CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

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Medical Review(s)

See Medical Review section of Action Package for review of financial disclosure information

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Memorandum

DATE: 2.6.02

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SUBJECT: Review of supplement: Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE, OASIS-4).

sNDA: NDA 20-839

RÉSUMÉ

This memorandum includes a recommendation supporting the approval of clopidogrel for the treatment of patients with Acute Coronary Syndrome (ACS). Appendix One contains the clinical review of the CURE trial, which randomized 12,562 patients diagnosed with ACS (including unstable angina pectoris/ UAP and MI without ST-segment elevation) to receive daily clopidogrel or a matching placebo. All patients were treated with aspirin (ASA) as tolerated, and were followed for at least 3 months. In this setting, in the patient population studied, the use of clopidogrel had a significant effect to reduce the incidence of the following two pre-specified primary endpoints of the trial, as defined in the protocol:

1) First occurrence of any component of the following during the period of follow-up: Cardiovascular death, Non-fatal MIs, Strokes.

2) First occurrence of any component of the following during the period of follow-up: Cardiovascular death, Non-fatal MIs, Strokes and Refractory cardiac ischemia.

Evidence supporting the efficacy of clopidogrel was seen across a broad range of patient demographics, including patients grouped according to gender, age (< or >65 years) and the receipt of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) while on study drug. Too few ethnic minorities were enrolled for an informative efficacy analysis in those populations.

The major safety concern identified in the trial was an increased incidence of bleeding adverse events in patients taking clopidogrel. No synergistic interactions with clopidogrel and other drugs or procedures affecting bleeding were identified. No episodes of thrombocytopenic purpura (TTP) or aplastic anemia were reported. No new safety concerns for clopidogrel were identified in the CURE trial database.

Reviews of the data by Biopharmaceutics, Chemistry, Pharmacology-Toxicology and Statistics have identified no issues precluding an approval decision. The CURE trial supports the approval of clopidogrel to reduce the occurrence of cardiovascular death, non-fatal MIs, strokes and refractory cardiac ischemia, as defined in the protocol.

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I. Background and Introduction

The CURE trial (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events) was designed to study the effects of long-term therapy with an antiplatelet medication on the occurrence of clinical cardiovascular events in patients presenting with signs and symptoms of Acute Coronary Syndrome (unstable angina pectoris/UAP, or myocardial infarction/MI without ST-segment elevation) who are also receiving ASA therapy. While there are previous trials examining the clinical effects of thienopyridines in other populations with cardiovascular disease, supporting a clinical benefit for these drugs, clopidogrel has not previously been tested in patients presenting with signs and symptoms of acute cardiac ischemia. Additional background information on previous trials of anti-platelet drugs in ACS is to be found in Appendix One.

II. Clinically Relevant Findings from Other Review Disciplines

The reader is referred to earlier reviews of the CAPRIE trial ("Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events") and to the approved clopidogrel label. Reviews of the data in the present supplement by the Biopharmaceutics, Chemistry, Pharmacology-Toxicology and Statistics disciplines have identified no issues precluding an approval decision. The reader is referred to the relevant reviews for details.

III. Human Pharmacokinetics and Pharmacodynamics

No new material relevant to human pharmacokinetics and pharmacodynamics was submitted as part of the current supplement. Plavix (clopidogrel bisulfate) is an inhibitor of ADP-induced platelet aggregation acting by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan. It is by preventing this platelet activation that clopidogrel is thought to reduce thrombotic events common to the pathophysiology of a variety of cardiovascular diseases, including MI, stroke, peripheral arterial occlusive disease.

Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation, but an active metabolite responsible for the activity of the drug has not been isolated. After repeated 75-mg oral doses of clopidogrel (base), plasma concentrations of the parent compound, which has no platelet inhibiting effect, are very low and are generally below the quantification limit , mg/L) beyond 2 hours after dosing. Clopidogrel is extensively metabolized by the liver. The main circulating metabolite is the carboxylic acid derivative, and it too has no effect on platelet aggregation.

The time-course of inhibition of platelet activation is one way to gauge the pharmacodynamic half-life of clopidogrel. Dose-dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of clopidogrel. Repeated doses of 75 mg clopidogrel per day inhibit ADP-induced platelet aggregation on the first day, and inhibition of platelet activation reaches steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg clopidogrel per day was between 40% and 60%. Platelet aggregation and bleeding time gradually return to baseline values after treatment is discontinued, generally in about 5 days.

IV. Description of Clinical Data and Sources

Sources of data for this review include the following:

1. Electronic submissions to NDA 20-839, including submissions through 1.28.02.
2. Reprints of CURE trial design and results (see references).
3. Copies of all DSMB minutes and relevant correspondence.
4. Statistical review of CURE by James Hung, Ph.D., dated 10.24.01.
5. CURE study report, submitted 10.5.01.

In general, the submission included baseline and follow-up data on the 12,562 patients randomized in CURE, from 482 centers in 28 countries. Adequate data were submitted to allow for sufficient assessment of both efficacy and safety of clopidogrel in these patients.

V. Clinical Review Methods

Review of primary efficacy outcomes and safety were conducted using the SAS datasets, published articles, finished study reports, minutes, and Case Report Forms (CRFs) submitted by the sponsor. The data sources are identified for each of the relevant tables in the review. Statistical methods applied are similarly identified as appropriate.

VI. Integrated Review of Efficacy

The reader is referred to Integrated Summary of Efficacy that appears at the end of Appendix One (CURE Study Review). The use of clopidogrel in CURE was associated with a significant decrease in the rate of occurrence for both of the pre-specified primary endpoints.

VII. Integrated Review of Safety

The reader is referred to Integrated Summary of Safety that appears at the end of Appendix One (CURE Study Review). The major safety concern regarding the use of clopidogrel in CURE is related to its pharmacodynamic effect as an inhibitor of platelet activation: bleeding. No synergistic drug-drug, drug-disease or drug-procedure interactions that increased bleeding risk were identified with clopidogrel in CURE. No novel safety concerns have been identified for clopidogrel in the CURE database.

VIII. Dosing, Regimen and Administration

A single dose of clopidogrel was compared with placebo in patients taking a background of ASA (75-325 mg) as tolerated. The dose of clopidogrel (Clopidogrel 300 mg oral loading dose on day one, then 75 mg per day chronically) differs from the approved dose (75 mg per day with no loading dose) by the use of a loading dose. The study protocol states the intent of the loading dose was 'to provide an immediate antiplatelet effect.'

IX. Use in Special Populations

Sufficient women and patients >65 years of age were enrolled in CURE to assess the efficacy of clopidogrel in those populations (favorable trends were seen for clopidogrel). Too few subjects from ethnic minorities, including African-Americans, were enrolled to assess the efficacy of clopidogrel in those populations. Specifics of enrollment can be found in Appendix One, section 2.4.

The efficacy of clopidogrel was sufficiently demonstrated in patients also receiving a classes of cardiovascular medications: beta-blockers, ACE-inhibitors, lipid-lowering agents, heparin and ASA.

The design of CURE excluded some relevant patient populations: patients who are intolerant or allergic to ASA, patients who received IV GPIIb/IIIa inhibitors for their presenting ACS, patients receiving oral anticoagulants, and those on chronic anti-platelet agents or NSAIDs. The efficacy of clopidogrel in ACS in these populations cannot be determined from CURE. Although patients who were intolerant on ASA were excluded from the trial, enough patients apparently discontinued ASA during the trial to detect a treatment effect for clopidogrel in patient not taking ASA.

X. Conclusions and Recommendations

The use of anti-platelet drugs in the treatment of ACS has been studied in many tens of thousands of patients (perhaps 100,000+), but have a mixed record. Trials in the short-term administration of the IV GPIIb/IIIa inhibitors have demonstrated efficacy for two drugs in this class (tirofiban, eptifibatide), but reported disappointing outcomes in a third agent (abciximab) in ACS. For the use of long-term anti-platelet therapy the data are similarly mixed. For ASA, a hallmark antiplatelet agent, meta-analyses suggest a robust efficacy in secondary prevention of cardiovascular events after an MI although the individual trials have a mixed set of outcomes. Another oral agent in the thienopyridine class, ticlopidine, has reported efficacy in secondary prevention in vascular disease but no trial data in ACS. Finally, there are a series of failed trials treating patients chronically with ACS with oral GPIIb/IIIa inhibitors. These trials have been halted due to an apparent excess of morbidity (especially bleeding) and mortality. Based on these data, then, there is substantial interest in additional investigations in the treatment of ACS with chronic oral anti-platelet therapies.

CURE was a multicenter, multinational, randomized, parallel-group, double-blind trial of clopidogrel versus placebo in patients with ACS who were also receiving ASA therapy. The primary objective of the study was to evaluate whether clopidogrel is superior to placebo in preventing ischemic cardiovascular complications in these patients during follow-up for between 3 and 12 months.

In CURE, clopidogrel had a significant effect to reduce the occurrence of the two pre-specified primary endpoints (Cardiovascular Death/MI/Stroke, or the same endpoints plus Refractory Ischemia). These data are summarized in tables 3.2.1 and 3.2.2 in Appendix One). For the occurrence of CV Death, MI and Stroke, clopidogrel use was associated with an absolute decrease in incidence of 1.7% (11.4% in placebo, 9.3% in clopidogrel) equating a relative risk (clopidogrel:placebo) of 0.80 (95% Confidence Interval 0.72-0.90). The most robust effect was seen on recurrent MIs (Relative Risk 0.77 (0.67-0.89), with less robust, but favorable, trend on the other components of the primary endpoints. Of interest, there was only a small effect of clopidogrel to reduce the incidence of 'Refractory Ischemia (recurrent angina requiring hospitalization or additional procedures), with a Relative Risk of 0.93 (95% CI 0.87-1.13). The CURE trial was large enough, and accumulated sufficient endpoints to allow informed assessment of a variety of demographics of interest for this endpoint, including patients undergoing percutaneous coronary intervention (PCI) or CABG. With the significant exception of some of the racial sub-groups (where too few patients were enrolled), clopidogrel had a consistent effect to reduce the incidence of clinical events, especially myocardial infarction (MI), across all of the major demographics of interest. This effect of clopidogrel appeared to persist throughout the duration of therapy (at least 3 months). There was no significant effect of clopidogrel on the need for mechanical interventions (*i.e.*, PCI with or without stenting, CABG), although the need for thrombolytics and IV GPIIb/IIIa inhibitors was reduced. The absence of an effect on the need for procedures has been seen in other trials of anti-platelet drugs in ACS suggesting that anti-platelet drugs have little effect on the need for further procedures. Why this is so, when both classes of anti-platelet drugs have a significant effect to reduce the incidence of recurrent MIs, is open to speculation.

The trial enrollment criteria are significant for the exclusion of the use of the following: IV GPIIb/IIIa inhibitors, oral anticoagulants and the chronic use of non-study anti-platelet drugs or NSAIDs. This limits the interpretation of the trial results in these populations. No issues were identified with regard to the conduct of the trial that limit the interpretation of either the efficacy or safety data.

The safety of clopidogrel in CURE is interesting both for what it showed (an expected increase in bleeding relative to placebo) and for what it didn't show (any cases of TTP or aplastic anemia). Importantly, with regard to bleeding, no synergistic interactions of clopidogrel with other drugs or procedures to increase the rate of bleeding were identified. When patients underwent cardiovascular procedures, the expected increase in bleeding occurred in patients taking either clopidogrel or placebo.

Where does this leave the treatment of ACS? First, based on CURE, the use of clopidogrel in association with ASA has a demonstrated clinical effect in the enrolled population to reduce cardiovascular morbidity during the 12 months following ACS. This efficacy extends to patients who undergo PCI and CABG while on clopidogrel. While not strictly relevant to the approval decision for clopidogrel in ACS, there is considerable interest in comparing the efficacy of clopidogrel with IV GPIIb/IIIa inhibitors in this setting. This trial minimized the use of IV GPIIb/IIIa inhibitors and prohibited their concomitant use at the time of randomization. As a result, no robust conclusions about their concomitant use can be drawn. Absent directly comparing the short-term administration of an IV GPIIb/IIIa inhibitor with the long-term administration of clopidogrel, any comparisons between these two classes of therapy in this conditions remain speculative.

XI. APPENDIX ONE: CURE STUDY REVIEW

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1.1 Title of Study

Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE), OASIS-4.

1.2 Sites of Investigation and Investigators

CURE was conducted in 428 centers in 28 countries.

1.3 Study Background

This trial was designed to study the effects of long-term therapy with an antiplatelet medication (a thienopyridine) in the secondary prevention of clinical vascular events in patients presenting with signs and symptoms of acute coronary syndrome (ACS). The table below summarizes the published data on the effects of thienopyridines (ticlopidine or clopidogrel) on vascular death, MI or stroke from a variety of trials enrolling patients with vascular disease, as summarized below.

Table 1.3.1 Published Effects of Thienopyridines in Patients with Vascular Disease[a].

Trial	Thienopyridine (n/N) %	Comparator (n/N) %	Hazard Ratio
TIA/ Stroke			
CATS (Ticlopidine vs placebo)	108/525 (20.6%)	134/528 (25.3%)	0.74
TASS (Ticlopidine vs. ASA)	370/1529 (24.2%)	395/1540 (25.6%)	0.93
CAPRIE (Clopidogrel vs. ASA)	939/9599 (9.8%)	1416/11126 (12.7%)	0.91
Unstable Angina			
Balsano (Ticlopidine vs Control)	23/314 (7.3%)	48/448 (10.7%)	0.49
Intermittent Claudication			
STIMS (Ticlopidine vs. Placebo)	91/346 (26.3%)	108/341 (31.7%)	0.77

a. References for these trials appear in Appendix One. Endpoints summarized are for vascular death, MI and stroke.

For the use of other drugs in similar settings, ASA has a meta-analysis suggesting a substantial effect in secondary prevention, but a database in which the largest trial reported no significant benefit of ASA vs. placebo (Ref. 9). There are other long-term trials in the use of similar anti-platelet agents that have raised significant safety concerns (*e.g.*, the oral GPIIb/IIIa inhibitors). The present trial was designed to test the utility of a thienopyridine in the long-term prevention of cardiovascular events and death in a population admitted with ACS.

1.4 Study Design

CURE was a multicenter, multinational, randomized, parallel-group, double-blind trial of clopidogrel versus placebo in patients with ACS (unstable angina or MI without ST-segment elevation) who are also receiving ASA therapy (75 to 325 mg per day, determined by the investigators). The primary objective of this study was to evaluate whether clopidogrel is superior to placebo in preventing ischemic complications in the patient population enrolled. Eligible patients were randomized to receive one of two treatments:

Clopidogrel 300 mg oral loading dose on day one, then 75 mg per day chronically.
Placebo

Patients were evaluated at time of hospital discharge, at the end of 1, 3, 6, 9 and 12 months and were followed for a minimum of 3 months. Since the endpoint was based on a time-to-event analysis, patients enrolled late in the trial did not have follow-up through 12 months.

The trial had two co-primary endpoints, based on outcome events as adjudicated blindly by a central events adjudication committee (EAC):

First occurrence of one of the following: Cardiovascular (CV) death, MI or Stroke during the period of follow-up.

First occurrence of one of the following: CV death, MI, Stroke or Refractory ischemia over the duration of the follow-up.

Concomitant Medications and Therapies

Patients who received PCI in the previous 3 months were not eligible for entry into CURE. Following randomization, if a patient underwent a coronary stenting procedure after starting study drug blinded medication was to be stopped for 2-4 weeks to allow for the open-label administration of a thienopyridine (ticlopidine or clopidogrel). At the end of that time, blinded study medication was to be re-started and the open-label drug stopped.

The use of GPIIb/IIIa inhibitors in the three days prior to admission was prohibited. Following randomization patients were allowed to receive them at the discretion of the investigators.

All patients were to receive ASA, and intolerance to ASA was an exclusion criterion.

Protocol Amendments

The first table summarizes the amendments and trial milestone for CURE.

Table 1.4.1 Milestones in CURE[a].

Date	Milestone/Amendment	Notes
12.98	Trial enrollment begins	
6.25.99	Meeting to discuss changes in patient population and increased trial size	Decision made not to enroll patients >60 years old without objective ECG signs of cardiac ischemia.
7.01.99	Protocol Amendment 1.1	1. Requires that all patients enrolled have either ECG or cardiac enzyme evidence of ischemia. 2. Allows the use of GPIIb/IIIa inhibitors 'as required during interventional procedures.' 3. Added 'recurrent angina during initial hospitalization' to endpoints
8.16.99	Amendment 1.1 implemented	Followed IRB review and approval. 3211 patients were enrolled prior to this date.
9.1.99	Sample size increased to 12,500	Approximately 3,500 patients were enrolled at this time.
7.25.00	Addition of Second Primary Endpoint	Specified level of statistical significance for both primaries, based on estimate of overlap between two endpoints of 0.55.

a. From DSMB and Operations Committee minutes and Dec. 11, 2001 submission from sponsor.

The CURE study was amended twice. The first amendment, on 9.1.99, increased the sample size was based on the observed event rates after approximately 3,500 patients had been enrolled.

The second amendment, on 7.25.2000 changed the designation of the secondary endpoint (CV death, MI, stroke or refractory ischemia) to a co-primary endpoint. To account for the co-primaries, the original primary endpoint (CV death, MI or stroke) was to be tested at $p = 0.045$ and the new co-primary endpoint (CV death, MI, stroke or refractory ischemia) would tested at $p = 0.01$. Per Dr. Hung, these alpha levels were determined through simulation studies taking into account the correlation between the two composite endpoints. The interim analysis boundaries were adjusted accordingly.

1.5 Primary and Secondary Endpoints

Primary Endpoint

First occurrence of any component of the following during the period of follow-up:

Cardiovascular Death.
Myocardial Infarction.
Stroke (ischemic, hemorrhagic or of uncertain type).

Secondary Endpoint

First occurrence of any component of the following during the period of follow-up:

Cardiovascular Death.
Myocardial Infarction.
Stroke (ischemic, hemorrhagic or of uncertain type).
Refractory Ischemia.

'Other' Outcomes

Cardiovascular Death.
Myocardial Infarction.
Stroke (ischemic, hemorrhagic or of uncertain type).
Recurrent angina during initial hospitalization
'Severe ischemia' during initial hospitalization.
Need for mechanical or chemical revascularization: PCI, CABG or thrombolytic.

Definitions of Study Outcomes

All events reported by the investigators were blindly adjudicated by the Events Adjudication Committee (EAC) using the definitions below. A list of the EAC is to be found in Appendix Three of this review.

Cardiovascular Death

All deaths except those due to a documented non-vascular cause.

Myocardial Infarction

MI requires the presence of at least two of the following:

- New onset or worsening chest pain characteristic of angina occurring at rest or with minimal exertion lasting 20 minutes or needed NTG or narcotic analgesia.
- Elevation of CK, CK-MB, troponin or other cardiac enzymes to at least 2X ULN (or >20% elevation above previous level if in-hospital MI).
- ECG changes c/w ischemia. ECG documentation is needed for this event.

Stroke

New focal neurologic deficit thought to be vascular in origin, with signs or symptoms lasting >24 hours. CT or MRI confirmation was 'strongly recommended' but not required. Strokes were further classified as definite hemorrhagic, ischemic, or unknown.

Refractory Ischemia

1. Chest pain with ECG changes lasting more than 5 minutes while on optimal therapy (including 2 anti-anginals with one being IV nitrate if possible), and leading to additional interventions (thrombolytics, cardiac catheterization, PCI, CABG) by midnight of the next calendar day. OR
2. Rehospitalization for unstable angina with symptoms and signs of angina.

Severe Ischemia

One episode of recurrent chest pain lasting >5 minutes on optimal therapy, with documentation of new ECG changes.

Recurrent Angina During Initial Hospitalization

Chest pain lasting >15 minutes requiring new anti-anginal medication with or without ECG changes.

Coronary Revascularization

PCI or CABG. Considered urgent if it occurred within one week of rehospitalization for ACS.

1.6 Inclusion/ Exclusion Criteria

Inclusion Criteria

In the original protocol, patients were eligible for enrollment if they fit into one of two categories, if they gave informed consent:

1. With ECG Changes

Chest pain with the onset of the most recent episode in ≤24 hours.
Chest pain consistent with angina, with

- New onset, or worsening pattern.
- Occurring at rest or with minimal exertion.
- Lasting 5 minutes or requiring NTG.
- ECG: ST-depression ≥1 mm
  ST-elevations of ≤1 mm.
  T-wave inversion of ≥2 mm.
  Hyperacute T-waves.

2. Without ECG Changes

Patients without ECG changes could be entered with:
Age >60 years of age
A history of one of the following:

- Prior MI.
- Prior revascularization procedure >3 months before entry.
- Prior cardiac catheterization showing 'significant' CAD.
- Positive exercise test.
- 'Other objective evidence of atherosclerotic vascular disease'.

At the time of the first amendment, the second criterion was modified, so that patients over the age of 60 were required to have either biochemical or ECG evidence of cardiac ischemia.

Exclusion Criteria

1. Age <21 years.
2. Previous 'disabling' stroke.
3. Previous intracranial hemorrhage or hemorrhagic stroke.
4. Co-morbid conditions limiting survival to <12 months.
5. NYHA Class IV CHF.
6. 'Uncontrolled' hypertension (HTN).
7. Current use of oral anticoagulants, non-study anti-platelet drugs or NSAIDs (used long-term).
8. Enrollment in other investigational trial.
9. GPIIb/IIIa use in previous 3 days.
10. PCI or CABG in previous 3 months.
11. Women of child-bearing potential not 'following an effective method of contraception'.
12. 'Geographical or social factors making study participation impractical'.
13. History or thrombocytopenia, neutropenia, ASA intolerance, or contraindications to clopidogrel or ASA.

1.7 Safety and Efficacy Endpoints Measured

Table 1.7.1 Efficacy and Safety Collection in CURE[a].

	Baseline	Hospital Discharge	1 Month	3 Month	6, 9 and 12 Months[b]
Hx, Physical	X				
ECG	X				
Vital Signs	X				
Labs	X				
Study Drug	X				
AEs		X			
Outcomes		X			

a. From final protocol dated 7.12.98.

Bleeding events

All bleeding events were recorded and classified by the investigators as:

- **Life-threatening:** Defined as fatal or leading to:
  - A drop in hemoglobin ≥5 g/dL.
  - Significant hypotension with need for inotropes.
  - Requiring surgery (other than vascular site repair).
  - Symptomatic intracranial hemorrhage.
  - Requiring transfusion of 4 or more units of red blood cells or equivalent whole blood.
- **Major**: Significantly disabling, intraocular bleeding leading to significant loss of vision or bleeding requiring transfusion of 2 or 3 units of red blood cells or equivalent whole blood.
- **Minor**: Any other bleeding requiring permanent or temporary discontinuation of the study drug.

All reports of suspected life-threatening and major bleeding events were blindly adjudicated by the Event Adjudication Committee (EAC). Any suspected life-threatening and major bleeds had to be reported as a SAE by the investigators, with the exception of hemorrhagic stroke which was a study outcome. Any other bleeding event was to be reported on the minor bleeding form of the CRF, but not on the AE form.

Follow-up for Adverse Events

Patients who stopped study drug for and AE were to be followed up at least until the event was resolved, or where possible until the end of the planned period of follow-up. In the case of an SAE, the subject had to be followed up until clinical recovery was complete and laboratory results had returned to normal, or until progression had been stabilized (the follow-up could continue after the patient had left the study).

1.8 Statistical Considerations and Interim Analyses

See the statistical review by James Hung, Ph.D. for CURE for additional details of the statistical plan. The population analyzed for the primary endpoint was an intention-to-treat population, defined as all-randomized patients. The primary analysis was the time-to-first occurrence of any component of the primary endpoint (Cardiovascular Death, Myocardial Infarction or Stroke). The rate of occurrence of the primary endpoint was assessed using log-rank statistics.

Interim Analyses

Two interim analyses were conducted at (roughly) 1/3 and 2/3 of the patients enrolled, conducted by the external statistician working with the DSMB. 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. 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.

Sample Size Calculations

Initially, the study was designed to include 9000 patients, based on a placebo event rate of 12-14% (from the OASIS registry of 8000 patients followed for 8-9 months).

1.8.1 Observed Relative Risk Reductions in CURE for 9,000 Patients Enrolled[a].

Endpoint	Control Event Rate	80% Power	90% Power
Primary Endpoint[b]	12%	15.4%	17.7%
	13%	14.8%	16.9%
	14%	14.1%	16.2%
Secondary Endpoint[c]	22%	13.2%	14.8%
	24%	12.5%	14.0%

a. From Final Protocol dated 8.12.98.
b. Alpha level 0.05 (two-sided).
c. Alpha level 0.01 (one-sided).

The total event rate was reviewed after 5000 patients were enrolled, and 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.

2.0 to 2.9 CURE Trial Conduct

Patients were recruited between 12.98 and 10.2000 at 482 centers in 28 countries by the OASIS Investigators (Organization to Assess Strategies for Ischemic Syndromes). The study end date was 12.6.2000. The data lock date for the study report was 12.6.2000.

2.1 Disposition of Subjects

The protocol called for 3 months of treatment in all patients, regardless of when they entered the trial, with follow-up for 12 months when possible.

Table 2.1.1 Patient Disposition in CURE[a].

	Clopidogrel	Placebo	Total
Randomized	6259	6303	12562
Randomized and Treated	6244	6287	12531
Completed 3 Months of Treatment	6037 (96.4%)	6048 (96.0%)	12085 (96.2%)
Completed Treatment	4939 (78.9%)	5114 (81.1%)	10053 (80.0%)
Completed Alive	4675 (74.7%)	4802 (76.2%)	9477 (75.4%)
Death While on Treatment	264 (4.2%)	312 (5.0%)	576 (4.6%)
Patient Discontinuations			
Adverse Event[b]	366 (5.8%)	247 (3.9%)	613 (4.9%)
Consent Withdrawal	596 (9.5%)	561 (8.9%)	1157 (9.2%)
Qualifying Condition Absent	70 (1.1%)	81 (1.3%)	151 (1.2%)
Intervention	21 (0.3%)	16 (0.3%)	37 (0.3%)
Contraindicated Concomitant Medications	123 (2.0%)	130 (2.1%)	253 (2.0%)
Patient Refusal or Noncompliance	54 (0.9%)	54 (0.9%)	108 (0.9%)
Missing Reasons	10 (0.2%)	4 (0.1%)	14 (0.1%)
Other	79 (1.3%)	94 (1.5%)	173 (1.4%)

a. Data from CURE study report, table (10.1) 2.
b. Includes AEs, SAEs, and bleeding events.

2.2 Subject Selection, Participation and Informed Consent

No information is available about the number of patients screened to obtain the enrolled population (n=12,562 subjects). All patients were to have completed an informed consent prior to the administration of study drug. The subject participation in CURE is summarized in the two tables below.

Table 2.2.1 Duration of Study Participation in CURE[a].

Metric of Exposure	Clopidogrel N=6259	Placebo N=6303	Total N=12562
Mean (Months ±SD)	9.4±3.4	9.4±3.5	9.4±3.4
Median (Months)	10.8	10.8	10.8

a. Data from CURE study report, table (10.1) 3.

Table 2.2.2 Patient Follow-up in CURE[a].

	Randomized	≥10 Days	≥30 Days	≥90 Days	≥180 Days	≥270 Days	≥365 Days	≥540 Days
Placebo	6303	6131	5943	5600	4441	3347	2183	11
Clopidogrel	6259	6080	5905	5585	4417	3276	2132	13

a. Data from sponsor's submission dated 12.11.01 and SAS sets, LASTDT minus RANDT.

2.3 Protocol Violations

Protocol violations were reported for around 7% of the randomized population, as shown in the table below. The largest group related to the enrollment, early in the trial, of patients >60 years of age without ECG or serum marker evidence of cardiac ischemia. No imbalance in the occurrence of protocol violations between the two study groups is evident.

Table 2.3.1 Protocol Violations in CURE[a].

Inclusion/Exclusion Violation	Clopidogrel N=6259	Placebo N=6303
Any Violation	459 (7.3%)	429 (6.8%)
Lack of Qualifying Symptoms	5 (0.8%)	8 (0.13%)
Time from Onset of Sxs to Enrollment >24 hours	126 (2.1%)	119 (1.9%)
No Cardiac Ischemia on ECG or Cardiac Enzymes[b]	312 (5.0%)	283 (4.5%)
Thrombocytopenia, High Risk of Bleeding or Contraindication to ASA or Clopidogrel	6 (0.10%)	7 (0.11%)
Contraindicated Medication used before Randomization	6 (0.1%)	7 (0.1%)
Concurrent Enrollment in Another Trial	2 (0.3%)	1 (0.02%)
PTCA/stent or CABG in 3 Months Prior to Enrollment	9 (0.14%)	12 (0.9%)
Written Consent Not Obtained	2 (0.03%)	2 (0.03%)
Received Wrong Study Medication[c]	11 (0.2%)	15 (0.2%)

a. Data from CURE study report, table (10.2.1)1.

b. Many of these patients would have been eligible under the original inclusion criteria (later changed to exclude those without ECG or enzyme evidence of ischemia).

c. Includes anyone who was identified as receiving wrong study drug at any time of the trial. Patients were analyzed in their originally assigned groups.

2.4 Subject Demographics & Baseline Characteristics

A total of 12,562 patients at 482 centers in 28 countries were randomized. The largest fraction (82%) of the enrolled population came from Europe, as shown in the first table below. The US population made up 3.7% of the enrollment.

Table 2.4.1 Nationality of Patients Enrolled in CURE[a].

Ethnicity[a]	# of Patients (% of total)
Arab	137 (1.1%)
Black African	69 (0.5%)
Chinese	18 (0.1%)
Colored African	93 (0.7%)
European	10308 (82.0%)
Japanese	8 (0.06%)
Malaysian	13 (0.1%)
Missing	4 (0.03%)
Native Latin/ North American/ Australian Aborigine	1325 (10.5%)
North American	2223 (17.7%)
Other	372 (2.9%)
Other Asian	29 (0.2%)
South Asian	186 (1.5%)
United States	462 (3.7%)

a. As identified from SAS 'Demographics' file identifiers.

The racial breakdown is summarized below. Caucasians were the predominate racial group, with small numbers of blacks or Orientals. Only 37 African-Americans were enrolled in the trial.

Table 2.4.2 Ethnicity of Patients Enrolled in CURE[a].

Race[a]	# of Patients (% of total)
Black[b]	69 (0.5%)
Caucasian[c]	10,308 (82.0%)
Missing	4 (0.03%)
Oriental	254 (2.0%)
Other	1927 (15.3%)

a. As identified from SAS 'Demographics' file identifiers.

b. There were 37 African-Americans enrolled in CURE (0.3% of total enrollment), 21 in Clopidogrel, 16 in Placebo.

c. There were 215 Caucasian-Americans enrolled in CURE (1.7% of enrollment), 108 in Clopidogrel, 107 in Placebo.

The next table summarizes additional baseline demographics for CURE. The majority of the patients (75%) carried the diagnosis of unstable angina pectoris (UAP) at baseline, and a smaller fraction (25%) had elevated cardiac enzymes without ST-segment elevation, suggesting non-Q-wave MI.

Table 2.4.3 Baseline Demographics of Patients Enrolled in CURE[a].

Demographic	Clopidogrel N=6259	Placebo N=6303
Age (years) means±sd	64.2±11	64.2±11
Gender: Female	2420 (38.7%)	2416 (38.3%)
Heart Rate (bpm) means±sd	73±15	73±15
Supine Systolic BP (mmHg)[c] means±sd	134±22	134±22
Supine Diastolic BP (mmHg)[c] means±sd	77±13	77±14
ECG Changes at Entry		
ST Segment Depression ≥1 mm	2642 (42.2%)	2646 (42%)
ST Segment Elevation ≤1 mm	203 (3.2%)	199 (3.2%)
Diagnosis at Entry		
UAP	4690 (74.9%)	4724 (74.9%)
Suspected MI	1569 (25.1%)	1579 (25.1%)
MI[b]	1624 (25.9%)	1659 (25.3%)
Elevated CPK or Troponin I or T ≥2X ULN	1584 (25.3%)	1592 (25.3%)

a. From CURE study report, table (10.4.2) 3.

b. Defined as MI with pain prior to randomization.

The majority of patients had their qualifying episode of pain between 12 and 24 hours prior to enrollment, as shown in the table below.

Table 2.4.4 Timing of Chest Pain Prior to Enrollment in CURE[a].

Hx of Demographic	Clopidogrel N=6259	Placebo N=6303
Time from onset of pain to randomization (hrs)		
Mean (hours) mean±sd	14.2±7.2	14.1±7.1
Median	14.8	14.5
Time from Pain to Enrollment		
<6 hours	1070 (17.1%)	1063 (16.9%)
6-12 hours	1430 (22.9%)	1490 (23.7%)
12-24 hours	3645 (58.3%)	3627 (57.6%)
>24 hours	111 (1.8%)	119 (1.9%)

a. From CURE study report, table (10.4.2) 2.

The past medical histories of the patients were significant for a majority with a history of smoking and hypertension, but only a small fraction with a history of CHF or strokes.

Table 2.4.5 Medical History of Randomized Patients in CURE[a].

Hx of Demographic	Clopidogrel N=6259	Placebo N=6303
MI	2029 (32.4%)	2015 (32.0%)
CABG or PCI	1107 (17.7%)	1139 (18.1%)
CVA	274 (4.4%)	232 (3.7%)
CHF	462 (7.4%)	492 (7.8%)
HTN	3750 (59.9%)	3841 (60.9%)
Diabetes	1405 (22.4%)	1435 (22.8%)
Current or former smoker	3790 (60.6%)	3841 (60.9%)

a. From CURE study report.

2.5 Concomitant Therapies at Baseline

At baseline the concomitant use of other medications was balanced between the two treatment groups.

Table 2.5.1 Medications at Time of Randomization in CURE[a].

Demographic	Clopidogrel N=6259	Placebo N=6303
ASA	4168 (66.6%)	4134 (65.6%)
Heparin or LWMH	4522 (72.3%)	4605 (73.1%)
ACE Inhibitor	2347 (37.5%)	2309 (36.6%)
Beta-blocker	3678 (58.8%)	3690 (58.5%)
Calcium-channel blocker	1784 (28.5%)	1771 (28.1%)
Lipid-lowering Agent	1599 (25.6%)	1586 (25.2%)
Intravenous Nitrate	2836 (45.3%)	2906 (46.1%)

a. From CURE study report table (10.4.3)1 and SAS datasets.

3.0 to 3.9 Efficacy Analyses of CURE

3.1 Interim Efficacy Analyses of CURE

Interim analyses of the primary and secondary efficacy variables were conducted 2.14.2000 and 6.29.2000, when approximately 1/3 and 2/3 of the patients had been enrolled. The results from those two analyses are summarized in the two tables below.

Table 3.1.1 CURE Interim Analysis Results as of 2.4.00[a].

	Placebo	Clopidogrel	Hazard Ratio (95% C.I.)	p-Value
Randomized	3589	3544		
Primary Endpoint[b]	274 (7.6%)	220 (6.2%)	0.80 (0.67-0.95)	0.0123
Secondary Endpoint[c]	477 (13.3%)	402 (11.3%)	0.83 (0.73-0.95)	0.0079

a. Data from DSMB minutes dated 2.14.00.
b. CV death, New MI, Stroke.
c. CV death, New MI, Stroke, Refractory Angina.

Table 3.1.2 CURE Interim Analysis Results as of 6.19.00[a].

	Placebo	Clopidogrel	Hazard Ratio (95% C.I.)	p-Value
Randomized	5338	5328		
Primary Endpoint[b]	458 (8.6%)	369 (6.9%)	0.80 (0.69-0.91)	0.0012
Secondary Endpoint[c]	779 (14.6%)	700 (13.1%)	0.89 (0.80-0.98)	0.0225

a. Data from DSMB minutes dated 6.29.00.
b. CV death, New MI, Stroke.
c. CV death, New MI, Stroke, Refiactory Angina.

After these latter results were available, the DSMB (minutes dated 6.29.00) 'noted that the efficacy analysis for premature termination in the protocol was met.' As the stopping rule in place also required that a second analysis, 3 months apart from the first, confirm the p-Value, the trial was continued. The DSMB minutes note that 'by the time a second analysis is conducted in 3 months time, all of the projected 12,500 patients are likely to be enrolled.'

3.2 Primary Efficacy Analyses of CURE

The primary analysis was the time-to-first occurrence of any component of the two primary endpoints:

Cardiovascular death, Myocardial Infarction or Stroke.
Cardiovascular death, Myocardial Infarction, Stroke or Refractory Ischemia.

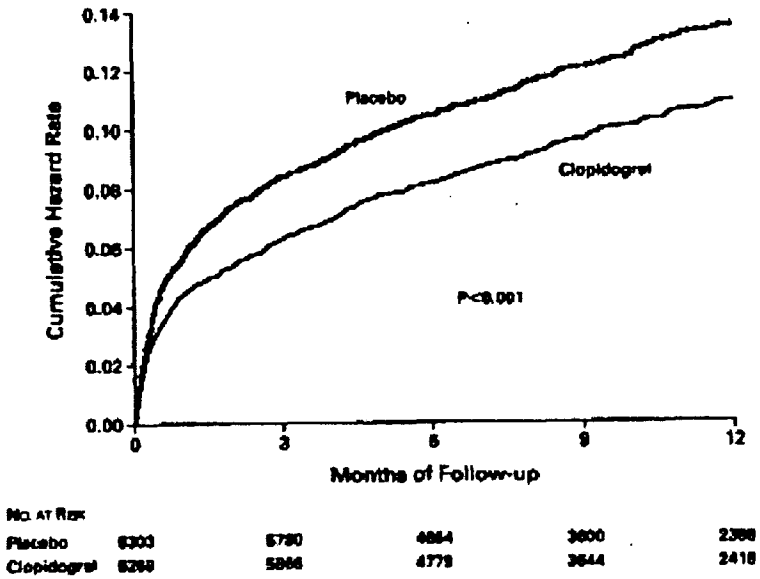
The rate of occurrence of the primary endpoint was to be assessed on all randomized patients, using log-rank statistics. The first table summarizes the incidence of the co-primary endpoints per the sponsor, counting only the first occurrence of any one of the composite clinical events. Favorable trends on all of the components of the primary endpoint were also evident, especially MI.

Table 3.2.1 Incidence of the Primary and Secondary Endpoints in CURE[a].

Endpoint[b]	Clopidogrel N=6259	Placebo N=6303	Relative Risk (95% CI)	p-Value
CV Death, MI, Stroke	582 (9.3%)	719 (11.4%)	0.80 (0.72-0.90)	<0.001 [c]
CV Death, MI, Stroke, Refractory Ischemia	1035 (16.5%)	1187 (18.8%)	0.86 (0.79-0.94)	<0.001 [c]
CV Death	318 (5.1%)	345 (5.5%)	0.93 (0.79-1.08)	
MI	234 (5.2%)	419 (6.7%)	0.77 (0.67-0.89)	
Q-Wave MI	116 (1.9%)	193 (3.1%)	0.60 (0.48-0.76)	
NQWMI	216 (3.5%)	242 (3.8%)	0.89 (0.74-1.07)	
Stroke	75 (1.2%)	87 (1.4%)	0.86 (0.63-1.18)	
Refractory Ischemia	544 (8.7%)	587 (9.3%)	0.93 (0.87-1.13)	

a. From NEJM article 345:494-502 (2001). Shown as means±sd.
b. See Trial Design section for definitions. Events are as designated by central adjudication committee.
c. p-Values per the sponsor from CURE study report 0.00009 and 0.00052 respectively.

The cumulative hazard ratio for the occurrence of the first primary endpoint (Death, MI, Stroke) is shown below. After an early separation the curve appear more or less parallel through the period of follow-up.



The next two tables, from Dr. Hung's statistical review, summarize his analyses of the primary endpoints and their individual components in CURE. The first table is based on events as adjudicated centrally (the pre-specified primary analysis. The statistical reviewer and the sponsor agree on the incidence and significance of the findings observed in CURE for both primary endpoints. Of interest, 89% of the deaths in the trial were adjudicated as cardiovascular deaths.

Table 3.2.2 Incidence of Adjudicated Clinical Events in CURE[a].

	Clopidogrel (N=6259)	Placebo (N=6303)	Hazard Ratio (95% CI)	p-Value[b]
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 Hospitalization	85 (1.4%)	126 (2.0%)	0.68 (0.52, 0.90)	--
After Hospitalization	459 (7.6%)	461 (7.6%)	0.99 (0.87, 1.13)	--
Other Endpoints				
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%)	ND	--

a. From statistical review by James Hung, Ph.D.
b. Nominal p-Value from log rank test.

3.3 Investigator-Designated Endpoints from CURE

The second table from Dr. Hung's statistical review summarizes the endpoints when the investigator-adjudicated endpoints are considered.

Table 3.3.1 Incidence of Investigator-Reported Clinical Events in CURE[a].

	Clopidogrel (N=6259)	Placebo (N=6303)	Hazard Ratio (95% CI)	p-Value[b]
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 Hospitalization	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)	
Other Endpoints				
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%)		

a. From statistical review by James Hung, Ph.D.
b. Nominal p-Value from log rank test.

3.4 Additional Efficacy Analyses from CURE

3.4a Other Pre-Specified Endpoint Analyses from CURE

The original secondary endpoint of CV death, MI, Stroke and Refractory Ischemia was ultimately made a co-primary. Other pre-specified endpoints, besides the components of the primary endpoints, were severe ischemia during initial hospitalization and mechanical or pharmacological coronary revascularization (PCI, CABG or thrombolytic therapy). There was a lower rate of reported severe ischemia during hospitalization (as opposed to 'refractory ischemia,') in the clopidogrel group. The risk of having mechanical or pharmacological coronary revascularization was not different between the two treatment groups.

Table 3.4a.1 Incidence of Additional Pre-specified Events (Adjudicated) in CURE[a].

	Clopidogrel (N=6259)	Placebo (N=6303)	Hazard Ratio (95% CI)	p-Value[a]
Severe Ischemia During Initial Hospitalization	176 (2.8%)	237 (3.8%)	0.74 (0.61, 0.90)	0.003
Mechanical or Pharmacological Coronary Intervention: PCI, CABG or Thrombolytics	2271 (36.3%)	2349 (37.3%)	0.96 (0.90, 1.01)	0.12

a. p-Values per FDA statistical review.

The table below summarizes the need for the individual components of mechanical or pharmacological coronary revascularization, along with the use of GPIIb/IIIa inhibitors following the initial hospitalization in CURE. Recall that the use of GPIIb/IIIa inhibitors during the 3 days prior to enrollment was an exclusion criteria in CURE. The use of surgical cardiac procedures (PCI, CABG) occurred with equal frequencies in the two treatment groups, although patients treated with clopidogrel were less likely to received thrombolytics or GPIIb/IIIa inhibitors.

Table 3.4a.2 Other Cardiovascular Procedures in CURE[a].

Endpoint	Clopidogrel	Placebo	Risk Reduction (95% C.I.)	p-Value
Any PCI	1313 (21.0%)	1345 (21.3%)	0.96	
PCI with Stent	1096 (17.5%)	1110 (17.6%)	0.99	
PCI without Stent	276 (4.4%)	311 (4.9%)	0.90	
CABG	1011 (16.2%)	1061 (16.8%)	0.96	
Thrombolytic Tx	71 (1.1%)	126 (2.0%)	43.3 (24.3, 57.5)	0.0001
IV GPIIb/IIIa Antagonist tx	369 (5.9%)	454 (7.2%)	18.2 (6.5, 28.3)	0.003

a. From CURE study report, Appendices 16.2.6.3.1 and 16.2.6.3.3. Information on 17 patients is missing from this analysis: 10 in clopidogrel, 7 in placebo.
b. Percutaneous Coronary Intervention (PCI) or coronary artery bypass grafting (CABG).

When the rates of percutaneous coronary intervention (PCI) or CABG during the initial hospitalization were examined, there was a numerical trend towards fewer procedures in the clopidogrel group. Following hospital discharge, the numerical trend instead favored the placebo group.

Table 3.4a.3 Other Cardiovascular Procedures During Initial Hospitalization in CURE[a].

Endpoint	Clopidogrel	Placebo
PCI/CABG Surgery	1302 (20.8%)	1430 (22.7%)
Any PCI	821 (13.1%)	909 (14.4%)
PCI With Stent	688 (11.0%)	748 (11.9%)
PCI Without Stent	133 (2.1%)	161 (2.6%)
CABG Surgery	487 (7.8%)	532 (8.4%)

a. From CURE study report, Appendices 16.2.6.3.1 and 16.2.6.3.3. Information on 3 patients is missing from this analysis.

Table 3.4a.4 Other Cardiovascular Procedures Following Initial Hospitalization in CURE[a].

Endpoint	Clopidogrel	Placebo
PCI/CABG Surgery	1076 (17.2%)	1053 (16.7%)
Any PCI	581 (9.3%)	556 (8.8%)
PCI with Stent	458 (7.3%)	429 (6.8%)
PCI without Stent	147 (2.4%)	155 (2.5%)
CABG Surgery	525 (8.4%)	532 (8.4%)

a. From CURE study report, Appendices 16.2.6.3.1 and 16.2.6.3.3. Information on 14 patients is missing from this analysis.

3.4b Additional Efficacy Analyses: Congestive Heart Failure

The investigators in CURE collected information on the occurrence of radiologic evidence of CHF during the initial hospitalization, as a check-box in the Case Report Form. These events were not further adjudicated. Fewer patients in the clopidogrel group were reported to have this finding, as summarized below, although hospitalizations for CHF were not different in the two treatment groups during follow-up. The meaning of this finding is obscure.

Table 3.4b.1 Congestive Heart Failure in CURE[a].

	Clopidogrel (N=6259)	Placebo (N=6303)	Hazard Ratio (95% CI), p-Value
Radiological Evidence of CHF[c]	229 (3.66)	280 (4.44)	17.6 (2.3, 30.6) 0.026
Hospitalizations for CHF[b]	155 (2.5%)	158 (2.5%)	--

a. Data from table (11.1.2) 5 in CURE study report.
b. Defined as lasting longer than 24 hours.
c. Check-box on CRF.

3.4c Subgroup Analyses of Efficacy

The consistency of the outcome was assessed by examining the incidence of the first primary endpoint in a variety of sub-groups, summarized below.

Subgroup Analyses by Demographics at Randomization

The FDA statistician analyzed the incidence of the endpoint of CV Death/ MI/ Stroke for selected demographic sub-populations, and the results are summarized below. Too few subjects from racial sub-groups were enrolled to allow any assessment of efficacy. Otherwise, the use of clopidogrel was associated with a favorable point estimate for the other relevant demographic populations, including those grouped according to gender and age (>65 years).

Table 3.4c.1 Incidence of CV death, MI and Stroke by Subgroup[a,b].

	Clopidogrel (N=6259)	Placebo (N=6303)	Hazard Ratio (95% CI)
Gender			
Male	351 (9.1%)	461 (11.9%)	0.77 (0.68, 0.88)
Female (n=4836)	231 (9.5%)	258 (10.7%)	0.89 (0.76, 1.06)
Race			
Caucasian (n=10308)	470 (9.1%)	568 (11.0%)	0.83 (0.74, 0.93)
Black n=69[c]	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)
Age			
< 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)
MI			
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)
Smoking Status			
Current (N = 2893)	89 (6.1%)	135 (9.4%)	0.63 (0.48,0.83)
Former (N = 4738)	240 (10.3%)	316 (13.1)	0.77 (0.65,0.91)
Never (N = 4928)	252 (10.2%)	268 (10.9%)	0.93 (0.79,1.11)

a. Analysis by James Hung, Ph.D., from his statistical review, based on adjudicated events. Smoking status from CURE study report, table (11.2.1) 1.

b. Demographics based on history/presence of the disease/procedure/concomitant meds at the time of randomization. Not all cells have information available from all patients.

c. 37 of these patients were from the U.S.

d. Refers to concomitant use of heparins. Some patients (n=2097) received both and are in both rows.

Table 3.4c.2 Incidence of CV death, MI and Stroke by Concomitant Drug Use[a,b].

	Clopidogrel (N=6259)	Placebo (N=6303)	Hazard Ratio (95% CI)
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)
'Statins'			
No, N=4461	10.9%	13.1%	0.83 (NA)
Yes, N=8101	8.4%	10.5%	0.80 (NA)
Heparins			
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)

a. Analysis by James Hung, Ph.D., from his statistical review, based on adjudicated events. Smoking status from CURE study report, table (11.2.1) 1

b. Demographics based on history/presence of the disease/procedure/concomitant meds at the time of randomization. Not all cells have information available from all patients.

c. 37 of these patients were from the U.S.

d. Refers to concomitant use of heparins. Some patients (n=2097) got both and are included in both rows.

The sponsor also analyzed the incidence of the first primary endpoint in several additional demographic subgroups of interest. In particular, the effect of receipt of heparinoids and IV GPIIb/IIIa inhibitors during the trial were analyzed. Recall that patients who had received GPIIb/IIIa inhibitors in the previous 3 days were not eligible for entry into the trial, although they were allowed to receive them as concurrent therapy for later procedures (Protocol Amendment 1.1). Clopidogrel use was associated with a reduction in the incidence of CV Death, MI and Stroke in these populations.

Table 3.4c.3 Incidence of CV death, MI and Stroke Therapies During CURE[a].

Demographic	Clopidogrel	Placebo	Hazard Ratio (95% C.I.)
IV GPIIb/IIIa Inhibitor During Trial			
No N=11739	524 (8.9%)	632 (10.8%)	0.80 (0.72, 1.09)
Yes N=823	58 (15.7%)	87 (19.2%)	0.80 (0.58, 1.13)
Heparins During Trial			
No N=950	23 (4.9%)	37 (7.8%)	0.62 (0.37, 1.05)
Yes N=11612	559 (9.7%)	682 (11.7%)	0.81 (0.73, 0.91)
Unfractionated Heparin[d] N=6536	343 (10.6%)	424 (12.9%)	0.81 (0.71, 0.94)
LMWH[d] N=7040	323 (9.2%)	411 (11.6%)	0.76 (0.67, 0.89)
CABG or PCI During Trial			
No N=7977	324 (8.1%)	397 (10.0%)	0.80 (0.69, 0.92)
Yes N=4584	258 (11.4%)	322 (13.8%)	0.82 (0.69, 0.96)
CABG During Trial			
No N=10481	434 (8.3%)	547 (10.4%)	0.78 (0.69, 0.89)
Yes N=2081	148 (14.6%)	172 (16.1%)	0.90 (0.72, 1.12)

a. From sponsor's submission dated 1.28.02.

Subgroup Analyses by Diagnosis at Time of Randomization

The sponsor conducted a series of sub-group analyses based on disease subgroup as well. The hazard ratio consistently favored clopidogrel across a broad range of demographics.

Table 3.4c.4 Incidence of CV Death, MI and Stroke by Subgroup in CURE[a].

	Clopidogrel (N=6259)	Placebo (N=6303)	Hazard Ratio (95% CI), p-Value[a]
Troponin Elevated at Randomization			
No (N = 9381)	413 (8.8%)	512 (10.9%)	0.80 (0.70,0.91) 0.928
Yes (N = 3176)	169 (10.7%)	207 (13.0%)	0.81 (0.66,0.99)
ST depression ≥1 mm at Randomization			
No (N = 7273)	271 (7.5%)	327 (8.9%)	0.83 (0.71,0.98) 0.549
Yes (N = 5288)	311 (11.8%)	392 (14.8%)	0.78 (0.67,0.90)
Diagnosis at Discharge			
Non Q-wave MI (N = 3295)	207 (12.7%)	258 (15.5%)	0.80 (0.67,0.97) 0.795
Unstable angina (N = 8298)	305 (7.3%)	362 (8.7%)	0.83 (0.71,0.97)
Other Diagnoses (N=968)	70 (15.1%)	99 (19.7%)	0.75 (0.55,1.02)
Diabetes			
No (N = 9721)	382 (7.9%)	480 (9.9%)	0.79 (0.69,0.90) 0.560
Yes (N = 2840)	200 (14.2%)	239 (16.7%)	0.84 (0.70,1.02)
Peripheral Arterial Disease			
No (N = 11515)	488 (8.5%)	620 (10.7%)	0.78 (0.70,0.88) 0.273
Yes (N = 1046)	94 (17.7%)	99 (19.2%)	0.93 (0.70,1.23)
Previous MI			
No (N = 8517)	329 (7.8%)	409 (9.5%)	0.81 (0.70,0.93) 0.904
Yes (N = 4044)	253 (12.5%)	310 (15.4%)	0.79 (0.67,0.94)
Previous Stroke			
No (N = 12055)	533 (8.9%)	667 (11.0%)	0.80 (0.71,0.90) 0.761
Yes (N = 506)	49 (17.9%)	52 (22.4%)	0.74 (0.50,1.10)

a. Data from CURE study report. p-Values are per the sponsor, and test each demographic for a significant interaction.

Efficacy Analyses in Geographic Subgroups

The FDA statistician, James Hung, Ph.D., analyzed the incidence of the primary endpoints grouped according to the country where the center was located. He concluded that '(t)here was no clear outlier that might suggest potential heterogeneity in the clopidogrel effect across the countries. The reader is referred to his analysis for details. The hazard ratios for the two primary endpoints were similar between US and non-US regions.

Table 3.4c.5 Incidence of Adjudicated Primary Events (US vs. Others)[a].

	Clopidogrel	Placebo	Hazard Ratio (95% CI)	p-Value[b]
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

a. From FDA statistical review. Nominal p-Value from log rank test.

The next table extends this analysis, summarizing the occurrence of the primary endpoints in the North American and U.S. populations. Too few events were reported in the Black population (39) in the United States to allow comparison of the treatment groups.

Table 3.4c.6 Primary Endpoints in North American Populations[a].

Endpoint	Placebo	Clopidogrel	Hazard Ratio, (95% CI)
CV Death, MI, Stroke			
North America n=2223	157 (13.9%)	113 (10.3%)	0.72 (0.57, 0.92)
U.S. n=462	36 (15.1%)	27 (12.1%)	0.79 (0.48, 1.29)
CV Death, MI, Stroke Refractory Ischemia			
North America n=2223	231 (20.5%)	184 (16.8%)	0.80 (0.66, 0.97)
U.S. n=462	48 (20.5%)	37 (20.1%)	0.80 (0.52, 1.23)

a. Data from NDA submission SE1-019.
b. 37 of these patients were from the U.S.

Efficacy Analyses by Entry Criteria

On 8.16.99 the CURE trial was amended to discontinue the enrollment of patients >60 years old without ECG changes (see Study Design section above), after enrollment of 3211 patients. The results prior to and after the amendments are summarized below. The reason for the substantially higher hazard ratio (that is, less robust efficacy) in the patients with ECG findings before the amendment (0.96) compared with the population after the amendment (0.78) is not apparent. Note also that the inclusion of 'Refractory Ischemia' in the endpoint had the effect of increasing the hazard ratio (comparing clopidogrel with placebo).

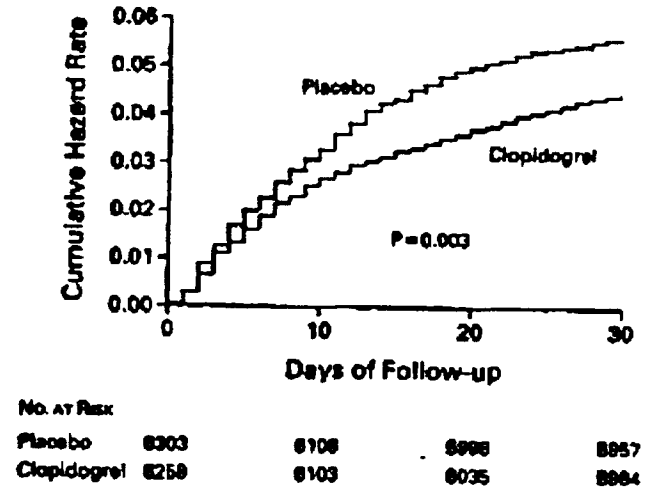
Table 3.4c.7 Primary Endpoints by Enrollment Criteria in CURE[a].

Endpoint	ECG Changes?	Clopidogrel	Placebo	Hazard Ratio, (95% CI)
MI, Stroke, Vascular Death				
Pre-Amendment	Yes (n=2595)	157 (12.1%)	163 (12.6%)	0.96 (0.77, 1.19)
	No[b] (n=616)	24 (7.5%)	30 (10.1%)	0.74 (0.43, 1.26)
Post-Amendment	Yes (n=8654)	381 (8.9%)	490 (11.2%)	0.78 (0.68, 0.89)
	No[c] (n=696)	20 (5.6%)	36 (10.5%)	0.52 (0.30, 0.89)
MI, Stroke, Vascular Death, Refractory Ischemia				
Pre-Amendment	Yes (n=2595)	272 (21.0%)	288 (22.2%)	0.93 (0.79, 1.10)
	No[b] (n=616)	41 (12.9%)	41 (13.8%)	0.92 (0.80, 1.08)
Post-Amendment	Yes (n=8654)	692 (16.1%)	813 (18.6%)	0.85 (0.77, 0.94)
	No[c] (n=696)	30 (8.5%)	45 (13.2%)	0.62 (0.39, 0.99)

a. Data from NDA submission SE1-019, 12.5.2001 response to Reviewer questions.
b. These patients had to be 60 with other history of cardiovascular disease.
c. These patients had to have elevations in cardiac enzymes if no ECG changes were present.

3.4d Temporal Trends in Efficacy of Clopidogrel

The trend towards fewer events in the clopidogrel group was evident early after starting treatment, as seen in the sponsor's time-to-event analysis for the first 14 days after randomization, shown below.



For CV Death/ MI/ Stroke, the benefit was similar within the first 30 days, and from 30 days to 1 year. For the endpoint of CV Death/ MI/ Stroke/ Refractory Ischemia, the benefit seen beyond 30 days was slightly less in the population remaining on study drug than that observed within the first 30 days.

Table 3.4d.1 Primary Endpoints in CURE from 0-30 Days and After 30 Days[a].

Endpoint	≤30 Days			>30 Days		
	Clopidogrel	Placebo	Hazard Ratio (95% CI)	Clopidogrel	Placebo	Hazard Ratio (95% CI)
MI/Stroke/CV death	272 (4.4%)	349 (5.5%)	0.78 (0.67, 0.91)	310 (5.0%)	370 (5.8%)	0.83 (0.71, 0.96)
MI (fatal or not)	158 (2.5%)	228 (3.6%)		165 (2.6%)	186 (2.95)	
Stroke (fatal or not)	26 (0.4%)	36 (0.57%)		38 (0.6%)	47 (0.8%)	
Other CV death	88 (1.4%)	85 (1.4%)		107 (1.7%)	137 (2.2%)	
MI/Stroke/CV death/ Refractory ischemia	487 (7.8%)	594 (9.4%)	0.82 (0.73, 0.93)	548 (8.8%)	593 (9.4%)	0.91 (0.81, 1.02)
MI (fatal or not) [b]	152 (2.4%)	208 (3.3%)		135 (2.2%)	155 (2.5%)	
Stroke (fatal or not) [b]	24 (0.4%)	35 (0.6%)		32 (0.5%)	37 (0.6%)	
Other CV death [b]	81 (1.3%)	82 (1.3%)		88 (1.4%)	110 (1.8%)	
Refractory ischemia	230 (3.7%)	269 (4.3%)		293 (4.7%)	291 (4.6%)	

a. Date from CURE study report, table (11.1.2) 1.

b. These are smaller than the corresponding rows for the first primary endpoint, as some patients experience more than one endpoint, with refractory ischemia being the first one temporally.

If all events occurring in the first 24 hours, 30 days and 365 days of therapy is examined, an early trend in favor of clopidogrel is seen, with a nominally significant difference seen through 365 days in the two treatment groups. The estimated benefit at 365 days is similar to that after 30 days in the population still on study drug,.

Table 3.4d.2 Incidence of Primary Endpoints Over Time in CURE[a].

	Clopidogrel (N=6259)	Placebo (N=6303)	Relative risk (95% CI)	p-Value[a]
CV death, MI, Stroke				
24 hours	38 (0.6%)	53 (0.8%)	0.78 (0.67, 0.92)	0.002
30 days	272 (4.3%)	349 (5.5%)	0.82 (0.73, 0.90)	0.001
365 days	582 (9.3%)	719 (11.4%)	0.72 (0.48, 1.09)	0.12
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

a. From the FDA Statistical Review by James Hung. Nominal p-Value from Chi-square test.

3.4e Additional Efficacy Analyses: Effect of Clopidogrel Use in Patients Undergoing PCI with Stent Placement

In CURE, if a patient required PCI with stent placement, their study drug was interrupted and they could be administered open-label clopidogrel at the discretion of the investigator. A total of 2658 of the 12562 patients randomized in CURE underwent PCI (1313 clopidogrel, 1345 placebo). The majority of these were done during the initial hospitalization (1730/2658, 65%). Consistent with the high use of stents in medical practice today, of the 2658 who underwent PCI 2,172 received a stent (82%). Characteristics of the two treatment groups subsets who underwent PCI are summarized below.

Table 3.4e.1 Demographics of the Sub-Set of CURE Patients Receiving PCI[a].

Demographics	Clopidogrel N=1313	Placebo N=1345
Age (mean ±SD)	61.6±11	61.4±11
Women (n/ % of total)	399 (30.3%)	405 (30.1%)
Diabetes	249 (19.0%)	255 (19.0%)
Previous MI	359 (27.3%)	349 (26.0%)
Previous PCI	176 (13.4%)	185 (13.8%)
Previous CABG	157 (12.0%)	175 (13.0%)
ST-Segment Depression on Admission	567 (43.2%)	571 (42.4%)
ST-Segment Elevation	65 (5.1%)	59 (4.4%)
Received Stents	1080 (82.4%)	1092 (81.3%)
Median Time after Randomization to PCI		
All PCI (day, range)	10 (5-30)	10 (5-25)
PCI during initial hospitalization	6 (3-10)	6 (4-10)
PCI after initial hospitalization	49 (23-89)	49 (24-106)
Open-label Thienopyridine Use		
Before PCI	344 (36.4%)	329 (24.7%)
Overall	1089 (82.9%)	1131 (84.1%)

a. From submission dated 12.10.01.

In the population who received PCI, the use of clopidogrel was associated with a reduced incidence of cardiovascular events that did not achieve nominal statistical significance although the point-estimates were similar to the overall trial results, as summarized below. In data not shown, the use of clopidogrel in patients who received a CABG during the trial was also associated with a reduced incidence of cardiovascular events.

Table 3.4e.2 Cardiovascular Events Before and After PCI in a Subset from CURE[a].

Endpoint	Clopidogrel N=1313	Placebo N=1345	Relative Risk (95% C.I.)
Events Before PCI			
CV Death/ MI/ Stroke	NA	NA[c]	NA
CV Death	NA	NA	NA
MI	47 (3.6%)	68 (5.1%)	0.68 (0.47-0.99)
MI or Refractory Ischemia[b]	159 (12.1%)	206 (15.3%)	0.76 (0.62-0.93)
Events To Day 30 After PCI			
CV Death/ MI/ Stroke	43 (3.3%)	62 (4.6%)	0.71 (0.48-1.05)
CV Death/ MI/ Stroke/Ref. Isch.	70 (5.3%)	84 (6.2%)	0.85 (0.62-1.17)
CV Death/ MI	38 (2.9%)	59 (4.4%)	0.66 (0.44-0.99)
CV Death	14 (1.1%)	13 (1.0%)	1.10 (0.52-2.35)
MI	28 (2.1%)	51 (5.4%)	0.56 (0.35-0.89)
MI or Refractory Ischemia[b]	57 (4.3%)	73 (5.4%)	0.80 (0.56-1.13)
Events From PCI to End of F/U			
CV Death/ MI/ Stroke	91 (6.9%)	117 (8.7%)	0.79 (0.60-1.05)
CV Death/ MI/ Stroke/Ref. Isch.	168 (12.8%)	199 (14.8%)	0.86 (0.70-1.06)
CV Death/ MI	79 (6.0%)	108 (8.0%)	0.75 (0.56-1.00)
CV Death	32 (2.4%)	31 (2.3%)	1.07 (0.65-1.75)
MI	59 (4.5%)	85 (6.4%)	0.71 (0.51-0.99)
MI or Refractory Ischemia[b]	141 (10.7%)	171 (12.7%)	0.84 (0.67-1.05)

a. From sponsor's submission dated 12.20.01.
b. Centrally-adjudicated endpoints as defined in Trial Design section above.
c. Not calculated as CV death was not definable prior to PCI.

The sponsor conducted a similar analysis focusing only one those patients who had their PCI during their initial hospitalization. No separate demographics are available for this sub-set of the patients who had PCI. Here again, a non-significant trend favoring clopidogrel is seen.

Table 3.4e.3 Cardiovascular Events Before and After PCI During Initial Hospitalization in CURE[a].

Endpoint	Clopidogrel N=821	Placebo N=909	Relative Risk (95% C.I.)
Events Before PCI			
CV Death/ MI/ Stroke	NA	NA[c]	NA
CV Death/ MI/ Stroke/ Refractory Ischemia	NA	NA	NA
CV Death/ MI	NA	NA	NA
CV Death	NA	NA	NA
MI	14 (1.7%)	35 (3.9%)	0.45 (0.24, 0.83)
MI or Refractory Ischemia[b]	52 (6.3%)	95 (10.5%)	0.61 (0.43, 0.85)
Events To Day 30 After PCI			
CV Death/ MI/ Stroke	34 (4.1%)	45 (5.0%)	0.84 (0.54, 1.30)
CV Death/ MI/ Stroke/ Refractory Ischemia	53 (6.5%)	62 (6.8%)	0.95 (0.66, 1.36)
CV Death/ MI	31 (3.8%)	43 (4.7%)	0.80 (0.50, 1.26)
CV Death	12 (1.5%)	12 (1.3%)	1.11 (0.50, 2.47)
MI	23 (2.8%)	36 (4.0%)	0.71 (0.42, 1.19)
MI or Refractory Ischemia[b]	42 (5.1%)	53 (5.8%)	0.88 (0.58, 1.31)
Events From PCI to End of F/U			
CV Death/ MI/ Stroke	63 (7.7%)	85 (9.4%)	0.82 (0.59, 1.14)
CV Death/ MI/ Stroke/ Refractory Ischemia	120 (14.6%)	144 (15.8%)	0.92 (0.72, 1.18)
CV Death/ MI	55 (6.7%)	77 (8.5%)	0.79 (0.56, 1.12)
CV Death	19 (2.3%)	26 (2.9%)	0.81 (0.45, 1.47)
MI	43 (5.2%)	59 (6.5%)	0.80 (0.54, 1.19)
MI or Refractory Ischemia[b]	102 (12.4%)	121 (13.3%)	0.93 (0.72, 1.21)

a. From sponsor's submission dated 1.14.02.
b. Centrally-adjudicated endpoints as defined in Trial Design section above.
c. Not calculated as CV death was not definable prior to PCI.

A similar analysis was conducted in patients <u>not</u> undergoing PCI during the period of follow-up in CURE. Their demographics and outcomes are summarized below.

Table 3.4e.4 Demographics of the Sub-Set of CURE Patients Not Receiving PCI[a].

	Clopidogrel N=4946	Placebo N=4958
Demographics		
Age (mean ±SD)	65±11	65±11
Women (n/ % of total)	2021 (41%)	2241 (45%)
Diabetes	1156 (23%)	1180 (24%)
Previous MI	1670 (34%)	1666 (34%)
Previous PCI	432 (9 %)	442 (9%)
Previous CABG	516 (10%)	532 (11%)
Current or Former Smoker	2882 (58%)	2892 (58%)
ST-Segment Depression on Admission	2129 (43%)	2123 (43%)
Diagnosis at Entry		
Unstable Angina	3763 (76%)	3757 (76%)
Suspected MI	1183 (22%)	1201 (24%)
Median Time From Pain Onset to Randomization (hours)	14±7	14±7

a. From sponsor's submission dated 12.20.01.

The use of clopidogrel was associated with a lower incidence of the primary endpoint that achieved nominal statistical significance in the population that did not receive PCI in CURE. Of interest, the magnitude of the risk reduction in the population not undergoing PCI (below) is similar to the magnitude of the reduction in the group that did undergo PCI.

Table 3.4e.5 Cardiovascular Events in Population Not Undergoing PCI in CURE[a].

Endpoint	Clopidogrel N=4946	Placebo N=4958	Relative Risk (95% C.I.)
Events To Day 30 After Entry			
CV Death/ MI/ Stroke	211 (4.3%)	255 (5.1%)	0.82 (0.69-0.91)
CV Death/ MI/ Stroke/ Refractory Ischemia	335 (6.8%)	389 (7.8%)	0.86 (0.74-0.94)
CV Death/ MI	191 (3.9%)	226 (4.6%)	0.84 (0.69, 1.02)
CV Death	117 (2.4%)	117 (2.4%)	1.02 (0.78, 1.30)
All-Cause Death	123 (2.5%)	119 (2.4%)	1.04 (0.67, 1.20)
MI	106 (2.1%)	142 (2.9%)	0.75 (0.58, 0.96)
Stroke	27 (0.5%)	34 (0.7%)	0.79 (0.48, 1.32)
Events To End of Follow-Up			
CV Death/ MI/ Stroke	456 (9.2%)	542 (10.9%)	0.83 (0.74, 0.94)
CV Death/ MI/ Stroke/ Refractory Ischemia	744 (15.0%)	1822 (16.6%)	0.90 (0.81, 0.99)
CV Death/ MI	423 (8.6%)	491 (9.9%)	0.86 (0.75, 0.97)
CV Death	286 (5.%)	314 (6.3%)	0.91 (0.77, 1.06)
All Cause Death	318 (4.5%)	354 (7.1%)	0.89 (0.77, 1.04)
MI	224 (4.5%)	270 (5.4%)	0.82 (0.69, 0.98)
Stroke	62 (1.3%)	73 (1.5%)	0.84 (0.60, 1.19)

a. From sponsor at reviewer's request.
b. Centrally-adjudicated endpoints as defined in Trial Design section above.

Data on the subset of patients who underwent CABG while on study drug is pending at the time of the submission of this review.

4.0 to 4.9 Safety Outcomes for CURE

The sources for the safety information below are the SAS datasets submitted by the sponsor as well as the study report submitted to the Agency.

4.1 Exposure Data from CURE

The exposure to study drug in CURE is summarized in the two tables below, first in terms of mean and median exposure and then in terms of the # of patients exposed to study drug for various categories of time.

Table 4.1.1 Duration of Exposure to Study Drug in CURE[a].

	Clopidogrel N=6259	Placebo N=6303	Total N=12562
Mean (Months ±SD)	9.4±3.4	9.35±3.5	9.4±3.4
Median (Months)	10.8	10.8	10.8

a. Data from CURE study report, table (10.1) 3.

Table 4.1.2 Duration of Exposure to Study Drug in CURE[a].

	≥3 Months	3-6 Months	6-9 Months	9-12 Months	≥12 Months
Placebo	780 (12.4%)	1153 (18.3%)	1104 (17.5%)	1083 (17.2%)	2183 (34.6%)
Clopidogrel	747 (11.9%)	747 (11.9%)	1155 (18.5%)	1048 (16.7%)	2132 (34.1%)

a. Data from CURE study report, table (12.1) 1.

4.2 Defined Safety Endpoints

The definitions used to adjudicate the bleeding adverse events reported to the DSMB are in the 'Safety and Efficacy Endpoints Measured' section above, along with the timing of the safety endpoint collection. The Adverse Events were spontaneously reported and then collected by the sponsor. Bleeding adverse events are discussed separately in section 4.3a.

4.2a Deaths

The table below summarizes all deaths reported during the CURE study period or after the end of the study (after 365 days or the study end date of 12.6.2000).

Table 4.2a.1 Deaths Reported in CURE[a].

	Clopidogrel N=6259	Placebo N=6303
Deaths During Study Period	359 (5.7%)	390 (6.2%)
CV Death During Study Period	311 (5.0%)	345 (5.5%)
Death on Treatment	314 (5.0%)	363 (5.8%)
Death Not on Treatment	45 (0.7%)	27 (0.4%)
Deaths Outside the Study Period	5 (0.08%)	5 (0.08%)
Total Deaths	364 (5.8%)	395 (6.3%)

a. Data from CURE study report.

4.2b SAEs

The next two tables summarize the SAEs reported by the investigators during the trial. Bleeding SAEs were the most commonly reported SAEs, occurring more frequently in the clopidogrel group.

Table 4.2b.1 Serious Adverse Events (SAEs) Reported at ≥1.0% Incidence in CURE[a].

	Clopidogrel N=6259	Placebo N=6303
All SAEs	881 (14.1%)	802 (12.7%)
Platelet, Bleeding and Clotting Disorders	275 (4.4%)	201 (3.2%)
Hemorrhage of Operative Wound	81 (1.3%)	69 (1.1%)
Gastrointestinal Hemorrhage	65 (1.0%)	32 (0.5%)
Respiratory System Disorders	163 (2.6%)	127 (2.0%)
Body as a Whole - General Disorders	93 (1.5%)	100 (1.6%)
Gastrointestinal System Disorders	81 (1.3%)	103 (1.6%)
Urinary System Disorders	64 (1.0%)	48 (0.8%)
Cardiovascular Disorders, General	59 (0.9%)	62 (1.0%)

a. Data from CURE study report.

Table 4.2b.2 Serious Adverse Events (SAEs) Reported at <1.0% Incidence in CURE[a].

	Clopidogrel N=6259	Placebo N=6303
CV Resistance Mechanism Disorders	48 (0.8%)	33 (0.5%)
Central and Peripheral Nervous System Disorders	41 (0.7%)	35 (0.6%)
Red Blood Cell Disorders	32 (0.5%)	39 (0.6%)
Neoplasms	31 (0.5%)	48 (0.8%)
Heart rate and Rhythm Disorders	26 (0.4%)	32 (0.5%)
Liver and Biliary System Disorders	26 (0.4%)	22 (0.4%)
Metabolic and Nutritional Disorders	26 (0.4%)	43 (0.7%)
Musculo-skeletal System Disorders	23 (0.4%)	19 (0.3%)
Myo-, Endo-, Pericardial and Valve Disorders	19 (0.3%)	18 (0.3%)
Psychiatric Disorders	19 (0.3%)	11 (0.2%)
Vascular (extracardiac) Disorders	17 (0.3%)	18 (0.3%)
Skin and Appendage Disorders	10 (0.2%)	7 (0.1%)
Application Site Disorders	9 (0.1%)	7 (0.1%)
Autonomic Nervous System disorders	8 (0.1%)	15 (0.2%)
White cell and RES Disorders	7 (0.1%)	8 (0.1%)
Reproductive Disorders, male	6 (0.1%)	9 (0.1%)
Vision disorders	6 (0.1%)	6 (0.1%)
Reproductive Disorders, Female	5 (0.1%)	4 (0.1%)
Endocrine Disorders	3 (0.05%)	2 (0.03%)
Collagen Disorders	0 (0.00%)	1 (0.02%)

a. Data from CURE study report.
b. RES = Reticuloendothelial system.

4.2c Adverse Events

Next the adverse events (AEs) will be summarized. Adverse events related to platelets, bleeding and clotting disorders were more frequent in the clopidogrel group. In particular, there were higher rates of bruising and gastrointestinal hemorrhage. In the 'body as a whole' organ class, there was an apparent increase in fatigue in the clopidogrel group.

Table 4.2c.1 Adverse Events Reported in CURE[a].

	Clopidogrel N=6259	Placebo N=6303
Any Class	2612 (41.7%)	2530 (40.1%)
Body as a Whole - General Disorders	524 (8.4%)	522 (8.8%)
Chest Pain	166 (2.6%)	176 (2.8%)
Fatigue	93 (1.5%)	64 (1.0%)
Pain	80 (1.3%)	90 (1.4%)
Fever	76 (1.2%)	66 (1.0%)
Influenza-Like Symptoms	68 (1.1%)	72 (1.1%)
Gastrointestinal System Disorders	735 (11.7%)	786 (12.5%)
Abdominal pain	145 (2.3%)	178 (2.8%)
Diarrhea	128 (2.0%)	140 (2.2%)
Dyspepsia	126 (2.0%)	118 (1.9%)
Nausea	121 (1.9%)	145 (2.3%)
Constipation	98 (1.6%)	119 (1.9%)
Vomiting	72 (1.2%)	77 (1.2%)
Respiratory System Disorders	557 (8.9%)	574 (9.1%)
Dyspnea	121 (1.9%)	117 (1.9%)
Pneumonia	100 (1.6%)	108 (1.7%)
Coughing	84 (1.3%)	77 (1.2%)
Bronchitis	71 (1.1%)	92 (1.5%)
Upper Respiratory Tract Infection	70 (1.1%)	60 (1.0%)
Nervous System Disorders	486 (7.8%)	493 (7.8%)
Headache	192 (3.1%)	201 (3.2%)
Dizziness	150 (2.4%)	127 (2.01%)
Platelet, Bleeding and Clotting Disorders	479 (7.6%)	324 (5.1%)
Bruise	123 (2.0%)	38 (0.6%)
Hemorrhage of Operative wound	81 (1.3%)	70 (1.1%)
Gastrointestinal Hemorrhage	65 (1.0%)	32 (0.5%)
Cardiovascular Disorders, General	254 (4.1%)	281 (4.5%)
Hypotension	62 (1.0%)	66 (1.0%)
Skin and Appendage Disorders	250 (4.0%)	221 (3.5%)
Rash	83 (1.3%)	66 (1.0%)
Musculo-Skeletal System Disorders	213 (3.4%)	213 (3.4%)
Back pain	64 (1.0%)	78 (1.2%)
Urinary System Disorders	213 (3.4%)	212 (3.4%)
Urinary Tract Infection	92 (1.5%)	91 (1.4%)
Psychiatric Disorders	196 (3.1%)	171 (2.7%)
Resistance Mechanism Disorders	182 (2.9%)	144 (2.3%)
Infection	84 (1.3%)	73 (1.2%)
Metabolic and Nutritional Disorders	170 (2.7%)	211 (3.4%)

a. Data from NDA supplement, Supportive Table 15.3.1.4.

Table 4.2c.1 Adverse Events Reported in CURE (cont)[a].

	Clopidogrel N=6259	Placebo N=6303
AEs: Secondary Terms Related to Organ Systems	164 (2.6%)	143 (2.3%)
Inflicted injury	68 (1.1%)	73 (1.2%)
Red Blood Cell Disorders	83 (1.3%)	109 (1.7%)
Anemia	73 (1.2%)	99 (1.6%)
Vascular (Extracardiac) Disorders	71 (1.1%)	65 (1.0%)
Liver and Biliary System Disorders	60 (1.0%)	50 (0.8%)
Vision Disorders	59 (0.9%)	60 (1.0%)
Heart Rate and Rhythm Disorders	58 (0.9%)	60 (1.0%)
Neoplasms	55 (0.9%)	60 (1.0%)
Autonomic Nervous System Disorders	45 (0.7%)	66 (1.0%)
Myo-, Endo-, Pericardial and valve AEs	38 (0.6%)	44 (0.7%)
Application Site Disorders	36 (0.6%)	35 (0.6%)
Endocrine Disorders	29 (0.5%)	27 (0.4%)
Reproductive Disorders, Male	28 (0.4%)	38 (0.6%)
White Cell and RES Disorders	19 (0.3%)	22 (0.4%)
Hearing and vestibular Disorders	17 (0.3%)	15 (0.2%)
Reproductive Disorders, female	13 (0.2%)	12 (0.2%)
Collagen Disorders	4 (0.1%)	1 (<0.1%)
Special Senses other, Disorders	3 (0.1%)	5 (0.1%)
Poison Specific Terms	2 (<0.1%)	1 (<0.1%)

a. Data from NDA supplement, Supportive Table 15.3.1.4.

4.2d Adverse Events Leading to Discontinuation

More individuals discontinued clopidogrel than placebo, related almost entirely to the increased number of bleeding adverse events.

Table 4.2d.1 Discontinuations in CURE[a].

	Clopidogrel N=6259	Placebo N=6303
Patients who permanently D/C'd study drug due to AEs	366 (5.8%)	247 (3.9%)
Hemorrhagic AEs	141 (2.3%)	68 (1.1%)
Non-Hemorrhagic AEs	168 (2.7%)	129 (2.0%)
Unspecified	57 (0.9%)	50 (0.8%)

a. Data from CURE study report and tables 15.3.1.4 and 15.3.2.4.

4.2e Laboratory AEs, Including ECGs

After the baseline laboratories, no pre-set collection of additional labs or ECGs after admission was dictated by the protocol, and no additional analyses of the spontaneous lab collections or ECGs has been performed by this reviewer. Analyses related to specific lab parameters that resulted in AEs are discussed below.

4.3 Comments on Specific Safety Parameters

Several specific safety concerns merit individual discussion: bleeding, hematological abnormalities not related to bleeding, renal toxicity, abnormal hepatic function and allergic reactions.

4.3a Bleeding Adverse Events

The incidence of bleeding events, measured variously, was higher in patients receiving clopidogrel, as summarized in the two tables below. The incidence of life-threatening bleeding (*e.g.*, retroperitoneal, intracranial) hemorrhage was low in both treatment groups with no clear excess in the clopidogrel group.

Table 4.3a.1 Patients with Bleeding Events in CURE[a].

	Clopidogrel (N=6259)	Placebo (N=6303)	Relative risk (95% CI)	p-Value
Life-Threatening or Major Bleeding (Adjud.)	231 (3.7%)	169 (2.7%)	1.38 (1.14, 1.68)	0.001
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
Bleeding Characteristics				
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 Txf[b] of ≥ 2 Units of Blood	178 (2.8%)	142 (2.3%)	1.26 (1.02, 1.57)	0.026
Necessitating Txf 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%)		
Symptomatic Intracranial Hemorrhage	7 (0.11%)	5 (0.08%)		
Hematuria	4 (0.1%)	5 (0.1%)		
Puncture Site	36 (0.6%)	22 (0.3%)		
Surgical Site	56 (0.9%)	53 (0.8%)		
Ulcer bleeding	24 (0.38%)	19 (0.30%)		

a. From SAS sets MAJBLD.SD2 and MINBLD.SD2. FDA statistical analysis, and from supplemental table 1)4. Nominal p- Value from unadjusted chi-square test.

b. Transfusion = txf.

c. Definitions used:

Life-threatening: Defined as fatal or leading to:

A drop in hemoglobin ≥5 g/dL.

Significant hypotension with need for inotropes.

Requiring surgery (other than vascular site repair).

Symptomatic intracranial hemorrhage.

Requiring txf of 4 or more units of red blood cells or equivalent whole blood.

Major: Significantly disabling, intraocular bleeding leading to significant loss of vision or bleeding requiring transfusion of 2 or 3 units of red blood cells or equivalent whole blood.

Minor: Any other bleeding requiring permanent or temporary discontinuation of the study drug.

Table 4.3a.2 Sponsor's Summary of Bleeding in CURE[a].

	Clopidogrel N=6259	Placebo N=6303	p-Value
Life-Threatening Bleeding[b]	135 (2.2%)	112 (1.8%)	0.125
Fatal Bleeding	11 (0.2%)	15 (0.2%)	
Non-Fatal Bleeding	125 (2.0%)	99 (1.6%)	
Major Bleeding	100 (1.6%)	65 (1.0%)	0.0053
Minor Bleeding	322 (5.1%)	153 (2.4%)	< 0.0001
Other Bleeding	727 (11.6%)	421 (6.7%)	
Characteristics of Bleeding			
Symptomatic Intracranial Hemorrhage	7 (0.11%)	5 (0.08%)	
Significant Hypotension Needing Inotropes	34 (0.54%)	34 (0.54%)	
Drop in Hemoglobin of at Least 5 g/dL	58 (0.93%)	57 (0.90%)	
Requiring 2-3 Units of Blood	80 (1.28%)	54 (0.86%)	
Requiring at least 4 Units of Blood	74 (1.18%)	60 (0.95%)	
Significantly Disabling	26 (0.42%)	16 (0.25%)	
Intraocular Bleeding with Significant Loss of Vision	3 (0.05%)	2 (0.03%)	

a. From Appendix 16.2.7.13 of CURE Supplement.

b. Definitions as in the table above.

The incidence of major bleeding and life-threatening bleeding occurring before and after 30 days for patients still on study drug are shown in the table below. In both periods there was excess life-threatening and major bleeding in the clopidogrel group.

Table 4.3a.3 Timing of Reported Bleeding Events in CURE[a].

	Clopidogrel N=6259	Placebo N=6303
Prior to 30 Days on Drug		
Life-Threatening Bleeding	81 (1.3%)	62 (1.0%)
Major Bleeding	48 (0.8%)	39 (0.6%)
After 30 Days		
Life-Threatening Bleeding	54 (0.9%)	50 (0.8%)
Major Bleeding	52 (0.8%)	26 (0.4%)

a. Data from CURE study report, table (12.2.1)2.

The sponsor also looked at the association of bleeding with procedures commonly received by patients with coronary artery disease as well as for a series of relevant patient demographics. For demographics, including age >65, gender, race, presence of diabetes or abnormal renal function at baseline (>150 µmol/l) there was no significant interaction with clopidogrel. There was also no evidence of a synergistic interaction between clopidogrel and other anti-platelet agents: NSAIDs, LMWHs or UFH, ASA, GPIIb/IIIa inhibitors, or oral anticoagulants (data not shown, see CURE submission supplemental table (1.)3. As seen below, the bleeding rates increased in patients undergoing these procedures for patients in both the clopidogrel and placebo groups, but the increase was proportional for both groups (that is, there was no interaction with clopidogrel and procedures to increase bleeding risk at a rate that was more than additive).

Table 4.3a.4 Use of Clopidogrel in Association With Procedures and Life-Threatening/Major Bleeding[a].

Procedure	Clopidogrel	Placebo	p-Value[c]
Any invasive cardiac surgical procedure[b]			
No (N = 5526)	57 (2.0%)	37 (1.4%)	0.688
Yes (N = 7036)	174 (5.0%)	132 (3.7%)	
PTCA/CABG surgery			
No (N = 7977)	97 (2.4%)	56 (1.4%)	0.112
Yes (N = 4585)	134 (5.9%)	113 (4.8%)	
PTCA			
No (N = 9901)	185 (3.7%)	128 (2.6%)	0.329
Yes (N = 2661)	46 (3.5%)	41 (3.0%)	
CABG surgery			
No (N = 10481)	134 (2.6%)	89 (1.7%)	0.475
Yes (N = 2081)	97 (9.6%)	80 (7.5%)	
Thrombolytic therapy			
No (N = 12365)	225 (3.6%)	154 (2.5%)	0.138
Yes (N = 197)	6 (8.4%)	15 (11.9%)	

a. Data from CURE study report, table (12.2.1)8.

b. Includes angiography, PTCA, CABG surgery, intra-aortic balloon pump and other vascular procedures.

c. For interaction with clopidogrel use.

4.3b Non-Bleeding Hematalogic Adverse Events

Non-hematologic AEs were infrequent in the CURE trial.

Table 4.3b.1 Hematologic AEs in CURE[a].

	Clopidogrel N=6259	Placebo N=6303
Thrombocytopenia	19 (0.3%)	24 (0.4%)
Thrombocytopenia as SAE	3 (<0.1%)	11 (0.2%)
Platelet Decreased	6 (0.1%)	7 (0.1%)
Thrombocythemia	0 (0.0%)	1 (<0.1%)

a. From CURE study report.

There were no reported case of Thrombotic Thrombocytopenic Purpura (TTP), Agranulocytosis, or Aplastic Anemia in CURE. In my review of the 14 cases of thrombocytopenia classified as severe by the investigators I found no clinical suggestion of TTP in any of the cases.

Table 4.3b.2 WBC Abnormalities in CURE[a].

	Clopidogrel N=6259	Placebo N=6303
Leukopenia	5 (0.1%)	3 (0.1%)
Neutropenia	3 (0.1%)	3 (0.1%)
Leukocytosis	2 (<0.1%)	3 (<0.1%)

a. Data from CURE study report, Appendices 16.2.7.7 and 16.2.7.8.

4.3c Renal Adverse Events

During the trial a concern was raised about a series of observed cases of renal failure in the blinded database (that is, no treatment attribution was known). The first table summarizes the reported adverse events related to renal function. There is no apparent association between clopidogrel and any of these metrics of renal function.

Table 4.3c.1 Renal AEs in CURE[a].

	Clopidogrel N=6259	Placebo N=6303
Any Abnormal Renal Fxn	33 (0.5%)	28 (0.4%)
BUN Increased	1 (<0.1%)	0 (0.00%)
NPN Increased	1 (<0.1%)	0 (0.00%)
Renal Failure Acute	13 (0.2%)	10 (0.2%)
Renal Function Abnormal	18 (0.3%)	19 (0.3%)
Uremia	1 (<0.1%)	0 (0.00%)

a. From sponsor's submission dated 12.20.01.

The next table summarizes the need for dialytic intervention and the occurrence of 'uremia' as an adverse event description term. A review of the CRFs revealed no cases of glomerulonephritis and glomerulonephritis was not included in any of the AE descriptions for "renal failure acute", "renal function abnormal", and "uraemia" per the sponsor. The individuals with acute renal failure on clopidogrel had underlying chronic renal insufficiency that worsened while on clopidogrel (4/5) or acute renal failure following a complicated CABG procedure (1/5).

Table 4.3c.2 Need for Dialysis and Uremia in CURE[a].

	Clopidogrel N=6259	Placebo N=6303
Uremia, with or without Dialysis	2 (0.03%)	7 (0.11%)
Acute Renal Failure with Dialysis	5 (0.08%)	4 (0.06%)

a. From sponsor's submission dated 12.20.01.

4.3d Abnormal Hepatic Function

The table below summarizes the occurrence of hepatic adverse events in CURE, including severe adverse events. Review of CRFs for the three individuals who developed severe hepatic impairment revealed that one of them had a bile-duct stricture thought to be related to a malignancy, one had an elevated ALT at admission (108 IU/L) related to prostate cancer with hepatic metastases, and one had elevated liver enzymes on therapy that improved after changing his 'statin'. No association of clopidogrel use with hepatic adverse events is apparent.

Table 4.3d.1 Abnormal Hepatic Function Reported in CURE[a].

	Clopidogrel N=6259		Placebo N=6303	
	All	Severe	All	Severe
Any Abnormal Hepatic Function	22 (0.4%)	3 (0.1%)	27 (0.4%)	1 (<0.1%)

a. Data from CURE study report and Appendix 16.2.7.10.

b. 'any abnormal hepatic function' included: bilirubinemia, GGT (gamma-glutamyl transferase) increased, hepatic function abnormal, hepatitis, hepatitis cholestatic, hepatocellular damage, jaundice, phosphatase alkaline increased, hepatic failure, and hepatic enzymes increased.

4.3e Allergic Reactions

Rashes as AEs were more common in the clopidogrel group in CURE. No cases of Stevens-Johnson Syndrome were reported. Allergic reactions were reported infrequently and at a similar frequency in the two groups.

Table 4.3e.1 Allergic Reactions Reported in CURE[a].

	Clopidogrel N=6259		Placebo N=6303	
	All	Severe	All	Severe
Any Rash[b]	143 (2.3%)	7 (0.1%)	102 (1.6%)	4 (0.1%)
Any Allergic Reaction[b]	24 (0.4%)	1 (<0.1%)	19 (0.3%)	2 (<0.1%)

a. Data from CURE study report and Appendix 16.2.7.10.

b. 'Any rash' included: rash, rash erythematous, rash maculo-papular, rash pustular, rash follicular, skin reaction localized, and urticaria. 'Any allergic reaction' included: allergic reaction, anaphylactoid reaction, anaphylactic shock, and allergy

5.0 Comparison of Clopidogrel and GPIIb/IIIa inhibitors in ACS

Comparison of the efficacy and safety of clopidogrel with the other therapies established for use in ACS (IV GPIIb/IIIa inhibitors) is complicated. The first issue of some interest is how the efficacy of chronic therapy with clopidogrel in CURE compares with the chronic outcomes from the earlier trials of IV IIb/IIIa inhibitors. For the ACS population, this comparison is necessarily limited to the PURSUIT (eptifibatide) and PRISM-PLUS (tirofiban) studies, as Reopro was not distinguished from placebo in the single study in ACS. The second issue of interest is how the bleeding rates for the short-term IV therapies compare with the bleeding rates during long-term therapy with clopidogrel. Recall that the risk of bleeding with clopidogrel does not appear to decrease with time (Table 4.3a.3 above).

5.1. Comparison of Clopidogrel Efficacy in CURE with IV GPIIb/IIIa Inhibitors in ACS

The first table below serves to highlight the observation that while events continued to occur during the trial follow-up, the Hazard Ratio remained fairly stable. It also serves to facilitate comparison of the incidence of outcomes with other trials (below).

Table 5.1.1 (from Table 3.4d.2) Incidence of Primary Endpoints Over Time in CURE[a].

	Clopidogrel (N=6259)	Placebo (N=6303)	Hazard Ratio (95% CI)	p-Value[b]
CV Death, MI, Stroke				
24 hours	38 (0.6%)	53 (0.8%)	0.78 (0.67, 0.92)	0.002
30 days	272 (4.3%)	349 (5.5%)	0.82 (0.73, 0.90)	0.001
365 days	582 (9.3%)	719 (11.4%)	0.72 (0.48, 1.09)	0.12

a. From the FDA Statistical Review by James Hung, Ph.D.

b. Reviewer's analysis: nominal p-value from Chi-square test.

The primary effect of clopidogrel in CURE was seen in the effect on reducing the occurrence of MIs, as summarized in the table below. As summarized below, this is also the pattern for the two IV GPIIb/IIIa inhibitors also studied in ACS. In contrast, no effect of these therapies on the need for later coronary interventions (PCI, CABG) is evident.

Table 5.1.2 (from Table 3.2.2) Incidence of Adjudicated Clinical Events in CURE[a].

	Clopidogrel (N=6259)	Placebo (N=6303)	Hazard Ratio (95% CI)	p-Value[b]
Primary Endpoint				
CV death, MI, Stroke	582 (9.3%)	719 (11.4%)	0.80 (0.72, 0.90)	< 0.0001
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
Other Endpoints				
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%)	ND	--
Mechanical Interventions[c]	2253 (36.0%)	2324 (36.9%)	0.96 (0.91, 1.02)	0.166

a. From statistical review by James Hung, Ph.D.

b. Nominal p-value from log rank test.

c. Percutaneous Coronary Intervention (PCI) or coronary artery bypass grafting (CABG).

Tirofiban Efficacy in ACS

The PRISM-PLUS trial randomized patients with ACS to receive either tirofiban or placebo on a background of heparin and ASA. The efficacy endpoint used in CURE is not available in the database from PRISM-PLUS, although the incidence of total mortality and non-fatal MI is, and is summarized below at 30 and 180 days following randomization. In PRISM-PLUS, while there was a robust effect on the incidence of non-fatal MI, no effect of tirofiban on the use of procedures following randomization was evident.

Table 5.1.3 Selected Outcomes from PRISM-PLUS[a].

	Tirofiban +Heparin N=773	Heparin N=797	Hazard Ratio, p-Value
Death/MI at 30 Days	67 (8.7%)	95 (11.9%)	0.73, p=0.060
Non-Fatal MI at 7 Days[c]	22 (2.9%)	49 (6.2%)	0.46, p<0.05
CABG, PCI, Atherectomy at 30 days[b]	444 (57.4%)	442 (55.5%)	1.03, p=0.44

a. Data from FDA review of NDA 20-912 (tirofiban), table 6.2.1.12.2d.1, 6.2.1.12.3.2 and 6.2.1.12.3.10.

b. The incidence of atherectomy in this trial was 5 (0.6%) and 8 (1.0%) in the two groups respectively and so contributes little to this endpoint.

c. Data from the per-protocol analysis population.

Eptifibatide Efficacy in ACS

The PURSUIT trial randomized patients with ACS to either eptifibatide or placebo on a background of heparin and ASA. The incidences of the primary endpoint (death/ MI) and non-fatal MI at 30 and 180 days are shown below. No information about the receipt of further cardiac procedures is available. Here again the effect of the GPIIb/IIIa inhibitor was most striking on the incidence of MI, especially through 180 days.

Table 5.1.4 Selected Outcomes from PURSUIT[a].

	Eptifibatide N=4722	Placebo N=4739	Hazard Ratio, p-Value
Death/MI at 30 Days	672 (14.2%)	745 (15.7%)	0.90, p=0.042
Death/MI at 180 Days	636 (13.6%)	567 (12.2%)	0.90, 0.028
Non-Fatal MI at 30 Days	507 (10.7%)	568 (12.0%)	0.89, p=NA
MI at 180 Days[b]	64 (8.3%)	84 (10.5%)	0.80, p=0.100

a. Data from PURSUIT FDA review by J. Hammond, M.D., dated 2.17.98 and PURSUIT FDA review by D.C. Throckmorton, M.D. dated 3.1.99.

b. Includes fatal and non-fatal MIs.

5.2 Comparison of Bleeding in CURE with IV IIb/IIIa Inhibitors in ACS

The primary safety concern for these compounds is the increased risk of bleeding associated with their use. The TIMI major bleeding criterion can be used to compare between studies, as the definitions used in CURE to describe bleeding don't correspond to the usual descriptions of bleeding. The rates for TIMI major and minor bleeding, as well as intracranial hemorrhage and retroperitoneal hemorrhage, are shown below. For comparison, the reported rates for PRISM-PLUS and PURSUIT are also summarized. Excluding the CABG population in PURSUIT (eptifibatide) the rates of TIMI Major bleeding are similar across all of the anti-platelet trials summarized. Life-threatening bleeding (retroperitoneal, intracranial) is rare in all three datasets, with slight numerical excess seen for the drug-treated groups in clopidogrel and eptifibatide.

Table 5.2.1 Bleeding in CURE[a].

	Clopidogrel N=6259	Placebo N=6303	p-Value
TIMI Major Bleeding[b]	68 (1.1%)	72 (1.1%)	0.76
TIMI Minor Bleeding[c]	172 (2.8%)	126 (2.0%)	0.006
TIMI Major Bleeding in Subset Undergoing PCI	11 (0.8%)	17 (1.3%)	0.28
TIMI Minor Bleeding in Subset Undergoing PCI	33 (2.5%)	24 (1.8%)	0.20
Intracranial Hemorrhage	7 (0.11%)	5 (0.08%)	0.56
Retroperitoneal Hemorrhage	8 (0.13%)	5 (0.08%)	0.40

a. From sponsor's submission dated 1.28.02.

b. Hemoglobin drop >5 g/dl, intracranial bleed or cardiac tamponade.

c. Hemoglobin drop >3 g/dl, spontaneous gross hematuria, hemetemesis, hemoptysis.

The incidence of TIMI Major bleeding was lower in the PRISM-PLUS trial with tirofiban, when compared with PURSUIT with eptifibatide (tables below). One part of the discrepancy is the high rate of bleeding in the patients in PURSUIT who underwent CABG. This can be seen in the analysis below that excludes those patients in PURUSIT. The reasons for this discrepancy are not evidently related to trial design or population. The use of heparin was mandated in PRISM-PLUS (tirofiban) but was optional in PURSUIT (eptifibatide). Additionally, all patients in PRISM-PLUS were expected to undergo angiography at 48 hours, where such interventions were optional in PURSUIT. These two factors would have been expected to increase the bleeding rate in the PRISM-PLUS trial; instead the opposite was reported. One aspect of this may be related to changes in the management of hemostasis, as seen in the final table below from the ESPRIT trial of eptifibatide following PCI and coronary stenting. In this most recent trial the rates of major bleeding are quite low, despite the invasive procedures all of the patients underwent.

Bleeding with Tirofiban in ACS

The rates of bleeding in the PRISM-PLUS trial are summarized in the table below.

Table 5.2.2 Bleeding in PRISM-PLUS (Tirofiban)[a].

	Tirofiban +Heparin N=773	Heparin N=797
TIMI Major Bleeding	11 (1.4%)	6 (0.8%)
TIMI Minor Bleeding	81 (10.5%)	64 (8.0%)
Intracranial Hemorrhage	0 (0%)	0 (0%)
Retroperitoneal Hemorrhage	0 (0%)	1 (0.1%)

a. Data from PRISM-PLUS FDA review by D. C. Throckmorton, M.D., dated 3.24.98.

Bleeding with Eptifibatide in ACS

The first table summarizes the bleeding reported in PURSUIT first in the total population and then in the population that did not undergo CABG. The rates for intracranial hemorrhage and retroperitoneal hemorrhage are from the whole population.

Table 5.2.3 Bleeding in PURSUIT (Eptifibatide)[a].

	Eptifibatide N=4679	Placebo N=4696
TIMI Major Bleeding	498 (10.8%)	425 (9.3%)
TIMI Minor Bleeding	604 (13.1%)	347 (7.6%)
TIMI Major Bleeding Excluding CABG	121 (3.1%)	50 (1.3%)
TIMI Minor Bleeding Excluding CABG	448 (11.5%)	190 (4.9%)
Intracranial Hemorrhage	5 (<0.1%)	3 (<0.1%)
Retroperitoneal Hemorrhage	3 (<0.1%)	3 (0.1%)

a. Data from PURSUIT FDA review by I. Hammond, M.D., dated 2.17.98.

Bleeding with Eptifibatide Following PCI with Stent Placement

The next table summarizes the bleeding rates for the ESPRIT trial, which compared eptifibatide and placebo in patients undergoing PCI with stent placement. This trial used a higher dose of eptifibatide (a second bolus) and a lower dose of heparin than in the earlier PURSUIT trial.

Table 5.2.4 Bleeding Adverse Events in ESPRIT (Eptifibatide)[a].

Bleeding Severity (TIMI Criteria)	Eptifibatide 180/2.0/180 N =1040	Placebo N = 1024
Major	13 (1.3%)	4 (0.4%)
Minor	29 (3.0%)	18 (2.0%)
Intracranial	2 (0.2%)	1 (0.1%)
Retroperitoneal	3 (0.3%)	0 (0%)

a. Data from ESPRIT study report, table 12-3.

6.0 Integrated Summary Of Efficacy

The CURE trial was designed to explore the clinical efficacy and safety of long-term use of thienopyridine anti-platelet drug in a patient population are relatively high risk for cardiovascular events (*i.e.*, following admission for ACS). Patients with either biochemical (CPK, troponin) or ECG evidence of cardiac ischemia who were otherwise eligible were randomized to blinded study drug (either clopidogrel or placebo), and then followed for clinical events for a minimum of 3 months. All patients received a background therapy of ASA if tolerated. Regarding the efficacy of clopidogrel in the CURE study:

1. Trial Design and Conduct

1a. The CURE trial was adequately designed to yield interpretable trial results. No trial design issues were identified that would systematically limit the interpretability of the study.

1b. Protocol violations were detected in approximately 7% of the enrollees. Most of the protocol violations (appr. 5%) were technical violations of the inclusion criteria, related to the enrollment, early in the trial, of patients >60 years of age without ECG or serum marker evidence of cardiac ischemia. No imbalance in the occurrence of protocol violations between the two study groups was evident. **(Table 2.3.1)**

1c. No substantive issues related to unblinding or of improper trial conduct related to the two interim analyses were identified. **(Section 3.1)**.

1d. Financial Disclosure information submitted by the sponsors is considered in a separate memorandum. While some individuals from sites enrolling a total of 806 patients (6.4% of total enrollment) failed to submit financial disclosure information, this is insufficient to alter the major findings of the CURE study.

2. Patient Exposure and Demographics

2a. A total of 12,562 patients were enrolled in CURED, and 12,085 received study drug and follow-up for three months. Overall the mean duration of exposure to study drug was 9.4 months in both treatment groups (**Tables 2.1.1 and 2.2.1**).

2b. Patients were enrolled at 482 centers in 28 countries. The largest fraction (82%) of the population came from Europe, with the U.S. population making up 3.7% of the enrollment (**Table 2.4.1, 2.4.2**). Most of the patients were Caucasian (82%), and male (61%), with a mean age at enrollment of 64. Only 37 African-Americans were enrolled in the trial, limiting any interpretation of efficacy and safety in this population (**Table 2.4.1**). The majority of patients (58%) had their qualifying episode of chest pain between 12 and 24 hours prior to enrollment (**Table 2.4.4**).

2c. The patients enrolled in the two treatment groups were well-balanced demographically according to gender, race, age, medical history, concomitant medications and clinical diagnosis at the time of admission (**Sections 2.4 and 2.5**). The largest fraction (75%) of the patients had a suspected diagnosis of unstable angina pectoris at the time of enrollment, with 25% with a suspected non-Q-wave MI (**Table 2.4.3**). The use of ASA (66%) and beta-blockers (59%) was common in the study, while ACE inhibitors (37%) and lipid-lowering agents (25%) were used less often (**Table 2.5.1**).

3. Primary Analyses of Efficacy

3a. The pre-specified primary efficacy analyses were the time-to-first occurrence of any component of the following two endpoints:

Cardiovascular death, Myocardial Infarction or Stroke.

Cardiovascular death, Myocardial Infarction, Stroke or Refractory Ischemia.

The rate of occurrence of the primary endpoints was to be assessed on all randomized patients, using log-rank statistics. The endpoints used were adjudicated centrally, based on the definitions in **Section 1.5** above. The use of clopidogrel was associated with a significantly lower incidence of both primary endpoints.

Table 6.1 (from Table 3.2.2) Incidence of Adjudicated Clinical Events in CURE[a].

	Clopidogrel (N=6259)	Placebo (N=6303)	Hazard Ratio (95% CI)	p-Value[b]
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

a. From statistical review by James Hung, Ph.D.

b. Nominal p-value from log rank test.

3b. Similar trends were observed when the events as designated by the investigators were used to calculate the incidence of the two endpoints (**Table 3.3.1**).

4. Additional Pre-Specified Efficacy Endpoints

4a. The only specified secondary endpoint from the original protocol was changed to a co-primary endpoint during the study. Additional endpoints of interest include the components of the primary endpoint.

Trends favoring clopidogrel for all of the components of the primary endpoint were evident, with nominal significant differences detected for both MI and Q-wave MI.

Table 6.2 (from Table 3.2.2) Incidence of Components of the Primary Endpoint in CURE[a].

	Clopidogrel (N=6259)	Placebo (N=6303)	Hazard Ratio (95% CI)	p-Value[b]
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

a. From statistical review by James Hung, Ph.D.
b. Nominal p-Value from log rank test.

4b. Additional pre-specified endpoints of interest also include the components of the primary endpoint and two additional pre-specified endpoints: severe ischemia during hospitalization and mechanical or pharmacological coronary revascularization (PCI, CABG or thrombolytic therapy. There was a lower rate of reported severe ischemia during hospitalization in the clopidogrel group. The risk of having mechanical or pharmacological coronary revascularization was not different between the two treatment groups.

Table 6.3 (from Table 3.4a.1) Incidence of Additional Pre-specified Events (Adjudicated) in CURE[a].

	Clopidogrel (N=6259)	Placebo (N=6303)	Hazard Ratio (95% CI)	p-Value[a]
Severe ischemia during hospitalization	176 (2.8%)	237 (3.8%)	0.74 (0.61, 0.90)	0.003
Mechanical or Pharmacological Coronary Intervention: PCI, CABG or Thrombolytics	2271 (36.3%)	2349 (37.3%)	0.96 (0.90, 1.01)	0.12

a. p-Values per FDA statistical review.

5. Additional Analyses of the Primary Endpoint in Demographic Subsets

5a. The incidences for the primary endpoints were analyzed for selected demographic sub-populations (**Section 3.4b**). Too few subjects from racial sub-groups other than Caucasians were enrolled to allow any assessment of efficacy in populations other than overall study population and Caucasians. Otherwise, the use of clopidogrel was associated with a favorable point estimate for the other relevant demographic populations, including those grouped according:

- gender.
- age (>65 years).
- concomitant medication use.
- medical and cardiac history, including prior receipt of cardiac procedures.

6. Durability of Clopidogrel Efficacy

6a. If the incidence of primary events occurring through the first 24 hours, 30 days and 365 days of therapy is examined, an early trend in favor of clopidogrel is seen, with a nominally significant difference seen through 365 days for the two treatment groups. There is no trend towards greater benefit at 365 days relative to 30 days in the population remaining on study drug (**Table 3.4c.2**).

7. Clopidogrel Use and Need for Cardiac Interventions

7a. During the period of follow-up, the use of other cardiac procedures (PCI, CABG) occurred with equal frequencies in the two treatment groups, although patients treated with clopidogrel were less likely to received thrombolytics or GPIIb/IIIa inhibitors (**Table 3.4d.1**).

8. Efficacy of Clopidogrel in the Sub-Set of Patients Undergoing PCI

8a. A total of 2,658 of the 12,562 patients randomized in CURE underwent PCI (1313 clopidogrel, 1345 placebo). The majority of these were done during the initial hospitalization (1730/2658, 65%). Consistent with the high use of stents in medical practice today, of the 2658 who underwent PCI 2,172 received a stent (82%). The demographics of the patients in this sub-set who received placebo and clopidogrel were similar (**Table 3.4e.1**). In this population, clopidogrel use was associated with a non-significant reduction in the incidence of the two primary endpoints of roughly the same magnitude as the size of the effect in the overall trial population (compare **Table 3.2.2** and **Tables 3.4e.2 and 3.4e.3**).

Table 6.4 (from Table 3.4e.2) Cardiovascular Events Before and After PCI in a Subset from CURE[a,b].

Endpoint From PCI to End of F/U	Placebo N=1345	Clopidogrel N=1313	Risk Reduction (95% C.I.)
CV Death/ MI/ Stroke	117 (8.7%)	91 (6.9%)	0.79 (0.60-1.05)
CV Death/ MI/ Stroke/ Refractory Ischemia	199 (14.8%)	168 (12.8%)	0.86 (0.70-1.06)

a. From sponsor's submission dated 12.20.01.
b. Centrally-adjudicated endpoints as defined in Trial Design section above.

9. Efficacy of Clopidogrel in the Sub-Set of Patients Not Undergoing PCI

9a. The use of clopidogrel was associated with a lower incidence of the primary endpoint that achieved nominal statistical significance in the population (n=9,904) that did not receive PCI in CURE.

Table 6.5 (from Table 3.4e.5) Cardiovascular Events in Population Not Undergoing PCI in CURE[a,b].

Events To End of Follow-Up	Clopidogrel N=4946	Placebo N=4958	Relative Risk (95% C.I.)
CV Death/ MI/ Stroke	456 (9.2%)	542 (10.9%)	0.83 (0.74, 0.94)
CV Death/ MI/ Stroke/ Refractory Ischemia	744 (15.0%)	1822 (16.6%)	0.90 (0.81, 0.99)

a. From sponsor at reviewer's request.
b. Centrally-adjudicated endpoints as defined in Trial Design section above.

10. Comparisons with other Anti-Platelet Agents

10a. The majority of clopidogrel's clinical effect was seen in the reduction of MIs during the period of follow-up (table 3.2.2), with no significant effect on the need for later interventions (PCI, CABG) (**Tables 5.1.2 and 5.1.3**). This pattern is similar to what has been seen for two GPIIb/IIIa inhibitors studied in patients with ACS: tirofiban (PRISM-PLUS, **Table 5.1.2**) and eptifibatide (PURSUIT, **Table 5.1.3**).

7.0 Integrated Summary of Safety

Regarding the safety of clopidogrel, derived from the data in the CURE study:

1. Dataset and Patient Exposures

1a. Datasets and patient exposure have been summarized in Integrated Review of Efficacy (**Tables 2.2.1, 2.2.2**).

2. Deaths in CURE

2a. There were 759 deaths reported in the CURE trial, including 749 that occurred while on study drug. There was a non-significant trend towards lower total mortality and cardiovascular mortality in the patients receiving clopidogrel. The large majority (89%) of the deaths during the study were adjudicated as cardiovascular deaths.

Table 7.1 (from Table 4.2a.1) Deaths Reported in CURE[a].

	Clopidogrel N=6259	Placebo N=6303
Deaths During Study Period	359 (5.7%)	390 (6.2%)
CV Deaths During Study Period	311 (5.0%)	345 (5.5%)

a. Data from CURE study report.

3. Serious Adverse Events in CURE

3a. There was a higher incidence of SAEs in the clopidogrel group, due to Bleeding SAEs which were more commonly reported in the clopidogrel group (**Section 4.2b**).

4. Adverse Events in CURE

4a. Adverse events related to platelets, bleeding and clotting disorders were more frequent in the clopidogrel group. In particular, there were higher rates of bruising and gastrointestinal hemorrhage. In the 'body as a whole' organ class, there was an apparent increase in fatigue reported in the clopidogrel group.

Table 7.2 (from Table 4.2c.1) Adverse Events Reported in CURE[a].

	Clopidogrel N=6259	Placebo N=6303
Any class	2612 (41.7%)	2530 (40.1%)
Body as a whole - General disorders	524 (8.4%)	522 (8.8%)
Fatigue	93 (1.5%)	64 (1.0%)
Platelet, bleeding and clotting disorders	479 (7.6%)	324 (5.1%)
Bruise	123 (2.0%)	38 (0.6%)
Hemorrhage of operative wound	81 (1.3%)	70 (1.1%)
Gastrointestinal hemorrhage	65 (1.0%)	32 (0.5%)

a. Data from NDA supplement, Supportive Table 15.3.1.4.

5. Adverse Events Associated with Discontinuations in CURE

5a. More individuals discontinued clopidogrel than placebo in CURE, related almost entirely to the increased number of bleeding adverse events.

Table 7.3 (from Table 4.2d.1) Discontinuations in CURE[a].

	Clopidogrel N=6259	Placebo N=6303
Patients who permanently D/C'd study drug due to AEs	366 (5.8%)	247 (3.9%)
Hemorrhagic AEs	141 (2.3%)	68 (1.1%)
Non-Hemorrhagic AEs	168 (2.7%)	129 (2.0%)

a. Data from CURE study report and tables 15.3.1.4 and 15.3.2.4.

6. Selected Adverse Events in CURE

Particular attention was paid to a group of adverse events for which concerns either existed related to other safety data or because of safety signals raised during the trial: bleeding, hematological abnormalities not related to bleeding, renal toxicity, abnormal hepatic function and allergic reactions. With the exceptions of bleeding and rashes (as a component of allergic reactions) no safety concern was seen in the CURE database **(Section 4.3)**.

6a. Bleeding adverse events, Life-threatening, Major and Minor as defined in the protocol, were reported more commonly in the clopidogrel group. While the majority of the bleeding was defined as minor, there were increases in the rates of reported major bleeding as well as bleeding requiring transfusion and bleeding defined as 'significantly disabling.' Intracranial hemorrhage was rare (7 events, 0.11% vs. 5 events, 0.08% in placebo).

Table 7.4 (from Table 4.3a.2) Bleeding in CURE[a].

	Clopidogrel N=6259	Placebo N=6303	p-Value
Life-Threatening Bleeding[b]	135 (2.2%)	112 (1.8%)	0.125
Fatal Bleeding	11 (0.2%)	15 (0.2%)	
Non-Fatal Bleeding	125 (2.0%)	99 (1.6%)	
Major Bleeding	100 (1.6%)	65 (1.0%)	0.0053
Minor Bleeding	322 (5.1%)	153 (2.4%)	< 0.0001
Other Bleeding	727 (11.6%)	421 (6.7%)	
Characteristics of Bleeding			
Symptomatic Intracranial Hemorrhage	7 (0.11%)	5 (0.08%)	
Requiring 2-3 Units of Blood	80 (1.28%)	54 (0.86%)	
Requiring at least 4 Units of Blood	74 (1.18%)	60 (0.95%)	
Significantly Disabling	26 (0.42%)	16 (0.25%)	

a. From Appendix 16.2.7.13 of CURE Supplement.

b. Definitions used:

Life-threatening: Defined as fatal or leading to:
- A drop in hemoglobin ≥5 g/dL.
- Significant hypotension with need for inotropes.
- Requiring surgery (other than vascular site repair).
- Symptomatic intracranial hemorrhage.
- Requiring txf of 4 or more units of red blood cells or equivalent whole blood.

Major: Significantly disabling, intraocular bleeding leading to significant loss of vision or bleeding requiring transfusion of 2 or 3 units of red blood cells or equivalent whole blood.

Minor: Any other bleeding requiring permanent or temporary discontinuation of the study drug.

6b. There is no evidence that the risk of bleeding decreases after chronic (>30 days) exposure to clopidogrel **(Table 4.3a.3)**.

6c. The sponsor examined the association of bleeding with procedures commonly received by patients with coronary artery disease as well as for a series of relevant patient demographics. For demographics, including age >65, gender, race, presence of diabetes or abnormal renal function at baseline (>150 µmol/l) there was no significant interaction with clopidogrel. There was also no evidence of a significant interaction between clopidogrel and other anti-platelet agents: NSAIDs, LMWHs or UFH, ASA, GPIIb/IIIa inhibitors, or oral anticoagulants. The bleeding rates increased in patients undergoing cardiac procedures for patients in both the clopidogrel and placebo groups (relative to those not undergoing the procedures), but the increase was proportional for both groups (that is, there was no interaction with clopidogrel and procedures to increase bleeding risk **(Table 4.3a.4)**.

7. Comparison of Safety in CURE with IV GPIIb/IIIa Inhibitors in ACS

7a. Comparison of the bleeding rates in trials of anti-platelet drugs with ACS is complicated by the changing management of hemostasis in these patients. Overall, while differences exist in the rates of TIMI Major bleeding among trials, there are no clear differences in the overall rates of clinically-significant bleeding between the acute use of IV GPIIb/IIIa inhibitors (PRISM-PLUS, PURSUIT) in ACS and the long-term use of clopidogrel in CURE **(Section 5.2)** that can be attributed to the individual drugs. In CURE, there was no excess incidence of TIMI Major or Minor bleeding in the clopidogrel arm compared with placebo **(Table 5.2.1)**.

7b. In the available trials in ACS, the rates of life-threatening bleeding (intracranial, retroperitoneal) were quite low in all treatment groups **(Table 5.2.1 to 5.2 4)**.

XII. Appendix Two: References

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XIII. APPENDIX THREE: Key Personnel

Data Safety and Monitoring Board

During Closed Sessions.

John Cairns
Rorbert Hart
Michael Gent
Thomas Ryan
Janet Wittes
Janice Pogue
Jack Hirsch
D. Georges Wyse (Chair)

During Open Sessions (additional to above)

C. Gaudin
J. Bouthier
M. Blumenthal
S. Yusuf

Steering Committee

Salim Yusuf, Chairman	Klas Maimberg	Susan Chrolavicius
Aldo Maggioni	Lars Ryden	Thomas Wittinger
Allen Kitching	Leopoldo Piegas	Tom Hess
Alvaro Avezum	Leszek Ceremuzynski	Vince Yacshyn
Andzej Budaj	M. Corrales	William Grossman
Athanase Pipilis	M. Natarajan	
Basil Lewis	Marc Sotty	
Bernie Garsh	Marcus Flather	
Cam Joyner	Maria Franzosi	
Christophe Gaudin	Matyas Keltai	
David Halon	Mel Blumenthal	
David Hunt	Michel Bertrand	
Ernesto Paolasso	Najam Awan	
Eva Sitkei	Nardev Kurmi	
Giannini Tognoni	Nicholas Karatzas	
Hans-Jurgen Rupprecht	Patrick Commerford	
Jacques Col	Petr Widimsky	
Janice Pogue	Rafael Diaz	
Jean Bouthier	Ron Peters	
Joao Morais	Shamir Mehta	
John Varigos	Sonia Anand	
Keith Fox	Steve Kopecky	

Event Adjudication Committee

Cam Joyner (chairman)	Klas Miamberg	Yun Chan
Akbar Panju	Leopoldo Piegas	
Aldo Maggioni	M. Corrales	
Alvaro Avezum	M. den Hartoog	
Andzej Budaj	Madhu Natarajan	
Athanase Piplis	Marcus Flather	
Basil Lewis	Marku Nieminen	
Catherine Demers	Matyas Keltai	
D.C.G. Basart	Michelle Galli	
David Halon	Nicholas Karatzas	
David Hunt	Petr Jansky	
Ernesto Paolasso	Patrick Commerford	
Eva Sitkei	Petr Widimsky	
Francesco Mauri	Pierre Auger	
Hans-Jurgen Rupprecht	Piotr Szymanski	
Hervert De Raedt	Rafael Diaz	
Jean-Francois Marquis	Ron J. G. Peters	
Joao Morais	Shamir Metha	
John Eikelboom	Thomas Wittlinger	
John Norris	Tiziano Moretti	
John Renkin	Vincent Valentin	
Juan Garcia-Guerrero	Wojciech Wasek	

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/s/

Doug Throckmorton
2/6/02 12:35:30 PM
MEDICAL OFFICER

Douglas C. Throckmorton, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
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Rockville, MD 20816
Tel (301) 594-5327, FAX (301) 594-5494

Memorandum

DATE: 1.30.02

FROM: Douglas C. Throckmorton. M.D., Deputy Division Director
Division of Cardio-Renal Drug Products, HFD-110

TO: Raymond Lipicky, M.D., Division Director
Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Plavix (clopidogrel) financial disclosure information for the CURE trial.

PURPOSE OF MEMO

This memorandum reflects the findings of my review of the submitted financial disclosure information for the investigators of the CURE trial. These materials, including FDA Form 3454, were submitted to the Agency on 8.21.01. The sponsors asserts that neither Sanofi-Synthelabo Inc. nor Bristol-Myers Squibb Company have entered into any financial arrangement with any clinical investigators as defined in 21 CFR 54, specifically:

- They have not entered into any financial agreement whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).
- Each listed clinical investigator required to disclose whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests.

  In this regard investigators from 28 sites (out of 428 sites that enrolled patients) did not submit the required financial information to the sponsor. Of these 63 individuals, only one [redacted] was a Principle Investigator. Sanofi-Synthelabo Inc. [redacted] do not believe any bias, intentional or unintentional, was introduced by these investigators.
- No investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

I find no evidence in the submitted information suggesting inappropriate or suspect financial arrangements between the sponsor (Sanofi-Synthelabo) and any of the investigators of the CURE trial. The sites with individuals who did not submit the required finacial information represent a small fraction of the individuals who contributed to the enrollment of patients in this trial.

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/s/

Doug Throckmorton
1/30/02 02:16:46 PM
MEDICAL OFFICER