar between US and non-US regions.

Table 4. Incidence of adjudicated primary events (US vs. Others)

	Clopidogrel (N=6259)	Placebo (N=6303)	Hazard ratio (95% CI)	p-value[$]
US	**(N=223)**	**(N=239)**		
CV death, MI, stroke	27 (12.1%)	36 (15.1%)	0.79 (0.48, 1.29)	0.34
CV death, MI, stroke, refractory ischemia	37 (16.6%)	48 (20.1%)	0.80 (0.52, 1.23)	0.31
NON-US	**(N=6036)**	**(N=6064)**		
CV death, MI, stroke	555 (9.2%)	683 (11.3%)	0.81 (0.72, 0.90)	< 0.0001
CV death, MI, stroke, refractory ischemia	998 (16.5%)	1139 (18.8%)	0.87 (0.80, 0.94)	0.0009

Reviewer's analysis $ nominal p-value from log rank test

Results By country

Figures 3 and 4 presented the relative risks of the two primary endpoints by country. There was no clear outlier that might suggest potential heterogeneity in the clopidogrel effect across the countries.

Subgroup results

There was no noticeable inconsistency in the results over the subgroups as seen in the following table and in Figure 4 of the NEJM article.

Table 5. Incidence of CV death, MI and stroke (adjudicated) by subgroup

	Clopidogrel (N=6259)	Placebo (N=6303)	Hazard ratio (95% CI)
Male	351 (9.1%)	461 (11.9%)	0.77 (0.68, 0.88)
Female	231 (9.5%)	258 (10.7%)	0.89 (0.76, 1.06)
Caucasian	470 (9.1%)	568 (11.0%)	0.83 (0.74, 0.93)
Black	0	1	
Oriental	16 (12.6%)	12 (9.4%)	1.33 (0.66, 2.70)
Other	96 (10.1%)	138 (14.1%)	0.72 (0.56, 0.92)
< 65 yrs of age	154 (5.2%)	228 (7.6%)	0.68 (0.56, 0.83)
≥ 65 yrs of age	428 (13.1%)	491 (14.9%)	0.87 (0.77, 0.99)
Diabetes			
No	382 (7.9%)	480 (9.8%)	0.80 (0.70, 0.91)
Yes	200 (14.2%)	239 (16.7%)	0.85 (0.72, 1.02)
Aspirin			
No	143 (6.9%)	171 (7.9%)	0.87 (0.70, 1.07)
Yes	439 (10.5%)	548 (13.3%)	0.79 (0.71, 0.89)
Heparin			
No	154 (8.9%)	175 (10.3%)	0.86 (0.70, 1.06)
Yes	428 (9.5%)	544 (11.8%)	0.80 (0.71, 0.90)
ACE inhibitor			
No	316 (8.1%)	419 (10.5%)	0.77 (0.67, 0.89)
Yes	266 (11.3%)	300 (13.0%)	0.87 (0.75, 1.02)
Beta blocker			
No	229 (8.9%)	280 (10.7%)	0.83 (0.70, 0.98)
Yes	353 (9.6%)	439 (11.9%)	0.81 (0.71, 0.92)
Myocardial Infarction			
No	329 (7.8%)	409 (9.5%)	0.82 (0.71, 0.94)
Yes	253 (12.5%)	310 (15.4%)	0.81 (0.69, 0.95)
Hypertension			
No	188 (7.5%)	268 (10.1%)	0.74 (0.62, 0.89)
Yes	394 (10.5%)	451 (12.4%)	0.85 (0.75, 0.96)
CABG or PTCA			
No	434 (8.3%)	547 (10.4%)	0.79 (0.70, 0.89)
Yes	148 (14.6%)	172 (16.1%)	0.91 (0.74, 1.11)

Reviewer's analysis

Secondary endpoints

The only initially specified secondary endpoint was designated as a co-primary endpoint in the protocol amendment. Other pre-specified endpoints, besides the components of the primary endpoints, were severe ischemia during hospitalization and mechanical or pharmacological coronary revascularization - PTCA, CABG or thrombolytic therapy. There seemed to be a lower risk of having severe ischemia during hospitalization in the clopidogrel group. The risk of having mechanical or pharmacological coronary revascularization appeared to be no different between the two treatment groups.

Table 6. Incidence of other pre-specified events (adjudicated)

	Clopidogrel (N=6259)	Placebo (N=6303)	Hazard ratio (95% CI)	p-value$
Severe ischemia during hospitalization	176 (2.8%)	237 (3.8%)	0.74 (0.61, 0.90)	0.003
Mechanical or pharmacological coronary revascularization - PTCA, CABG or thrombolytic therapy	2271 (36.3%)	2349 (37.3%)	0.96 (0.90, 1.01)	0.12

Reviewer's analysis $ nominal p-value from log-rank test

The NEJM article reported that significantly fewer patients in the clopidogrel group than in the placebo group had severe ischemia, recurrent angina, or radiological evidence of heart failure, and underwent coronary revascularization during the initial period of hospitalization. Only severe schemia during hospitalization was pre-specified.

Safety results

Major bleeding and minor bleeding were more common in the clopidogrel group (Table 7). The numbers presented in the NEJM article deviate slightly from those in Table 7 which were generated from the sponsor's data sets, MAJBLD.SD2 and MINBLD.SD2. The results of the analysis of investigators' reported major bleeding (not reported in this review) are similar to those from adjudicated major bleeding events reported in Table 7.

Table 7. Number (%) of patients with bleeding complications

	Clopidogrel (N=6259)	Placebo (N=6303)	Relative risk (95% CI)	p-value
Major Bleeding (adjudicated)	231 (3.7%)	169 (2.7%)	1.38 (1.14, 1.68)	0.001
Necessitating transfusion of ≥ 2 units of blood	178 (2.8%)	142 (2.3%)	1.26 (1.02, 1.57)	0.026
Life-threatening	135 (2.2%)	112 (1.8%)	1.21 (0.95, 1.56)	0.13
Fatal	11 (0.2%)	15 (0.2%)		
Causing 5 g/dl drop in hemoglobin level	58 (0.9%)	61 (1.0%)		
Requiring surgical intervention	49 (0.8%)	44 (0.7%)		
Causing hemorrhagic stroke	7 (0.1%)	4 (0.1%)		
Requiring inotropic agents	34 (0.5%)	34 (0.5%)		
Necessitating transfusion of ≥ 4 units of blood	75 (1.2%)	61 (1.0%)		
Non-life-threatening	96 (1.5%)	57 (0.9%)	1.70 (1.22, 2.35)	0.001
Site of major bleeding				
Gastrointestinal	83 (1.3%)	47 (0.7%)		
Retroperitoneal	8 (0.1%)	5 (0.1%)		
Hematuria	4 (0.1%)	5 (0.1%)		
Puncture site	36 (0.6%)	22 (0.3%)		
Surgical site	56 (0.9%)	53 (0.8%)		
Other	40 (0.6%)	37 (0.6%)		

Minor bleeding	316 (5.0%)	152 (2.4%)	2.09 (1.73, 2.53)	<0.001
Total with bleeding complications	529 (8.5%)	316 (5.0%)	1.69 (1.47, 1.93)	<0.001

Reviewer's analysis $ nominal p-value from chi-square test

3. REVIEWER'S COMMENTS

Designation of the pre-specified secondary endpoint – CV death, MI, stroke or refractory ischemia to a co-primary endpoint occurred after the second interim analysis and in less than three months before the trial end. It was not clear whether such a change might have been influenced by observing the trends shown in interim analyses. Traditionally, this type of change could post a problem with statistical inference. This potential problem becomes a moot issue in the CURE study since both primary endpoints have very small p-values.

The results of the investigators' reported events are similar to those of the EC adjudicated events. This adds a lot of comfort.

4. CONCLUSIONS

The rate of the composite endpoint of CV death, nonfatal MI, or stroke was significantly lower in the clopidogrel group. The rate of the composite endpoint of CV death, nonfatal MI, stroke, or refractory ischemia was also significantly lower in the clopidogrel group. The effect of clopidogrel appeared to be constant over the duration of the trial. There was no evidence that US results differ from non-US results. Nor was there noticeable inconsistency in the results over the subgroups. These treatment differences seemed to be largely attributed to the treatment difference in nonfatal MI. The clopidogrel effect on reduction of refractory ischemia appeared to be little.

For the pre-specified other endpoints, the risk of severe ischemia during hospitalization seemed to be lower in the clopidogrel group. The risk of having mechanical or pharmacological coronary revascularization appeared to be no different between the two treatment groups. The results of the unspecified endpoints reported in the NEJM article should not be included in the drug label.

Major bleeding and minor bleeding were more common in the clopidogrel group.

5. APPENDIX

Table A.1 Additional baseline variables

	Clopidogrel (N=6259)	Placebo (N=6303)
Age		
< 65 yrs	2980 (47.6%)	3016 (47.9%)
≥ 65 yrs	3279 (52.3%)	3287 (52.1%)
Race		
Caucasin	5150 (82.3%)	5158 (81.8%)
Black	33 (0.5%)	36 (0.6%)
Oriental	127 (2.0%)	127 (2.0%)
Others	947 (15.1%)	980 (15.6%)
Missing	2	2

Reviewer's analysis

Table A.2 Distribution of time (days) to non-event censoring

	CV death, MI, stroke		CV death, MI, stroke, refractory ischemia	
	Clopidogrel (N=6259)	Placebo (N=6303)	Clopidogrel (N=6259)	Placebo (N=6303)
# of censored cases	5677 (90.7%)	5584 (88.6%)	5224 (83.5%)	5116 (81.2%)
Max				
99th %tile	365	365	365	365
95th	365	365	365	365
90th	365	365	365	365
75th	365	365	365	365
50th	336	337.5	334	335
Mean	288	288	287	287
25th	214	212.5	211	210
10th	140	140	140	139
5th	113	112	113	111
1st	92	92	92	92
Min				

Reviewer's analysis

Figure 1. Log(-log(Survival Probability)) for CV death, MI or stroke (Reviewer's analysis)

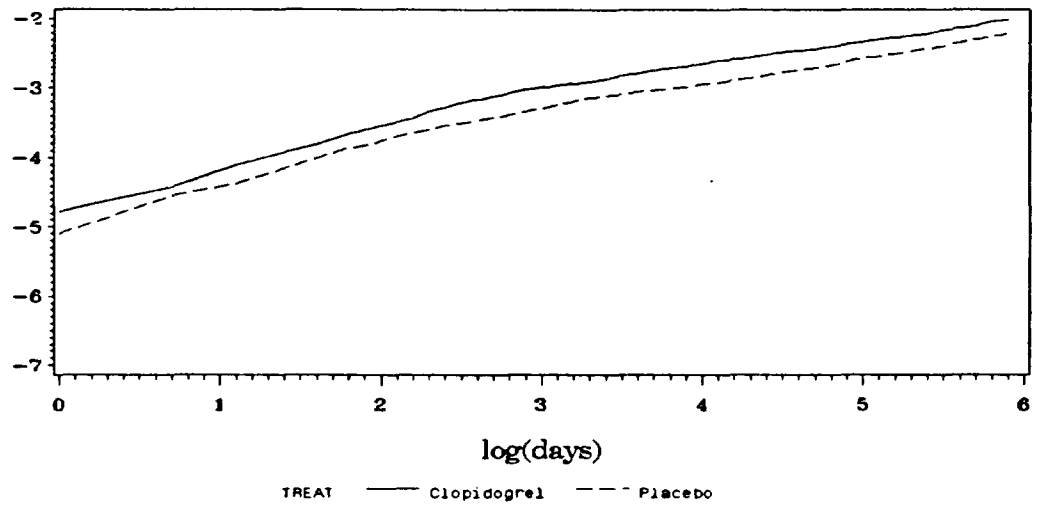


Figure 2. Log(-log(Survival Probability)) for CV death, MI, stroke or refractory ischemia (Reviewer's analysis)

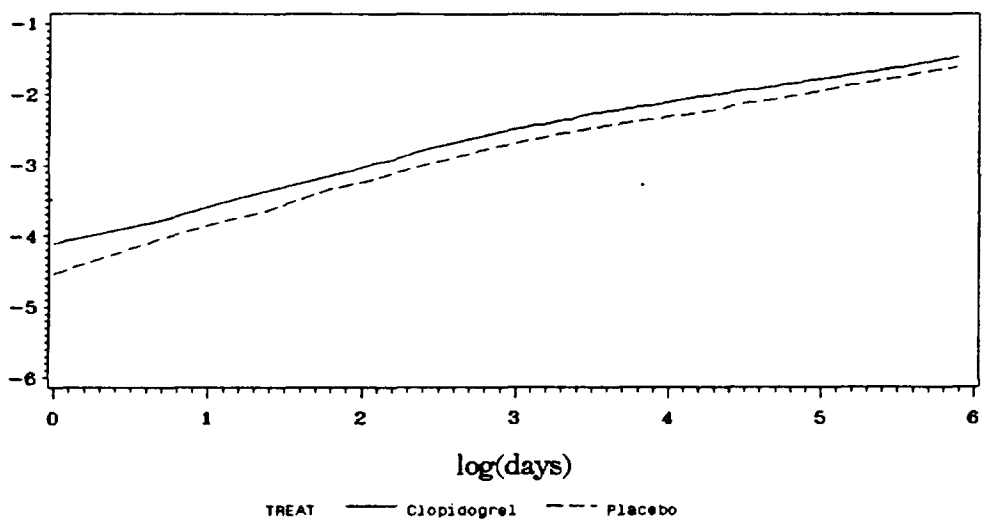


Figure 3. Relative risk of adjudicated event of CV death, MI or stroke by country (Reviewer's analysis)

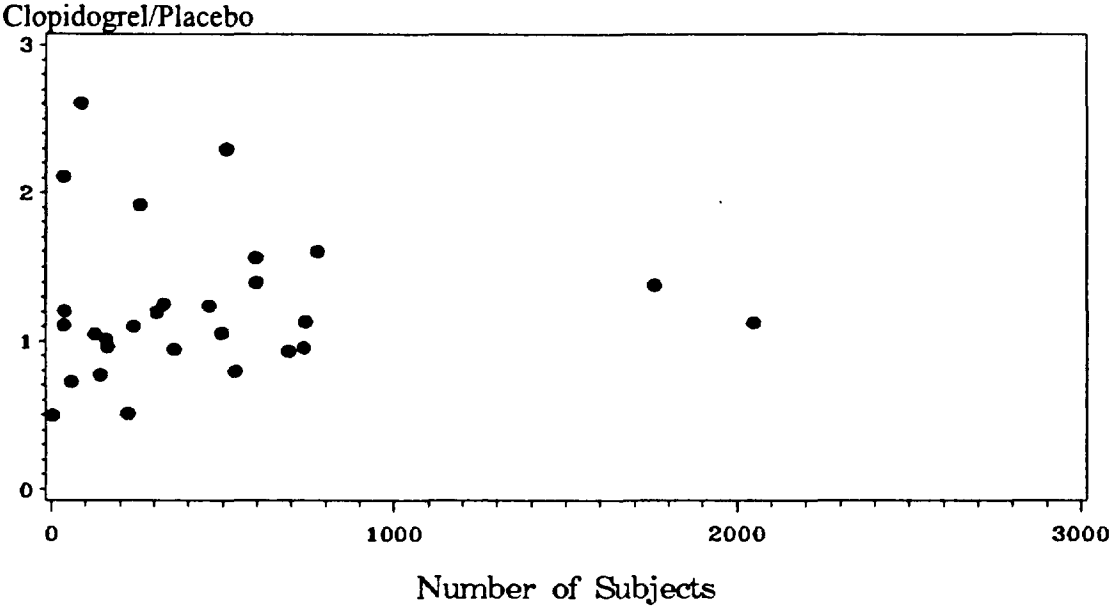
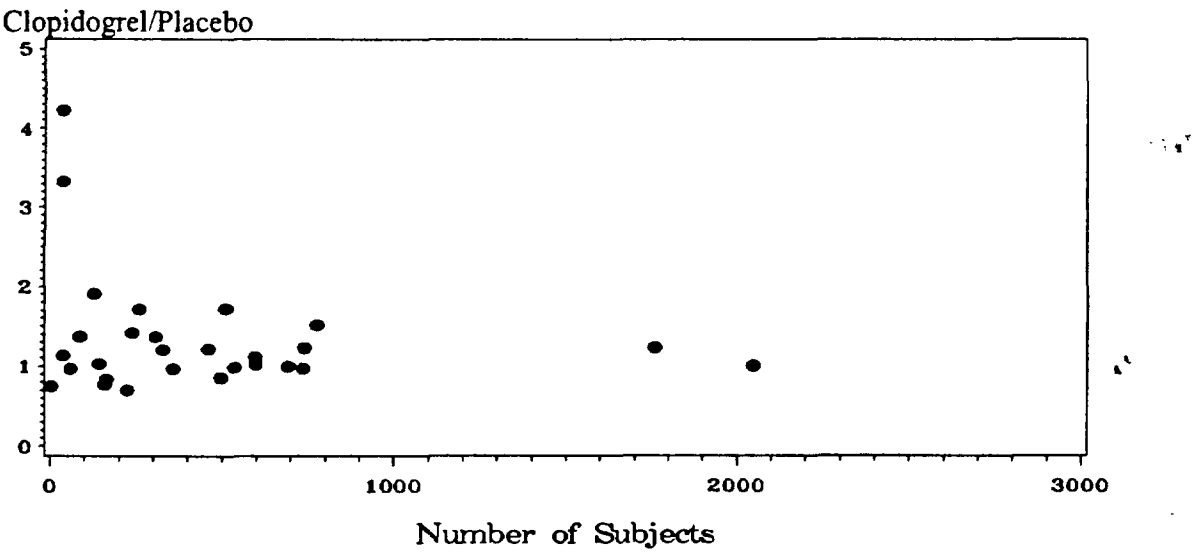


Figure 4. Relative risk of adjudicated event of CV death, MI, stroke or refractory ischemia by country (Reviewer's analysis)



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

James Hung
11/13/01 12:04:03 PM
BIOMETRICS

George Chi
11/13/01 12:19:11 PM
BIOMETRICS