CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-839 / S-034

Trade Name: Plavix

Generic Name: clopidogrel bisulfate

Sponsor: Sanofi-Aventis

Approval Date: August 17, 2006

Indications: For patients with ST-segment elevation acute myocardial infarction, Plavix has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, reinfarction or stroke. This benefit is not known to pertain to patients who receive primary angioplasty.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-839 / S-034

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-839/S-034

Sanofi-Aventis Inc.
Attention: Mr. Christopher Graham
300 Somerset Corporate Boulevard
P.O. Box 6977
Bridgewater, NJ 08807

Dear Mr. Graham:

Please refer to your supplemental new drug application dated November 17, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) 75 mg Tablets. Please note that this letter supersedes the previous letter issued August 17, 2006.

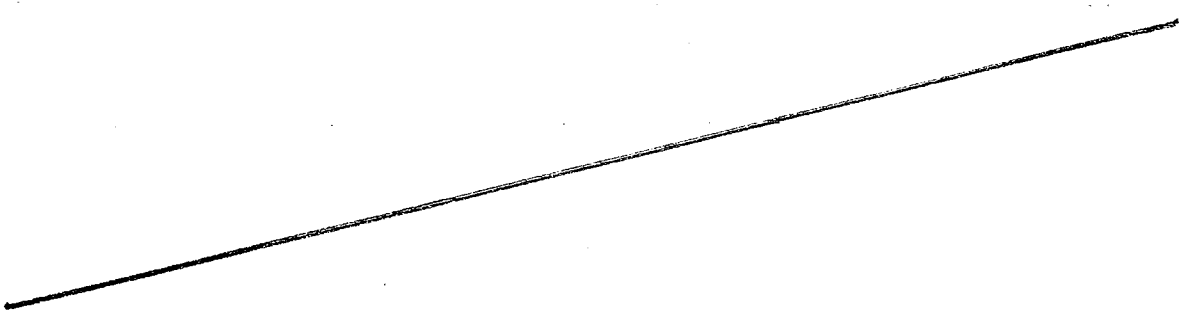
We acknowledge receipt of your electronic submissions dated December 13, 2005 and January 3, 10, March 22, April 25, May 16, July 5(3) and 14, and August 4 and 7, 2006.

This supplemental new drug application provides for the following new use of Plavix (clopidogrel bisulfate) 75 mg tablets:

> For patients with ST-segment elevation acute myocardial infarction, Plavix has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction or stroke. This benefit is not known to pertain to patients who receive primary angioplasty.

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the following agreed-upon labeling text:

In the **CLINICAL STUDIES** section, revise the order of the studies listed. The paragraph should be revised from:



b(4)

To read as follows:

"The clinical evidence for the efficacy of Plavix is derived from four double-blind trials involving 81,090 patients: the CAPRIE study (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events), a comparison of Plavix to aspirin, and the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events), the COMMIT/CCS-2 (Clopidogrel and Metoprolol in Myocardial Infarction Trial / Second Chinese Cardiac Study) studies comparing Plavix to placebo, both given in combination with aspirin and other standard therapy and CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy – Thrombolysis in Myocardial Infarction)."

All other labeling will remain the same.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert submitted electronically on August 16, 2006).

Please submit the FPL electronically according to the guidance for industry entitled, "Providing Regulatory Submissions in Electronic Format – NDA."

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. Please refer to our letter dated October 4, 2005 waiving the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Cardiovascular and Renal Products and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call:

Ms. Meg Pease-Fye, M.S.
Regulatory Project Manager
(301) 796-1130

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: approved agreed-upon labeling

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/s/

Norman Stockbridge
8/17/2006 08:03:11 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-839/S-034

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/s/

Norman Stockbridge
8/17/2006 08:02:11 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-839 / S-034

LABELING

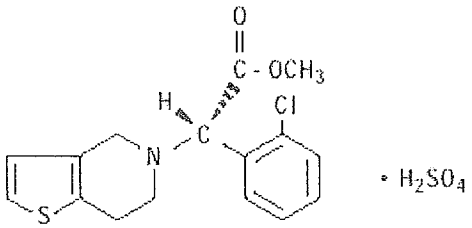
Rx only

PLAVIX®
clopidogrel bisulfate tablets

DESCRIPTION

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. Chemically it is methyl (+)-(*S*)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4*H*)-acetate sulfate (1:1). The empirical formula of clopidogrel bisulfate is $C_{16}H_{16}ClNO_2S \cdot H_2SO_4$ and its molecular weight is 419.9.

The structural formula is as follows:



Clopidogrel bisulfate is a white to off-white powder. It is practically insoluble in water at neutral pH but freely soluble at pH 1. It also dissolves freely in methanol, dissolves sparingly in methylene chloride, and is practically insoluble in ethyl ether. It has a specific optical rotation of about +56°.

Plavix for oral administration is provided as pink, round, biconvex, debossed film-coated tablets containing 97.875 mg of clopidogrel bisulfate which is the molar equivalent of 75 mg of clopidogrel base.

Each tablet contains hydrogenated castor oil, hydroxypropylcellulose, mannitol, microcrystalline cellulose and polyethylene glycol 6000 as inactive ingredients. The pink film coating contains ferric oxide, hypromellose 2910, lactose monohydrate, titanium dioxide and triacetin. The tablets are polished with Carnauba wax.

CLINICAL PHARMACOLOGY

Mechanism of Action

Clopidogrel is an inhibitor of platelet aggregation. A variety of drugs that inhibit platelet function have been shown to decrease morbid events in people with established cardiovascular atherosclerotic disease as evidenced by stroke or transient ischemic attacks, myocardial infarction, unstable angina or the need for vascular bypass or angioplasty. This indicates that platelets participate in the initiation and/or evolution of these events and that inhibiting them can reduce the event rate.

Pharmacodynamic Properties

Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. 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. Clopidogrel also inhibits platelet aggregation induced by agonists other than ADP by blocking the amplification of platelet activation by released ADP. Clopidogrel does not inhibit phosphodiesterase activity.

Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan.

Dose dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of Plavix. Repeated doses of 75 mg Plavix per day inhibit ADP-induced platelet aggregation on the first day, and inhibition reaches steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg Plavix 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.

Pharmacokinetics and Metabolism

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 (0.00025 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. It represents about 85% of the circulating drug-related compounds in plasma.

Following an oral dose of ^{14}C-labeled clopidogrel in humans, approximately 50% was excreted in the urine and approximately 46% in the feces in the 5 days after dosing. The elimination half-life of the main circulating metabolite was 8 hours after single and repeated administration. Covalent binding to platelets accounted for 2% of radiolabel with a half-life of 11 days.

Effect of Food: Administration of Plavix (clopidogrel bisulfate) with meals did not significantly modify the bioavailability of clopidogrel as assessed by the pharmacokinetics of the main circulating metabolite.

Absorption and Distribution: Clopidogrel is rapidly absorbed after oral administration of repeated doses of 75 mg clopidogrel (base), with peak plasma levels (≅3 mg/L) of the main circulating metabolite occurring approximately 1 hour after dosing. The pharmacokinetics of the main circulating metabolite are linear (plasma concentrations increased in proportion to dose) in the dose range of 50 to 150 mg of clopidogrel. Absorption is at least 50% based on urinary excretion of clopidogrel-related metabolites.

Clopidogrel and the main circulating metabolite bind reversibly *in vitro* to human plasma proteins (98% and 94%, respectively). The binding is nonsaturable *in vitro* up to a concentration of 100 µg/mL.

Metabolism and Elimination: *In vitro* and *in vivo*, clopidogrel undergoes rapid hydrolysis into its carboxylic acid derivative. In plasma and urine, the glucuronide of the carboxylic acid derivative is also observed.

Special Populations

Geriatric Patients: Plasma concentrations of the main circulating metabolite are significantly higher in elderly (≥75 years) compared to young healthy volunteers but these higher plasma levels were not associated with differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.

Renally Impaired Patients: After repeated doses of 75 mg Plavix per day, plasma levels of the main circulating metabolite were lower in patients with severe renal impairment (creatinine clearance from 5 to 15 mL/min) compared to subjects with moderate renal impairment (creatinine clearance 30 to 60 mL/min) or healthy subjects. Although inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy volunteers, the prolongation of bleeding time was similar to healthy volunteers receiving 75 mg of Plavix per day.

Gender: No significant difference was observed in the plasma levels of the main circulating metabolite between males and females. In a small study comparing men and women, less inhibition of ADP-induced platelet

aggregation was observed in women, but there was no difference in prolongation of bleeding time. In the large, controlled clinical study (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events; CAPRIE), the incidence of clinical outcome events, other adverse clinical events, and abnormal clinical laboratory parameters was similar in men and women.

Race: Pharmacokinetic differences due to race have not been studied.

CLINICAL STUDIES

The clinical evidence for the efficacy of Plavix is derived from four double-blind trials involving 81,090 patients: the CAPRIE study (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events), a comparison of Plavix to aspirin, and the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events), the COMMIT/CCS-2 (Clopidogrel and Metoprolol in Myocardial Infarction Trial / Second Chinese Cardiac Study) studies comparing Plavix to placebo, both given in combination with aspirin and other standard therapy and CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy – Thrombolysis in Myocardial Infarction).

Recent Myocardial Infarction (MI), Recent Stroke or Established Peripheral Arterial Disease

The CAPRIE trial was a 19,185-patient, 304-center, international, randomized, double-blind, parallel-group study comparing Plavix (75 mg daily) to aspirin (325 mg daily). The patients randomized had: 1) recent histories of myocardial infarction (within 35 days); 2) recent histories of ischemic stroke (within 6 months) with at least a week of residual neurological signs; or 3) objectively established peripheral arterial disease. Patients received randomized treatment for an average of 1.6 years (maximum of 3 years).

The trial's primary outcome was the time to first occurrence of new ischemic stroke (fatal or not), new myocardial infarction (fatal or not), or other vascular death. Deaths not easily attributable to nonvascular causes were all classified as vascular.

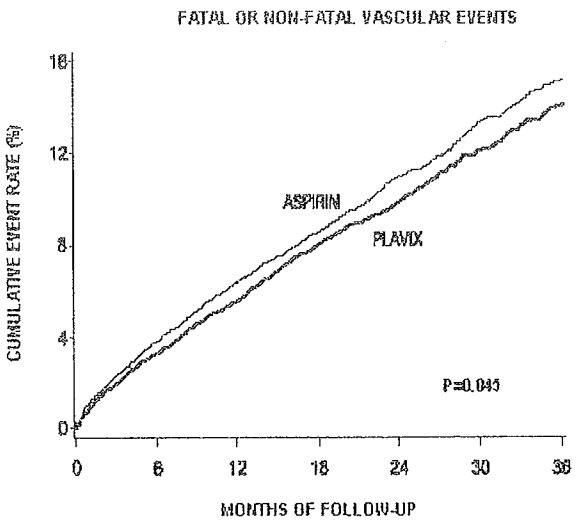
Table 1: Outcome Events in the CAPRIE Primary Analysis

	Plavix	aspirin
Patients	9599	9586
IS (fatal or not)	438 (4.6%)	461 (4.8%)
MI (fatal or not)	275 (2.9%)	333 (3.5%)
Other vascular death	226 (2.4%)	226 (2.4%)
Total	939 (9.8%)	1020 (10.6%)

As shown in the table, Plavix (clopidogrel bisulfate) was associated with a lower incidence of outcome events of every kind. The overall risk reduction (9.8% vs. 10.6%) was 8.7%, P=0.045. Similar results were obtained when all-cause mortality and all-cause strokes were counted instead of vascular mortality and ischemic strokes (risk reduction 6.9%). In patients who survived an on-study stroke or myocardial infarction, the incidence of subsequent events was again lower in the Plavix group.

The curves showing the overall event rate are shown in Figure 1. The event curves separated early and continued to diverge over the 3-year follow-up period.

Figure 1: Fatal or Non-Fatal Vascular Events in the CAPRIE Study



Although the statistical significance favoring Plavix over aspirin was marginal (P=0.045), and represents the result of a single trial that has not been replicated, the comparator drug, aspirin, is itself effective (vs. placebo) in reducing cardiovascular events in patients with recent myocardial infarction or stroke. Thus, the difference between Plavix and placebo, although not measured directly, is substantial.

The CAPRIE trial included a population that was randomized on the basis of 3 entry criteria. The efficacy of Plavix relative to aspirin was heterogeneous across these randomized subgroups (P=0.043). It is not clear whether this difference is real or a chance occurrence. Although the CAPRIE trial was not designed to evaluate the relative benefit of Plavix over aspirin in the individual patient subgroups, the benefit appeared to be strongest in patients who were enrolled because of peripheral vascular disease (especially those who also had a history of myocardial infarction) and weaker in stroke patients. In patients who were enrolled in the trial on the sole basis of a recent myocardial infarction, Plavix was not numerically superior to aspirin.

In the meta-analyses of studies of aspirin vs. placebo in patients similar to those in CAPRIE, aspirin was associated with a reduced incidence of thrombotic events. There was a suggestion of heterogeneity in these studies too, with the effect strongest in patients with a history of myocardial infarction, weaker in patients with a history of stroke, and not discernible in patients with a history of peripheral vascular disease. With respect to the inferred comparison of Plavix to placebo, there is no indication of heterogeneity.

Acute Coronary Syndrome

The CURE study included 12,562 patients with acute coronary syndrome without ST segment elevation (unstable angina or non-Q-wave myocardial infarction) and presenting within 24 hours of onset of the most recent episode of chest pain or symptoms consistent with ischemia. Patients were required to have either ECG changes compatible with new ischemia (without ST segment elevation) or elevated cardiac enzymes or troponin I or T to at least twice the upper limit of normal. The patient population was largely Caucasian (82%) and included 38% women, and 52% patients ≥65 years of age.

Patients were randomized to receive Plavix (300 mg loading dose followed by 75 mg/day) or placebo, and were treated for up to one year. Patients also received aspirin (75-325 mg once daily) and other standard therapies such as heparin. The use of GPIIb/IIIa inhibitors was not permitted for three days prior to randomization.

The number of patients experiencing the primary outcome (CV death, MI, or stroke) was 582 (9.30%) in the Plavix-treated group and 719 (11.41%) in the placebo-treated group, a 20% relative risk reduction (95% CI of 10%-28%; p=0.00009) for the Plavix-treated group (see Table 2).

At the end of 12 months, the number of patients experiencing the co-primary outcome (CV death, MI, stroke or refractory ischemia) was 1035 (16.54%) in the Plavix-treated group and 1187 (18.83%) in the placebo-treated group, a 14% relative risk reduction (95% CI of 6%-21%, p=0.0005) for the Plavix-treated group (see Table 2).

In the Plavix-treated group, each component of the two primary endpoints (CV death, MI, stroke, refractory ischemia) occurred less frequently than in the placebo-treated group.

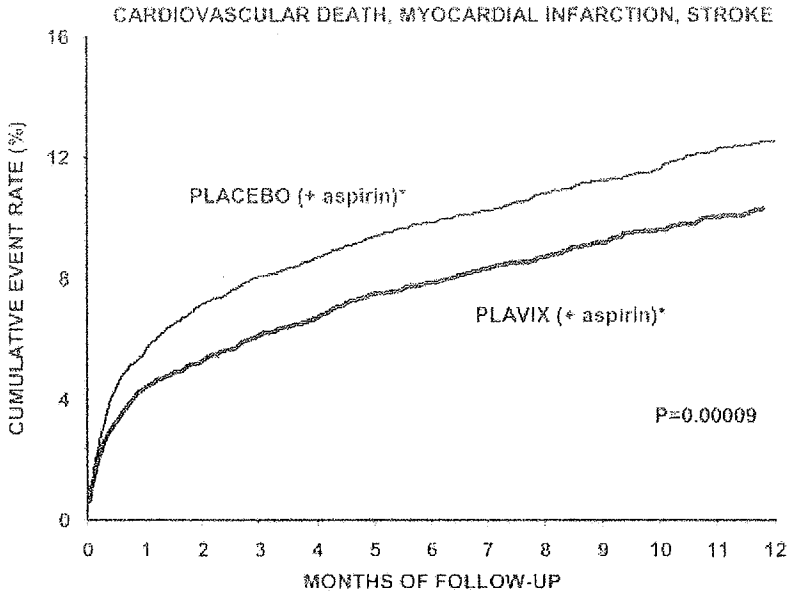
Table 2: Outcome Events in the CURE Primary Analysis

Outcome	Plavix (+ aspirin)* (n=6259)	Placebo (+ aspirin)* (n=6303)	Relative Risk Reduction (%) (95% CI)
Primary outcome (Cardiovascular death, MI, Stroke)	582 (9.3%)	719 (11.4%)	20% (10.3, 27.9) P=0.00009
Co-primary outcome (Cardiovascular death, MI, Stroke, Refractory Ischemia)	1035 (16.5%)	1187 (18.8%)	14% (6.2, 20.6) P=0.00052
All Individual Outcome Events:†			
CV death	318 (5.1%)	345 (5.5%)	7% (-7.7, 20.6)
MI	324 (5.2%)	419 (6.6%)	23% (11.0, 33.4)
Stroke	75 (1.2%)	87 (1.4%)	14% (-17.7, 36.6)
Refractory ischemia	544 (8.7%)	587 (9.3%)	7% (-4.0, 18.0)

* Other standard therapies were used as appropriate.
† The individual components do not represent a breakdown of the primary and co-primary outcomes, but rather the total number of subjects experiencing an event during the course of the study.

The benefits of Plavix (clopidogrel bisulfate) were maintained throughout the course of the trial (up to 12 months).

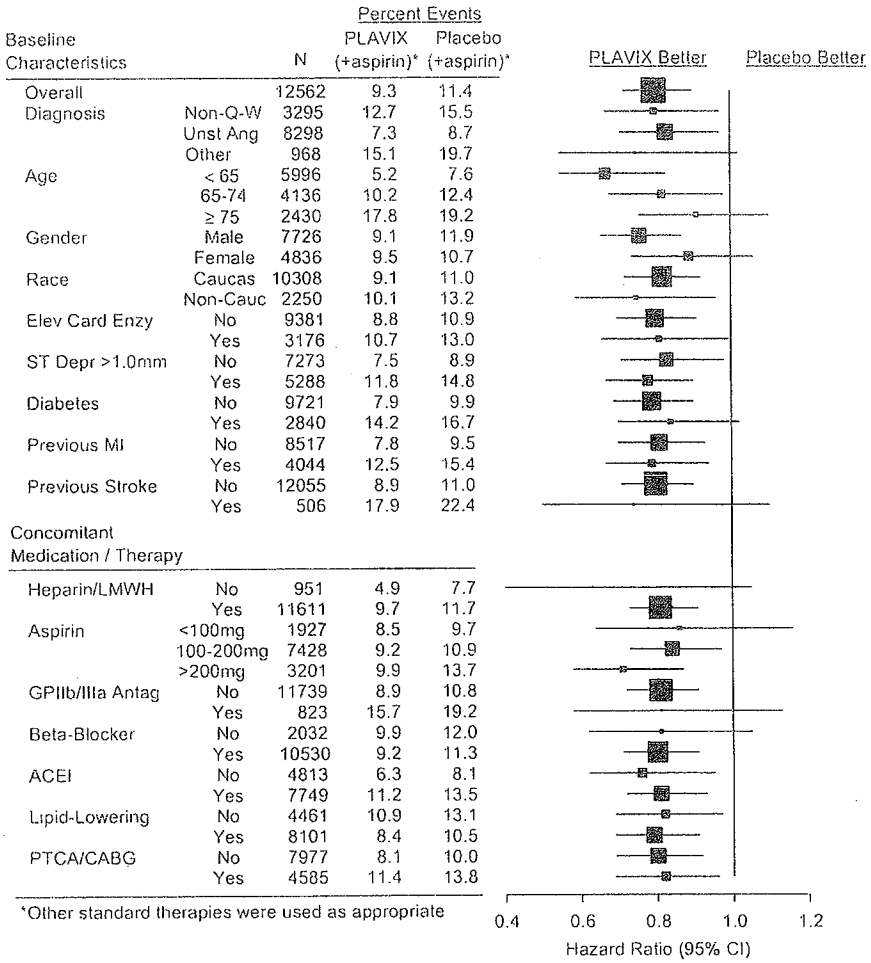
Figure 2: Cardiovascular Death, Myocardial Infarction, and Stroke in the CURE Study



*Other standard therapies were used as appropriate

In CURE, the use of Plavix was associated with a lower incidence of CV death, MI or stroke in patient populations with different characteristics, as shown in Figure 3. The benefits associated with Plavix were independent of the use of other acute and long-term cardiovascular therapies, including heparin/LMWH (low molecular weight heparin), IV glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, lipid-lowering drugs, beta-blockers, and ACE-inhibitors. The efficacy of Plavix was observed independently of the dose of aspirin (75-325 mg once daily). The use of oral anticoagulants, non-study anti-platelet drugs and chronic NSAIDs was not allowed in CURE.

Figure 3. Hazard Ratio for Patient Baseline Characteristics and On-Study Concomitant Medications/Interventions for the CURE Study



The use of Plavix in CURE was associated with a decrease in the use of thrombolytic therapy (71 patients [1.1%] in the Plavix group, 126 patients [2.0%] in the placebo group; relative risk reduction of 43%, P=0.0001), and GPIIb/IIIa inhibitors (369 patients [5.9%] in the Plavix group, 454 patients [7.2%] in the placebo group, relative risk reduction of 18%, P=0.003). The use of Plavix in CURE did not impact the number of patients treated with CABG or PCI (with or without stenting), (2253 patients [36.0%] in the Plavix group, 2324 patients [36.9%] in the placebo group; relative risk reduction of 4.0%, P=0.1658).

In patients with ST-segment elevation acute myocardial infarction, safety and efficacy of clopidogrel have been evaluated in two randomized, placebo-controlled, double-blind studies, COMMIT – a large outcome study conducted in China – and CLARITY – a supportive study of a surrogate endpoint conducted internationally.

The randomized, double-blind, placebo-controlled, 2x2 factorial design COMMIT trial included 45,852 patients presenting within 24 hours of the onset of the symptoms of suspected myocardial infarction with supporting ECG abnormalities (*i.e.*, ST elevation, ST depression or left bundle-branch block). Patients were randomized to receive Plavix (75 mg/day) or placebo, in combination with aspirin (162 mg/day), for 28 days or until hospital discharge whichever came first.

The co-primary endpoints were death from any cause and the first occurrence of re-infarction, stroke or death.

The patient population included 28% women, 58% patients ≥ 60 years (26% patients ≥ 70 years) and 55% patients who received thrombolytics, 68% received ace-inhibitors, and only 3% had percutaneous coronary intervention (PCI).

As shown in Table 3 and Figures 5 and 6 below, Plavix significantly reduced the relative risk of death from any cause by 7% (p = 0.029), and the relative risk of the combination of re-infarction, stroke or death by 9% (p = 0.002).

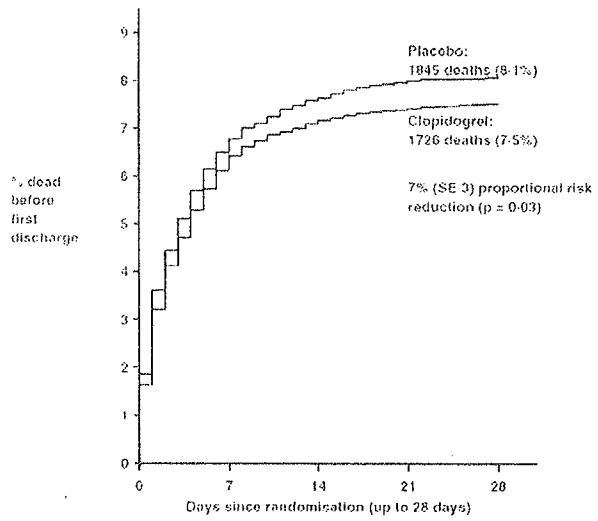
Table 3: Outcome Events in the COMMIT Analysis

Event	Plavix (+ aspirin) (N = 22961)	Placebo (+ aspirin) (N = 22891)	Odds ratio (95% CI)	p-value
Composite endpoint: Death, MI, or Stroke*	2121 (9.2%)	2310 (10.1%)	0.91 (0.86, 0.97)	0.002
Death	1726 (7.5%)	1845 (8.1%)	0.93 (0.87, 0.99)	0.029
Non-fatal MI**	270 (1.2%)	330 (1.4%)	0.81 (0.69, 0.95)	0.011
Non-fatal Stroke**	127 (0.6%)	142 (0.6%)	0.89 (0.70, 1.13)	0.33

*The difference between the composite endpoint and the sum of death+non-fatal MI+non-fatal stroke indicates that 9 patients (2 clopidogrel and 7 placebo) suffered both a non-fatal stroke and a non-fatal MI.

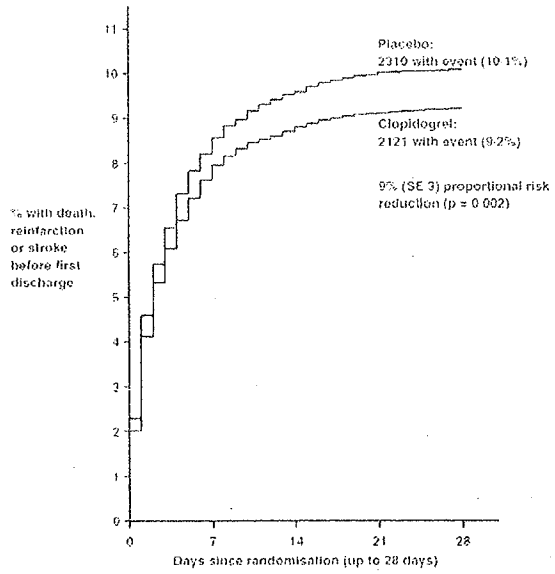
** Non-fatal MI and non-fatal stroke exclude patients who died (of any cause).

Figure 4: Cumulative Event Rates for Death in the COMMIT Study*



* All treated patients received aspirin.

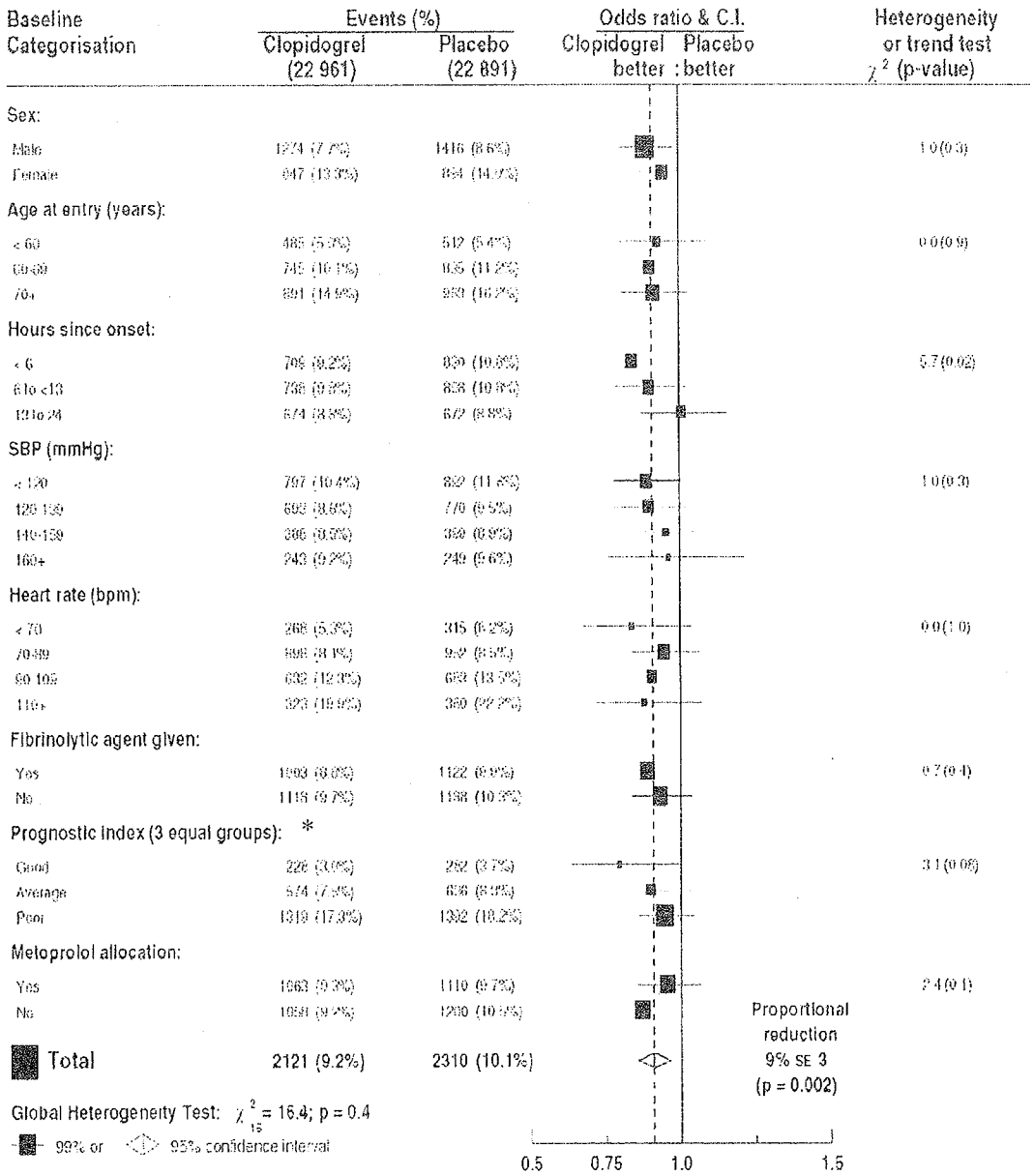
Figure 5: Cumulative Event Rates for the Combined Endpoint Re-Infarction, Stroke or Death in the COMMIT Study*



* All treated patients received aspirin.

The effect of Plavix did not differ significantly in various pre-specified sub-groups as shown in Figure 6. Additionally, the effect was similar in non-prespecified subgroups including those based on infarct location, Killip class or prior MI history. Such sub-group analyses should be interpreted very cautiously.

Figure 6: Effects of Adding PLAVIX to Aspirin on the Combined Primary Endpoint across Baseline and Concomitant Medication Subgroups for the COMMIT Study



*Three similar-sized prognostic index groups were based on absolute risk of primary composite outcome for each patient calculated from baseline prognostic variables (excluding allocated treatments) with a Cox regression model.

The randomized, double-blind, placebo-controlled CLARITY trial included 3,491 patients, 5% U.S., presenting within 12 hours of the onset of a ST elevation myocardial infarction and planned for thrombolytic therapy. Patients were randomized to receive Plavix (300-mg loading dose, followed by 75 mg/day) or placebo until angioplasty, discharge, or Day 8. Patients also received aspirin (150 to 325 mg as a loading dose, followed by 75 to 162 mg/day), a fibrinolytic agent and, when appropriate, heparin for 48 hours. The patients were followed for 30 days.

The primary endpoint was the occurrence of the composite of an occluded infarct-related artery (defined as TIMI Flow Grade 0 or 1) on the predischarge angiogram, or death or recurrent myocardial infarction by the time of the start of coronary angiography.

The patient population was mostly Caucasian (89.5%) and included 19.7% women and 29.2% patients ≥ 65 years. A total of 99.7% of patients received fibrinolytics (fibrin specific: 68.7%, non- fibrin specific: 31.1%), 89.5% heparin, 78.7% beta-blockers, 54.7% ACE inhibitors and 63% statins.

The number of patients who reached the primary endpoint was 262 (15.0%) in the Plavix-treated group and 377 (21.7%) in the placebo group, but most of the events related to the surrogate endpoint of vessel patency.

Table 4: Event Rates for the Primary Composite Endpoint in the CLARITY Study

	Clopidogrel 1752	Placebo 1739	OR	95% CI
Number (%) of patients reporting the composite endpoint	262 (15.0%)	377 (21.7%)	0.64	0.53, 0.76
Occluded IRA				
N (subjects undergoing angiography)	1640	1634		
n (%) patients reporting endpoint	192 (11.7%)	301 (18.4%)	0.59	0.48, 0.72
Death				
n (%) patients reporting endpoint	45 (2.6%)	38 (2.2%)	1.18	0.76, 1.83
Recurrent MI				
n (%) patients reporting endpoint	44 (2.5%)	62 (3.6%)	0.69	0.47, 1.02

*The total number of patients with a component event (occluded IRA, death, or recurrent MI) is greater than the number of patients with a composite event because some patients had more than a single type of component event.

INDICATIONS AND USAGE

Plavix (clopidogrel bisulfate) is indicated for the reduction of atherothrombotic events as follows:

- **Recent MI, Recent Stroke or Established Peripheral Arterial Disease**
  For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, Plavix has been shown to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.

- **Acute Coronary Syndrome**
  For patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-Q-wave MI) including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (with or without stent) or CABG, Plavix has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI, or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia

  For patients with ST-segment elevation acute myocardial infarction, Plavix has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction or stroke. This benefit is not known to pertain to patients who receive primary angioplasty.

CONTRAINDICATIONS

The use of Plavix is contraindicated in the following conditions:

Hypersensitivity to the drug substance or any component of the product.
Active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

WARNINGS

Thrombotic thrombocytopenic purpura (TTP): TTP has been reported rarely following use of PLAVIX, sometimes after a short exposure (< 2 weeks). TTP is a serious condition and requires urgent referral to a hematologist for prompt treatment. It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever. TTP was not seen during clopidogrel's clinical trials, which included over 17,500 clopidogrel-treated patients. In world-wide postmarketing experience, however, TTP has been reported at a rate of about four cases per million patients exposed, or about 11 cases per million patient-years. The background rate is thought to be about four cases per million person-years. (See **ADVERSE REACTIONS**.)

PRECAUTIONS

General

Plavix prolongs the bleeding time and therefore should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions (particularly gastrointestinal and intraocular). If a patient is to undergo elective surgery and an antiplatelet effect is not desired, Plavix should be discontinued 5 days prior to surgery.

Due to the risk of bleeding and undesirable hematological effects, blood cell count determination and/or other appropriate testing should be promptly considered, whenever such suspected clinical symptoms arise during the course of treatment (see **ADVERSE REACTIONS**).

In patients with recent TIA or stroke who are at high risk of recurrent ischemic events, the combination of aspirin and Plavix has not been shown to be more effective than Plavix alone, but the combination has been shown to increase major bleeding.

GI Bleeding: In CAPRIE, Plavix was associated with a rate of gastrointestinal bleeding of 2.0%, vs. 2.7% on aspirin. In CURE, the incidence of major gastrointestinal bleeding was 1.3% vs 0.7% (Plavix + aspirin vs. placebo + aspirin, respectively). Plavix should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions should be used with caution in patients taking Plavix.

Use in Hepatically Impaired Patients: Experience is limited in patients with severe hepatic disease, who may have bleeding diatheses. Plavix should be used with caution in this population.

Use in Renally-impaired Patients: Experience is limited in patients with severe renal impairment. Plavix should be used with caution in this population.

Information for Patients

Patients should be told that they may bleed more easily and it may take them longer than usual to stop bleeding when they take Plavix or Plavix combined with aspirin, and that they should report any unusual bleeding to their physician. Patients should inform physicians and dentists that they are taking Plavix and/or any other product known to affect bleeding before any surgery is scheduled and before any new drug is taken.

Drug Interactions

Study of specific drug interactions yielded the following results:

Aspirin: Aspirin did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation. Concomitant administration of 500 mg of aspirin twice a day for 1 day did not significantly increase the prolongation of bleeding time induced by Plavix. Plavix potentiated the effect of aspirin on collagen-induced platelet aggregation. Plavix and aspirin have been administered together for up to one year.

Heparin: In a study in healthy volunteers, Plavix did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Coadministration of heparin had no effect on inhibition of platelet aggregation induced by Plavix.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): In healthy volunteers receiving naproxen, concomitant administration of Plavix was associated with increased occult gastrointestinal blood loss. NSAIDs and Plavix should be coadministered with caution.

Warfarin: Because of the increased risk of bleeding, the concomitant administration of warfarin with Plavix should be undertaken with caution. (See **PRECAUTIONS–General.**)

Other Concomitant Therapy: No clinically significant pharmacodynamic interactions were observed when Plavix was coadministered with **atenolol, nifedipine,** or both atenolol and nifedipine. The pharmacodynamic activity of Plavix was also not significantly influenced by the coadministration of **phenobarbital, cimetidine** or **estrogen**.

The pharmacokinetics of **digoxin** or **theophylline** were not modified by the coadministration of Plavix (clopidogrel bisulfate).

At high concentrations *in vitro*, clopidogrel inhibits P_{450} (2C9). Accordingly, Plavix may interfere with the metabolism of **phenytoin, tamoxifen, tolbutamide, warfarin, torsemide, fluvastatin,** and many **non-steroidal anti-inflammatory agents,** but there are no data with which to predict the magnitude of these interactions. Caution should be used when any of these drugs is coadministered with Plavix.

In addition to the above specific interaction studies, patients entered into clinical trials with Plavix received a variety of concomitant medications including **diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents** (including **insulin**), **thrombolytics, heparins** (unfractionated and LMWH), **GPIIb/IIIa antagonists, antiepileptic agents** and **hormone replacement therapy** without evidence of clinically significant adverse interactions.

There are no data on the concomitant use of oral anticoagulants, non study oral anti-platelet drugs and chronic NSAIDs with clopidogrel.

Drug/Laboratory Test Interactions

None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of tumorigenicity when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats at dosages up to 77 mg/kg per day, which afforded plasma exposures >25 times that in humans at the recommended daily dose of 75 mg.

Clopidogrel was not genotoxic in four *in vitro* tests (Ames test, DNA-repair test in rat hepatocytes, gene mutation assay in Chinese hamster fibroblasts, and metaphase chromosome analysis of human lymphocytes) and in one *in vivo* test (micronucleus test by oral route in mice).

Clopidogrel was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg per day (52 times the recommended human dose on a mg/m^2 basis).

Pregnancy

Pregnancy Category B. Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/kg/day (respectively, 65 and 78 times the recommended daily human dose on a mg/m^2 basis), revealed no evidence of impaired fertility or fetotoxicity due to clopidogrel. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, Plavix should be used during pregnancy only if clearly needed.

Nursing Mothers

Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the nursing woman.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

Geriatric Use

Of the total number of subjects in the CAPRIE, CURE and CLARITY controlled clinical studies, approximately 50% of patients treated with Plavix were 65 years of age and older, and 15% were 75 years and older. In COMMIT, approximately 58% of the patients treated with Plavix were 60 years and older, 26% of whom were 70 years and older.

The observed risk of thrombotic events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in Figures 3 and 7 for the CURE and COMMIT trials, respectively (see **CLINICAL STUDIES**). The observed risk of bleeding events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in Tables 4 and 5 for the CURE and COMMIT trials, respectively (see **ADVERSE REACTIONS**).

ADVERSE REACTIONS

Plavix has been evaluated for safety in more than 42,000 patients, including over 9,000 patients treated for 1 year or more. The clinically important adverse events observed in CAPRIE, CURE, CLARITY and COMMIT are discussed below.

The overall tolerability of Plavix in CAPRIE was similar to that of aspirin regardless of age, gender and race, with an approximately equal incidence (13%) of patients withdrawing from treatment because of adverse reactions.

Hemorrhagic: In CAPRIE patients receiving Plavix, gastrointestinal hemorrhage occurred at a rate of 2.0%, and required hospitalization in 0.7%. In patients receiving aspirin, the corresponding rates were 2.7% and 1.1%, respectively. The incidence of intracranial hemorrhage was 0.4% for Plavix compared to 0.5% for aspirin.

In CURE, Plavix use with aspirin was associated with an increase in bleeding compared to placebo with aspirin (see Table 4). There was an excess in major bleeding in patients receiving Plavix plus aspirin compared with placebo plus aspirin, primarily gastrointestinal and at puncture sites. The incidence of intracranial hemorrhage (0.1%), and fatal bleeding (0.2%), were the same in both groups.

The overall incidence of bleeding is described in Table 5 for patients receiving both Plavix and aspirin in CURE,

Table 5: CURE Incidence of bleeding complications (% patients)

Event	Plavix (+ aspirin)* (n=6259)	Placebo (+ aspirin)* (n=6303)	P-value
Major bleeding †	3.7 ‡	2.7 §	0.001
Life-threatening bleeding	2.2	1.8	0.13
Fatal	0.2	0.2	
5 g/dL hemoglobin drop	0.9	0.9	
Requiring surgical intervention	0.7	0.7	
Hemorrhagic strokes	0.1	0.1	
Requiring inotropes	0.5	0.5	
Requiring transfusion (≥4 units)	1.2	1.0	
Other major bleeding	1.6	1.0	0.005
Significantly disabling	0.4	0.3	
Intraocular bleeding with significant loss of vision	0.05	0.03	
Requiring 2-3 units of blood	1.3	0.9	
Minor bleeding ¶	5.1	2.4	<0.001

*Other standard therapies were used as appropriate.
†Life threatening and other major bleeding.
‡Major bleeding event rate for Plavix + aspirin was dose-dependent on aspirin: <100 mg=2.6%; 100-200 mg= 3.5%; >200 mg=4.9%
Major bleeding event rates for Plavix + aspirin by age were: <65 years = 2.5%, ≥65 to <75 years = 4.1%, ≥75 years 5.9%
§Major bleeding event rate for placebo + aspirin was dose-dependent on aspirin: <100 mg=2.0%; 100-200 mg= 2.3%; >200 mg=4.0%
Major bleeding event rates for placebo + aspirin by age were: <65 years = 2.1%, ≥65 to <75 years = 3.1%, ≥75 years 3.6%
¶Led to interruption of study medication.

Ninety-two percent (92%) of the patients in the CURE study received heparin/LMWH, and the rate of bleeding in these patients was similar to the overall results.

There was no excess in major bleeds within seven days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (event rate 4.4% Plavix + aspirin; 5.3% placebo + aspirin). In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for Plavix + aspirin, and 6.3% for placebo + aspirin.

In CLARITY, the incidence of major bleeding (defined as intracranial bleeding or bleeding associated with a fall in hemoglobin > 5 g/dL) was similar between groups (1.3% versus 1.1% in the Plavix + aspirin and in the placebo + aspirin groups, respectively). This was consistent across subgroups of patients defined by baseline characteristics, and type of fibrinolytics or heparin therapy. The incidence of fatal bleeding (0.8% versus 0.6% in the Plavix + aspirin and in the placebo + aspirin groups, respectively) and intracranial hemorrhage (0. 5% versus 0.7%, respectively) was low and similar in both groups.

The overall rate of noncerebral major bleeding or cerebral bleeding in COMMIT was low and similar in both groups as shown in Table 5 below.

Table 6: Number (%) of Patients with Bleeding Events in COMMIT

Type of bleeding	Plavix (+ aspirin) (N = 22961)	Placebo (+ aspirin) (N = 22891)	P-value
Major* noncerebral or cerebral bleeding**	134 (0.6%)	125 (0.5%)	0.59
Major noncerebral	82 (0.4%)	73 (0.3%)	0.48
Fatal	36 (0.2%)	37 (0.2%)	0.90
Hemorrhagic stroke	55 (0.2%)	56 (0.2%)	0.91
Fatal	39 (0.2%)	41 (0.2%)	0.81
Other noncerebral bleeding (non major)	831 (3.6%)	721 (3.1%)	0.005
Any noncerebral bleeding	896 (3.9%)	777 (3.4%)	0.004

* Major bleeds are cerebral bleeds or non-cerebral bleeds thought to have caused death or that required transfusion.

** The relative rate of major noncerebral or cerebral bleeding was independent of age. Event rates for Plavix + aspirin by age were: <60 years = 0.3%, ≥60 to <70 years = 0.7%, ≥70 years 0.8%. Event rates for placebo + aspirin by age were: <60 years = 0.4%, ≥60 to <70 years = 0.6%, ≥70 years 0.7%.

Adverse events occurring in ≥2.5% of patients on Plavix in the CAPRIE controlled clinical trial are shown below regardless of relationship to Plavix. The median duration of therapy was 20 months, with a maximu 3 years.

Table 7: Adverse Events Occurring in ≥2.5% of Plavix Patients in CAPRIE

Body System Event	% Incidence (% Discontinua Plavix [n=9599]	Aspirin [n=9586]
Body as a Whole– general disorders		
Chest Pain	8.3 (0.2)	8.3 (0.3)
Accidental/Inflicted Injury	7.9 (0.1)	7.3 (0.1)
Influenza-like symptoms	7.5 (<0.1)	7.0 (<0.1)
Pain	6.4 (0.1)	6.3 (0.1)
Fatigue	3.3 (0.1)	3.4 (0.1)
Cardiovascular disorders, general		
Edema	4.1 (<0.1)	4.5 (<0.1)
Hypertension	4.3 (<0.1)	5.1 (<0.1)
Central & peripheral nervous system disorders		
Headache	7.6 (0.3)	7.2 (0.2)
Dizziness	6.2 (0.2)	6.7 (0.3)
Gastrointestinal system disorders		
Any event	27.1(3.2)	29.8 (4.0)
Abdominal pain	5.6 (0.7)	7.1 (1.0)
Dyspepsia	5.2 (0.6)	6.1 (0.7)
Diarrhea	4.5 (0.4)	3.4 (0.3)
Nausea	3.4 (0.5)	3.8 (0.4)
Metabolic & nutritional disorders		
Hypercholesterolemia	4.0 (0)	4.4 (<0.1)
Musculo-skeletal system disorders		
Arthralgia	6.3 (0.1)	6.2 (0.1)
Back Pain	5.8 (0.1)	5.3 (<0.1)
Platelet, bleeding, & clotting disorders		
Purpura/Bruise	5.3 (0.3)	3.7 (0.1)
Epistaxis	2.9 (0.2)	2.5 (0.1)
Psychiatric disorders		
Depression	3.6 (0.1)	3.9 (0.2)
Respiratory system disorders		
Upper resp tract infection	8.7 (<0.1)	8.3 (<0.1)
Dyspnea	4.5 (0.1)	4.7 (0.1)
Rhinitis	4.2 (0.1)	4.2 (<0.1)
Bronchitis	3.7 (0.1)	3.7 (0)
Coughing	3.1 (<0.1)	2.7(<0.1)
Skin & appendage disorders		
Any event	15.8 (1.5)	13.1 (0.8)
Rash	4.2 (0.5)	3.5 (0.2)
Pruritus	3.3 (0.3)	1.6 (0.1)
Urinary system disorders		
Urinary tract infection	3.1 (0)	3.5 (0.1)

No additional clinically relevant events to those observed in CAPRIE with a frequency ≥ 2.5%, have been reported during the CURE and CLARITY controlled studies. COMMIT collected only limited safety data.

Other adverse experiences of potential importance occurring in 1% to 2.5% of patients receiving Plavix (clopidogrel bisulfate) in the controlled clinical trials are listed below regardless of relationship to Plavix. In general, the incidence of these events was similar to that in patients receiving aspirin (in CAPRIE) or placebo + aspirin (in the other clinical trials).

Autonomic Nervous System Disorders: Syncope, Palpitation. *Body as a Whole-general disorders:* Asthenia, Fever, Hernia. *Cardiovascular disorders:* Cardiac failure. *Central and peripheral nervous system disorders:* Cramps legs, Hypoaesthesia, Neuralgia, Paraesthesia, Vertigo. *Gastrointestinal system disorders:* Constipation, Vomiting. *Heart rate and rhythm disorders:* Fibrillation atrial,. *Liver and biliary system disorders:* Hepatic enzymes increased. *Metabolic and nutritional disorders:* Gout, hyperuricemia, non-protein nitrogen (NPN) increased. *Musculo-skeletal system disorders:* Arthritis, Arthrosis. *Platelet, bleeding & clotting disorders:* GI hemorrhage, hematoma platelets decreased. *Psychiatric disorders:* Anxiety, Insomnia. *Red blood cell disorders:* Anemia. *Respiratory system disorders:* Pneumonia, Sinusitis. *Skin and appendage disorders:* Eczema, Skin ulceration. *Urinary system disorders:* Cystitis. *Vision disorders:* Cataract, Conjunctivitis.

Other potentially serious adverse events which may be of clinical interest but were rarely reported (<1%) in patients who received Plavix in the controlled clinical trials are listed below regardless of relationship to Plavix. In general, the incidence of these events was similar to that in patients receiving aspirin (in CAPRIE) or placebo + aspirin (in the other clinical trials).

Body as a whole: Allergic reaction, necrosis ischemic. *Cardiovascular disorders:* Edema generalized. *Gastrointestinal system disorders:* Peptic, gastric or duodenal ulcer, gastritis, gastric ulcer perforated, gastritis hemorrhagic, upper GI ulcer hemorrhagic. *Liver and Biliary system disorders:* Bilirubinemia, hepatitis infectious, liver fatty. *Platelet, bleeding and clotting disorders:* hemarthrosis, hematuria, hemoptysis, hemorrhage intracranial, hemorrhage retroperitoneal, hemorrhage of operative wound, ocular hemorrhage, pulmonary hemorrhage, purpura allergic, thrombocytopenia. *Red blood cell disorders:* Anemia aplastic, anemia hypochromic. *Reproductive disorders, female:* Menorrhagia. *Respiratory system disorders:* Hemothorax. *Skin and appendage disorders:* Bullous eruption, rash erythematous, rash maculopapular, urticaria. *Urinary system disorders*: Abnormal renal function, acute renal failure. *White cell and reticuloendothelial system disorders:* Agranulocytosis, granulocytopenia, leukemia, leukopenia, neutropenia.

Postmarketing Experience

The following events have been reported spontaneously from worldwide postmarketing experience:

- *Body as a whole:*
  - hypersensitivity reactions, anaphylactoid reactions, serum sickness
- *Central and Peripheral Nervous System disorders:*
  - confusion, hallucinations, taste disorders
- *Hepato-biliary disorders:*
  - abnormal liver function test, hepatitis (non-infectious), acute liver failure
- *Platelet, Bleeding and Clotting disorders:*
  - cases of bleeding with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal hemorrhage)
  - agranulocytosis, aplastic anemia/pancytopenia, thrombotic thrombocytopenic purpura (TTP) – some cases with fatal outcome- (see **WARNINGS**).
  - conjunctival, ocular and retinal bleeding
- *Respiratory, thoracic and mediastinal disorders:*
  - bronchospasm, interstitial pneumonitis
- *Skin and subcutaneous tissue disorders:*
  - angioedema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, lichen planus
- *Renal and urinary disorders:*
  - glomerulopathy, increased creatinine levels
- *Vascular disorders:*
  - vasculitis, hypotension
- *Gastrointestinal disorders:*

- colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis

• *Musculoskeletal, connective tissue and bone disorders:*

- myalgia

OVERDOSAGE

Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. A single oral dose of clopidogrel at 1500 or 2000 mg/kg was lethal to mice and to rats and at 3000 mg/kg to baboons. Symptoms of acute toxicity were vomiting (in baboons), prostration, difficult breathing, and gastrointestinal hemorrhage in all species.

Recommendations About Specific Treatment:

Based on biological plausibility, platelet transfusion may be appropriate to reverse the pharmacological effects of Plavix if quick reversal is required.

DOSAGE AND ADMINISTRATION

Recent MI, Recent Stroke, or Established Peripheral Arterial Disease

The recommended daily dose of Plavix is 75 mg once daily.

Acute Coronary Syndrome

For patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-Q-wave MI), Plavix should be initiated with a single 300-mg loading dose and then continued at 75 mg once daily. Aspirin (75 mg-325 mg once daily) should be initiated and continued in combination with Plavix. In CURE, most patients with Acute Coronary Syndrome also received heparin acutely (see **CLINICAL STUDIES**).

For patients with ST-segment elevation acute myocardial infarction, the recommended dose of Plavix is 75 mg once daily, administered in combination with aspirin, with or without thrombolytics. Plavix may be initiated with or without a loading dose (300 mg was used in CLARITY; see **CLINICAL STUDIES**).

Plavix can be administered with or without food.

No dosage adjustment is necessary for elderly patients or patients with renal disease. (See **Clinical Pharmacology: Special Populations.**)

HOW SUPPLIED

Plavix (clopidogrel bisulfate) is available as a pink, round, biconvex, film-coated tablet debossed with "75" on one side and "1171" on the other. Tablets are provided as follows:

NDC 63653-1171-6 bottles of 30
NDC 63653-1171-1 bottles of 90
NDC 63653-1171-5 bottles of 500
NDC 63653-1171-3 blisters of 100

Storage

Store at 25° C (77° F); excursions permitted to 15°–30° C (59°–86° F) [See USP Controlled Room Temperature].

Distributed by:
Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership
New York, NY 10016

sanofi-synthelabo

Bristol-Myers
Squibb Company

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Revised XXXX

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-839 / S-034

MEDICAL REVIEW(S)

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memorandum

NDA: 20-839 (clopidogrel; Plavix))

Sponsor: Sanofi-Aventis

Review date: 28 August 2006

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 20-839

HFD-110/Pease-Fye
HFD-110/Lemtouni
HFD-710/Zhang

This memo documents the Division's decision to approve supplement 034, granting an indication for Plavix in the treatment of ST elevation acute myocardial infarction in patients not receiving primary angioplasty. My comments are based on the primary reviews of Drs. Lemtouni (clinical reviews dated 5 May 2006 and 12 July 2006) and Zhang (statistical review dated 27 April 2006 and 12 July 2006).

Clopidogrel inhibits ADP-dependent platelet aggregation by binding to the glycoprotein GPIIa/IIIb complex. Prior to the action on this supplement, it carried indications for use in reducing the combined end point of vascular death, MI, and stroke in patients with recent MI or stroke or with peripheral vascular disease, and to reduce the combined end point of cardiovascular death, MI, stroke, or recurrent ischemia in the setting of acute coronary syndrome.

The indication covered by supplement 034 was supported by two studies, briefly described below.

COMMIT/CCS-2 (hereafter referenced as COMMIT) enrolled subjects with ST elevation acute myocardial infarction within 24 hours of the onset of symptoms. Subjects (N=45852) were randomized to clopidogrel 75 mg/d (no loading dose) or placebo and to metoprolol 50 mg or placebo in a factorial design. All received background aspirin 162 mg/d. Most received ACE inhibitors (68%) and thrombolytics (55%), but only 3% had percutaneous coronary intervention.

COMMIT was conducted in a large number of sites in China. DSI inspected 5 sites with large enrollment (together representing about 2% of total enrollment) and uncovered no major issues regarding data integrity. Study enrollment increased from about 30000 to the final 45000 and there was some initial concern because of heterogeneity in the results between the first 30000 and the last 15000. However, the decision to increase enrollment was made very early (i.e., not just after the first 30000 subjects were enrolled), and the heterogeneity (still unexplained) emerges within the first 30000 subjects, so this is no longer considered troubling.

COMMIT had hypotheses relating to both metoprolol and clopidogrel. It is generally considered to be unnecessary to adjust study alpha for two such independent assessments. COMMIT also had two primary end points relating to clopidogrel—all-cause mortality and the composite of death, reinfarction, and stroke. There was apparently no clear plan to adjust alpha between these end points or to evaluate them sequentially, but this turns out not to be a serious problem, either. There were no secondary end points. Follow-up was 30 days.

Overall mortality was 8.1% on placebo and 7.5% on clopidogrel for a 7% reduction in odds ratio (p=0.029). Combined death, MI, or stroke occurred in 10.1% on placebo and 9.2% on clopidogrel for a 9% reduction in odds ratio (p=0.002). Thus, most of the events were fatal. Nonfatal recurrent MI comprised 10-15% of events, and was significantly reduced on clopidogrel (nominally 19%; p=0.011). Nonfatal strokes were only about 5% of total events, and there was a nonsignificant trend for fewer such events on clopidogrel.

(Had one decided this study's primary end points should be assessed sequentially, both would have been significant, regardless of the order of evaluation. Had alpha as much as 0.002 been allocated to the composite end point, it would have been considered significant. One might have concluded that a formal test for mortality would not have been significant using the remaining alpha or, treating mortality as a component of the successful end point, using the same alpha allocated to the composite. However, one would still have to describe the composite end point as having been partially driven by effects on mortality. I think the labeling would have been very similar in almost any reasonable analysis plan.)

The second study was CLARITY, in which subjects (N=3491) were enrolled within 6 hours of STEMI, treated with aspirin (150 or 325 mg) and unfractionated or low-molecular-weight heparin, and randomized to clopidogrel (300-mg loading dose plus 75 mg/d) or to placebo, prior to thrombolysis and, at >48 hours, coronary angioplasty (urgent angiography was an exclusion criterion). Follow-up was 30 days.

The primary end point was a composite of death, recurrent MI, and patency of the infarct-related artery (IRA) at the earliest of angiography, day 8, or hospital discharge.

Sample size was, in two steps, roughly tripled from the original protocol, in part because of an event rate that was lower than expected, but also to achieve greater power (or detect a smaller treatment effect). The latter raises some issues with regard to preservation of study alpha, but this turns out not to be a serious issue in this case.

This study was conducted multinationally and it was not inspected.

The event rates in CLARITY were 21.7% on placebo and 15.0% on clopidogrel for a 36% reduction in odds ratio ($p=3.6 \times 10^{-7}$). About 70% of the events were IRA occlusions, with the remainder being about equally split between recurrent MI (which trended favorably on clopidogrel) and mortality (which trended adversely on clopidogrel).

Because patency of the infarct-related artery is not considered to be sufficient to predict clinical benefit, the CLARITY result is considered supportive, and it is COMMIT that is the main basis for the regulatory decision.

The major issue with COMMIT was whether the effects it found were likely to apply to the US setting. Differences in practice included the delay in thrombolysis (longer in China), the choice of thrombolytic, use of PCI (rare in China), and the use of antilipid drugs (lower in China). The sponsor attempted to address this matter in a submission dated 17 May 2006.

- There were similar effects of clopidogrel in CLARITY whether subjects received thrombolytics or not, and if they did, regardless of class.
- Results in COMMIT were best among subjects treated within the first 6 hours.
- There is a trend in CURE, CLARITY, and COMMIT for the effects of clopidogrel to be larger among patients who received thrombolytics and antilipid drugs.

I believe these data are adequately persuasive that the effects seen in COMMIT (and somewhat supported by CLARITY) are relevant to the US, in a setting of STEMI when PCI is not imminent.

Use of clopidogrel in this setting had only hints of usual adverse hemorrhagic events; event rates were pretty similar on drug and placebo, making one wonder if more aggressive therapy would improve the net outcome.

Dr. Temple has made several suggestions that might be effected by requesting a labeling supplement. He notes that the STEMI trial descriptions and indications might reasonably have headings distinct from ACS (where they now appear). In addition, he recommends that the label call some attention to the apparently progressively better effect of clopidogrel the sooner the enrollment. I believe the two headings are a good idea, but the trend for earlier being better is difficult to validate and seems likely to be how it will be implemented in the US, without further advice.

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/s/

Norman Stockbridge
8/28/2006 06:56:13 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	sNDA
Submission Number	20839
Submission Code	034
Letter Date	11/17/05
Stamp Date	11/17/05
PDUFA Goal Date	August 17
Reviewer Name	Salma Lemtouni, M.D., M.P.H.
Review Completion Date	7/03/06
Established Name	Clopidogrel
Trade Name	Plavix
Therapeutic Class	Platelet aggregation inhibitor
Applicant	Sanofi-aventis
Priority Designation	P
Formulation	Oral
Dosing Regimen Loading:	300 mg, maintenance: 75 mg
Indication	Acute MI
Intended Population	ST-elevation MI

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ACS	acute coronary syndrome
AE(s)	adverse event(s)
ASA	acetylsalicylic acid (aspirin)
AV	atrioventricular
BBB	bundle branch block
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events
CCS-1	First Chinese Cardiac Study
CCS-2	Second Chinese Cardiac Study
CI	confidence interval
COMMIT	Clopidogrel and Metoprolol in Myocardial Infarction Trial
CRF	case report form
CT	computed tomography
CURE	Clopidogrel in Unstable angina to prevent recurrent ischemic Events
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
HR	heart rate
IC	informed consent
ISIS-2	Second International Study of Infarct Survival
ITT	intent-to-treat
MI	myocardial infarction
MRI	magnetic resonance imaging
QD	once daily
PCT	platelet count
PTCA	percutaneous transluminal coronary angioplasty
SAE(s)	serious adverse event(s)
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SFDA	The State Food and Drug Administration (China)
STEMI	ST-elevation myocardial infarction
TFC	TIMI frame count
TFG	TIMI flow grade
TMPG	TIMI myocardial perfusion grade
WBC	white blood cell

1 Executive summary

1.1 Recommendation on Regulatory Action

For the management of ST segment elevation acute myocardial infarction, clopidogrel without the loading dose was shown to reduce the combined outcome of death, reinfarction and stroke in a population ethnically homogeneous (Chinese) that was sub-optimally managed by US medical standards. Per the findings of post-hoc analyses of CLARITY and CURE, and the findings from observational studies, clopidogrel seems to have an extra benefit even in patients who are optimally treated with state of the art management therapies and procedures.

CLARITY with its primary composite outcome results driven by the degree of patency of the infarct related artery is not conclusive with regard to the clinical benefit a patient with STEMI would derive from clopidogrel, especially in the light of an absence of a significant difference between clopidogrel and placebo in the incidence of death and/or recurrent MI, and of ST segment resolution at the study time point. Worth mentioning is the adverse trend of death, myocardial rupture and hemopericardium on clopidogrel compared to placebo in the short-term (within the first week of randomization) and a beneficial trend on mortality and reinfarction at the 30-days follow-up, even if patients were no longer taking study drug.

COMMIT on the other hand met its primary objectives of reducing the composite of mortality, re-infarction and stroke, and all cause mortality in a non-optimally managed (per US medical practice standards) STEMI population. COMMIT was conducted in a population one hundred percent Chinese and in a medical setting that is substantially different from that of the US. The most important differences are the timing of the study drug intake relative to the beginning of symptoms and the rate of PTCA implementation which raise two questions. The first being whether meeting the primary objective outcome resulted from an effect of the study drug on the thromboembolus responsible for the index event which qualified the study subjects for enrollment; and the second whether the findings of COMMIT are applicable to patients in an average US acute myocardial infarction management practice. An additional difference was the omission of the clopidogrel loading dose, and one would wonder whether an added-risk from the loading dose, were it given, would have offset the benefit that was observed in the COMMIT population.

Whether the difference in the primary events in COMMIT was due to an effect that clopidogrel had on the atherothrombus that caused the index event or whether it had an effect on subsequent atherothrombi either in the infarct-related artery or other arteries in this high risk population, it seems that clopidogrel has a benefit in the STEMI population.

The trends of a beneficial effect on Day 30 in combination of an apparent adverse trend early on clopidogrel in CLARITY, also suggest a potential lack of effect on the index event, but a potential beneficial effect on subsequent atherothrombotic events.

Given that clopidogrel was shown to be effective in preventing adverse outcomes in the ACS (STEMI and NSTEMI) population with PCI, thrombolytics and statins (see 11 Response to FDA

Request for Information, page 76), generalizing findings from the COMMIT population to the US population seems less of a concern.

What remains to be demonstrated is whether giving a loading dose and a longer-duration ((> 4 days (average extent of exposure in CLARITY)) of the maintenance dose to a more optimally treated American population, with anticoagulants and thrombolytics on board, will be safe and won't offset the benefit observed without a loading dose in the Chinese population that was not as aggressively managed (as subjects in the CLARITY study) and received the study drug for an average of 14 days. Could it be that the early trends of increased mortality, cardiac rupture and hemopericardium in the CLARITY population were due to too much inhibition of platelet aggregation?

One last point, the COMMIT population was hospitalized on average 5 days longer than the CLARITY population. How would a shorter hospitalization time and lesser in-hospital medical supervision affect the safety outcome especially in a population that might be given the loading dose of clopidogrel and the maintenance dose for as long as 30 days?

1.2 Recommendation on Postmarketing Actions

To determine whether clopidogrel in its loading and maintenance (300/75 mg) dose formulation has an acceptable benefit/risk profile (as observed with its maintenance, without a loading, dose) in a population that is medically and procedurally aggressively treated and which is not medically supervised in a hospital setting for as long as the population that generated the beneficial effect findings, some postmarketing program assessing the benefit/risk profile in the US is strongly recommended. This is especially important if the duration of therapy will be longer than what was observed in CLARITY (mean exposure of 4 days).

1.2.1 Risk Management Activity

NA

1.2.2 Required Phase 4 Commitments

NA

1.2.3 Other Phase 4 Requests

NA

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Clopidogrel, marketed as Plavix, is an oral antiplatelet of the thienopyridine class that is currently indicated for acute coronary syndrome with unstable angina and NSTEMI.

The proposed new indication is ST elevation acute MI. COMMIT and CLARITY were two trials that enrolled subjects presenting with such condition with a total of 49,500 subjects.

COMMIT was a randomized, double-blind, placebo-controlled, 2 x 2 factorial trial that was conducted solely in China investigating two active treatments, clopidogrel and metoprolol in the prevention of death, reinfarction and/or stroke in subject admitted to the hospital for acute MI confirmed with ECG abnormalities. About a total of 46,000 patients subjects were randomized within 24 hour of the beginning of their symptoms to either clopidogrel 75 mg and ASA 162 mg or placebo and ASA 162 mg (and also to metoprolol or placebo), and followed for an average of one month. The study had two co-primary endpoints, a composite of death, reinfarction or stroke; and all-cause mortality.

CLARITY was an international, multicenter, randomized, double-blind, placebo-controlled clinical trial comparing clopidogrel plus ASA with ASA alone in subjects with STEMI treated with fibrinolysis. About 3,500 subjects were randomized within 6 hours of the onset of a qualifying STEMI in a 1:1 ratio to receive either clopidogrel, as a loading does of 300 mg and a maintenance dose of 75 mg, and aspirin, or placebo and aspirin. Subjects were to be followed for a maximum of eight days. The primary efficacy endpoint was the composite of an occluded infarct-related artery (defined as TIMI Flow Grade 0 or 1) on the pre-discharge angiogram or death or recurrent MI by the end of the calendar day following angiography, or by day 8 or hospital discharge (whichever comes first) for subjects who do not undergo angiography.

Other sources of data used include two postmarketing studies (MATCH and CHARISMA) and only summaries concerning bleeding from these two studies are reported in this review.

1.3.2 Efficacy findings

1.3.2.1 COMMIT Findings

COMMIT evaluated the effect of clopidogrel, omitting the 300 mg loading dose, on all-cause mortality and on the composite of death, re-infarction and stroke in subjects presenting with STEMI, but excluded and discontinued subjects who needed angioplasty.

As can be seen from Figure 1 page 15 and Figure 2 page 15, clopidogrel significantly reduced the risk of the composite outcome by 9% (p-value = 0.002) compared to placebo, and marginally significantly reduced the risk of death by 7% (p-value = 0.03).

As can be seen from Table 1 page 16, most of the effect on the composite outcome was mediated through the effect on death and myocardial reinfarction as a first occurrence of the composite. The effect on stroke was not different between the treatment arms.

Figure 3 page 16 and Figure 4 page 16, show that the effect of clopidogrel on the composite outcome was observed immediately starting on day 0, waning around day 2 and 3 with no difference between the two treatment arms and reappearing around day 4. The effect on the coprimary outcome of death was annulled from day 2 to day 7 before it reappeared around day 8.

Figure 1. Cumulative event rate of the combined endpoint in COMMIT (death, reinfarction or stroke)

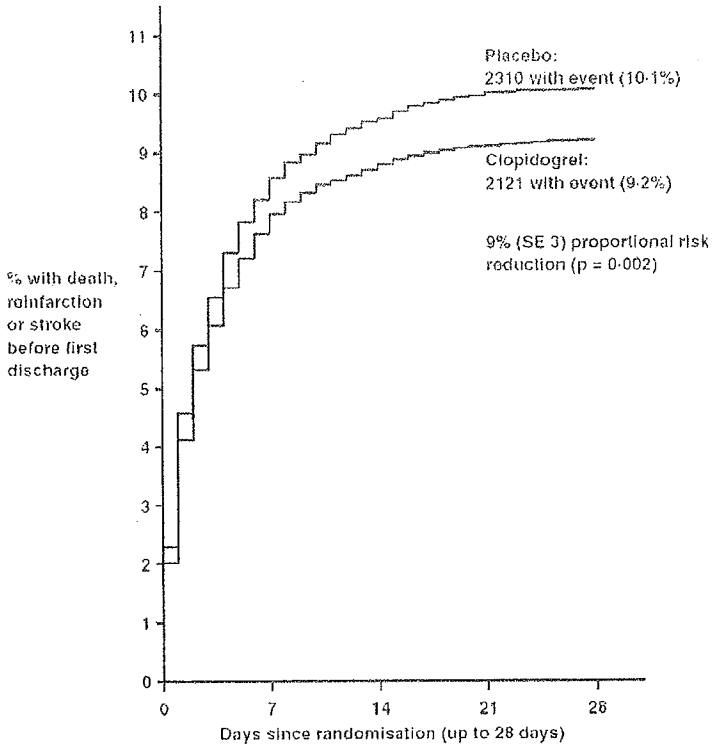


Figure 2. Cumulative event rate of death in COMMIT

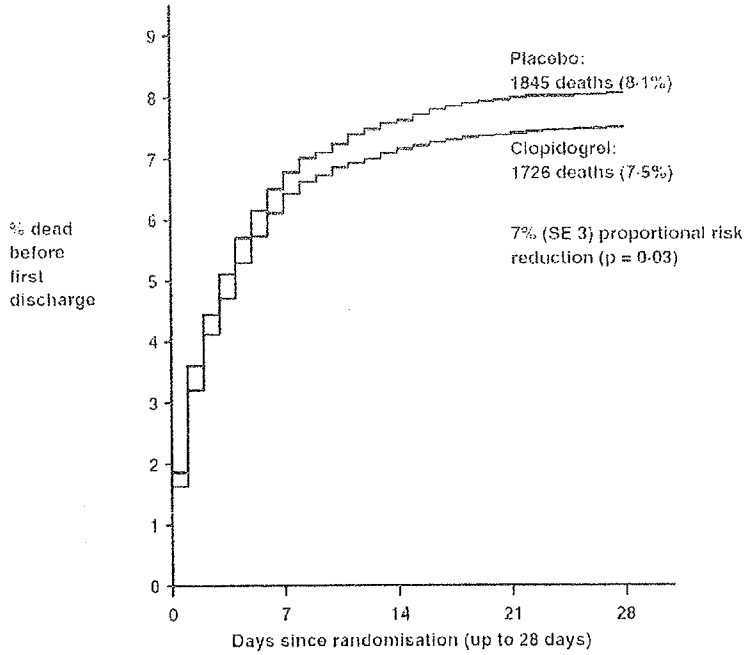


Table 1. Summary of frequency of the components of the primary endpoint

	Clopidogrel 75 mg	Placebo	Odds Ratio
Event N (%)	(N = 22961)	(N = 22891)	[95% CI]
Composite endpoint	2121 (9.2%)	2310 (10.1%)	0.91 [0.86, 0.97]
Death	1726 (7.5%)	1845 (8.1%)	0.93 [0.87, 0.99]
All re-MI	465	538	0.86 [0.73,0.98]
All strokes	214	246	0.87 [0.68,1.05]

Figure 3. Composite primary endpoint by day of the outcome event in COMMIT

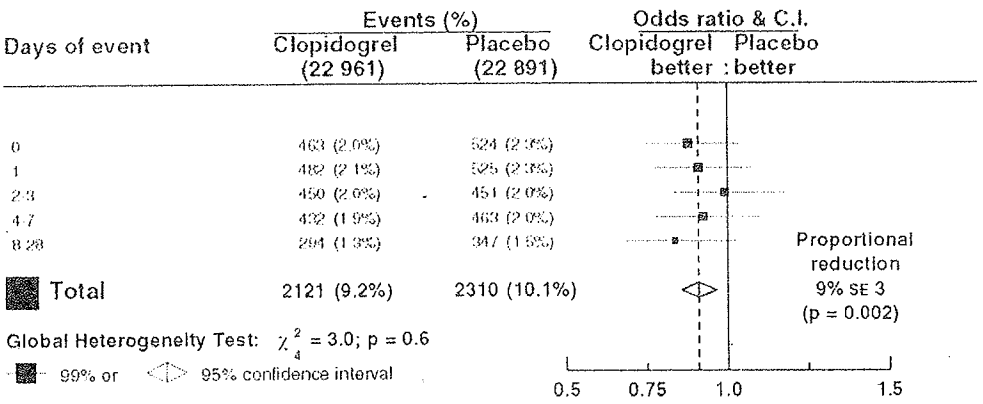


Figure 4. Mortality from any cause by day of the outcome event in COMMIT

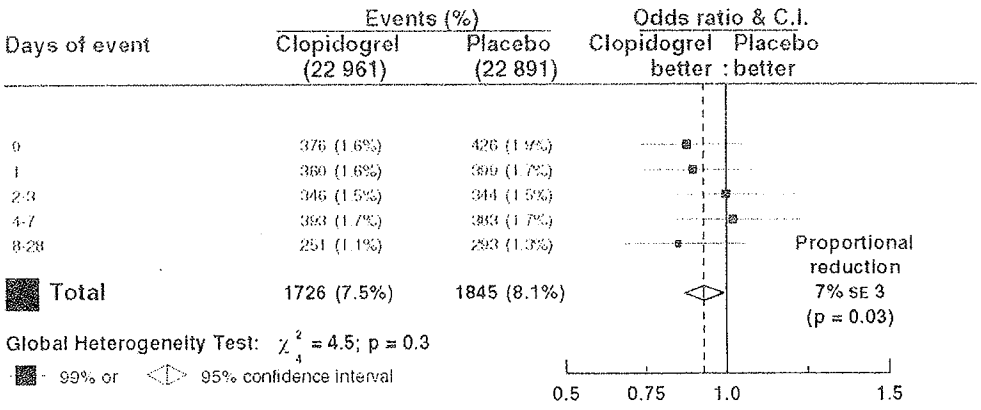


Figure 5. Composite endpoint by subgroups of baseline characteristics in COMMIT

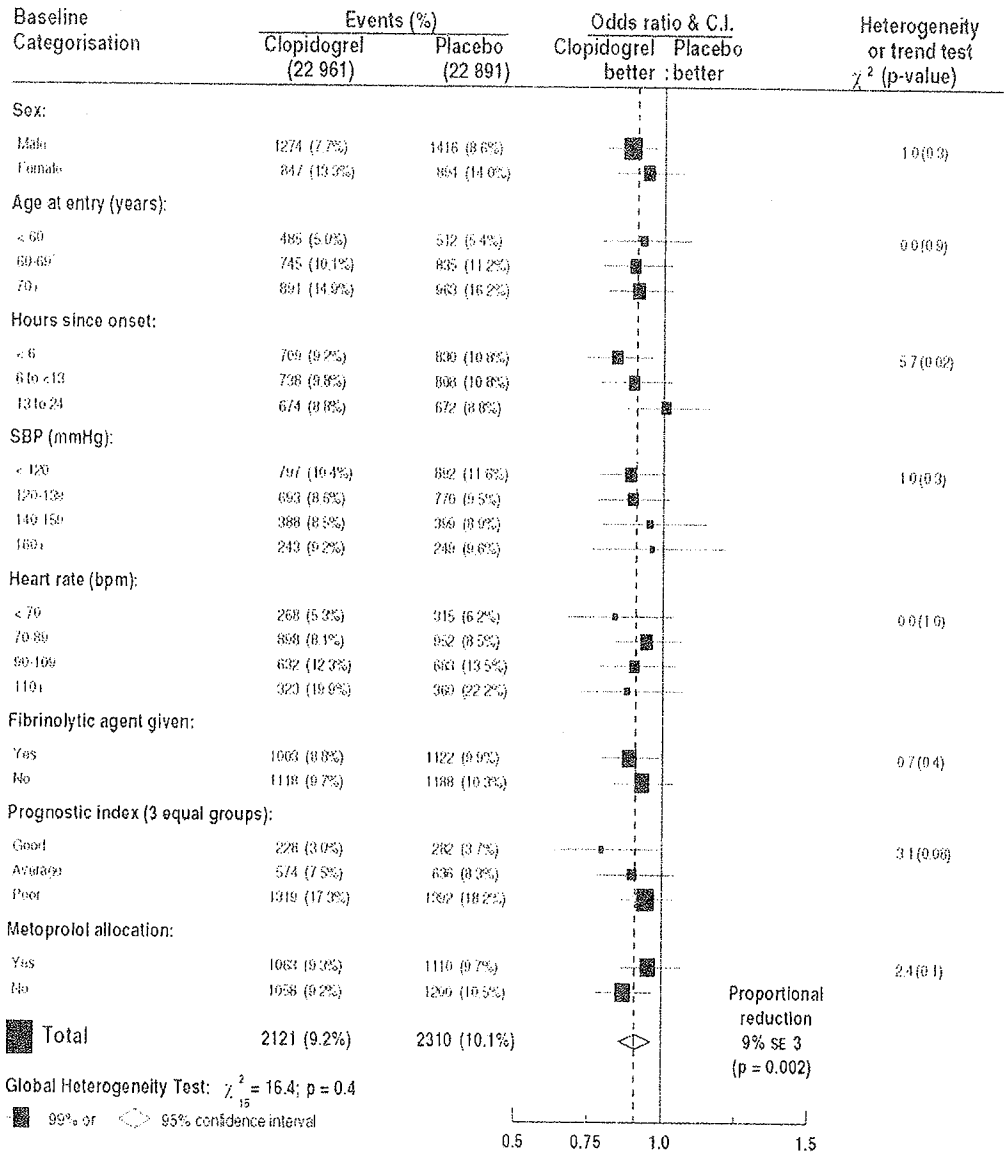
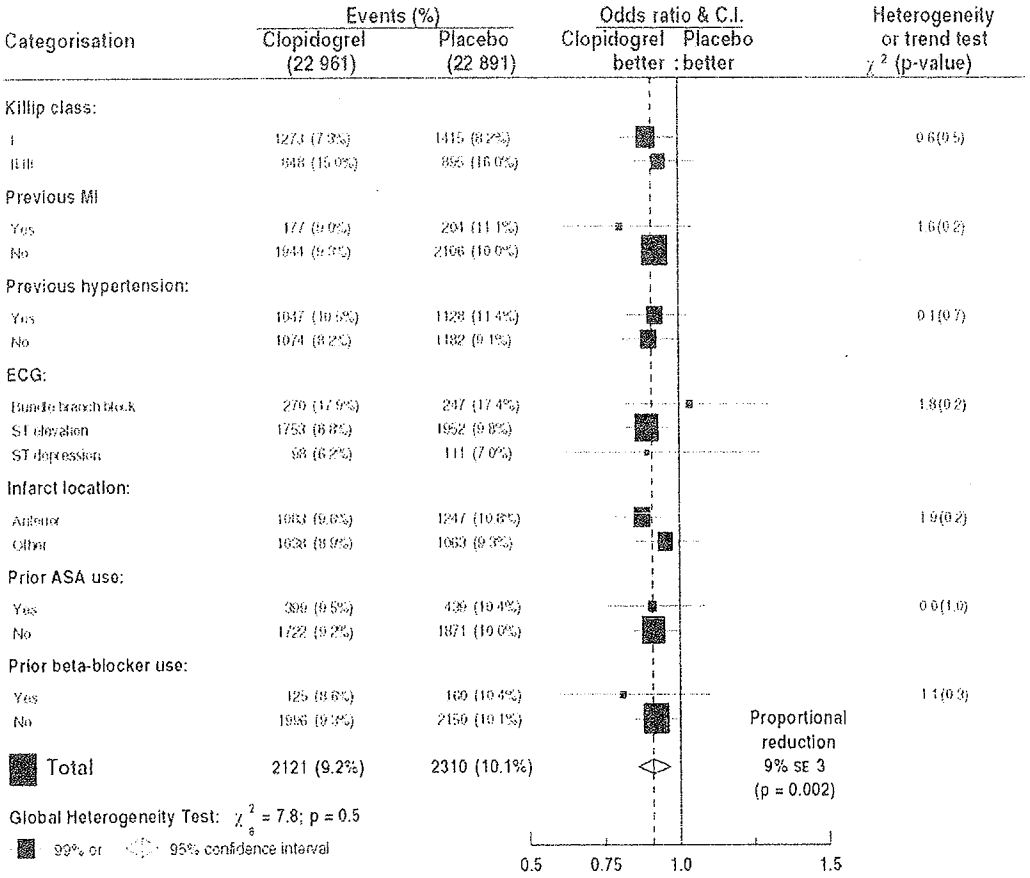


Figure 6. Composite endpoint by additional subgroups of baseline characteristics in COMMIT



As can be seen above, all subgroups trended in the right direction except for subjects whose randomization was delayed by 13 hours post beginning of symptoms and subjects with bundle branch block.

1.3.2.2 Discussion of COMMIT findings

These findings were driven by a prominent effect in subjects who were randomized within 13 hours of the beginning of symptoms (subgroup pre-specified analyses). No effect was observed in the subgroup (N=15328) where randomization to study drug occurred more than 13 hours since beginning of symptoms (Figure 5 page 17).

Clopidogrel and ASA were expected to act through the inhibition of platelet aggregation and the subsequent formation of new thromboemboli, but the findings discussed above limiting the effectiveness to the subgroup randomized within 13 hours is not supportive of this mechanism, and rather mimics the effect of thrombolysis in STEMI which ceases to have an effect after the first few hours. Also of note, two thirds of the subjects with delayed study therapy (> 13 hours) were not given fibrinolytics.

Most of the effect in this study was observed in subjects with anterior MI, and since this is usually more severe than non-anterior MI, the lack of effect past 13 hours post-randomization could be explained by the postponement of randomization in non-severe cases.

Also, the observed waning and disappearance of the effect of clopidogrel on both co-primary endpoints (Figure 3 page 16 and Figure 4 page 16) around the time when clopidogrel was expected to reach steady state and optimal pharmacodynamic effect, is interesting.

1.3.2.2 CLARITY findings

Table 2. Odds ratio of the primary composite endpoint (occurrence of an occluded IRA on the predischarge angiogram, or death or recurrent MI) in CLARITY

Primary efficacy endpoint	Clopidogrel N = 1752	Placebo N = 1739	p value	OR	95% CI
Number (%) of patients reporting the endpoint	262 (15.0)	377 (21.7)	0.00000036	0.64	0.53,0.76

Source: Sponsor's analysis

Table 3. Odds ratio of the primary composite endpoint in CLARITY by pre-angiography PTCA (Analysis by Dr. Zhang)

	Angioplasty prior to angiography				No angioplasty prior angiography			
	Clopidogrel N=964	Placebo N=966	OR	p-value	Clopidogrel N=788	Placebo N=773	OR	p-value
Number (%) reporting endpoint	147	222	0.66	<0.001	115	155	0.73	0.007

Source: Sponsor's analysis

Table 4. Individual components of the composite endpoint in CLARITY (ITT)

	Clopidogrel 1752	Placebo 1739
Occluded IRA		
N (subjects undergoing angiography)	1640	1634
n (%) patients reporting endpoint	192 (11.7)	301 (18.4)
Death		
n (%) patients reporting endpoint	45 (2.6)	38 (2.2)
Recurrent MI		
n (%) patients reporting endpoint	44 (2.5)	62 (3.6)

Source: Sponsor's analysis

Figure 7. Kaplan-Meir curve for death or recurrent MI up to day 30 in CLARITY (note: study drug was taken for a maximum of 8 days)

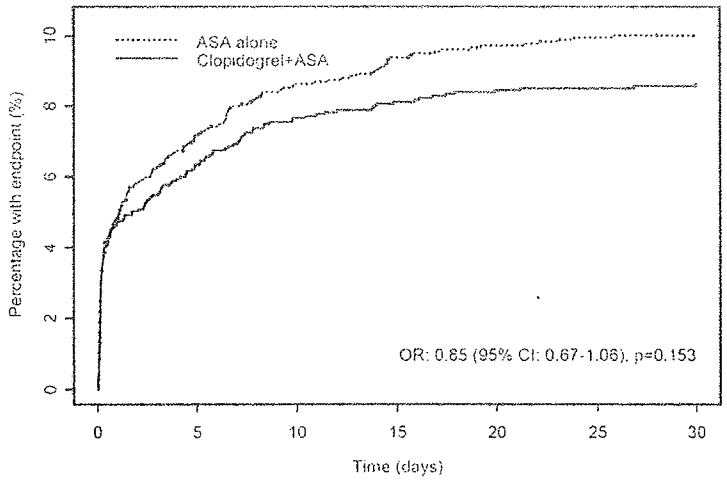


Table 5. Secondary endpoint analyses in CLARITY

Secondary efficacy endpoint	Clopidogrel	Placebo	p value	Mean difference	95% CI
Adjusted mean ST segment resolution of an ECG at 180 minutes after the first dose of study drug	N = 1068 53.01	N = 1021 55.12	0.223	-2.11	-5.50,1.28
	Clopidogrel	**Placebo**	**p value**	**OR**	**95% CI**
Number (%) of patients with occluded IRA on pre-discharge angiogram	N = 1640 192 (11.7%)	N = 1634 301 (18.4%)	<0.001	0.59	0.48,0.72
Number (%) of patients with death, recurrent MI, or recurrent myocardial ischemia (severe or leading to revascularization) by the time of the start of pre-discharge angiography	N = 1752 145 (8.3%)	N = 1739 162 (9.3%)	0.274	0.88	0.69,1.11

Source: Sponsor's analysis

Since the first secondary endpoint (ST segment resolution) was not statistically significant, testing of other secondary endpoints is not relevant because of the hierarchy testing procedure.

1.3.2.3 Discussion of CLARITY findings

CLARITY met its primary objective of a statistically significant difference between the treatment arms in the primary composite outcome (Table 2 page 19), occlusion of the infarct-related artery (IRA) or death or re-infarction. The difference in the primary outcome was robust and consistent across all subgroup categories (Figure 10 page 72 and Figure 11 page 73). This difference in effect was driven by the effect on the component of occluded IRA (Table 4 page19). Total number of events from the other two components constituted less than one third of the overall number of events.

Mortality (at the primary time point) a component of the composite outcome trended in the wrong direction ((45 (2.6%) and 38 (2.2%) see Table 4 page 19 for clopidogrel and placebo

respectively)), and the degree of ST segment resolution at 180 minutes post first dose of study drug (a secondary endpoint) was not different between the two treatment arms. These findings led to the question of whether the degree of patency of the infarct related artery is a good marker of a beneficial outcome in the general STEMI population represented by the study population.

> At the 30-day follow-up, however, the trends for death or recurrent MI trended toward a beneficial effect on clopidogrel, see Source: Sponsor's analysis

Figure 7 page 19.

1.3.3 Safety

Clopidogrel has been marketed for years and millions of subjects have been exposed to this drug, but its interaction with other anticoagulants and antithrombotics and fibrinolytics that are commonly used for the management of STEMI with regard to the risk of bleeding has not been investigated.

Data collection in COMMIT was limited because this study was focused on the evaluation of efficacy rather than safety. The report of serious adverse events was left to the discretion of the interpretation of the investigator which was based on their judgment of the relatedness to the study drug. The protocol specified that only serious adverse events judged by the investigator to be study drug related were to be reported.

Also, the loading dose was omitted in COMMIT, therefore the findings on bleeding and other adverse events know to be related to clopidogrel do not represent an accurate picture of what would happen when clopidogrel is taken by millions of STEMI patients.

As a result, the findings from this study should be interpreted cautiously with regard to the conclusion on the safety of clopidogrel in the STEMI population.

1.3.3.1 Bleeding

Bleeding is an important side effect of clopidogrel and it is the focus of this safety review. The COMMIT study by design collected limited information on bleeding. Information on major and other non-cerebral bleeding was collected under "Possible side-effects of trial treatment"; and information on stroke of probable hemorrhagic origin was collected under "Major events after randomization in hospital".

CLARITY on the other hand was more comprehensive in the collection of adverse events than COMMIT.

Bleeding was reported as a cause of death in COMMIT in 19 (0.1%) subjects on clopidogrel and 18 (0.1%) subjects on placebo; and in CLARITY in 13 (0.8%) subjects on clopidogrel and 10 (0.6%) subjects on placebo.

Bleeding was reported as a serious adverse event in CLARITY in 58 (3.4%) on clopidogrel and in 37 (2.2%) on placebo with 8 (0.4%) intracranial on clopidogrel compared to 12 (0.7%) on placebo; and 12 (0.7%) hemopericardium on clopidogrel compared to 3 (0.2%) on placebo;

Bleeding as a cause of study discontinuation was reported in COMMIT in 429 (1.9%) subjects on clopidogrel compared to 364 (1.6%) subjects on placebo with the majority of discontinuations due to non-cerebral hemorrhage (87% and 90% on clopidogrel and placebo respectively); around 6% (in each group) due to cerebral hemorrhage and the remaining (26 (6%) on clopidogrel and 14 (4%) on placebo) due to "high risk of bleeding".

In CLARITY, bleeding led to discontinuation in 29 (1.8%) subjects on clopidogrel compared to 27 (1.6%) subjects on placebo.

Except for intracranial hemorrhage where an excess was observed on placebo compared to clopidogrel, all bleeds were higher on clopidogrel compared to placebo.

The most common bleeds in CLARITY were gastrointestinal ((18 (1.0%) vs. 10 (0.6%)), followed by catheter site ((13 (0.8%) vs. 6 (0.4%)) and pericardial ((12 (0.7%) vs. 3 (0.2%)). Bleeding in subjects 70 years of age or older was more than 3 times higher on clopidogrel compared to placebo (23 (1.3%) vs. 7 (0.4%) respectively).

1.3.3.2 Other adverse events

COMMIT had the statistical power to possibly quantify the risk of TTP, liver failure and aplastic anemia, but COMMIT was not focused on hypotheses testing. Besides, when the study started, TTP was not yet determined to be an adverse event of clopidogrel.

No cases of thrombotic thrombocytopenic purpura were reported in either study and the numbers of subjects with thrombocytopenia in CLARITY were similar on both treatment arms.

There was a doubling of cardiac rupture on clopidogrel compared to placebo in CLARITY, but the numbers were small.

1.3.4 Dosing Regimen and Administration

Per the CURE trial findings optimal inhibition of platelet aggregation by clopidogrel is accomplished by delivering the 300 mg loading dose before initiation of the 75 mg maintenance dose.

1.3.5 Drug-Drug Interactions

NA

1.3.6 Special Populations

The findings of CURE showed that elderly patients (75 years of age and older) benefited less and were at a higher risk of bleeding than younger patients.

1.4 Generalizability of the Efficacy Findings

1.4.1 Factors that might affect the generalizability of the findings of COMMIT to a non-Chinese population and a US-type medical standards and practice

Table 6. Comparison of selected demographics and other baseline characteristics in COMMIT and CLARITY

	COMMIT	CLARITY
Ethnicity		
Caucasian	0%	90%
Asian	100%	2%
Other	0%	10%
Gender		
Male	72%	80%
Female	28%	20%
Age (yrs)		
Mean (SD)	61.3 (11.8)	57.4 (10.3)
Range	15.4-100.3	18-79
Mean SBP (SD) mmHg	128 (22.5)	135 (22.7)
Mean DBP (SD) mmHg	81 (14.5)	81 (14.3)
HR mean (SD) bpm	82 (17.2)	75 (17.3)
Prior MI	8%	9%
History of hypertension	43%	43%
Infarct location		
Anterior	54	41%
Non-anterior	46	59%
Duration of hospitalization		
Mean (SD) (days)	14.9 (7.8)	9.18 (6.16)

Table 7. Comparison of selected medical characteristics in COMMIT and CLARITY

	COMMIT[1]	CLARITY
Randomization within 6 hours	34%	91%
Randomization > 13 hours	33.4%	NA
Mean (SD) hours since onset	10.3 (6.7)	2.8 (2.1)
Use of nitrates	94%	72%
Fibrinolytics	55%	100%
Antiarrhythmics	22.3	9%
Diuretics	23%	18%
ACE-I	68%	55%
CCB	11.8	5%
Need for PTCA	3%[2]	56%
PTCA during index hospitalization[3]	0%	56%

[1] Urokinase, a fibrinolytic is commonly used in China while streptokinase is more commonly used in this country.
[2]These were discontinued from the protocol;
[3]Other cases of revascularizations such as those performed during a subsequent period of hospitalization (5%), as a scheduled day case (3%) and other (0.6%) are not included.

As can be seen from the table above, there are some substantial differences between the medical management of STEMI in the Chinese population and the Western population.

For the applicability of the findings of COMMIT in the US two questions remain unanswered:

1. Quantification of the added harm or benefit of the loading dose on the objectives targeted by COMMIT in a STEMI population medically managed per US medical standards;
2. Interaction and the quantification of interaction between clopidogrel and angioplasty;

1.4.2 Relevance of the Findings of CLARITY to a STEMI population

The findings of CLARITY are not conclusive with regard to how much clinical benefit is gained by reinstituting epicardial blood flow, especially in the context of an absence of a significant difference in the other components of the composite endpoint.

2 Introduction and background

Dose-dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses and 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 Days 3 and 7. At steady state, the average inhibition level observed with a dose of 75 mg 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.

Early use of ASA has become routine for a wide range of patients admitted to hospital with suspected or definite acute MI as a result of the findings of the Second International Study of Infarct Survival (ISIS-2), where one month of daily ASA (162 mg) reduced the risk of early death by approximately 25% and the risks of nonfatal reinfarction and stroke by approximately 50% in 17000 patients with suspected acute MI.

Both clopidogrel and ASA are approved for the reduction of cardiovascular events in acute coronary syndrome patients. It is believed by the sponsor that unstable angina and acute MI (with or without ST-segment elevation) share a common underlying pathophysiology and represent different degrees of the same disease. Therefore, it was hypothesized that the combination clopidogrel/ASA would have an effect in STEMI as it did in ACS.

2.1 Product Information

NA

2.2 Currently Available Treatment for Indications

ASA is the only other anti-platelet indicated in the treatment of acute ST elevation MI. Other non-platelet-targeted therapies include fibrinolytics and anti-coagulants.

2.3 Availability of Proposed Active Ingredient in the United States

Clopidogrel is currently marketed in the US and many other countries including China for the indication of acute coronary syndrome with unstable angina and NSTEMI.

2.4 Important Issues with Pharmacologically Related Products

NA

2.5 Presubmission Regulatory Activity

COMMIT was not under IND, but when the study was completed the Sponsor proposed the submission of this study for the support of an indication in acute ST elevation MI. The results of COMMIT were presented to the Agency in a meeting and it was recommended that a supplemental NDA be submitted containing the findings of COMMIT.

In the minutes of the pre-NDA meeting in July of 2005, the Agency commented that COMMIT was the only outcome study and it was conducted in a non-U.S. population. Therefore, Agency needs to be convinced that it is relevant despite differences in clinical practice and, consequently, will predict benefit to the U.S. population. The agency required that this argument be addressed clearly and in detail.

2.6 Other Relevant Background Information

NA

3 Significant findings from other review disciplines

3.1 CMC (and Product Microbiology, if Applicable)

NA

3.2 Animal Pharmacology/Toxicology

NA

4 Data sources, review strategy, and data integrity

4.1 Sources of Clinical Data

Sources of efficacy review depended on the pivotal studies, CLARITY and COMMIT. One of these studies, COMMIT, was conducted solely in China.

Sources for safety review relied mostly on the two pivotal studies, but findings published from other studies not submitted with this application, CHARISMA and MATCH, were also used especially with regard to bleeding.

4.2 Tables of Clinical Studies

Table 8. List of (submitted) clinical studies in acute ST elevation MI

Study	Study drug	Design	Objective	Duration	Population
COMMIT	Clopidogrel 75 mg + ASA	R, DB, PC	1. Death or re-infarction or stroke; 2. all deaths	Discharge up to Day 28	45852 Acute MI with ECG abnormalities

Study	Study drug	Design	Objective	Duration	Population
CLARITY	Clopidogrel 300 mg (loading dose), and 75 mg thereafter	R, DB, PC	Occluded infarct related artery or death or recurrent MI	Angiography, discharge up to Day 8	3491 STEMI treated with fibrinolytics

Table 9. Other studies used for safety review

Study	Study drug	Design	Objective	Duration	Population
MATCH	ASA 75 mg or placebo + Clopidogrel 75 mg	R, DB, PC	Ischemic stroke or MI or Vascular death or re-hospitalization for acute ischemic events	18 months	7599 recent IS or TIA + at least one vascular risk factor
CHARISMA	+ ASA 75-162 mg	R, DB, PC	MI or stroke or CV death	30 months	15603 at high risk of atherothrombotic events

IS: ischemic stroke
TIA: transient ischemic attack

4.3 Review Strategy

Safety from the pivotal studies was summarized for each study separately for a number of reasons including the omission of the loading dose in the COMMIT trial, differences in concomitant use of products that affect the outcome of bleeding and other differences that are inherent to a different study population.

Adverse events were blindedly re-coded by the reviewer and safety summary tables were generated.

Additional safety data from literature regarding bleeding was also summarized.

4.4 Data Quality and Integrity

Five investigation centers in China, for COMMIT, were audited by Dr. Gan of DSI. Centers were selected based on the number of subjects enrolled and on the observed effect of treatment. The comments from the audit were that there was sufficient documentation to assure that study subjects existed, eligibility criteria were fulfilled, assigned study medication was received and adverse events were adequately reported.

4.5 Compliance with Good Clinical Practices

In COMMIT, the informed consent method was left to the discretion of the study investigator to be obtained either in writing or orally from patients or their relatives. Per the following language, it seems that the consent was not obtained from some patients in certain circumstances: "since any delays starting treatment may lead to lives being lost, it may not be considered appropriate to discuss the various treatment options in prolonged detail. The degree and timing of consent is, therefore, left to individual doctors to decide of individual patients, in the light of local requirements and advice from any relevant local ethical committee".

Per the submission report, data from two centers were omitted from analyses because major GCP violations were detected.

The concept of obtaining an informed consent before enrollment into a study is a western concept that might not have fit well with the Chinese practice especially if it were going to delay delivery of the study drug that was going to be tested in a condition as acute as MI.

The purpose of COMMIT was to test a hypothesis not to change the conduct of a whole medical system. Therefore, the absence of diligence in consenting subjects with a rapidly evolving condition before study enrollment does not seem as grave as it would have been if the system were familiar and set for obtaining consent from every patient. B

4.6 Financial Disclosures

Sanofi-Synthelabo stated that they have not entered into any financial arrangement with any clinical investigators as defined in 21 CFR 54.

Some investigators did not provide financial equity ownership disclosure despite many attempts on the part of the Sponsor.

5 Clinical pharmacology

NA

6 Integrated review of efficacy

6.1 Indication

6.1.1 Methods

6.1.2 General Discussion of Endpoints

COMMIT

The primary endpoints for the clopidogrel treatment comparison were two: the composite of death, reinfarction or stroke; and death.

CLARITY

The primary endpoint was the composite of death or recurrent MI (by the time of the start of predischarge angiogram) or occlusion (TIMI Flow Grade 0 or 1) of the infarct related artery on the predischarge angiogram.

6.1.3 Study Design

6.1.3.1 COMMIT

COMMIT/CCS-2 "A randomized trial of clopidogrel plus aspirin (ASA) versus ASA alone and of metoprolol versus placebo, among patients with suspected acute myocardial infarction (MI)"

First patient was enrolled on July 30 1999 and last patient was completed on February 28 2005.

It was stated[1] that the trial was set jointly by the Clinical Trial Service Unit (Clinical Trial Service Unit) at the University of Oxford and the Beijing coordinating center based at the Fuwai Hospital, Chinese Academy of Medical Sciences, and that the general structure of the study was planned independently of the companies funding the study (Astra-Zeneca and Sanofi) who had no representatives in its organization and who were to remain blinded to the results as they accumulated.

This study was not conducted under an IND, therefore, the protocol was not submitted for review before initiation of the study. The protocol was published during the first year of randomization by the Second Chinese Cardiac Study (CCS-2) Collaborative Group[1].

This was a randomized, double-blind, placebo-controlled, 2 x 2 factorial trial investigating two active treatments, clopidogrel and metoprolol in the prevention of death, reinfarction and/or stroke in subject admitted to the hospital for acute MI confirmed with ECG abnormalities. The study was conducted solely in China. Subjects were randomized within 24 hour of the beginning of their symptoms in a 2 x 2 factorial design to clopidogrel or placebo, and metoprolol or placebo.

After randomization, subjects were to first receive their daily ASA 162 mg and clopidogrel 75 mg or ASA 162 mg and placebo, followed by three IV injections two to three minutes apart of either metoprolol 5 mg or placebo. The injections could be halted or stopped all together if blood pressure and/or heart rate were affected adversely.

Metoprolol 50 mg tablet or placebo was to be started 15 minutes after the last injection and given every 6 hours for the remaining of first day and the second day.

From the third day on, metoprolol 200 mg or placebo was to be given qd until Day 28 or discharge or death whichever came first.

All other patient management was at the discretion of the treating physician except that non-trial antiplatelets and betablockers were to be avoided during the 4-week trial duration.

At discharge or death a single page discharge form was to be filled with brief detail on compliance with study treatment, other treatment received during hospitalization, possible trial treatment side effects, major clinical events and cause of death if patient died. No post-hospital follow-up was required.

Subjects presenting within 24 hours of symptoms of suspected AMI with ECG abnormalities (ST elevation, ST depression or BBB) were considered for inclusion, provided that the treating doctor considered that there was no clear indication or contraindication to the trial therapy.

Reasons for exclusion from the trial were not pre-specified by the protocol but were at the discretion of the physician. Examples were given such as low benefit in subjects at low risk of death, or anticipated high risk of adverse events including previous allergy to aspirin, active bleeding or active hemostatic disorder, SBP < 100 mmHg, heart rate < 50 bpm, third degree heart block or cardiogenic shock.

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[1] Second Chinese Cardiac Study (CCS-2) Collaborative Group; Journal of Cardiovascular Risk 2000, 7:435-441

Random allocation and blinding of the study treatment at each participating center seem to have been conducted adequately by using pre-packed, sequentially numbered trial drug packs that had been prepared and sealed, in cases of 8 packs each, centrally. The physician responsible removed the next available randomization pack, completed the one-page entry form attached to the outside of the randomization pack before removing the box of trial treatments from the pack. A copy of the form was to be returned together with a copy of the most recent pre-entry ECG sheet on the day of study entry to the coordinating center in Beijing.

The choice of the clopidogrel dose, 75 mg, was based on the experience with the CAPRIE trial. By the time results of CURE became available showing the benefit of clopidogrel as a loading dose of 300 mg plus a 75 mg maintenance dose, 15000 subjects had already been enrolled in COMMIT, and the decision was not to amend the protocol.

The choice of ASA dose was based on the ISIS-2 study, where ASA at a dose of 162 mg daily was shown to be highly effective in the emergency treatment of acute MI[2].

Patients and investigators, the Clinical Trial Service Unit, both companies (Sanofi-Synthelabo Research and AstraZeneca) and all committees except the DSMB and statistician who performed interim analyses were blinded to the study drug identity for individual patients.

Concomitant fibrinolytic therapy, where indicated, was strongly encouraged. All other aspects of patient management were entirely at the discretion of the patient's own physician, except that nontrial beta-blocker and antiplatelet therapy were to be avoided during the scheduled treatment period (i.e., up to 4 weeks in the hospital) unless they were considered to be clearly indicated.

[2] ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction. ISIS-2. Lancet 1988;2(8607):349-60.

Figure 8. Schema of study design

	Clopidogrel plus aspirin	Aspirin alone	
Metoprolol	(i) **11500 patients** Active-clopidogrel plus aspirin + Active-metoprolol	(ii) **11500 patients** Placebo-clopidogrel plus aspirin + Active-metoprolol	Subtotal 1: 23 000 allocated **active-metoprolol**
No metoprolol	(iii) **11500 patients** Active-clopidogrel plus aspirin + Placebo-metoprolol	(iv) **11500 patients** Placebo-clopidogrel plus aspirin + Placebo-metoprolol	Subtotal 2: 23 000 allocated placebo-metoprolol
	Subtotal A: 23 000 allocated **active-clopidogrel** plus aspirin	Subtotal B: 23 000 allocated placebo-clopidogrel plus aspirin	

I. Efficacy evaluation

1. Primary efficacy variables

Primary efficacy was assessed based on the occurrence of two coprimary endpoints during the scheduled trial treatment period defined as randomization through Day 28, hospital discharge or death, and these endpoints were the composite of death, reinfarction or stroke; and all-cause mortality.

2. Secondary efficacy variables

The other planned efficacy outcomes included:

-any reinfarction (fatal and nonfatal);

-any stroke;

-any pulmonary embolism;

-other major clinical events in hospital during the scheduled treatment period that were explicitly recorded (i.e., cardiogenic shock, heart failure requiring persistent treatment, presumed cardiac rupture, ventricular fibrillation/other cardiac arrest);

II. Safety evaluation

Safety was assessed based on the incidence of bleeding and other adverse events.

All bleeding events were recorded as 1 of 3 types:

-major noncerebral bleeding (fatal or nonfatal requiring transfusion);

-other noncerebral bleeding;

-hemorrhagic stroke;

Other adverse events collected are:

-persistent hypotension (SBP <90 mmHg);

-bradycardia (heart rate persistently <40 beats/minute);

-"volunteered AEs";

Only SAEs that were both unexpected (unexpected AEs were defined as those that would not be expected among patients given antiplatelet therapy[3] or beta-blocker for suspected acute MI) and believed with a reasonable probability to be due to study treatment were to be reported. Per this definition and per the timing of COMMIT, many of the adverse events that were determined to be caused by clopidogrel in the post-marketing phase, e.g., TTP would have been missed.

III. Statistical analyses

It was stated that the statistical analysis plan has been revised blind to the specific treatment results (Data Analysis Plan, page 1006, EFC7018 \\CDSESUB1\N20839\S_034\2005-11-17).

1. Sample size

Original sample size calculation was based on the findings of the first Chinese cardiac study where an in-hospital death rate among subjects with acute MI was expected to be around 10% even in the presence of antiplatelet and/or fibrinolytic therapy.

If clopidogrel plus ASA produced a 10% reduction in mortality, then 15000 subjects in each treatment arm would be needed with a mortality rate of 9% (1350 out of 15000) on clopidogrel vs. 10% (1500) on placebo to show a statistically significant difference between the treatment groups (two-sided p-value = 0.003).

A further 4% of the patients were expected to experience non-fatal events including MI or stroke. It was then hypothesized that an overall risk reduction of 11% of the composite of death, reinfarction or stroke would be observed if active treatment with clopidogrel reduced major non-fatal events by 15%.

Later, after enrollment of 15,000 subjects, it was decided that the sample size needed to be increased because the overall event rates (8% for mortality and 10% for the combined outcome) observed were lower than anticipated (10% for mortality and 14% for the combined outcome), and there was concern that there was not enough power to meet the coprimary endpoint of mortality. Table below shows numbers of anticipated major events in a population of 46000 patients with suspected acute infarction.

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[3] Based on findings of trials that studied non-thionopyridin antiplatelets;

Table 10. Anticipated major efficacy events in the COMMIT population

Event	Proportional Risk Reduction	Active (23000)	Control (23000)	Two-sided p-values
Death	10%	2070 (9.0%)	2300 (10.0%)	0.003
Nonfatal re-infarction or stroke/arrest	15%	782 (3.4%)	920 (4.0%)	0.006
Total: death, re-infarction or stroke/arrest	11%	2530 (12.4%)	3220 (14.0%)	<0.0001

Source: Sponsor's analyses

2. Data analyses

Although patients in COMMIT/CCS-2 were randomized among four treatment groups in a 2 x 2 factorial design with placebo control, it was assumed that the intake of metoprolol by half of the subjects on clopidogrel would not interfere with the accurate assessment of the effect of clopidogrel on the study outcomes. Therefore, a two-way instead of a four-way comparison was planned for the evaluation of efficacy.

Information would be provided about whether the combined proportional effects of clopidogrel and metoprolol are approximately multiplicative.

All analyses were to be based on the ITT (randomly allocated study treatments including completers and dropouts). For each particular outcome or group of outcomes, the analysis would be of the number of patients suffering such an outcome at least once during the scheduled trial treatment period (randomization to whichever comes first of death in hospital, first discharge alive from hospital or day 28).

For the primary analyses, the comparisons would involve comparing the survival curves for the two treatment using "logrank" analyses of the two co-primary end-points, and all time-to-event analyses would be based on the first relevant event. If a patient is discharged alive before day 28 without a relevant event, the logrank analysis would treat this patient as if he were event-free up to day 28 (rather than censoring on the day of discharge) even if he/she had an event after discharge and before Day 28. If the time of an event is unknown for a particular patient, then it would be assumed to have been as early as possible given whatever information is available.

The effect of treatment was to be presented as odds ratio (clopidogrel vs. placebo) and absolute benefit per 1000 subjects (placebo minus clopidogrel).

No adjustment for multiplicity was to be made to the first co-primary endpoint. If the p-value of the second co-primary endpoint were more extreme than that for the first co-primary, the p-value for the latter was to be used in discussing the significance of the effects of treatment on it.

3. Interim analyses

It was stated that interim analyses of the primary endpoint (and other information such as serious adverse events believed by the physician responsible to be due to the trial treatment) were to be performed at regular intervals during the trial period and reviewed by an independent Data Monitoring Committee.

4. Subsidiary comparisons

The principal subsidiary comparisons were, as specified in the published protocol, the effects of clopidogrel on the combined end-point and on death, during days 0-1, days 2-7 and days 8-28 of the scheduled treatment period.

Other subsidiary outcomes analyzed using log-rank analysis (as for the primary endpoints) were MI (separating fatal and non-fatal); and stroke (separating ischemic versus hemorrhagic; with and without CT/MRI confirmation; with and without residual handicap).

Other subsidiary outcomes (where time to event was not collected or used) analyzed using ordinary odds ratio calculations and (95% CIs) were persistent hypotension; bradycardia; cardiogenic shock; heart failure requiring persistent treatment; presumed cardiac rupture; ventricular fibrillation; other cardiac arrest; and pulmonary embolus.

5. Subgroup analyses

Additional analyses of the effect of clopidogrel on the composite endpoint in population subgroups including:

-age: <60, 60-69, 70+;
-hours since onset of symptoms: <6, 6 to <13, 13 to 24;
-systolic blood pressure: <120, 120-139, 140-159, 160+;
-heart rate <70, 70-89, 90-109, 110+ bpm;
-Fibrinolytic therapy intake;
-Randomization to metoprolol;
-Prognosis defined as good, average and poor (three similar sized groups based on absolute risk) constructed using the prognostic index based on baseline characteristics using Cox regression analyses to identify and find the best fit for predictive variables (of the overall risk of death, reinfarction or stroke) and derive the coefficient of prediction.

Other non-prespecified subgroups of interest (defined according to baseline characteristics) included Killip class: I, II/III; previous MI: yes, no; history of hypertension: yes, no; ECG change including bundle branch block (BBB), ST elevation, ST depression; infarct location: anterior vs. other; prior ASA: yes, no; prior beta-blocker: yes, no.

6.1.3.2 CLARITY

CLARITY-TIMI 28 – "Clopidogrel as Adjunctive Reperfusion Therapy – Thrombolysis in Myocardial Infarction - 28: A randomized, double-blind, placebo-controlled trial comparing clopidogrel plus ASA versus ASA alone in patients with acute STEMI treated with fibrinolytic therapy"

This was an international, multicenter, randomized, double-blind, placebo-controlled clinical trial comparing clopidogrel plus ASA with ASA alone in subjects with STEMI treated with fibrinolysis.

Within 6 hours of the onset of a qualifying STEMI, subjects were to be randomized in a 1:1 ratio to receive either clopidogrel or placebo. All subjects were also to receive daily aspirin for the duration of the study.

Subjects were to receive study drug up to and including the day of angiography. For subjects who do not undergo angiography, administration of study drug was to continue up to and including day 8 or discharge from the hospital, whichever came first.

Coronary angiography was to be performed during the index hospitalization between 48 and 192 hours after the start of study medication to determine late patency of the infarct related artery. Also, 12-lead ECGs were to be obtained at baseline and at 90 and 180 minutes after administration of the loading dose of study drug to assess early reperfusion.

The loading dose (300 mg) was to be administered with the start of fibrinolysis, and subjects were to take 1 tablet (clopidogrel 75 mg or placebo) daily thereafter.

The dose of ASA depended on previous intake. If no ASA was taken within the previous 24 hours, 150-325 mg was to be given and if ASA was taken within 24 hours, 150-162 mg was to be given. This initial dose was to be chewed or given IV, and 75-162 mg was to be given daily thereafter.

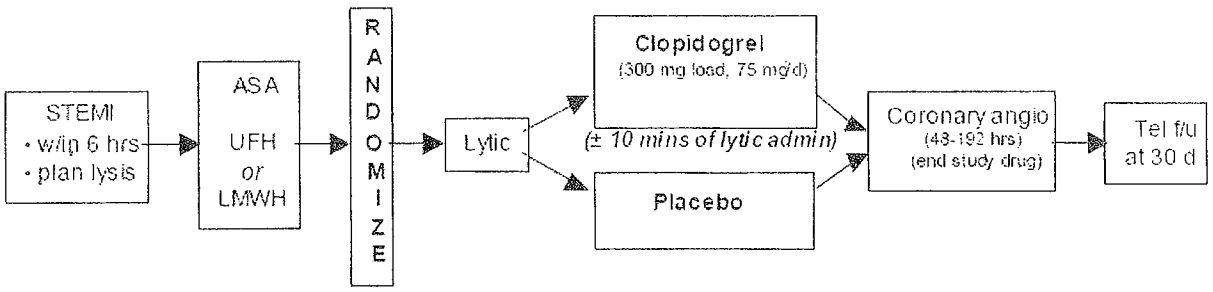
For subjects who undergo coronary stenting at the time of their initial angiogram, it is recommended that blinded study drug be discontinued and open-label clopidogrel be administered after the initial angiogram with a loading dose of 300 mg, followed by 75 mg daily.

Study drug was to be discontinued after angiography. In subjects who did not undergo angiography, it was to be discontinued after Day 8 or hospital discharge, whichever came first.

Other circumstances in which study drug was to be discontinued included CABG where study medication was to be withheld 5 days prior the procedure; need for chronic oral anticoagulation; major and unprovoked minor bleeding; and evidence of neutropenia (neutrophil count <1500/mm3), thrombocytopenia (platelet count <100,000/mm3) or thrombotic thrombocytopenic purpura (TTP).

All subjects were to be followed for 30 days through telephone contact regardless of whether or not they continued on the study drug.

Figure 9. Schema of study design



To be included were subjects 18 to 75 years of age with onset of ischemic discomfort at rest within 12 hours of randomization; symptoms of prolonged (>20 minutes) ischemic discomfort at rest associated with electrocardiographic evidence of new ST segment elevation ≥0.10 mV (80 msec after the J point) in at least 2 contiguous limb leads or ≥0.20 mV in at least 2 contiguous precordial (chest) leads, or left bundle branch block not known to be old; with a fibrinolytic agent (alteplase, reteplase, tenecteplase, or streptokinase), an anticoagulant (if receiving a fibrin-specific fibrinolytic), and ASA as planned treatment;

To be excluded were subjects with the intention of performing early coronary angiography (within 48 hours of fibrinolysis); treatment within 7 days prior to enrollment or planned treatment with clopidogrel or ticlopidine; contraindication to fibrinolysis; treatment with >4000 U bolus of UFH in patients ≤ 67 kg or treatment with 5000 U bolus of UFH in patients > 67 kg within 6 hours; treatment with >30 mg IV or >1.1 mg/kg SC of enoxaparin within 8 hours; or treatment with >130 U/kg of dalteparin within 8 hours; planned use of a glycoprotein IIb/IIIa inhibitor as part of the initial pharmacologic reperfusion therapy; anticipated use of urokinase as fibrinolytic; prior CABG; evidence of cardiogenic shock or acute pulmonary edema requiring intubation or an intra-aortic balloon pump; known serum creatinine >2.5 mg/dL; known hepatic insufficiency; platelet count <100,000 / mm^3; prior hypersensitivity (i.e., allergic reaction) to ASA, ticlopidine, or clopidogrel, prior neutropenia or heparin-induced thrombocytopenia; pregnancy or women of child-bearing potential who are not using an acceptable contraceptive method; previous enrollment in CLARITY-TIMI 28;

Protocol-specific major clinical events, including non-fatal recurrent myocardial infarction, stroke, and major hemorrhagic events were to be adjudicated by the trial's clinical event committee.

Use of non-study drug clopidogrel or ticlopdine was prohibited, except following coronary stenting.

Use of GP IIb/IIIa inhibitors (e.g., abciximab, eptifibatide, and tirofiban) was permitted only after the initial coronary angiogram is obtained;

All subjects were to be treated with one of the standard, approved fibrinolytic regimens at the discretion of the treating physician (e.g. alteplase, reteplase, tenecteplase, streptokinase).

All subjects receiving a fibrin-specific fibrinolytic (i.e., alteplase, reteplase, tenecteplase) were to be treated with a heparin regimen.

Subjects were to have three 12-lead study ECGs performed at pre-randomization and 90 and 180 minutes after administration of the study drug loading dose. These ECGs were to be sent to a blinded-TIMI ECG Core Laboratory for analysis.

The following laboratory parameters were to be evaluated at local clinical laboratories:
-complete blood count (CBC) with differential at baseline;
-coagulation parameters (PT, aPTT) at baseline and aPTT at 3 hours after the initiation of fibrinolysis;

-ACT (activated clotting time) to be measured (not in subjects receiving LMWH) prior to anticoagulation at the start of catheterization for angiography;
-CK-MB and troponin after the initiation of fibrinolysis: five times over 48 hours (i.e., approximately every 8 hours); post-revascularization: three times over the subsequent 24 hours (i.e., approximately every 8 hours); in suspected recurrent ischemia or reinfarction: 3 times over the subsequent 24 hours following onset of symptoms;

Interim clinical endpoints and adverse events were to be collected via a 30-day follow-up phone call, and medical records were to be retrieved and reviewed for events that resulted in hospitalization.

Subjects were to undergo coronary angiography during the index hospitalization between 48 and 192 hours after the start of study medication. TIMI Flow Grade (TFG) in the infarct-related artery was to be read by the TIMI Angiographic Core Laboratory, which was to be blinded to treatment assignment and clinical endpoints.

Cardiac catheterization before 48 hours was permitted in subjects who developed cardiogenic shock or persistent hemodynamic instability, manifest clear clinical evidence of failed reperfusion (e.g., persistent severe chest pain and <50% resolution of ST segment elevation), or develop recurrent ischemia as documented by recurrent ischemic ECG changes and ischemic chest pain.

Table 11. CLARITY-Study flow-chart

Evaluation/Procedure	Baseline	Time 0	90 min	180 min	24-48 hrs	Daily	Angiogram (Day 3-8)	Discharge	Day 30 Tele FU
Screening	x								
Informed Consent	x								
Medical History	x								
Physical Exam	x								
12-lead ECG	x		x	x					
Continuous ECG (selected sites)		x	x	x	x	x	x		
Hematology	x								
Coagulation parameters	x			x	x				
Myonecrosis markers	x				x		x		
Ischemia, myonecrosis, hemostatic, inflammatory, and neurohormonal markers (selected sites)	x						x		
ASA	x					x	x	x	x
Anticoagulant	x	x	x	x	x				
Randomization	x								
Fibrinolytic	x								
Study Drug		x				x	x		
Angiography							x		
Clinical events		x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x
Pharmacogenomic Informed Consent/Blood sample (selected sites)	x								

I. Efficacy Objectives

The primary objective of this study was to demonstrate in subjects with acute STEMI treated with fibrinolytic therapy that the combination of clopidogrel plus ASA would reduce the proportion of subjects who have an occluded infarct-related artery (defined as TIMI Flow Grade 0 or 1) on the pre-discharge angiogram, who die or have a recurrent MI by the end of the calendar day following angiography or by hospital discharge, whichever comes first[4].

The secondary objectives of this study were to demonstrate that clopidogrel plus ASA would reduce the proportion of subjects with an occluded infarct-related artery on the pre-discharge angiogram; improve early reperfusion as indicated by the degree of ST segment resolution on a 12-lead ECG at 180 minutes after study drug loading dose as compared to baseline; and that proportion of subjects who survive without recurrent MI or severe recurrent myocardial ischemia were higher with the combination of clopidogrel/ASA by the end of the calendar day following angiography or by hospital discharge, whichever came first[4].

Other objectives were of scientific interest and were to be examined as exploratory analyses, see 10.3 Other endpoints to be explored in CLARITY page 61.

II. Safety Objectives

The primary safety objective was to compare the treatment groups with regard to the rate of TIMI major bleeding;

The secondary safety objective was to evaluate the rate of intracranial hemorrhage, all stroke, all bleeding, or thrombocytopenia;

III. Statistical analyses

1. Sample size

A sample size of 1100 subjects per arm (or a total of 2200 subjects) would afford 82% power to detect a 5% absolute reduction (24% relative reduction) from 21% to 16% in the rate of the primary efficacy endpoint using a two-sided p=0.05 level test. This power calculation incorporated a continuity correction and assumed a dropout rate of 5%.

The event rate of death, recurrent MI, or TFG 0/1 in placebo was approximated from STEMI trials using UFH in which angiography revealed that approximately 20% of the subjects would be found to have TFG of 0/1 in the infarct-related artery (IRA), both at 60-90 minutes and at 5-7 days after randomization in these trials.

Populations considered for analyses included:

-ITT population in which subjects would be analyzed according to the study medication to which they were randomized irrespective of whether they received it;

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[4] For subjects who do not undergo angiography, day 8 or hospital discharge, whichever comes first, was to be used;

-Angiographic endpoints were to be assessed in subjects who were randomized and underwent angiography;

-Secondary analyses were to be performed in the ITT population in which a closed infarct-related artery was to be imputed for subjects who die prior to angiography.

-treated population was to consist of all subjects randomized who have received at least one dose of study medication. Safety analyses were to be conducted according to the study medication received;

-per-protocol population was to consist of the treated population excluding subjects who had major protocol violations (defined as those that interfere with the evaluation of the primary efficacy parameter). Major protocol violations were to be defined prior to unblinding of the study database. Secondary efficacy analyses were to be performed in this population to assess the robustness of the treatment effect;

2. Primary Efficacy Endpoints

The primary endpoint of this trial is the composite of an occluded infarct-related artery (defined as TIMI Flow Grade 0 or 1) on the pre-discharge angiogram or death or recurrent MI by the end of the calendar day following angiography[5].

Secondary Efficacy Endpoints

-TIMI Flow Grade 0 or 1 in the IRA on the pre-discharge angiogram;

-Death, recurrent MI, or recurrent myocardial ischemia (severe or leading to urgent revascularization) by the end of the calendar day following angiography[5];

-Degree of ST segment resolution at 180 minutes after study drug loading dose;

3. Efficacy Analyses

a. Primary Analyses

The primary endpoint was to be analyzed using logistic regression analysis with adjustment for type of fibrinolytic (fibrin-specific vs. non-fibrin specific), type of anticoagulant (UFH vs. LMWH vs. none) and infarct location (anterior vs. non-anterior), and tested at a significance level of <0.05. Additional analyses were to be conducted adjusting for any differences in baseline characteristics deemed clinically significant using a covariate-adjusted logistic regression model.

b. Secondary Analyses

-Angiographic (TFG 0/1 in the IRA) and clinical (death, MI, or recurrent myocardial ischemia) secondary efficacy endpoints were to be analyzed using the logistic regression model described in the primary analysis.

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[5] For subjects who do not undergo angiography, day 8 or by hospital discharge, whichever comes first, was to be used;

-Electrocardiographic secondary endpoint (degree of ST segment resolution at 180 minutes after study drug loading dose) were to be analyzed using a linear regression model with adjustment for type of fibrinolytic, type of anticoagulant, and infarct location.

-Additional analyses, if appropriate, were to be conducted adjusting for any additional differences in baseline characteristics deemed clinically significant using a covariate-adjusted regression model.

c. Subgroup Analyses

Analyses computing rates of the primary and secondary endpoints and point estimates with 95% confidence intervals for the effect of clopidogrel were to be conducted by type of fibrinolytic, type of anticoagulant, infarct location, randomization in ambulance/mobile care vs. in hospital, and by age and sex.

4. Safety analyses

Safety analyses were to be performed for major bleeding, all bleeding, stroke, intracranial hemorrhage, and thrombocytopenia. Additional analyses were to evaluate procedure- and non-procedure-related bleeding events. Incidence of AEs and SAEs were to be summarized by treatment group.

5. Interim analyses

An interim safety evaluation was performed by the DSMB on 14 April 2004. Partially blinded (treatment groups coded as Drug X and Drug Y) tabular summaries of stroke/ICH (total, hemorrhagic, and non-hemorrhagic), bleeding events (TIMI major and TIMI minor), and death for 1628 patients prepared by a Nottingham Clinical Research Limited's statistician not involved in the day-to-day activities of the study were reviewed and the recommendation was that the study should continue as planned.

6.1.4 Efficacy Findings

See 1.3 Summary of Clinical Findings page 13.

6.1.5 Clinical Microbiology

NA

6.1.6 Efficacy Conclusions

Both CLARITY and COMMIT despite significantly meeting their primary objectives did not demonstrate that clopidogrel is clinically beneficial in ST elevation acute myocardial infarction in subjects optimally managed by the state of the art treatment regimens.

There is no data that support that late patency of the infarct-related artery as is shown by CLARITY is correlated with a beneficial clinical outcome.

Extrapolating the findings of COMMIT to a STEMI population that is managed more aggressively and with all available treatment modalities as is the case with patients in the US would be unwise since it is not known whether clopidogrel would add anything to the state of the

art treatment modalities applied in this country. Also, it is not known how the interaction between a strong antiplatelet such as clopidogrel with its loading dose regimen and clothing/coagulation inhibitors would manifest.

7 Integrated review of safety

For all safety analyses in the CLARITY study, the dataset analyzed was the Treated Population which was constituted of 1733 subjects on clopidogrel and 1719 on placebo. Four patients randomized to clopidogrel and 8 patients randomized to placebo received incorrect study drug and for safety analyses they were included in the group according to the study drug received.

7.1 Methods and Findings

Table 12. Proportion of patients with treatment-emergent AEs leading to death, any treatment-emergent SAEs, or AEs leading to permanent discontinuation in CLARITY

	Clopidogrel N = 1733	Placebo N = 1719
Patients with TEAEs		
Angiography[1]	817 (47.1)	821 (47.8)
End of follow-up	983 (56.7)	981 (57.1)
Patients with TESAE		
Angiography1	306 (17.7)	314 (18.3)
End of follow-up2	431 (24.9)	452 (26.3)
Patients with TEAEs with an outcome of death by end of follow-up[2]	78 (4.5)	79 (4.6)
Patients with AEs leading to permanent discontinuation by end of follow-up[2]	119 (6.9)	147 (8.6)

Source: Sponsor's analyses

[1] Events from the time of first dose of study drug until the calendar day following pre-discharge angiography, or by Day 8 or hospital discharge, whichever came first, for patients who did not undergo an angiography;

[2] Events from the time of first dose of study drug until end of follow-up, Day 30;

7.1.1 Deaths

A. COMMIT

Table 13. Death by cause in COMMIT

Event	Clopidogrel (N = 22961)	Placebo (N = 22891)
All death[1]	1726 (7.5)	1845 (8.1)
Arrhythmia	432 (1.9)	454 (2.0)
Asystole	642 (2.8)	697 (3.0)
Cardiac rupture	188 (0.8)	210 (0.9)
Cardiogenic shock	503 (2.2)	562 (2.5)
Reinfarction	113 (0.5)	101 (0.4)
Stroke	72 (0.3)	87 (0.4)
Pulmonary embolus	26 (0.1)	18 (0.1)
Severe bleeding	19 (0.1)	14 (0.1)
Other cardiac	21 (0.1)	18 (0.1)
Other noncardiac (see Table 18 page 68)	26 (0.1)	53 (0.2)

Source: Sponsor's analyses

[1] Some deaths had more than one cause reported

B. CLARITY

Table 14. Number of patients who reported serious adverse event with an outcome of death up to the end of follow-up (Day 30) CLARITY

Preferred term of AEs leading to death	Clopidogrel 1733 N (%)	Placebo 1719 N (%)
All adverse events leading to death	78 (4.5)	79 (4.6)
Bleeding	13 (0.8)	10 (0.6)
Non-bleeding	75 (4.3)	71 (4.1)
Cardiovascular disorders	34 (2.0)	34 (2.0)
Cardiac failure	32 (1.8)	32 (1.9)
Cardiac failure left	1 (0.1)	3 (0.2)
Ventricular septal defect	5 (0.3)	2 (0.1)
Heart rate and rhythm	42 (2.4)	41 (2.4)
Arrhythmia	2 (0.1)	4 (0.2)
Arrhythmia ventricular	0 (0.0)	1 (0.1)
AV block	0 (0.0)	2 (0.1)
AV block complete	6 (0.3)	4 (0.2)
Cardiac arrest	30 (1.7)	28 (1.6)
Fibrillation atrial	1 (0.1)	0 (0.0)
Fibrillation ventricular	13 (0.8)	13 (0.8)
Tachycardia ventricular	9 (0.5)	4 (0.2)
Myo-, endo-, pericardial and valve disorders	24 (1.4)	21 (1.2)
Myocardial rupture (post infarct)	16 (0.9)	9 (0.5)
Myocardial infarction	6 (0.3)	8 (0.5)
Pericardial effusion	2 (0.1)	3 (0.2)
Angina pectoris	1 (0.1)	4 (0.2)
Coronary artery disorder	1 (0.1)	0 (0.0)
Resistance mechanism disorders	1 (0.1)	1 (0.1)
Sepsis	1 (0.1)	1 (0.1)
Vascular (extracardiac) disorders	4 (0.2)	2 (0.1)
Cerebrovascular disorder	2 (0.1)	2 (0.1)
Vascular disorder	2 (0.1)	0 (0.0)
Platelet, bleeding and clotting disorders	13 (0.8)	11 (0.6)
Hemopericardium	9 (0.5)	3 (0.2)
Cerebral hemorrhage	1 (0.1)	7 (0.4)
Embolism pulmonary	1 (0.1)	0 (0.0)
GI hemorrhage	1 (0.1)	0 (0.0)
Haematemesis	1 (0.1)	0 (0.0)
Hemorrhage intracranial	1 (0.1)	0 (0.0)
Thrombosis coronary	0 (0.0)	1 (0.1)
Body as a whole - general disorders	1 (0.1)	2 (0.1)
Death	0 (0.0)	2 (0.1)
Sudden death	1 (0.1)	0 (0.0)
CNS disorders	0 (0.0)	1 (0.1)
Convulsions grand mal	0 (0.0)	1 (0.1)

Preferred term of AEs leading to death	Clopidogrel 1733 N (%)	Placebo 1719 N (%)
Respiratory system disorders	2 (0.1)	4 (0.2)
Hypoxia	0 (0.0)	1 (0.1)
Pneumonia	1 (0.1)	0 (0.0)
Pneumonitis	0 (0.0)	1 (0.1)
Respiratory insufficiency	1 (0.1)	2 (0.1)
Urinary system disorders	0 (0.0)	1 (0.1)
Renal failure acute	0 (0.0)	1 (0.1)

Source: Sponsor's analyses

-Myocardial rupture and expectedly hemopericardium caused more deaths on clopidogrel than on placebo.
-VT caused twice as many deaths on clopidogrel;

7.1.2 Other Serious Adverse Events

A. COMMIT

Serious adverse events were not collected in the COMMIT trial. Only those SAEs that were both "unexpected" (defined as those that would not be expected among patients given antiplatelet therapy[6] or beta-blocker for suspected acute MI) and believed with a reasonable probability to be due to study treatment were to be reported.

At the time of design of COMMIT, a number of adverse events that became later known to be associated with clopidogrel were not taken into account and thus were not investigated.

B. CLARITY

Table 15. Serious adverse events observed up to the end of the day following angiography, or Day 8 or hospital discharge whichever came first in CLARITY

SOC Preferred term	Clopidogrel 1733 N (%)	Placebo 1719 N (%)
All treated patients	1733	1719
All adverse events	306 (17.7)	314 (18.3)
Application Site Disorders	1 (0.1)	0 (0.0)
Injection site bleeding	1 (0.1)	0 (0.0)
Autonomic Nervous System Disorders	1 (0.1)	0 (0.0)
Syncope	1 (0.1)	0 (0.0)
Body as a Whole - General Disorders	3 (0.2)	1 (0.1)
Allergic reaction	1 (0.1)	0 (0.0)
Chest pain	2 (0.1)	0 (0.0)
Death	0 (0.0)	1 (0.1)
Cardiovascular Disorders General,	55 (3.2)	67 (3.9)
Cardiac failure	45 (2.6)	60 (3.5)
Cardiac failure left	3 (0.2)	4 (0.2)
Heart disorder	1 (0.1)	0 (0.0)

[6] Based on findings of trials that studied non-thionopyridin antiplatelets;

SOC Preferred term	Clopidogrel 1733 N (%)	Placebo 1719 N (%)
Hypertension aggravated	3 (0.2)	1 (0.1)
Hypotension	5 (0.3)	2 (0.1)
Ventricular septal defect	5 (0.3)	2 (0.1)
CNS Disorders	3 (0.2)	1 (0.1)
Convulsions	1 (0.1)	0 (0.0)
Convulsions grand mal	0 (0.0)	1 (0.1)
Encephalopathy	2 (0.1)	0 (0.0)
Gastro-Intestinal System Disorders	3 (0.2)	2 (0.1)
Duodenal ulcer hemorrhagic	1 (0.1)	0 (0.0)
Gastric ulcer hemorrhagic	0 (0.0)	1 (0.1)
Gastritis hemorrhagic	2 (0.1)	1 (0.1)
Heart Rate and Rhythm Disorders	82 (4.7)	90 (5.2)
Arrhythmia	1 (0.1)	1 (0.1)
Arrhythmia nodal	0 (0.0)	1 (0.1)
Arrhythmia ventricular	0 (0.0)	1 (0.1)
AV block	3 (0.2)	4 (0.2)
AV block complete	10 (0.6)	11 (0.6)
Bradycardia	4 (0.2)	1 (0.1)
Cardiac arrest	29 (1.7)	29 (1.7)
Fibrillation atrial	6 (0.3)	5 (0.3)
Fibrillation ventricular	39 (2.3)	42 (2.4)
Tachycardia ventricular	19 (1.1)	16 (0.9)
Liver and Biliary System Disorders	0 (0.0)	1 (0.1)
Cholelithiasis	0 (0.0)	1 (0.1)
Metabolic and Nutritional Disorders	1 (0.1)	0 (0.0)
Diabetes mellitus	1 (0.1)	0 (0.0)
Myo-, Endo-, Pericardial and Valve Disorders	152 (8.8)	180 (10.5)
Angina pectoris	63 (3.6)	68 (4.0)
Angina pectoris aggravated	7 (0.4)	9 (0.5)
Coronary artery disorder	0 (0.0)	1 (0.1)
Myocardial infarction	49 (2.8)	79 (4.6)
Myocardial ischemia	12 (0.7)	13 (0.8)
Myocardial rupture (post infarct)	15 (0.9)	8 (0.5)
Pericardial effusion	4 (0.2)	3 (0.2)
Pericarditis	5 (0.3)	7 (0.4)
Neoplasms	4 (0.2)	2 (0.1)
Carcinoma	1 (0.1)	0 (0.0)
Colon carcinoma	0 (0.0)	1 (0.1)
GI neoplasm malignant	2 (0.1)	0 (0.0)
Neoplasm malignant	1 (0.1)	1 (0.1)
Rectal carcinoma	0 (0.0)	1 (0.1)
Platelet, Bleeding and Clotting Disorders	56 (3.2)	37 (2.2)
Cerebral hemorrhage	6 (0.3)	13 (0.8)
Embolism limb	1 (0.1)	1 (0.1)
Epistaxis	2 (0.1)	1 (0.1)
GI hemorrhage	6 (0.3)	4 (0.2)
Gingival bleeding	0 (0.0)	1 (0.1)

SOC Preferred term	Clopidogrel 1733 N (%)	Placebo 1719 N (%)
Haemarthrosis	0 (0.0)	1 (0.1)
Haematemesis	4 (0.2)	1 (0.1)
Haematoma	2 (0.1)	1 (0.1)
Haematuria	3 (0.2)	0 (0.0)
Hemorrhage intracranial	2 (0.1)	0 (0.0)
Hemorrhage NOS	2 (0.1)	0 (0.0)
Hemorrhage rectum	2 (0.1)	1 (0.1)
Hemopericardium	10 (0.6)	3 (0.2)
Hemorrhage of operative wound	15 (0.9)	4 (0.2)
Oral hemorrhage	1 (0.1)	0 (0.0)
Thrombocytopenia	6 (0.3)	6 (0.3)
Thrombosis coronary	0 (0.0)	1 (0.1)
Psychiatric Disorders	1 (0.1)	0 (0.0)
Dementia	1 (0.1)	0 (0.0)
Red Blood Cell Disorders	1 (0.1)	4 (0.2)
Anemia	1 (0.1)	4 (0.2)
Reproductive Disorders, Female	0 (0.0)	1 (0.1)
Endometrial hyperplasia	0 (0.0)	1 (0.1)
Resistance Mechanism Disorders	3 (0.2)	1 (0.1)
Sepsis	3 (0.2)	1 (0.1)
Respiratory System Disorders	9 (0.5)	7 (0.4)
Apnea	1 (0.1)	0 (0.0)
Bronchitis	1 (0.1)	0 (0.0)
Chest x-ray abnormal	1 (0.1)	0 (0.0)
Hemothorax	1 (0.1)	1 (0.1)
Hypoxia	0 (0.0)	1 (0.1)
Pneumonia	0 (0.0)	2 (0.1)
Pneumonia lobar	1 (0.1)	1 (0.1)
Pneumonitis	0 (0.0)	1 (0.1)
Pulmonary edema	3 (0.2)	0 (0.0)
Respiratory insufficiency	2 (0.1)	1 (0.1)
Secondary Terms	1 (0.1)	1 (0.1)
Alcohol problem	1 (0.1)	0 (0.0)
Post-operative wound infection	0 (0.0)	1 (0.1)
Skin and Appendage Disorders	1 (0.1)	0 (0.0)
Angioedema	1 (0.1)	0 (0.0)
Urinary System Disorders	0 (0.0)	2 (0.1)
Renal failure acute	0 (0.0)	2 (0.1)
Vascular (Extracardiac) Disorders	6 (0.3)	7 (0.4)
Cerebrovascular disorder	3 (0.2)	7 (0.4)
Peripheral ischemia	1 (0.1)	0 (0.0)
Vascular disorder	2 (0.1)	0 (0.0)

Source: Sponsor's analyses

-Hemopericardium was reported as SAE in (10 vs. 3) three as many times reported on clopidogrel as on placebo;

-Hemorrhage of operative wound and hematemesis were reported as SAEs in (15 vs. 4) four as many subjects on clopidogrel;

-Ventricular septal defect was reported as SAE in (5 vs. 2) twice and a half as many subjects on clopidogrel;

-Myocardial rupture was reported as SAE in (15 vs. 8) almost twice as many subjects on clopidogrel;

-Other hemorrhages including GI, hematuria were reported as SAEs more commonly on clopidogrel;

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

A. COMMIT

Table 16. Main reasons for stopping study drug prematurely in COMMIT

Reason for discontinuation	Clopidogrel	Placebo
PTCA or stent	684 (3.0)	713 (3.1)
Adverse event	549 (2.4)	494 (2.2)
MI not confirmed	103 (0.4)	90 (0.4)
Patient refusal	40 (0.2)	35 (0.2)
Other	233 (1.0)	233 (1.0)

Source: Sponsor's analyses

-The main reason for discontinuation in COMMIT was PTCA or need for a stent, followed by adverse events; detailed information on adverse events was not collected;

B. CLARITY

Table 17. Reason for discontinuation in CLARITY

Reason for discontinuation	Clopidogrel 1733	Placebo 1719
Patients permanently discontinued	69 (4.0)	64 (3.7)
AE/SAE	35 (50.7)	31 (48.4)
Subject no longer meets study criteria	4 (5.8)	6 (9.4)
Subject withdrew consent	8 (11.6)	4 (6.3)
Administrative	22 (31.9)	22 (34.4)
Other	0 (0.0)	1 (1.6)

Source: Sponsor's analyses

7.1.3.2 Adverse events associated with dropouts

A. COMMIT

Table 18. Discontinuations due to adverse events by reason in the COMMIT study

	Clopidogrel N=22961	Placebo N=22891	OR
Non-cerebral bleeding	375 (1.63)	326 (1.42)	1.15

	Clopidogrel N=22961	Placebo N=22891	OR
Non-MI/suspected non-MI	103 (0.45)	90 (0.39)	1.14
Non-specific symptoms (nausea, cough, pain)	85 (0.37)	79 (0.35)	1.07
Cannot swallow(coma, vomiting, psychiatric disorder)	45 (0.2)	47 (0.21)	0.95
No use of study drug due to serious complications including death	30 (0.13)	40 (0.17)	0.75
Hemorrhagic or mixed stroke	27 (0.12)	24 (0.1)	1.12
High risk of bleeding (easy bruising, etc)	26 (0.11)	14 (0.06)	1.85
Risk factor for bleeding(Ulcer, aneurysm; etc)	23 (0.1)	24 (0.1)	0.96
Allergy/skin pruritus	21 (0.09)	24 (0.1)	0.87
Low WBC and/or Low PCT	17 (0.07)	15 (0.07)	1.13
Cardiac failure/cardiac failure aggravation/reduced cardiac function	16 (0.07)	13 (0.06)	1.23
Acute GI (appendicitis; pancreatitis, gastric perforation, etc)	5 (0.02)	5 (0.02)	1.00
Cardiac arrest	3 (0.01)	2 (0.01)	1.50
Cerebral infarction	3 (0.01)	2 (0.01)	1.50
Pericarditis/Pericarditic fluid	3 (0.01)	2 (0.01)	1.50
Prolonged coagulating time	3 (0.01)	5 (0.02)	0.60
Thrombolytic therapy/heparin	3 (0.01)	5 (0.02)	0.60
Abnormal liver function (Hepatitis)	2 (0.01)	6 (0.03)	0.33
Acute pancreatitis	2 (0.01)	0 (0)	-
Hemolytic anemia/Hb Urine/drug-induced haemolysis	2 (0.01)	1 (0)	1.99
Renal failure	1 (0)	4 (0.02)	0.25
Cerebral tumor (bleeding)	1 (0)	0 (0)	-
Re-infarct	0 (0)	7 (0.03)	0.00
Gout	0 (0)	1 (0)	0.00

Source: Reviewer's analyses

B. CLARITY

Table 19. Adverse events leading to permanent discontinuation of study drug in CLARITY

SOC Preferred term	Clopidogrel 1733		Placebo 1719	
	No. of reports	No. of pts (%)	No. of reports	No. of pts (%)
All adverse events	140	119 (6.9)	172	147 (8.6)
Non-bleeding	114	100 (5.8)	148	126 (7.3)
Myocardial infarction	34	34 (2.0)	55	55 (3.2)
Angina pectoris	31	31 (1.8)	31	31 (1.8)
Bleeding	26	25 (1.4)	24	23 (1.3)
Cardiac failure	6	6 (0.3)	20	17 (1.0)
Myocardial ischemia	6	6 (0.3)	10	10 (0.6)
Cerebral hemorrhage	6	6 (0.3)	11	11 (0.6)
Fibrillation ventricular	5	5 (0.3)	7	7 (0.4)
Tachycardia ventricular	4	4 (0.2)	2	2 (0.1)
Angina pectoris aggravated	4	4 (0.2)	4	4 (0.2)
GI hemorrhage	4	4 (0.2)	4	4 (0.2)
Hemorrhage of operative wound	4	4 (0.2)	1	1 (0.1)
Hypotension	2	2 (0.1)	1	1 (0.1)

SOC Preferred term	Clopidogrel 1733		Placebo 1719	
	No. of reports	No. of pts (%)	No. of reports	No. of pts (%)
Cardiac arrest	2	2 (0.1)	3	3 (0.2)
Hepatic enzymes increased	2	2 (0.1)	0	0 (0.0)
Pericarditis	2	2 (0.1)	1	1 (0.1)
Haematemesis	2	2 (0.1)	1	1 (0.1)
Haematoma	2	2 (0.1)	0	0 (0.0)
Hemopericardium	2	2 (0.1)	0	0 (0.0)
Angioedema	2	2 (0.1)	0	0 (0.0)
Vascular disorder	2	2 (0.1)	0	0 (0.0)
Cardiac failure left	1	1 (0.1)	1	1 (0.1)
Ventricular septal defect	1	1 (0.1)	2	2 (0.1)
Duodenal ulcer hemorrhagic	1	1 (0.1)	0	0 (0.0)
Duodenitis	1	1 (0.1)	0	0 (0.0)
Dyspepsia	1	1 (0.1)	0	0 (0.0)
Gastritis hemorrhagic	1	1 (0.1)	0	0 (0.0)
Gastroesophageal reflux	1	1 (0.1)	0	0 (0.0)
AV block complete	1	1 (0.1)	1	1 (0.1)
Back pain	1	1 (0.1)	0	0 (0.0)
GI neoplasm malignant	1	1 (0.1)	0	0 (0.0)
Neoplasm malignant	1	1 (0.1)	0	0 (0.0)
Epistaxis	1	1 (0.1)	0	0 (0.0)
Hemorrhage intracranial	1	1 (0.1)	0	0 (0.0)
Hemorrhage NOS	1	1 (0.1)	0	0 (0.0)
Anemia	1	1 (0.1)	1	1 (0.1)
Respiratory insufficiency	1	1 (0.1)	1	1 (0.1)
Oliguria	1	1 (0.1)	0	0 (0.0)
Cerebrovascular disorder	1	1 (0.1)	0	0 (0.0)
Chest pain	0	0 (0.0)	1	1 (0.1)
Chest pain precordial	0	0 (0.0)	1	1 (0.1)
Hypertension aggravated	0	0 (0.0)	1	1 (0.1)
Gastric ulcer hemorrhagic	0	0 (0.0)	1	1 (0.1)
Fibrillation atrial	0	0 (0.0)	1	1 (0.1)
Coronary artery disorder	0	0 (0.0)	1	1 (0.1)
Pericardial effusion	0	0 (0.0)	1	1 (0.1)
Haematuria	0	0 (0.0)	2	2 (0.1)
Hemorrhage rectum	0	0 (0.0)	1	1 (0.1)
Oral hemorrhage	0	0 (0.0)	1	1 (0.1)
Thrombocytopenia	0	0 (0.0)	1	1 (0.1)
Depression	0	0 (0.0)	1	1 (0.1)
Hemothorax	0	0 (0.0)	1	1 (0.1)
Renal failure acute	0	0 (0.0)	1	1 (0.1)

Source: Sponsor's analyses

7.1.3.3 Other significant adverse events

1. Bleeding

A. Bleeding in CLARITY

Table 20. Adjudicated TIMI bleeding in CLARITY

Safety endpoint	Clopidogrel N = 1733	Placebo N = 1719	OR	p value	95 CI
N (%) of patients reporting any bleeding	302 (17.4)	221 (12.9)	1.43	<0.001	1.19,1.73
Adjudicated bleeding	67 (3.9)	44 (2.6)	1.51	-	-
Major	23 (1.3)	19 (1.1)	1.20	-	-
Minor	17 (1.0)	9 (0.5)	1.87	-	-
Minimal	28 (1.6)	16 (0.9)	1.74	-	-
None	1 (0.1)	1 (0.1)	0.99	-	-
Non-adjudicated bleeding	246 (14.2)	185 (10.8)	1.32	-	-

Source: Sponsor's analyses

Table 21. Adjudicated stroke

Event (%)	Clopidogrel N = 1733	Placebo N = 1719	p value	OR	95% CI
Stroke/ICH	10 (0.6)	21 (1.2)	0.048	0.47	0.20,1.05
ICH	8 (0.5)	12 (0.7)	0.380	0.66	0.23,1.76

Source: Sponsor's analyses

Table 22. Bleeding in CLARITY by site

Site of bleeding	Clopidogrel 1733	Placebo 1719	OR
Gastrointestinal	18 (1.04)	10 (0.58)	1.79
Catheter site	13 (0.75)	6 (0.35)	2.15
Pericardial	12 (0.69)	3 (0.17)	3.97
Other	11 (0.63)	8 (0.47)	1.36
Intracranial	8 (0.46)	12 (0.7)	0.66
Genitourinary	6 (0.35)	4 (0.23)	1.49
Subcutaneous	3 (0.17)	1 (0.06)	2.98
Retroperitoneal	0 (0)	1 (0.06)	0.00

Source: Sponsor's analyses

-Except for intracranial, the risk of bleeding in all other sites especially pericardial, catheter and gastrointestinal was higher on clopidogrel;

Table 23. Bleeding by intensity and seriousness in CLARITY

Intensity	Clopidogrel 1733	Placebo 1719	OR
Mild	5 (0.29)	9 (0.52)	0.55
moderate	35 (2.02)	16 (0.93)	2.17
Severe	27 (1.56)	20 (1.16)	1.34
Not serious	9 (0.52)	8 (0.47)	1.12
Serious	58 (3.35)	37 (2.15)	1.55

Source: reviewer's analysis

A slight increase in serious bleeding on clopidogrel compared to placebo was observed;

Table 24. Bleeding by age quartiles in CLARITY

Age	Clopidogrel 1733	Placebo 1719	OR
<60	19 (1.1)	10 (0.58)	1.88
60-65	9 (0.52)	11 (0.64)	0.81
66-70	16 (0.92)	16 (0.93)	0.99
>=70	23 (1.33)	7 (0.41)	3.26

Source: reviewer's analysis

Bleeding risk is greater in the oldest subjects of the study population and this is consistent with the findings of the CURE study;

Table 25. Bleeding by weight quartiles in CLARITY

Weight in Kg	Clopidogrel 1733	Placebo 1719	OR
< 68	14 (0.81)	12 (0.7)	1.16
>= 68 and <76.4	16 (0.92)	11 (0.64)	1.44
>=76.4 and <85	15 (0.87)	9 (0.52)	1.65
>=85	21 (1.21)	9 (0.52)	2.31

Source: reviewer's analysis

As body weight increased, the risk of bleeding increased; this could be explained by the added risk of bleeding from increasing doses (weight adjusted) of concomitant fibrinolytics and/or anticoagulants in this population;

B. Bleeding in COMMIT

Table 26. Bleeding (cerebral vs. non-cerebral) in COMMIT

	Clopidogrel N=22999	Placebo N=23065	OR
Any bleeding	927 (4.0)	819 (3.6)	1.13
Major noncerebral bleed	71 (0.31)	66 (0.29)	1.07
Other noncerebral bleed	843 (3.7)	722 (3.1)	1.16
Stroke, probably hemorrhagic	56 (0.24)	56 (0.24)	1.0

Source: reviewer's analysis

Table 27. Bleeding by age quartiles in COMMIT

Any bleed[1] by age in years	Placebo	Clopidogrel	OR
All ages N	22999	23065	
Bleeding	819 (3.6)	927 (4.0)	1.13
<=52.73 years N	5699	5811	
Bleeding	150 (2.63)	143 (2.46)	0.93
>52.73 <=62.92 years N	5810	5711	
Bleeding	173(2.98)	233 (4.08)	1.37
>62.92 <=70.2 years N	5732	5785	
Bleeding	228 (3.98)	271 (4.68)	1.18
>70.2 years N	5754	5755	
Bleeding	268 (4.66)	280 (4.87)	1.04

Source: reviewer's analysis

[1]Includes major and other non-cerebral + hemorrhagic stroke

The above analyses show no difference in the risk of bleeding between the different age groups in the COMMIT population. This could be explained by the omission of the loading dose in this study and/or the scarcity of the data collected.

Table 28. Major non-cerebral bleeding by age quartiles

Major non-cerebral bleed	Clopidogrel N=22999	Placebo N=23065	OR
All ages	71 (0.31)	66 (0.29)	1.07
Age <=52.73	5 (0.09)	7 (0.12)	0.75
52.73< age <=62.92	12 (0.21)	17 (0.29)	0.72
62.92< age <=70.2	24 (0.41)	23 (0.4)	1.03
Age > 70.2	30 (0.52)	19 (0.33)	1.58

Source: reviewer's analysis

C. Bleeding in other studies

Summarized safety from published findings of MATCH and CHARISMA follow:

Table 29. Bleeding in the MATCH study[7]

Bleeding Events	Clopidogrel + ASA N (%)	Clopidogrel + placebo N (%)	Diff. bet treatments [CI]	p
Life-threatening	96 (3)	49 (1)	2.6% [0.64,1.88]	<0.0001
Fatal	16 (<1)	11 (<1)	0.13% [-0.14,0.40]	
Non-fatal	81 (2)	38 (1)	1.15% [0.59,1.79]	
Symptomatic intracranial	40 (1)	25 (1)	0.40% [-0.01,0.82]	
Major	73 (2)	22 (1)	1.36% [0.86,1.86]	<0.0001
Minor	120 (3)	39 (1)	2.16% [1.51,2.81]	<0.0001

[7] Hans-Christoph Diener; Lancet 2004:364:331-37

Table 30. Bleeding (adjudicated) in the CHARISMA study[8]

Bleeding Events N (%)	Clopidogrel (n=1659)	Placebo (n=1625)	RR (95% CI)	p
Fatal	7 (0.4)	5 (0.2)	1.71 (0.50,5.84)	0.38
Primary ICH	7 (0.4)	6 (0.4)	1.14 (0.38,3.39)	0.81
GUSTO severe bleeding	34 (2.0)	20 (1.2)	1.67 (0.96,2.88)	0.07
GUSTO moderate bleeding	36 (2.2)	22 (1.4)	1.60 (0.95,2.71)	0.08

2. Thrombocytopenia

Table 31. Incidence of thrombocytopenia in the CLARITY trial

	Clopidogrel	Placebo
Total number of patients	1733	1719
Number of patients reporting endpoint	6 (0.3%)	6 (0.3%)
Number of patients reporting severe thrombocytopenia	1 (0.1%)	2 (0.1%)
Number of patients reporting profound thrombocytopenia	1 (0.1%)	0 (0.0%)

7.1.4 Other Search Strategies

Other search strategies used included literature reporting of findings from other studies conducted for marketing purposes[7,8].

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

The methods of eliciting adverse events in the two pivotal studies were different which led to separate summarization of their safety.

COMMIT had an abbreviated CRF, the protocol did not specify that other adverse events be collected beside those that were serious (believed to be unexpected and related to the study), leading to death or discontinuation, and was not organized to deal with the multitude of common adverse events to which the study population was predisposed.

Very few adverse events were reported spontaneously (volunteered), summarized in table below, and these are non-informative because they do not reflect the incidence of common adverse event in the whole study population.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

All reported adverse events in CLARITY were re-coded by the reviewer, blinded to treatment allocation, into preferred-term categories.

7.1.5.3 Incidence of common adverse events

[8] Bhatt DL, Fox KA, Hacke W, et al. 2006, in press

See 7.1.5.4 Common adverse event tables below.

7.1.5.4 Common adverse event tables

A. COMMIT

Table 32. Volunteered adverse events in COMMIT

Event Class	Clopidogrel (N = 22961)	Placebo (N = 22891)
Any	542(2.4)	509 (2.2)
AV Block	372 (1.6)	355 (1.6)
Other Vascular	90 (0.4)	83 (0.4)
Hematological	3 (0.0)	5 (0.0)
Respiratory	30 (0.1)	28 (0.1)
Gastrointestinal	2 (0.0)	1 (0.0)
Allergic	13 (0.1)	11 (0.0)
Other	32 (0.1)	26 (0.1)

Source: Sponsor's analyses

B. CLARITY

Table 33. Number of patients who reported TEAEs (≥ 2.5%) in CLARITY

	Clopidogrel		Placebo	
All treated patients	No. of reports	1733	No. of reports	1719
All adverse events	1810	817 (47.1)	1810	821 (47.8)
Hypotension	112	107 (6.2)	96	92 (5.4)
Cardiac failure	103	98 (5.7)	121	111 (6.5)
Angina pectoris	97	96 (5.5)	136	118 (6.9)
Tachycardia ventricular	93	89 (5.1)	76	75 (4.4)
Headache	89	86 (5.0)	84	80 (4.7)
Chest pain	80	72 (4.2)	86	70 (4.1)
Bradycardia	58	55 (3.2)	44	44 (2.6)
Fever	54	53 (3.1)	56	53 (3.1)
Fibrillation ventricular	53	52 (3.0)	53	51 (3.0)
Vomiting	51	50 (2.9)	39	39 (2.3)
Myocardial infarction	50	50 (2.9)	79	79 (4.6)
Nausea	42	41 (2.4)	48	48 (2.8)
Fibrillation atrial	39	37 (2.1)	45	44 (2.6)

Source: Sponsor's analyses

7.1.5.5 Identifying common and drug-related adverse events

Bleeding is a common adverse event of clopidogrel especially in elderly subjects, but the CLARITY (the more reliable of the two studies with regard to adverse event ascertainment) did not show a big difference between the treatment arms. The CLARITY population was exposed to a number of anti-clotting, antithrombotic and anti-coagulation drugs and was closely observed

and monitored for bleeding, also exposure to the study drug was short with a maximum of eight day which could explain the absence of a difference in bleeding between the two treatment arms.

7.1.5.6 Additional analyses and explorations

As was shown by age analyses of CURE data, elderly subjects in CLARITY bled more than younger subjects.

7.1.6 Less Common Adverse Events

The adverse events that are observed rarely on clopidogrel and that were identified in its postmarketing phase include the following:

-thrombocytopenia: was ascertained in CLARITY only and the incidence was similar in both active and control treatment groups;

-TTP: none was reported in the CLARITY study population, and it is not sure whether it was ascertained in the COMMIT study population;

-hepatic failure: only one case reported in the CLARITY study population, and none in the COMMIT study population;

7.1.7 Laboratory Findings

No laboratory data were collected for COMMIT or CLARITY.

7.1.8 Vital Signs

NA

7.1.9 Electrocardiograms (ECGs)

NA

7.1.10 Immunogenicity

NA

7.1.11 Human Carcinogenicity

NA

7.1.12 Special Safety Studies

NA

7.1.13 Withdrawal Phenomena and/or Abuse Potential

NA

7.1.14 Human Reproduction and Pregnancy Data

NA

7.1.15 Assessment of Effect on Growth

b(4)

7.1.16 Overdose Experience

NA

7.1.17 Postmarketing Experience

Clopidogrel has been approved and marketed for ACS and there have been about —— people exposed worldwide.

b(4)

7.2 Adequacy of Patient Exposure and Safety Assessments

Clopidogrel has been approved for ACS and there is ample experience with its safety profile, and as a result, the two studies that were submitted for this sNDA focused mostly on efficacy.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

In reviewing safety, data from submitted studies CLARITY and COMMIT and from post marketing studies, MATCH[9] and CHARISMA[10], and known post marketing experience were used to draw conclusions on safety.

7.2.1.1 Study type and design/patient enumeration

See Table 8. List of (submitted) clinical studies in acute ST elevation MI, page 25; and Table 9. Other studies used for safety review page 26.

7.2.1.2 Demographics

See 10.5.2 Demographics page 63.

7.2.1.3 Extent of exposure (dose/duration)

Table 34. Extent of exposure to study drug in CLARITY

Extent of exposure	Clopidogrel N= 1733	Placebo N=1719	Overall N=3452
Number of days			
1	283 (16.3)	329 (19.1)	612 (17.7)
2	74 (4.3)	76 (4.4)	150 (4.3)
3	210 (12.1)	203 (11.8)	413 (12.0)
4	334 (19.3)	286 (16.6)	620 (18.0)
5	263 (15.2)	253 (14.7)	516 (14.9)
6	205 (11.8)	218 (12.7)	423 (12.3)
7	184 (10.6)	177 (10.3)	361 (10.5)
8	123 (7.1)	116 (6.7)	239 (6.9)

[9] Hans-Christoph Diener; Lancet 2004:364:331-37;
[10] Bhatt DL, Fox KA, Hacke W, et al. 2006, in press;

Extent of exposure	Clopidogrel N= 1733	Placebo N=1719	Overall N=3452
>=9	57 (3.3)	61 (3.5)	118 (3.4)
Mean	4.5	4.4	4.4
Median (SD)	4 (2.3)	4 (2.4)	4 (2.3)
Range	1.0-13.0	1.0-13.0	1.0-13.0

Table 35. Extent of exposure to study drug in COMMIT

Durationa (days)	Clopidogrel (N = 22961)	Placebo (N = 22891)	Overall (N = 45852)
Mean (SD)	14.9 (7.9)	14.9 (7.8)	14.9 (7.8)
Median	14.0	14.0	14.0

Extent of exposure was estimated using the duration of hospitalization because no exposure information was available for approximately 7% of patient who prematurely discontinued treatment.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Safety findings, especially bleeding, from two other studies were summarized in this review, and these are described briefly below. These were not integrated with the primary source data because they were conducted in populations that are slightly different from the ones studied for the indication under review. Also these studies were conducted for postmarketing purposes and can stand on their own especially with regard to bleeding.

7.2.2.1 Other studies

MATCH (Management of ATherothrombosis with Clopidogrel in High-risk patients with recent transient ischemic attack or ischemic stroke) study randomized, double-blind placebo-controlled trial that was conducted in high-risk cerebrovascular patients receiving clopidogrel 75 mg. Included were subjects with either recent TIA or ischemic stroke plus at least one cardiovascular risk factors.

The primary endpoint was the composite of MI or ischemic stroke, or vascular death or re-hospitalization for an acute ischemic event. The study enrolled 7599 subjects and followed them for an average of 17.5 months.

CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) was a randomized, double-blind, placebo-controlled trial that was conducted in subjects with at least one of the following: documented coronary disease and/or documented cerebrovascular disease and/or documented symptomatic PAD and/or two major or one major and two minor or three minor risk factors.

Subjects with requirement for clopidogrel, need for chronic therapy with high dose (162 mg/day) ASA or non-steroidal anti-inflammatory drug, current use of oral anti-thrombotic medications with intention for long-term treatment, planned revascularization procedure were excluded.

The primary endpoint was the composite of first occurrence of MI, stroke or cardiovascular death. The study enrolled 16603 subjects and followed them for an average of 30 months.

7.2.2.2 Postmarketing experience

Post-marketing experience established an association between clopidogrel and TTP; liver failure; pancreatitis; agranulocytosis; autoimmune-type disorders including vasculitis, lichen planus, toxic epidermal necrolysis and interstitial pneumonitis; and glomerulopathy and increased creatinine.

In the postmarketing phase it was shown (MATCH data) that the addition of ASA to clopidogrel added no benefit to subjects with recent TIA and stroke; instead, it increased their risk of fatal and major bleeding.

Clopidogrel was shown (CHARISMA data) to be associated with increased risk of all cause mortality and cardiovascular mortality (RR=1.41, CI: [1.02,1.95]) and RR=1.74, CI: [1.16, 2.62]) respectively) in subjects characterized as having multiple risk factors but no ACS or STEMI.

7.2.3 Adequacy of Overall Clinical Experience

COMMIT, the largest clopidogrel clinical trial to have been conducted and the only study that could have evaluated the incidence and possibly confirmed the risk of at least some of the adverse events that were observed in its postmarketing-phase, failed to accomplish this goal. Except for bleeding adverse events and efficacy parameters, COMMIT is practically useless in answering some of the safety questions that were not answered by previous less powered trials.

CLARITY adequately assessed some of the adverse events that were experienced by its study population, but was underpowered for testing causality associations.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

NA

7.2.5 Adequacy of Routine Clinical Testing

NA

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

NA

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

NA

7.2.8 Assessment of Quality and Completeness of Data

One of the main studies in this program, COMMIT, is lacking in adverse event evaluation.

7.2.9 Additional Submissions, Including Safety Update

No additional submissions were planned and this was communicated to the Division because both studies were completed by the time of the initial submission.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.3.1 Bleeding

See

7.1.3.3 Other significant adverse events page 48;

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Data were not pooled across the COMMIT and CLARITY studies because the level of adverse evaluation was different.

7.4.1.1 Pooled data vs. individual study data

NA

7.4.1.2 Combining data

NA

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

NA

7.4.2.2 Explorations for time dependency for adverse findings

COMMIT exposed subjects for an average of less than a month and CLARITY for an average of less than one week, and the difference in exposure between subjects in each study was not big enough to explore the effect of duration on the risk of adverse events in the STEMI population.

7.4.2.3 Explorations for drug-demographic interactions

Per findings of CURE, subjects 75 years of age and older bled more often and experienced more severe bleeding than younger subjects. Similarly an age dose-response was observed for bleeding in the CLARITY population.

7.4.2.4 Explorations for drug-disease interactions

NA

7.4.2.5 Explorations for drug-drug interactions

All subjects randomized into COMMIT and CLARITY were suspected for an acute MI which dictate medical conducts and procedures that could magnify the risk and severity of bleeding.

7.4.3 Causality Determination

NA

8 Additional clinical issues

8.1 Dosing Regimen and Administration

The current label says: Plasma concentrations of the main circulating metabolite are significantly higher in elderly (≥75 years) compared to young healthy volunteers but these higher plasma levels were not associated with differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.

Per the findings of CURE, the risk of bleeding increased with age, and the label was modified to reflect this risk as an added footnotes to Table / CURE Incidence of bleeding complications (% patients) of the label. b(4)

Clopidogrel was investigated and is indicated in ACS as a loading dose of 300 mg and a maintenance dose of 75 mg. No dose formulation lower than 75 mg was investigated, and the investigation of omitting the loading dose, especially in patients at high risk of bleeding events, including the elderly, was not investigated.

8.2 Drug-Drug Interactions

NA

8.3 Special Populations

Per the label, plasma concentrations were studied in the elderly and even if the main circulating metabolites were higher, the effect of Plavix on coagulation parameters was not different from those in young healthy volunteers. However, in CURE there was excess bleeding, including major, in elderly subjects and these findings were not volunteered by the sponsor.

Of interest, especially in the light of what we know from CURE and the findings of MATCH and CHARISMA, is the bleeding safety of clopidogrel in elderly and women.

8.4 Pediatrics

For its current indication, reduction of atherothrombotic events, a waver was granted for studying clopidogrel in pediatrics.

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b(4)

8.5 Advisory Committee Meeting

NA

8.6 Literature Review

NA

8.7 Postmarketing Risk Management Plan

NA

8.8 Other Relevant Materials

Two studies (MATCH and CHARISMA) that are relevant especially to safety have been conducted, their findings have been published, and findings on bleeding are summarized in this review.

9 Overall assessment

9.1 Conclusions

COMMIT has shown that clopidogrel, without the loading dose, reduced mortality and re-infarction following ST segment elevation acute myocardial infarction in a Chinese population that was not managed optimally by US medical-care standards which raises the question of whether clopidogrel would add extra benefit to a STEMI population treated optimally and whether the use of clopidogrel in its loading dose regimen would be safe in this population.

CLARITY showed that clopidogrel reduced the rate of TIMI flow grade 0/1 occlusion in the infarct related artery, but the question remains whether these findings translate to a clinical benefit.

9.2 Recommendation on Regulatory Action

The use of clopidogrel in the STEMI population is approvable. The final decision on its approvability should await the submission and review of a proposed plan to postmarket-assess the benfit/risk profile of clopidogrel in a regimen that includes a loading and longer duration maintenance dose, see 9.3 Recommendation on Postmarketing Action below.

9.3 Recommendation on Postmarketing Action

The sponsor should attempt to assess the safety of the formulation and regimen of clopidogrel that include a loading dose and a longer (> one week) duration maintenance dose in a Western STEMI population.

9.4 Comments to Applicant

The sponsor should provide a proposal for assessing the benefit/risk profile of clopidogrel in a regimen that include a loading and longer (than what was observed in CLARITY) duration maintenance dose in a Western STEMI population for review.

10 Appendices

10.1 Protocol

10.1.1 COMMIT study protocol

See 6.1.3.1 COMMIT page 27.

10.1.2 CLARITY study protocol

See 6.1.3.2 CLARITY page 33.

10.2 Study amendments

10.2.1 COMMIT study amendments

Sample size

The decision to change the sample size was made by the steering committee early in the progress of the study (end of year 2000). The planned sample size was increased from 20,000 – 30,000 to 40,000 because the overall, blinded, event rate observed in the study (8% for mortality and 10% for the combined outcome of death, reinfarction or stroke) was lower than that anticipated (10% for mortality and 14% for the combined outcome) in the published study protocol.

In a letter dated 14 February 2003 from the cochairman of the Steering Committee to the Principal Investigator, it was recommended to recruit as many as 48,000 patients, up to a fixed closure date for the study at the time of the Chinese spring festival in 2005 (09 February 2005).

10.2.2 CLARITY study amendments

Table 36. Protocol amendments of CLARITY

Reasons for Amendment
28 February 2003
Increased sample size from 2200 to 3000 randomized patients and number of sites from 220 to 290;
Adjusted power calculations based on increase in sample size;
Redefined primary and secondary efficacy objectives and outcomes to include patients who died or had a recurrent MI by the time of the start of coronary angiography instead of by the end of the calendar day following angiography;
Added exclusion criterion of anticipated use of urokinase for fibrinolysis;
Specified that aPTT determination was required only for those
patients receiving UFH;
Specified that serial CK-MB and/or troponin measurements were required for patients with suspected recurrent ischemia or reinfarction;
Specified that blinded study drug therapy could be initiated before all baseline laboratory results were obtained, and if these results were subsequently found to be abnormal, study drug could be suspended;
Changed the dosing regimen for ASA to an initial dose of 150-500 mg (instead of 150-325 mg) for patients not receiving ASA within the previous 24 hours and oral or IV administration;
Redefined stroke to also include any event that resulted in death within 24 hours and was due to a cerebral lesion of vascular origin;
Clarified the requirement that Investigators report all clinical events and SAEs, using the Alert Report Booklet;

Reasons for Amendment
Added ability to randomize a patient in an ambulance or mobile care unit and defined the place of randomization as an element for subgroup analysis;
Provided additional guidelines for dosing with dalteparin and nadroparin.
30 December 2003
Changed the primary inclusion criterion to include patients with new LBBB in addition to those with new ST segment elevation on their ECG;
Specified that patients were to be randomized within 12 hours (instead of 6 hours) after the onset of symptoms;
Changed the guideline for the timing for administration of the loading dose of blinded study drug to be from within 10 to 45 minutes of the start of fibrinolysis;
Changed exclusion criterion #2 to treatment with clopidogrel or ticlopidine within 7 days (instead of within 10 days) prior to enrollment;
Changed exclusion criterion #4 with regard to UFH dosing to be consistent with most recent STEMI guidelines, making dosing based on weight, and added restriction concerning treatment with >90 anti-Xa IU/kg nadroparin;
Deleted exclusion criteria for PCI within prior 3 months, LBBB or paced rhythm precluding identification of MI location, history of drug or alcohol abuse, and hemodynamically significant valvular heart disease, endocarditis, hypertrophic cardiomyopathy, restrictive cardiomyopathy, or complex or cyanotic congenital heart disease;
Changed exclusion criterion #9 to specify evidence of cardiogenic shock or acute pulmonary edema requiring intubation or an IABP (instead of diuretic use);
Changed exclusion criterion #11 to reflect a known serum creatinine >2.5 mg/dL (instead of >2 mg/dL);
Clarified that a unique Patient Number was to be assigned at the time of randomization instead of at the time written informed consent was obtained;
Updated dosing regimen for ASA to be consistent with most recent STEMI guidelines;
Clarified that only SAEs were to be reported using the Alert Report Booklet;
Specified maintenance of a separate database for continuous ECG, serum biomarkers, static ECG (for exploratory analysis), and genomics, with analysis and reporting of data from these substudies separated from the main study;
28 July 2004
Increased total expected number of randomized patients from 3000 to 3500;
Adjusted power calculations based on increase in sample size.

10.3 Other endpoints to be explored in CLARITY

-Any reinfarction (separating fatal and non-fatal);

-Any stroke (separating ischemic or not; with and without CT/MRI confirmation; with and without residual handicap);

-Any pulmonary embolus (separating fatal and non-fatal);

-Any "major" (i.e. fatal or non-fatal transfused) non-cerebral bleed;

-Any non-cerebral bleed (including the previously analyzed major bleeds);

-Other major clinical events in hospital during the scheduled treatment period that were explicitly recorded (i.e. cardiogenic shock, heart failure requiring persistent treatment, presumed cardiac rupture, VF/other cardiac arrest);

10.4 Substudies in CLARITY

Planned substudies included assessments of silent ischemia using continuous ECG monitoring and exploratory evaluation of various serum biomarkers. The analyses and reporting of these substudies would be separate from the main study analyses.

Blood samples from baseline and at the start of angiography were to be collected for the assessment of existing cardiac biomarkers including CK-MB, total cardiac troponin I and T, troponin TIC complex, myoglobin, B-type natriuretic peptide, C-reactive protein, IL-6, CD40L, and potentially other novel biomarkers characterized during or after completion of this study. All blood samples for the biomarker substudy were to be sent to the core laboratory for analysis.

For sites participating in the continuous ECG monitoring substudy, a blood sample for markers of ischemia was to be obtained at the end of the monitoring period and sent to the TIMI Biomarker Core Laboratory for analysis.

10.5 Results

10.5.1 Disposition

10.5.1.1 COMMIT population disposition

Table 37. Treatment compliance and main reasons for stopping study drug prematurely in COMMIT

Category	Clopidogrel	Placebo
Randomized	N = 22961	N = 22891
Treatment not started	109 (0.5)	116 (0.5)
Treatment completed	21241 (92.5)	21210 (92.7)
Completed follow-up	22959	22891
Unknown	2	0
Treatment discontinued	1609 (7.0)	1565 (6.8)
Reason for discontinuation		
PTCA or stent	684 (3.0)	713 (3.1)
Adverse event	549 (2.4)	494 (2.2)
MI not confirmed	103 (0.4)	90 (0.4)
Patient refusal	40 (0.2)	35 (0.2)
Other	233 (1.0)	233 (1.0)

Source: Sponsor's analyses

10.5.1.2 CLARITY population disposition

Table 38. Disposition of the CLARITY population

	Clopidogrel	Placebo
Patients Randomized	1752	1739
Patients Randomized and treated	1729 (98.7)	1723 (99.1)
Patients Randomized and not treated	23 (1.3)	16 (0.9)
Up to Angiography, Day 8 or hospital discharge (whichever comes first) when no angiogram date available Patients completing treatment	1622 (93.8)	1623 (94.2)

	Clopidogrel	Placebo
Death up to angiography	45 (2.6)	38 (2.2)
Patients permanently discontinuing study drug	69 (4.0)	64 (3.7)
Reason for discontinuation		
AE/SAE	35 (50.7)	31 (48.4)
Subject no longer meets study criteria	4 (5.8)	6 (9.4)
Subject withdrew consent	8 (11.6)	4 (6.3)
Administrative	22 (31.9)	22 (34.4)
Other	0 (0.0)	1 (1.6)
Randomization up to Day 30 assessment date		
Patients completing follow-up	1669 (95.3)	1658 (95.3)
Patients not completing follow-up but not reported dead	3 (0.2)	1 (0.1)
Death during follow-up	80 (4.6)	80 (4.6)

10.5.2 Demographics

10.5.2.1 COMMIT population demographics

Table 39. Demographic and other baseline characteristics of the COMMIT study population

Characteristic	Clopidogrel 75 mg (N = 22961)	Placebo (N = 22891)	All patients
Sex - n (%)			
Female	6366 (27.7)	6393 (27.9)	12759 (27.8)
Male	16595 (72.3)	16498 (72.1)	33093 (72.2)
Age at entry (yr) - n (%)			
< 60	9624 (41.9)	9463 (41.3)	19087 (41.6)
60-69	7361 (32.1)	7470 (32.6)	14831 (32.3)
70 +	5976 (26.0)	5958 (26.0)	11934 (26.0)
Age at entry (yr)			
Mean (SD)	61.3 (11.9)	61.4 (11.8)	61.3 (11.8)
Range	15.4-100.3	15.4-99.3	15.4-100.3
SBP (mmHg) - n (%)			
< 120	7690 (33.5)	7709 (33.7)	15399 (33.6)
120-139	8092 (35.2)	8108 (35.4)	16200 (35.3)
140-159	4549 (19.8)	4471 (19.5)	9020 (19.7)
160+	2630 (11.5)	2603 (11.4)	5233 (11.4)
SBP (mmHg)			
Mean (SD)	128.2 (22.6)	128.2 (22.5)	128.2 (22.5)
Range	60.0-250.0	60.0-250.0	60.0-250.0
DBP (mmHg) - n (%)			
< 70	3584 (15.6)	3535 (15.4)	7119 (15.5)
70-79	6194 (27.0)	6190 (27.0)	12384 (27.0)
80-89	6002 (26.1)	6070 (26.5)	12072 (26.3)
90+	7181 (31.3)	7096 (31.0)	14277 (31.1)
DBP (mmHg)			
Mean (SD)	81.0 (14.6)	80.9 (14.4)	81.0 (14.5)
Range	40.0-177.0	40.0-180.0	40.0-180.0

Characteristic	Clopidogrel 75 mg (N = 22961)	Placebo (N = 22891)	All patients
HR (bpm) - n (%)			
< 70	5094 (22.2)	5043 (22.0)	10137 (22.1)
70-89	11101 (48.3)	11161 (48.8)	22262 (48.6)
90-109	5140 (22.4)	5069 (22.1)	10209 (22.3)
110+	1626 (7.1)	1618 (7.1)	3244 (7.1)
Heart rate (bpm)			
Mean (SD)	82.2 (17.2)	82.1 (17.2)	82.1 (17.2)
Range	40-228	40-225	40-228
Killip class - n (%)			
I	17320 (75.4)	17283 (75.5)	34603 (75.5)
II	4601 (20.0)	4504 (19.7)	9105 (19.9)
III	1040 (4.5)	1104 (4.8)	2144 (4.7)
Disease history			
Prior MI	1972 (8.6)	1846 (8.1)	3818 (8.3)
History of hypertension	9935 (43.3)	9903 (43.3)	19838 (43.3)

10.5.2.2 CLARITY population demographics

Table 40. Baseline demographic characteristics in the CLARITY, ITT population

	Clopidogrel N=1752	Placebo N=1739
Age (yrs)		
n with data	1752	1739
<65	1219 (69.6)	1252 (72.0)
>= 65	533 (30.4)	487 (28.0)
Mean	57.7	57.2
Median	58	57
sd	10.3	10.3
Range	28-78	18-79
Gender		
n with data	1752	1739
Female	352 (20.1)	336 (19.3)
Male	1400 (79.9)	1403 (80.7)
Race		
n with data	1752	1739
Asian/oriental	43 (2.5)	30 (1.7)
Black	28 (1.6)	35 (2.0)
Caucasian	1569 (89.6)	1556 (89.5)
Other	112 (6.4)	118 (6.8)
BMI (kg/m2)		
n with data	1658	1648
Normal (<= 25)	489 (29.5)	487 (29.6)
Overweight (>25-30)	775 (46.7)	774 (47.0)
Obese (>30)	394 (23.8)	387 (23.5)
Mean	27.5	27.4

	Clopidogrel N=1752	Placebo N=1739
Median	26.9	26.8
sd	4.3	4.4
Range	16.3-53.2	15.4-66.7
SBP		
Mean (sd)	133.9 (23.48)	135.4 (23.21)
Range	60,210	65,215
DBP		
Mean (sd)	80.3 (14.95)	81.3 (14.54)
Range	15,130	40, 125
HR		
Mean (sd)	75.49 (18.26)	75.25 (17.78)
Range	30,160	30,161
Killip class		
I	1376 (78.5)	1348 (77.5)
II	129 (7.4)	134 (7.7)
III	3 (0.2)	2 (0.1)

10.5.3 Efficacy

See 6.1.4 Efficacy Findings page 39.

10.5.4 Safety

See 7.1.1 Deaths page 40; 7.1.2 Other Serious Adverse Events page 42; 7.1.3 Dropouts and Other Significant Adverse Events page 45; 7.1.5 Common Adverse Events page 51; and 7.3.1 Bleeding page 56;

10.5.5 Other findings

All the findings below came from Sponsor analyses.

10.5.5.1 COMMIT

Table 41. Qualifying events of entry in the COMMIT study

Qualifying Event	Clopidogrel (N = 22961)	Placebo (N = 22891)	All patients (N = 45852)
Hours since onset			
Mean (SD)	10.3 (6.7)	10.3 (6.7)	10.3 (6.7)
Range	0.2-24.0	0.1-24.0	0.1-24.0
Hours since onset - n (%)			
< 6	7745 (33.7)	7707 (33.7)	15452 (33.7)
6 to < 13	7567 (33.0)	7505 (32.8)	15072 (32.9)
13 to 24	7649 (33.3)	7679 (33.5)	15328 (33.4)
Final diagnosis of initial MI - n (%)			
Confirmed MI	22002 (95.8)	21946 (95.9)	43948 (95.8)
Suspected MI	410 (1.8)	404 (1.8)	814 (1.8)
Unstable angina	288 (1.3)	308 (1.3)	596 (1.3)

Other	261a (1.1)	233 (1.0)	494 (1.1)

Table 42. Baseline ECG characteristics in COMMIT

ECG Abnormality	Clopidogrel 75 mg (N = 22961)	Placebo (N = 22891)	Overall (N = 45852)
Bundle branch block	1505 (6.6)	1423 (6.2)	2928 (6.4)
ST elevation: Anterior alone	11314 (49.3)	11515 (50.3)	22829 (49.8)
ST elevation: Inferior alone	6570 (28.6)	6386 (27.9)	12956 (28.3)
ST elevation: Anterior and Inferior	941 (4.1)	873 (3.8)	1814 (4.0)
ST elevation: Other	1052 (4.6)	1104 (4.8)	2156 (4.7)
ST depression, without ST elevation	1579 (6.9)	1590 (6.9)	3169 (6.9)

Table 43. Patient and other baseline characteristics by use of anticoagulants in COMMIT

Category	Prior Lytics Use		(N = 45852)
	Yes (N = 22794)	No (N = 23058)	
Sex - n (%)			
Female	5249 (23.0)	7510 (32.6)	12759 (27.8)
Male	17545 (77.0)	15548 (67.4)	33093 (72.2)
Age at entry (yr) - n (%)			
< 60	10951 (48.0)	8136 (35.3)	19087 (41.6)
60-69	7495 (32.9)	7336 (31.8)	14831 (32.3)
70 +	4348 (19.1)	7586 (32.9)	11934 (26.0)
Age at entry (yr)			
Mean (SD)	59.3 (11.5)	63.3 (11.8)	61.3 (11.8)
Range	15.4-99.9	20.2-100.3	15.4-100.3
SBP (mmHg)			
Mean (SD)	125.9 (21.1)	130.5 (23.6)	128.2 (22.5)
Range	60.0-250.0	60.0-250.0	60.0-250.0
DBP (mmHg)			
Mean (SD)	80.3 (14.2)	81.6 (14.8)	81.0 (14.5)
Range	40.0-170.0	40.0-180.0	40.0-180.0
Heart rate (bpm)			
Mean (SD)	81.0 (16.5)	83.3 (17.8)	82.1 (17.2)
Range	40.0-228.0	40.0-220.0	40.0-228.0
Killip class - n (%)			
I	17775 (78.0)	16828 (73.0)	34603 (75.5)
II	4128 (18.1)	4977 (21.6)	9105 (19.9)
III	891 (3.9)	1253 (5.4)	2144 (4.7)
Disease history			
Prior MI	1652 (7.2)	2166 (9.4)	3818 (8.3)
History of hypertension	9588 (42.1)	10250 (44.5)	19838 (43.3)
Neither MI nor hypertension	12392 (54.4)	11752 (51.0)	24144 (52.7)
Hours since onset			
Mean (SD)	8.6 (6.2)	12.0 (6.8)	10.3 (6.7)
Range	0.1-24.0	0.2-24.0	0.1-24.0

Category	Prior Lytics Use		(N = 45852)
	Yes (N = 22794)	No (N = 23058)	
Hours since onset - n (%)			
< 6	9954 (43.7)	5498 (23.8)	15452 (33.7)
6 to < 13	7622 (33.4)	7450 (32.3)	15072 (32.9)
13 to 24	5218 (22.9)	10110 (43.8)	15328 (33.4)
Final diagnosis of initial MI n (%)			
Confirmed MI	22428 (98.4)	21520 (93.3)	43948 (95.8)
Suspected MI	176 (0.8)	638 (2.8)	814 (1.8)
Other	190 (0.8)	900 (3.9)	1090 (2.4)
ECG abnormality			
Bundle branch block	1307 (5.7)	1621 (7.0)	2928 (6.4)
ST elevation: Anterior alone	12033 (52.8)	10796 (46.8)	22829 (49.8)
ST elevation: Inferior alone	7250 (31.8)	5706 (24.7)	12956 (28.3)
ST elevation: Anterior and Inferior	951 (4.2)	863 (3.7)	1814 (4.0)
ST elevation: Other	874 (3.8)	1282 (5.6)	2156 (4.7)
ST depression, without ST elevation	379 (1.7)	2790 (12.1)	3169 (6.9)

Table 44. Duration of hospitalization for patients still alive at Day 28

Duration (days)	Clopidogrel (N = 22961)	Placebo (N = 22891)	Overall (N = 45852)
Mean (SD)	14.9 (7.9)	14.9 (7.8)	14.9 (7.8)
Median	14.0	14.0	14.0

Days: number of days from admission to discharge for those discharged alive at or before Day 28; otherwise 28 days

Table 45. Use of non-trial anti-platelets and beta-blockers in the hospital in COMMIT

Medication	Clopidogrel 75 mg (N = 22961)	Placebo (N = 22891)	Overall (N = 45852)
Nontrial antiplatelet agents	2305 (10.0%)	2280 (10.0%)	4585 (10.0%)
Nontrial beta-blockers	2464 (10.7%)	2538 (11.1%)	5002 (10.9%)

Table 46. Use of other therapies in the hospital in COMMIT

Medication N (%)	Clopidogrel 75 mg	Placebo	Overall (N = 45852)
All patients	22961	22891	
Fibrinolytic agents before/after entry	12468 (54.3)	12499 (54.6)	24967 (54.5)
Patients randomized < 13 hours after onset of MI	15312	15212	
Fibrinolytic agents before/after entry	9548 (62.4)	9631 (63.3)	19179 (62.8)
Patients randomized ≥ 13 hours after onset of MI	7649	7679	
Fibrinolytic agents before/after entry	2920 (38.2)	2868 (37.3)	5788 (37.8)

Medication N (%)	Clopidogrel 75 mg	Placebo	Overall (N = 45852)
Anticoagulants	17022 (74.1)	17157 (75.0)	34179 (74.5)
Anti-arrhythmics	5150 (22.4)	5093 (22.2)	10243 (22.3)
ACE inhibitors	15649 (68.2)	15638 (68.3)	31287 (68.2)
Nitrates (oral or i.v.)	21615 (94.1)	21590 (94.3)	43205 (94.2)
Diuretics	5344 (23.3)	5344 (23.3)	10688 (23.3)
Calcium antagonists	2701 (11.8)	2705 (11.8)	5406 (11.8)

Table 47. Selected medication use prior to randomization in COMMIT

Medication N (%)	Clopidogrel 75 mg (N = 22961)	Placebo (N = 22891)
ASA	4214 (18.4)	4230 (18.5)
Beta-blocker	1457 (6.3)	1533 (6.7)
Fibrinolytic agent in all patients	11407 (49.7)	11387 (49.7)
Fibrinolytic agent in patients randomized < 13 hours after onset of MI	8780 (38.2)	8796 (38.4)
Fibrinolytic agent in patients randomized ≥ 13 hours after onset of MI	2627 (11.4)	2591 (11.3)

Table 48. Cause of deaths "Other noncardiac" in COMMIT

Subject ID	Treatment	Cause of Death
05003-043	Clopidogrel 75 mg	unexpected accidents
10017-020	Clopidogrel 75 mg	anoxic encephalopathy
10027-001	Clopidogrel 75 mg	Severe anemia
10027-007	Clopidogrel 75 mg	Renal failure
11011-048	Clopidogrel 75 mg	Multi-organ failure
11012-028	Clopidogrel 75 mg	Renal failure
11026-033	Clopidogrel 75 mg	Transfusion reaction
11047-005	Clopidogrel 75 mg	Ketoacidosis
11061-048	Clopidogrel 75 mg	Ketoacidosis
11061-061	Clopidogrel 75 mg	Ketoacidosis
13004-016	Clopidogrel 75 mg	Renal failure
21005-054	Clopidogrel 75 mg	Tumor metalease
21068-002	Clopidogrel 75 mg	Renal failure
25004-029	Clopidogrel 75 mg	Tumor metalease
25016-102	Clopidogrel 75 mg	Ketoacidosis
25086-001	Clopidogrel 75 mg	Septicaemia
45028-015	Clopidogrel 75 mg	Transfusion reaction
45028-267	Clopidogrel 75 mg	epilepsy seizure
51006-104	Clopidogrel 75 mg	Renal failure
57004-038	Clopidogrel 75 mg	Renal failure
61034-008	Clopidogrel 75 mg	Tumor metalease
71013-009	Clopidogrel 75 mg	Infection/shock

Subject ID	Treatment	Cause of Death
81004-003	Clopidogrel 75 mg	Ketoacidosis
83002-037	Clopidogrel 75 mg	Infection/shock
83008-018	Clopidogrel 75 mg	Giving up treatment(relative/patient)
83008-063	Clopidogrel 75 mg	Multi-organ failure
03030-007	Placebo	Phosphate poisoning
05010-030	Placebo	Renal failure
05031-009	Placebo	Infection/shock
05099-014	Placebo	Renal failure
05111-015	Placebo	unexpected accidents
10006-043	Placebo	ARDS
10032-006	Placebo	Tumor metalease
10046-145	Placebo	Renal failure
10053-030	Placebo	anoxic encephalopathy
11023-135	Placebo	Tumor metalease
11033-063	Placebo	Multi-organ failure
11038-010	Placebo	unexpected accidents
11042-023	Placebo	Septicaemia
11054-223	Placebo	Renal failure
13021-081	Placebo	Unknown
15025-027	Placebo	overdose
15034-030	Placebo	Multi-organ failure
15042-034	Placebo	Multi-organ failure
21006-124	Placebo	Multi-organ failure
21016-006	Placebo	Multi-organ failure
25009-158	Placebo	Severe anemia
25039-029	Placebo	Tumor metalease
25039-056	Placebo	Infection/shock
25071-013	Placebo	Ketoacidosis
25100-015	Placebo	Ketoacidosis
25123-498	Placebo	Renal failure
25129-201	Placebo	Renal failure
25136-011	Placebo	Ketoacidosis
25144-004	Placebo	Renal failure
25159-013	Placebo	Tumor metalease
31010-181	Placebo	Renal failure
35012-014	Placebo	anoxic encephalopathy
40001-024	Placebo	Tumor metalease
41010-005	Placebo	Acute pancreatitis
43030-035	Placebo	Renal failure
45011-002	Placebo	Tumor metalease
45035-084	Placebo	Tumor metalease
45040-008	Placebo	Multi-organ failure
45046-024	Placebo	Renal failure
45047-015	Placebo	Infection/shock

Subject ID	Treatment	Cause of Death
45047-070	Placebo	Emotional disturbance
61001-005	Placebo	Renal failure
61007-004	Placebo	Renal failure
61013-001	Placebo	hyperkalemia
61016-006	Placebo	Multi-organ failure
61044-010	Placebo	Renal failure
71002-016	Placebo	Intracranial tumors
73014-071	Placebo	Multi-organ failure
73020-008	Placebo	Tumor metalease
81002-012	Placebo	Multi-organ failure
81004-054	Placebo	Renal failure
83002-014	Placebo	Multi-organ failure
83002-016	Placebo	Suicide

Source: Sponsor analyses

10.5.5.2 CLARITY

Table 49. Cardiovascular medical history (ITT population) in CLARITY

	Clopidogrel 1752	Placebo 1739	Overall 3491
Number of patients who reported at least one medical abnormality	1384 (79.0)	1402 (80.6)	2786 (79.8)
History of hypertension	750 (42.8)	764 (43.9)	1514 (43.4)
Previous documented MI	159 (9.1)	159 (9.1)	318 (9.1)
Angina pectoris	402 (22.9)	402 (23.1)	804 (23.0)
Prior congestive heart failure	28 (1.6)	26 (1.5)	54 (1.5)
Atrial fibrillation	24 (1.4)	30 (1.7)	54 (1.5)
Peripheral arterial disease	69 (3.9)	81 (4.7)	150 (4.3)
Venous thromboembolic disease	18 (1.0)	22 (1.3)	40 (1.1)
Hypertension	750 (42.8)	764 (43.9)	1514 (43.4)
Hyperlipidemia	564 (32.2)	574 (33.0)	1138 (32.6)
Family history of CAD	665 (38.0)	594 (34.2)	1259 (36.1)
Diabetes mellitus	289 (16.5)	286 (16.4)	575 (16.5)
Prior coronary angiography	143 (8.2)	148 (8.5)	291 (8.3)
Percutaneous coronary intervention	84 (4.8)	85 (4.9)	169 (4.8)

Table 50. Summary of qualifying events (ITT population) in CLARITY

	Clopidogrel 1752	Placebo 1739	Overall 3491
Hours since onset of ischemic symptoms to randomization			
n with data	1751	1739	3490
<2	491 (28.0)	533 (30.6)	1024 (29.3)
2 to <4	775 (44.3)	746 (42.9)	1521 (43.6)
4 to <6	331 (18.9)	309 (17.8)	640 (18.3)

	Clopidogrel 1752	Placebo 1739	Overall 3491
6 to <9	111 (6.3)	113 (6.5)	224 (6.4)
9 to <12	42 (2.4)	31 (1.8)	73 (2.1)
>=12	1 (0.1)	7 (0.4)	8 (0.2)
Mean (hours)	3.3	3.3	3.3
Median	2.8	2.7	2.8
sd	2.0	2.1	2.1
Range	0.0-18.3	0.0-23.2	0.0-23.2
Number (%) of patients admitted to hospital prior to symptom onset	39 (2.2)	45 (2.6)	84 (2.4)

Table 51. Baseline distribution of factors used in the efficacy analyses (ITT population) in CLARITY

	Clopidogrel 1752	Placebo 1739
Type of fibrinolytic used		
n with data	1752	1739
Fibrin specific	1206 (68.8)	1191 (68.5)
Non-fibrin specific	542 (30.9)	542 (31.2)
None	4 (0.2)	6 (0.3)
Anticoagulant used up to two hours post-randomization		
n with data	1752	1739
UFH	808 (46.1)	792 (45.5)
LMWH	528 (30.1)	506 (29.1)
UFH+LMWH	85 (4.9)	90 (5.2)
None	331 (18.9)	351 (20.2)
Infarct location		
n with data	1752	1739
Anterior	722 (41.2)	697 (40.1)
Non-anterior	1030 (58.8)	1042 (59.9)

Table 52. Baseline ST deviation in CLARITY

	Clopidogrel	Placebo
Baseline sum of ST deviation		
n with data	1540	1501
Mean	12.9	13.2
Median	10.8	10.8
sd	8.7	8.6
Range	0.5-77.9	2.0-65.5

Table 53. Medications taken concomitantly with the study drug in CLARITY

	Clopidogrel	Placebo
Beta blockers	1371 (79.2)	1345 (78.3)
Nitrates	1253 (72.4)	1238 (72.1)
Calcium channel blockers	88 (5.1)	76 (4.4)

	Clopidogrel	Placebo
Antiarrhythmics	126 (7.3)	142 (8.3)
Statins	1105 (63.8)	1067 (62.1)
Other lipid lowering agents	49 (2.8)	42 (2.4)
ACE inhibitors	969 (56.0)	917 (53.4)
Angiotensin receptor blockers	26 (1.5)	29 (1.7)
Diuretics	316 (18.3)	291 (16.9)
Cardiac glycoside and/or other inotropes	80 (4.6)	71 (4.1)
NSAIDs	86 (5.0)	97 (5.6)
Anti-diabetic medications (not mutually exclusive)	309 (17.9)	297 (17.3)
Ticlopidine	10 (0.6)	4 (0.2)
Open label clopidogrel	61 (3.5)	62 (3.6)

Table 54. Compliance with study drug in CLARITY

Total number of patients	Clopidogrel 1733	Placebo 1719
When was study medication stopped compared to the earliest of angiography/Day 8/hospital discharge/death		
Same calendar day	1331 (76.8)	1355 (78.8)
Day before, <= 24 hours	243 (14.0)	221 (12.9)
Day before, >24 hours	92 (5.3)	79 (4.6)
More than 1 day before	67 (3.9)	64 (3.7)

Figure 10. Primary analysis by baseline characteristic subgroups in CLARITY

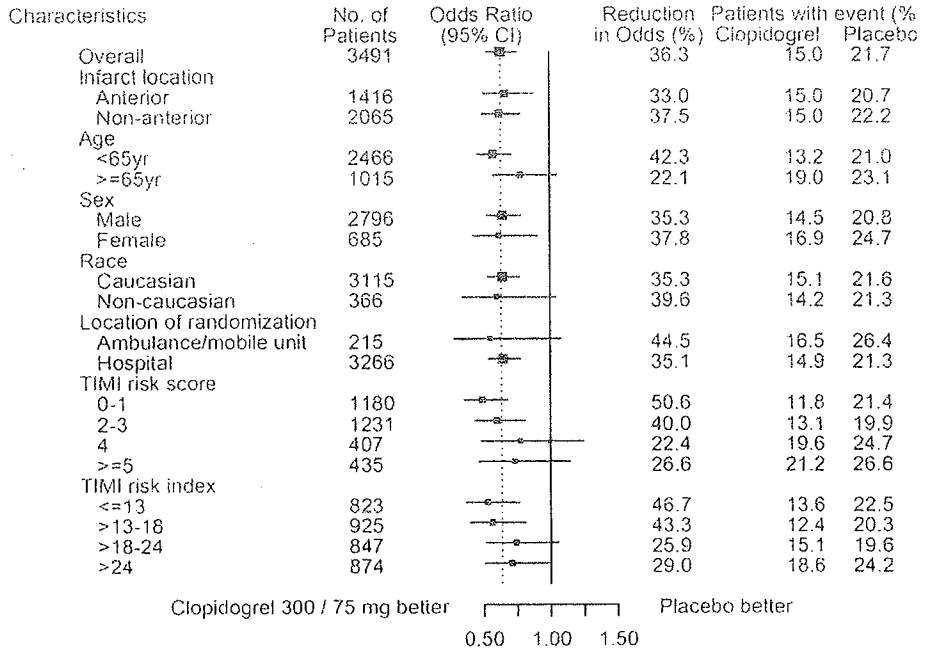
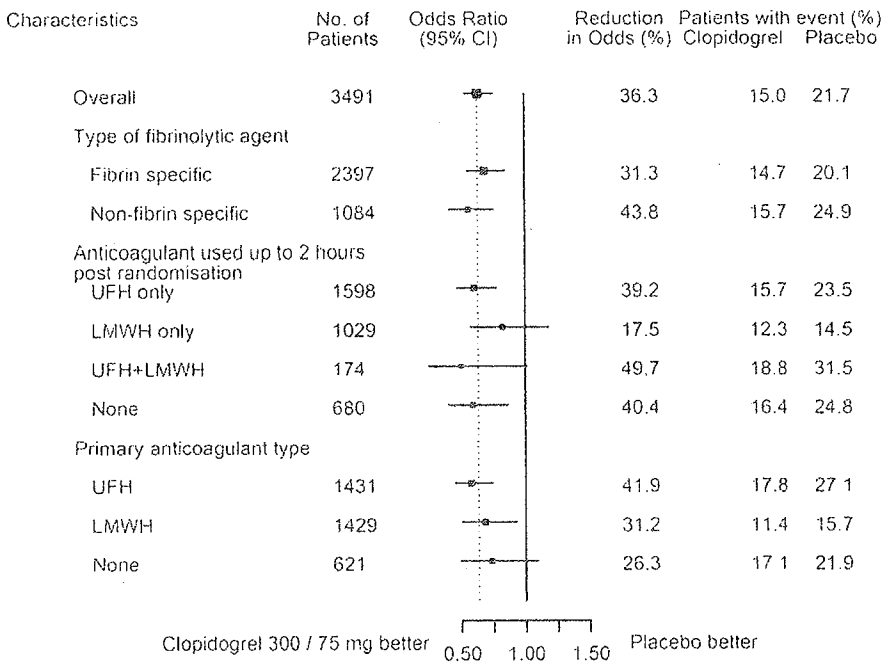


Figure 11. Primary analysis by the use of other concomitant therapy subgroups in CLARITY



10.5.6 Other studies (MATHCH and CHARISMA) general findings

Table 55. MATCH baseline characteristics

	clopidogrel + Placebo N=3802	clopidogrel + ASA N=3797
Age (mean)	66.1	66.5
Female	37.0%	37.0%
Qualifying event		
TIA	21.0	21.0
Stroke	79	79
Hypertension	78.2	78.3
Diabetes	68.4	68.4
Hypercholesterolemia	57.0	56.0
Smoking	47.0	48.0
Previous TIA	19.0	19.0
Angina pectoris	12.0	12.7
Symptomatic PAD	10.2	10.2
Previous MI	5.0	4.6

Table 56. CHARISMA baseline characteristics

	clopidogrel N=7802	Placebo N=7801
Age (median)	64.0	64.0
Female	29.7	29.8
Ethnicity		
Caucasian	80.4	79.9
Hispanic	10.0	10.7
Asian	5.0	5.0
Black	3.2	3.0
Other	1.5	1.4
Inclusion group		
Documented CVD	77.7	78.1
Multiple risk factor	21.3	20.8
Smoking		
Current	20.1	20.3
Former	48.8	48.7

10.6 Study Committees

10.6.1 COMMIT study committees

The Steering Committee was co-chaired by Professor Li-Sheng Liu and Professor Rory Collins and also included one principal study coordinator/international liaison representative (Zheng-Ming Chen), 2 clinical coordinators, 1 administrative coordinator, 2 statisticians, and other members from the People's Republic of China. This Committee was responsible for the major organizational and policy decisions and provided the scientific and strategic direction of the trial

and met about once a year. Additional statistical advice was obtained from Sir Richard Peto (Oxford University, United Kingdom).

COMMIT Data Safety Monitoring Board (DSMB)

A DSMB composed of 2 members (Peter Sandercock and T.H. Lam) and co-chaired by Drs. Peter Sleight and Stephen MacMahon was responsible for monitoring safety. About once a year during the study, an independent Clinical Trial Service Unit statistician prepared interim reports for the DSMB that included analyses of the primary endpoints and other information, if available, such as unexpected serious adverse events (SAEs) believed by the physician to be related to the trial treatments (as defined in the protocol). In light of these analyses, the DSMB provided advice to the Chairmen of the Steering Committee.

COMMIT DSMB minutes

-12/06/2001, 11785 subjects had been recruited and no modifications were recommended;

-04/30/2002, 20056 subjects had been recruited and it was agreed that the trial should continue to its planned sample size;

-9/11/2003, no safety concerns were observed;

-11/07/2004, data from 42217 discharge forms were considered, the decision for the study to continue unchanged was unanimous, and it was stated that the study was going to closeout in the Spring of 2005;

Of interest is the absence of a mention of the sample size amendment in the minutes of the DSMB.

10.6.2 CLARITY study committees

Four independent committees were formed for CLARITY including the Operations Committee, Steering Committee, Clinical Events Committee (CEC), and Data and Safety Monitoring Board (DSMB).

11 Response to FDA Request for Information

11.1 Question 1

Relevance of the results of the COMMIT trial to the US population based on therapy used in an acute setting [acute coronary syndrome (ACS)/ST-elevation myocardial infarction (STEMI)]: percutaneous coronary intervention (PCI), thrombolytic and lipid lowering agents.

11.1.1 Sponsor's response/Arguments

The Applicant has approached this question from two points of view. First, we consider that the treatment of acute MI in China is not significantly different from treatment in the US. Secondly, we provide information to argue that clopidogrel is effective with or without the use of PCI, fibrinolytics or lipid lowering agents.

First argument: CLARITY supports the applicability of the COMMIT/CCS-2 data in a Western international setting

--The prognostic significance of "open arteries" following reperfusion therapy after STEMI had been well documented in many trials.

-- Although EFC5133 (CLARITY-TIMI 28) was not powered to look at effects of clopidogrel on clinical endpoints, the composite clinical endpoint of death or recurrent MI at 30 days did show a favorable trend [odds ratio (OR)=0.85; confidence interval (CI) 95%: 0.67,1.06] consistent with the clinical benefit established in the COMMIT/CCS-2 population (2).

-- The findings of COMMIT and CLARITY are complementary and entirely consistent with each other. The significant improvement in the primary outcome of patency of the IRA in EFC5133 (CLARITY-TIMI 28) correlates to the significant (p=0.002) reduction in the primary composite endpoint.

Second argument: Legitimacy of extrapolating data from the Chinese population to the US population

--The patient population studied was very similar to those seen in routine practice, not only in China but also in Western populations (such as documented in the GRACE registry), allowing the results to be extrapolated from the Chinese population to the US population (1).

--The baseline characteristics of patients included in EFC7018 (COMMIT/CCS-2) did not differ from data reported for Western patients, in registries such as the GRACE registry or in clinical studies such as ASSENT-3 (3), with a majority of male patients and a mean age of 61-64 years [Table (1.) 1].

Table (1.) 1 - Summary of baseline demographics data (ITT population) - EFC5133 (CLARITY-TIMI 28), EFC7018 (COMMIT/CCS-2), ASSENT-3, and GRACE

Parameter	EFC5133[a] (CLARITY-TIMI 28)	EFC7018 (COMMIT/CCS-2)	ASSENT-3	GRACE[g]
	Overall N =3491	Overall N =45852	Overall N = 6095	Overall N=6625
Sex - n (%)				
Female	688 (19.7%)	12759 (27.8%)	1435 (23.5%)	1921 (29%)
Male	2803 (80.3%)	33093 (72.2%)	4660 (76.5%)	4704 (71%)
Age (years)[b]				
< 60	1973 (56.5%)	19087 (41.6%)	NA	NA
60-69	1019 (29.2%)	14831 (32.3%)	NA	NA
70 +	499 (14.3%)	11934 (26.0%)	767[e] (12.6%)	NA
Mean age (SD)	57.4 (10.3)	61.3 (11.8)	61 (13)	64
Range	18-79	15.4-100.3	NA	54-74
SBP (mmHg)				NA
Mean (SD)	134.5 (22.7)[c]	128.2 (22.5)	133-134 (22)	
Range	60.0-215.0	60.0-250.0	NA	
HR (bpm)			NA	NA
Mean (SD)	75.0 (17.3)[d]	82.1 (17.2)		
Range	30.0-161.0	40-228		
Killip class				NA
I	3202 (92.0%)	34603 (75.5%)	5347 (87.7%)	
II	274 (7.9%)	9105 (19.9%)	674 (11.1%)[f]	
III	5 (0.1%)	2144 (4.7%)	NA	
IV	1(0.03%)	NA	23 (0.4%)	

All treated patients received daily ASA (162 mg) in EFC7018 (COMMIT/CCS-2).
[a] With background acetylsalicylic acid (ASA) and initial fibrinolytic therapy.
[b] For EFC5133 (CLARITY-TIMI-28), overall age categories of <65 years [2471(70.8%)] and 65-75 years [1017 (29.1%)], 2 patients aged 78 years and 1 patient aged 79 years.
[c] In EFC5133 (CLARITY-TIMI 28), n with data was overall 3490 patients.
[d] In EFC5133 (CLARITY-TIMI 28), n with data was overall 3479 patients.
[e] Number (%) of patients >75 years.
[f] Data for pooled II/III classes.
[g] Data from (1)
HR = heart rate; NA = not available/not applicable; SBP = systolic blood pressure; SD = standard deviation.

Third argument: Legitimacy of extrapolating data from a population treated under different medical practice standards to the US population

--The effect of clopidogrel in COMMIT was shown in the presence (RRR of 11%) or absence (RRR of 6%) of finbrinolytics;

--There was no systematic collection in COMMIT/CCS-2 study of the use of PCI or lipid lowering agents. According to an epidemiological study conducted in China, 48.9% of STEMI patients received PCI as reperfusion therapy which does not differ from what is observed in the Western countries (4)(5)(6).

--PCI was undertaken in 35.8% of patients compared to 21.7% before publication of the Chinese guidelines (7) in 2001.

--Over a period of 3-years from 1999 to 2001, the Chinese registry showed that stents were implanted in 81% of the PCI procedures performed, which is similar to the rate observed in the US (84%) (8)(9). Literature data also shows that the use of lipid lowering agents in China is 72.5-93.0% (4).

--To address more specifically the question raised by the Division, the Applicant performed additional analyses of the clinical endpoints collected at Day 30 in the EFC5133 (CLARITY-TIMI 28) study, in which the type of lytic and lipid lowering agents were collected. In order to facilitate the comparability with the EFC7018 (COMMIT/CCS-2) study, the composite endpoint of cardiovascular death, recurrent MI or stroke was analyzed, as well as the composite endpoint of death, recurrent MI or stroke [identical to the one studied in the EFC7018 (COMMIT/CCS-2) study], according to PCI, type of thrombolytic used (fibrin specific or non-fibrin specific) and the use or not of statin [Table (1.) 2].

--These data show that there is a consistent trend towards a clinical benefit for clopidogrel versus placebo independent of the type of fibrinolytic used and whether or not a statin was used and in case of PCI.

--We also looked at the CURE study in non-ST-elevation myocardial infarction (NSTEMI) ACS patients. The analyses performed in the CURE study with the primary composite endpoint at 30 days [Table (1.) 3] are consistent with those in the EFC5133 (CLARITY-TIMI 28) study. In addition, there was no interaction identified with PCI.

--The combination of a statin and clopidogrel has also been evaluated in the GRACE (Global Registry of Acute Coronary Events) registry, showing that statin have a statistically significant effect on top of clopidogrel (associated with ASA) on the clinical outcomes of patients with NSTEMI (log-rank test RRR=22.8, $p<0.0001$ for the 6-month mortality with clopidogrel plus statin versus clopidogrel without statin] (10).

Table (1.) 2 - Summary of clinical endpoints (death, recurrent MI, stroke including TIA) at Day 30 - EFC5133 (CLARITY-TIMI 28)

Clinical endpoints	Clopidogrel[a] (N=1748)	Placebo[a] (N=1733)	p-value	OR	95% CI	Interaction p-value
CV death, recurrent MI, stroke (incl. TIA)	159 (9.1%)	189 (10.9%)	0.072	0.82	(0.65, 1.02)	NA
PCI						
Yes	71/934 (7.6%)	111/929 (11.9%)	0.002	0.62	(0.45, 0.84)	0.011
No	88/814 (10.8%)	78/804 (9.7%)	0.557	1.10	(0.80,1.52)	
Thrombolytic Use:						
Fibrin	112/1206 (9.3%)	135/1191 (11.3%)	0.105	0.80	(0.62, 1.05)	0.840
Non-fibrin	47/542 (8.7%)	54/542 (10.0%)	0.422	0.85	(0.56, 1.28)	
Statin Use:						
Yes	62/1106 (5.6%)	77/1072 (7.2%)	0.130	0.77	(0.54, 1.08)	0.577
No	97/642 (15.1%)	112/661 (16.9%)	0.365	0.87	(0.65, 1.17)	
Death, recurrent MI, stroke (incl. TIA)	162 (9.3%)	189 (10.9%)	0.104	0.83	(0.67, 1.04)	NA
PCI						
Yes	71/934 (7.6%)	111/929 (11.9%)	0.002	0.62	(0.45, 0.84)	0.007
No	91/814 (11.2%)	78/804 (9.7%)	0.412	1.14	(0.83, 1.58)	
Thrombolytic Use:						
Fibrin	112/1206 (9.3%)	135/1191 (11.3%)	0.105	0.80	(0.62, 1.05)	0.631
Non-fibrin	50/542 (9.2%)	54/542 (10.0%)	0.628	0.90	(0.60, 1.36)	
Statin Use:						
Yes	65/1106 (5.9%)	77/1072 (7.2%)	0.213	0.80	(0.57, 1.13)	0.731
No	97/642 (15.1%)	112/661 (16.9%)	0.365	0.87	(0.65, 1.17)	

[a] Patients who did not receive fibrinolytics are excluded from these analyses.
TIA = transient ischemic attack
CV = cardiovascular

Results are similar when TIA events were excluded.

Table (1.) 3 - Summary of the first co-primary endpoint (cardiovascular death, MI, stroke) in the first 30 days by subgroups - CURE

	No. (%) With Event			
	Clopidogrel	Placebo	Hazard Ratio (95% CI)	p-Value for Interaction
PCI				
Yes (N=1730)	46/821(5.60%)	76/909 (8.36%)	0.66 (0.46, 0.95)	0.302
No (N=10832)	226/5438 (4.16%)	273/5394 (5.06%)	0.82 (0.69, 0.98)	
Lipid lowering drug use				
Yes (N=7042)	138/3531(3.91%)	186/3511(5.30 %)	0.73 (0.59, 0.91)	0.413
No (N=5520)	134/2728 (4.91%)	163/2792(5.84 %)	0.84 (0.67, 1.05)	

In conclusion, the Applicant believes that the results of the EFC7018 (COMMIT/CCS-2) study are relevant to the US population receiving a background therapy including PCI, thrombolytics and lipid lowering agents.

11.1.2 Reviewer's comments

First argument, CLARITY supports the applicability of the COMMIT/CCS-2 data in a Western international setting

CLARITY could be supportive of the applicability of COMMIT's findings to the extent of the clinical findings in CLARITY. TIMI flow grade is a surrogate endpoint that does not add a lot of credibility to the supportive role of CLARITY for the following reasons:

--TIMI flow grade is a measure of epicardial not microvascular perfusion which can be evaluated using myocardial blush grade. The most commonly researched prognostic TIMI flow surrogate factor is TIMI flow 3, complete patency. Even at this level of patency, it was estimated that 1 out of 4 patients who achieve a brisk epicardial TIMI 3 coronary flow do not show tissue reperfusion. The reversal of and/or salvage of myocardial tissue injury depends on the timing of the institution of flow and extend of microscopic damage of cardiac and capillary endothelial cells. Microvascular damage is more pronounced in the subendocardium and with longer periods of coronary occlusion[11].

--ST segment resolution a strong indicator of the quality of reperfusion and that was shown to be significantly correlated with one-year mortality rates was not different between the treatment arms, see Table 5 page 20.

--The rate of angina pectoris at the time point was not different between the treatment groups see Table 33 page 52.

--Up to the primary study-time point, clinical parameters including death and cardiac rupture trended in favor of placebo see Table 4 page 19 and Table 15 page 42.

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[11] Flavio Ribichini, Valeria Ferrero, and William Wijns. Reperfusion Treatment of ST-Elevation Acute Myocaridal Infarction. Progress in Cardiovascular Disease 47: 131-157, 2004.

Second argument: Legitimacy of extrapolating Chinese data to US population

This was not raised as a major issue for this application.

Third argument: Legitimacy of extrapolating data from a Chinese medical practice standards to populations treated under western medical practice standards

--The more pronounced effect of clopidogrel in the group who received fibrinolytics in COMMIT is reassuring because unless contra-indicated, fibrinolytics are regularly used in the STEMI US population.

--Data on clinical practice in China, but what COMMIT study data portray, are not relevant to the issue at hand.

--Post hoc analyses evaluating the effect of clopidogrel by PCI, lytics and statin use on the composite endpoint of cardiovascular death, recurrent MI or stroke as well as the composite endpoint of death, recurrent MI or stroke (COMMIT's primary endpoint) in CLARITY at the 30-day time-point and showing favorable trends in the groups whose management included PCI, lytics and statins does not confirm the benefit of clopidogrel in these subgroups but are reassuring in the sense that they did not trend in the wrong direction.

--The findings from CURE (NSTEMI) are also reassuring with regard to the effect of clopidogrel on the composite of cardiovascular death, MI and stroke in the presence of PCI and lipid lowering drugs.

--The association observed between statins plus clopidogrel and 6-month mortality in the GRACE registry population could not be used as evidence of the favorable effect of this combination because the study was observational. In light of other findings, this information is somewhat supportive.

--No literature was submitted for the effect of clopidogrel in combination with PCI, but the ACC/AHA guidelines recommendation language was submitted. The recommendations classify the use of clopidogrel in patients for whom PCI is planned as Class I that is the "Benefit >>> Risk, Procedure/Treatment SHOULD be performed/administered". "For patients who have undergone diagnostic cardiac catheterization and for whom PCI is planned, clopidogrel should be started and continued for at least 1 month after bare metal stent implantation and for several months after drug-eluting stent implantation (3 months for sirolimus, 6 months for paclitaxel) and up to 12 months in patients who are not at high risk for bleeding. (Level of Evidence: B)"

11.2 Question 2

The Division would like the Applicant to give their interpretation of the COMMIT results in patients who received or did not receive metoprolol.

11.2.1 Sponsor's response

--The Applicant would like to emphasize that the metoprolol component used in the factorial design was designed to assess the balance of risks and benefits of adding early intravenous then oral metoprolol in STEMI patients (11). As presented in the EFC7018 (COMMIT/CCS-2)

publication (12) and in [Figure (2.) 1], from a statistical standpoint, the effect of clopidogrel was not significantly modified by random allocation to early use of metoprolol (p=0.1). Although the point estimates of the treatment effect in the subgroups are somewhat different, they are both in the same direction (quantitative difference; RRR 4% vs. 12%) and the confidence intervals overlap to a great extent. Given the overall result and lack of statistical interaction, it can be concluded that the benefit of clopidogrel is largely independent of whether or not beta-blockers are given as part of the background therapy, which is consistent with previous observation in the CURE study [Table (2.) 1]. We are unaware of any pharmacokinetic or pharmacodynamic interaction between clopidogrel and betablockers and no explanation other than play of chance can explain this observation. Moreover, contrary to previous perceptions (based on much smaller trials in much lower risk patients), early beta-blocker therapy did not reduce mortality in EFC7018 (COMMIT/CCS-2) (7.7% metoprolol vs. 7.8% placebo, OR=0.99, p=0.7], chiefly because of a significant excess of cardiogenic shock that counterbalanced the apparent reductions in the risks of re-infarction and of ventricular fibrillation (11).

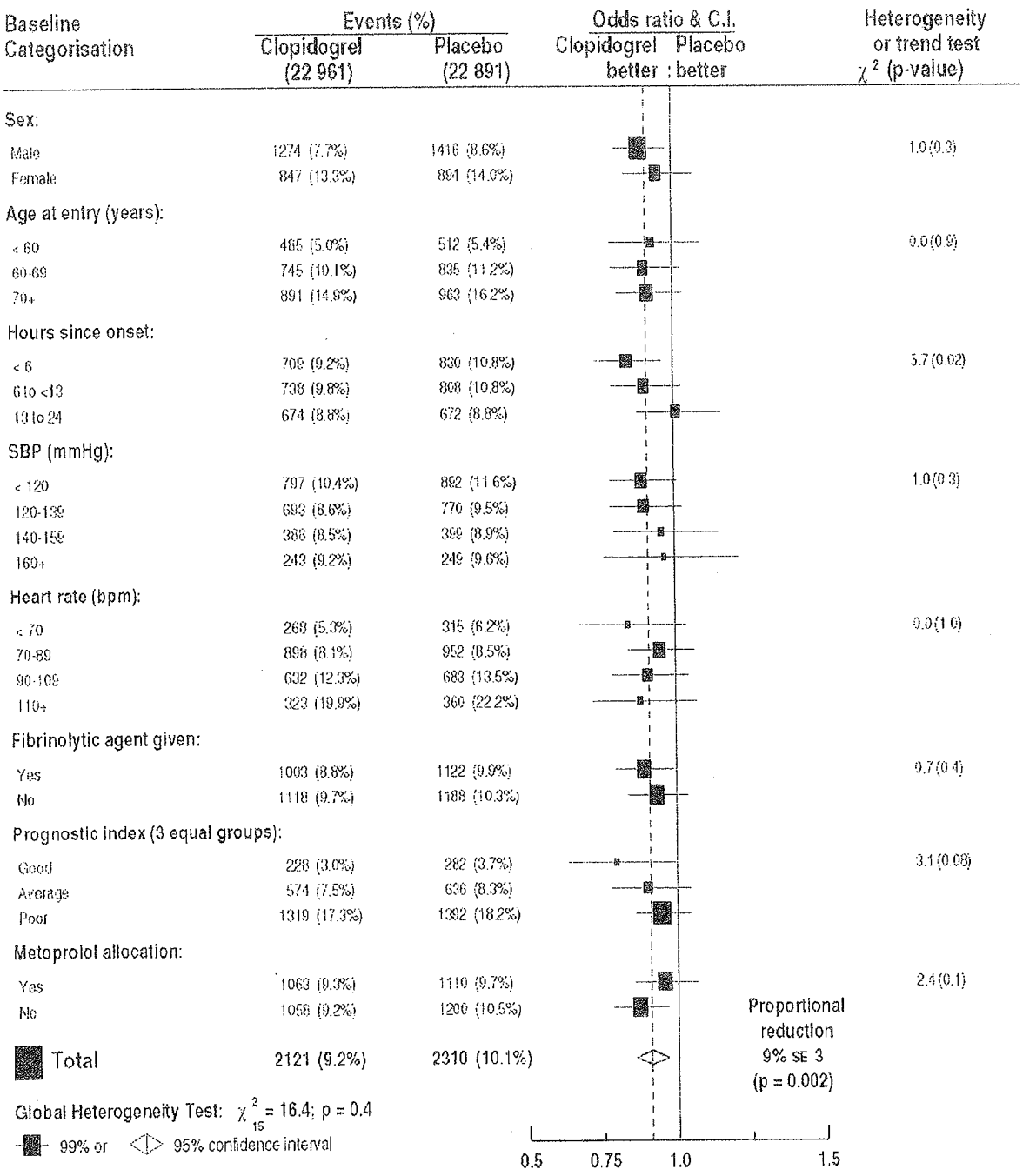

Figure (2.) 1 - Proportional effects of adding clopidogrel to aspirin on the combined coprimary endpoint (death, reinfarction, stroke) by the protocol-specified subgroups of baseline characteristics - EFC7018 (COMMIT/CCS-2)

Table (2.) 1 - Summary of first co-primary endpoint (cardiovascular death, MI, stroke) in the first 30 days according to beta-blocker use - CURE

Interaction Variable	No. (%) With Event			
	Clopidogrel	Placebo	Hazard Ratio (95% CI)	p-Value for Interaction
Betablocker use				
Yes (N=10186)	223/5079(4.39%)	274/5107 (5.37%)	0.81 (0.68, 0.97)	0.295
No (N=2376)	49/1180 (4.15%)	75/1196 (6.27%)	0.66 (0.46, 0.94)	

11.2.2 Reviewer's comments

The sponsor argues that statistically speaking, the effect of clopidogrel was not significantly modified by random allocation to early use of metoprolol because point estimates of the treatment effect in the subgroups are both in the same direction even though they are somewhat different.

The sponsor adds:

> -that given the lack of statistical interaction, they concluded that the benefit of clopidogrel is largely independent of whether or not beta-blockers are given as part of the background therapy;
>
> -these findings are consistent with previous observation in the CURE study;
>
> -they are unaware of any pharmacokinetic or pharmacodynamic interaction between clopidogrel and betablockers and no explanation other than play of chance can explain the observation.

--The sponsor contradicts itself by stating that this must have been a play of chance and by stating that this has been seen in the CURE population which assumes an underlying explanation or mechanism even if the sponsor is not aware of it.

--Although there is a difference in the magnitude of effect between the subgroups in the CURE study (Table (2.) 1), subjects on betablockers benefited statistically significantly from the addition of clopidogrel. These findings are not supportive of why no effect was observed in the subgroup on metoprolol in COMMIT. As can be seen from the table below, subjects on metoprolol in COMMIT did not seem to derive any benefit from clopidogrel unlike what the sponsor believes.

Table 57. Effect of Clopidogrel on the Combined Coprimary Endpoint by metoprolol intake in COMMIT Study

		N	Hazard Ratio	95% CI	p-value
Metoprolol	Yes	22929	0.952	(0.875, 1.036)	0.256
	No	22923	0.871	(0.802, 0.947)	0.001

In conclusion, the sponsor did not provide a satisfactory interpretation of the COMMIT results in patients who received of did not receive metoprolol.

11.3 Question 3

The Division identified some disparity between the 30,000 first patients and the 15,000 following patients, and required clarifications on how the sample size was determined.

11.3.1 Sponsor's response

The decision to go beyond the initial sample size was made very early on and was not dependent at all on the use of any interim results. The possible need to increase the sample size was clearly foreseen before the first patient was randomized and was stated clearly at various meetings between the Steering Committee members. The reason was a recommendation by the co-chairman of the Steering Committee and the Principal Investigator to increase the power for the endpoint of all-cause mortality. Assumptions regarding the event rate and effect size for the primary endpoint of death, non-fatal MI or non-fatal stroke were not changed. At the time the contract between CTSU-Oxford (sponsor of the study) and the Applicant (sanofi-aventis for clopidogrel) , as well as Astra-Zeneca for metoprolol, was signed, there were uncertainties on the way enrollment in the study would go, and so only 20,000 patients could be guaranteed by the study sponsor (CTSU-Oxford). Hence, the initial target was to be 20-30,000 patients.

After about one year of enrollment into the study, when approximately 8000 patients were randomized (December 2000), CTSU-Oxford was confident that a goal of 40,000 patients was achievable. The co-chairman of the Steering Committee and the Principal Investigator formally recommended the increase to the Applicant in December 2000 (letter dated 05 December 2000). This was agreed a few months later by the Applicant, and then a newsletter informed the investigators.

No protocol amendment was submitted at any time that would have affected the selection of the patient population, and the participating sites were not changed. A blinded analysis of baseline characteristics by groups of 5000 patients over the recruitment period was performed by the Applicant. This analysis does not show any specific changes in baseline characteristic of patients at the time-points described above [Table (3.) 1].

Table (3.) 1 - Baseline characteristics by groups of 5000 patients over the study - EFC7018 (COMMIT/CCS-2)

Parameter	Patients 1 - 5000	Patients 5001 - 10000	Patients 10001 - 15000	Patients 15001 - 20000	Patients 20001 - 25000	Patients 25001 - 30000	Patients 30001 - 35000	Patients 35001 - 40000	Patients 40001 - 45852
AGE (mean)	60	61	61	61	61	62	61	62	62
SEX (FEMALE)	26.0%	27.4%	26.5%	26.7%	28.7%	28.2%	27.4%	29.7%	29.7%
Previous MI	8.2%	7.8%	7.4%	8.5%	7.8%	8.4%	8.7%	9.4%	8.8%
Previous Hypertension	41.4%	42.3%	41.5%	44.0%	43.4%	44.1%	43.9%	43.7%	44.9%
Aspirin use pre admission	16.9%	16.0%	16.8%	18.2%	19.0%	20.2%	19.4%	19.9%	19.2%
Fibrinolytic given	54.2%	53.3%	54.0%	52.0%	48.6%	47.0%	48.3%	45.1%	45.5%
Beta blocker use pre admission	6.3%	5.5%	5.8%	6.6%	6.3%	6.9%	7.1%	7.5%	6.7%
Killip Class I	74.9%	74.8%	74.5%	74.2%	75.9%	76.1%	77.0%	75.2%	76.5%
Killip Class II	19.8%	20.2%	20.2%	21.5%	19.6%	19.5%	18.9%	20.0%	19.1%
Killip Class III	4.4%	4.3%	4.6%	3.9%	3.9%	4.1%	3.8%	4.5%	4.1%
Killip Class Not Known	0.9%	0.7%	0.7%	0.5%	0.5%	0.3%	0.3%	0.3%	0.3%
Hrs since onset of pain (mean)	10.1	10.4	10.3	10.5	10.5	10.6	10.1	10.5	10.4
Heart rate (mean)	83	82	82	83	82	83	81	82	82
Systolic BP (mean)	128	128	128	129	128	128	129	128	128
Diastolic BP (mean)	82	82	81	81	81	81	81	80	80
Bundle branch block	7.2%	7.1%	5.8%	7.0%	6.3%	6.9%	6.2%	5.9%	5.3%
ST elevation, anterior alone	57.9%	56.4%	52.6%	53.9%	53.1%	51.6%	53.9%	52.8%	52.6%
ST elevation, inferior alone	32.2%	31.0%	32.2%	28.1%	28.9%	29.0%	29.9%	30.9%	30.0%
ST elevation, anterior & inferior	5.0%	5.0%	4.5%	4.8%	4.5%	4.5%	4.2%	4.7%	3.8%
ST elevation, other	19.9%	19.2%	18.2%	18.6%	15.0%	17.4%	18.0%	13.6%	13.1%
ST depression, without ST elevation	6.4%	7.4%	7.8%	10.0%	10.9%	10.2%	9.2%	9.0%	10.5%

11.3.2 Reviewer's comments

--The sponsor argues that the decision to change the sample size was made early in the program before the first 30,000 subject mark was reached. They stated that the change was formally recommended by the co-chairman of the Steering Committee and the Principal Investigator to the Applicant in December 2000 (letter dated 05 December 2000). This was agreed a few months later by the Applicant, and then a newsletter informed the investigators.

--The Applicant submitted a letter dated of December 5, 2000 and signed by Drs. Peto, Collins and Chen stating that a sample size of 20-30,000 might not have enough power for the co-primary endpoint of death and seeking agreement that the new recruitment target be 40,000.

--The table above comparing baseline parameters for every subsequent 5000 patients is not helpful because it is not comparing baseline parameters by treatment group. Eyeballing the table, the differences between the first 30,000 and the last 15,000 were the distributions of fibrinolytic intake (5% less use in the last cohort) and ST elevation "other" (3% less in the last cohort).

11.4 Overall comments

The sponsor had demonstrated that PCI, thrombolytic and lipid lowering agents do not interact adversely with clopidogrel in subjects with STEMI.

The sponsor did not adequately explain why there was a difference in effect on clopidogrel by metoprolol intake.

It appears that the finding differences between the first 30,000 and the last 15,000 cohorts are chance findings. There is enough documentation that the decision to change the sample size was made long before the 30,000 mark was reached.

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29 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__√__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical-__1__

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Salma Lemtouni
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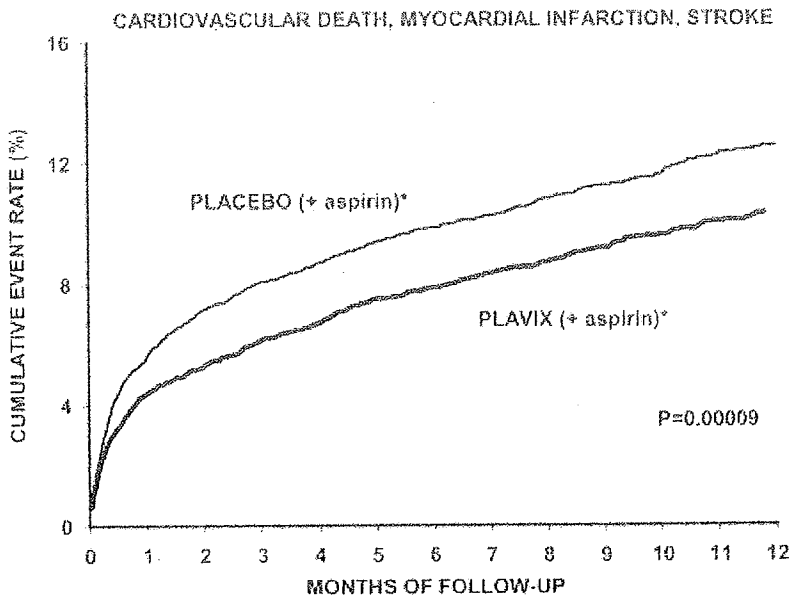
MEDICAL OFFICER

Figure 2: Cardiovascular Death, Myocardial Infarction, and Stroke in the CURE Study



*Other standard therapies were used as appropriate

ACS	acute coronary syndrome
AE(s)	adverse event(s)
ASA	acetylsalicylic acid (aspirin)
AV	atrioventricular
BBB	bundle branch block
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events
CCS-1	First Chinese Cardiac Study
CCS-2	Second Chinese Cardiac Study
CI	confidence interval
COMMIT	Clopidogrel and Metoprolol in Myocardial Infarction Trial
CRF	case report form
CT	computed tomography
CURE	Clopidogrel in Unstable angina to prevent recurrent ischemic Events
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
HR	heart rate
IC	informed consent
ISIS-2	Second International Study of Infarct Survival
ITT	intent-to-treat
MI	myocardial infarction
MRI	magnetic resonance imaging
QD	once daily
PCT	platelet count
PTCA	percutaneous transluminal coronary angioplasty
SAE(s)	serious adverse event(s)
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SFDA	The State Food and Drug Administration (China)
STEMI	ST-elevation myocardial infarction
TFC	TIMI frame count

TFG	TIMI flow grade
TMPG	TIMI myocardial perfusion grade
WBC	white blood cell

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

For the management of ST elevation acute myocardial infarction clopidogrel was not studied and was not shown to reduce the risk of adverse outcomes from the index event in patients treated optimally with state of the art management of STEMI. Therefore, it is not known whether the addition of clopidogrel would add any clinical benefit on top of the arsenal of a US-type medical management of STEMI.

CLARITY with its primary composite outcome results driven by the degree of patency of the infarct related artery is not conclusive with regard to the clinical benefit a patient with STEMI would derive from clopidogrel especially in the light of an absence of a significant difference between clopidogrel and placebo in the incidence of death and/or recurrent MI, and of ST segment resolution. Therefore, CLARITY is not considered supportive for a beneficial effect of clopidogrel in STEMI.

COMMIT on the other hand met its primary objectives of reducing the composite of mortality, re-infarction and stroke, and all cause mortality in a non-optimally managed (per US medical practice standards) STEMI population. COMMIT was conducted in a population one hundred percent Chinese and in a medical setting that is substantially different from that of the US. The most important differences are the timing of the study drug intake relative to the beginning of symptoms and the rate of PTCA implementation which raise two questions. The first being whether meeting the primary objective outcome resulted from an effect of the study drug on the thromboembolus responsible for the index event which qualified the study subjects for enrollment; and the second whether the findings of COMMIT are applicable to patients in an average US acute myocardial infarction management practice.

Therefore, neither COMMIT nor CLARITY provided solid proof that clopidogrel could reduce the risk of undesirable outcomes of STEMI in an optimally treated population.

1.2 Recommendation on Postmarketing Actions

NA

1.2.1 Risk Management Activity

NA

1.2.2 Required Phase 4 Commitments

NA

1.2.3 Other Phase 4 Requests

NA

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Clopidogrel, marketed as Plavix, is an oral antiplatelet of the thienopyridine class that is currently indicated for acute coronary syndrome with unstable angina and NSTEMI.

The proposed new indication is ST elevation acute MI. COMMIT and CLARITY were two trials that enrolled subjects presenting with such condition with a total of 49,500 subjects.

COMMIT was conducted in China and enrolled about 46,000 patients and followed them for an average of one month, while CLARITY enrolled about 35,00 subjects and followed them for an average of eight days.

Other sources of data used include two postmarketing studies (MATCH and CHARISMA) and only summaries concerning bleeding from these two studies are reported in this review.

1.3.2 Efficacy findings

1.3.2.1 COMMIT Findings

COMMIT evaluated the effect of clopidogrel, omitting the 300 mg loading dose, on all-cause mortality and on the composite of death, re-infarction and stroke in subjects presenting with STEMI, but excluded and discontinued subjects who needed angioplasty.

As can be seen from Figure 1 page 15 and Figure 2 page 15, clopidogrel significantly reduced the risk of the composite outcome by 9% (p-value = 0.002) compared to placebo, and marginally significantly reduced the risk of death by 7% (p-value = 0.03).

As can be seen from Table 1 page 16, most of the effect on the composite outcome was mediated through the effect on death and myocardial reinfarction as a first occurrence of the composite. The effect on stroke was not different between the treatment arms.

Figure 3 page 16 and Figure 4 page 16, show that the effect of clopidogrel on the composite outcome was observed immediately starting on day 0, waning around day 2 and 3 with no difference between the two treatment arms and reappearing around day 4. The effect on the coprimary outcome of death was annulled from day 2 to day 7 before it reappeared around day 8.

Figure 1. Cumulative event rate of the combined endpoint in COMMIT (death, reinfarction or stroke)

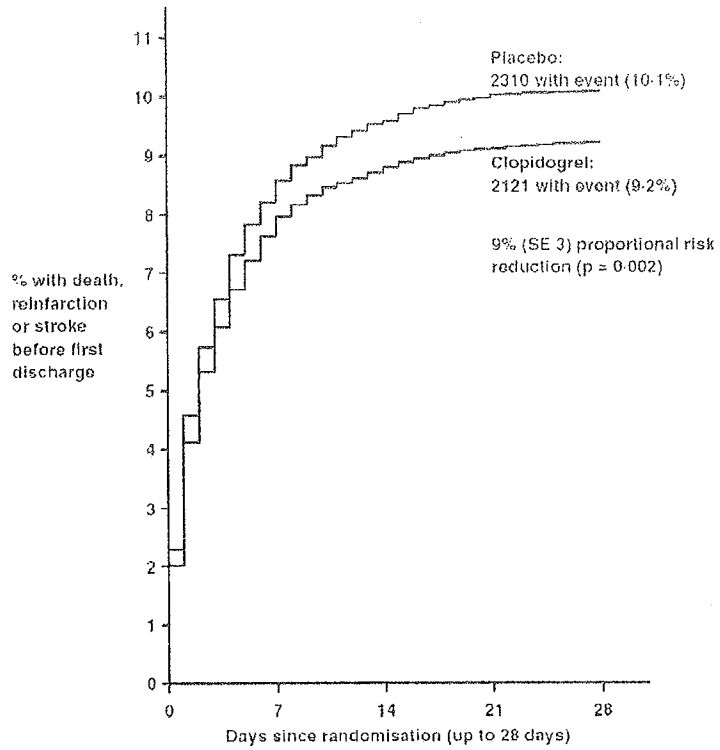


Figure 2. Cumulative event rate of death in COMMIT

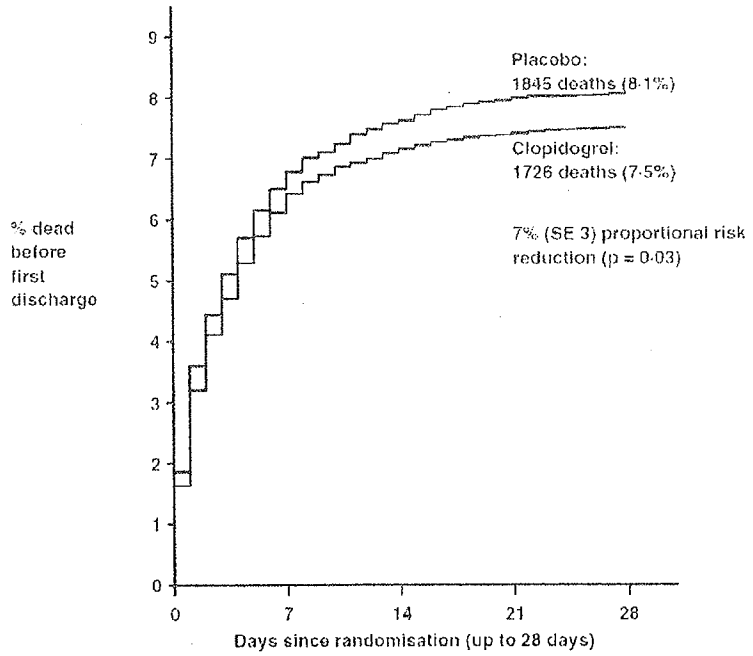


Table 1. Summary of frequency of the components of the primary endpoint

	Clopidogrel 75 mg*	Placebo*	Odds Ratio
Event N (%)	(N = 22961)	(N = 22891)	[95% CI]
Composite endpoint	2121 (9.2%)	2310 (10.1%)	0.91 [0.86, 0.97]
Death	1726 (7.5%)	1845 (8.1%)	0.93 [0.87, 0.99]
All re-MI	465	538	0.86 [0.73,0.98]
All strokes	214	246	0.87 [0.68,1.05]

Figure 3. Composite primary endpoint by day of the outcome event in COMMIT

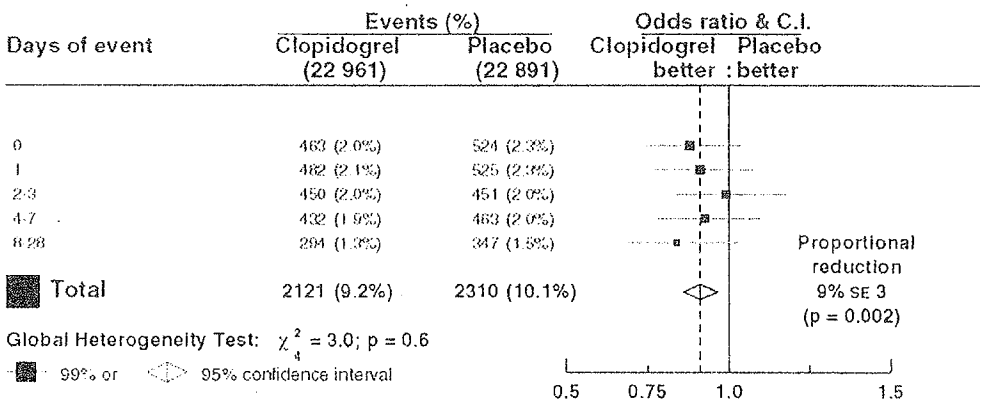


Figure 4. Mortality from any cause by day of the outcome event in COMMIT

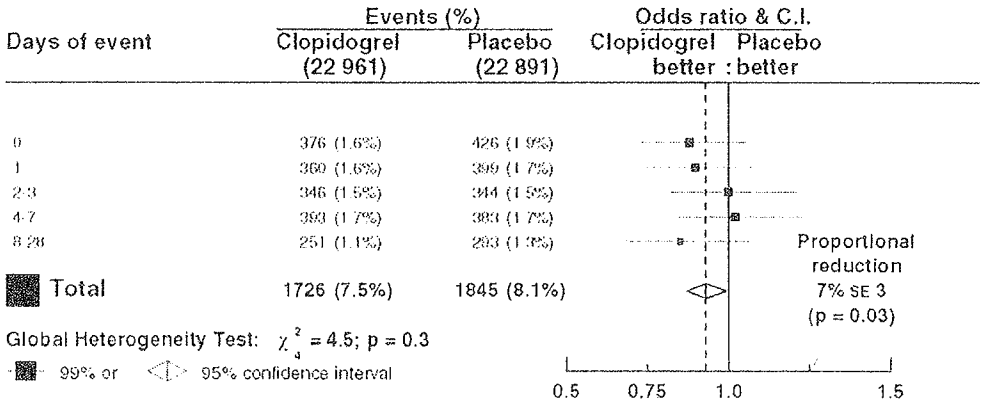


Figure 5. Composite endpoint by subgroups of baseline characteristics in COMMIT

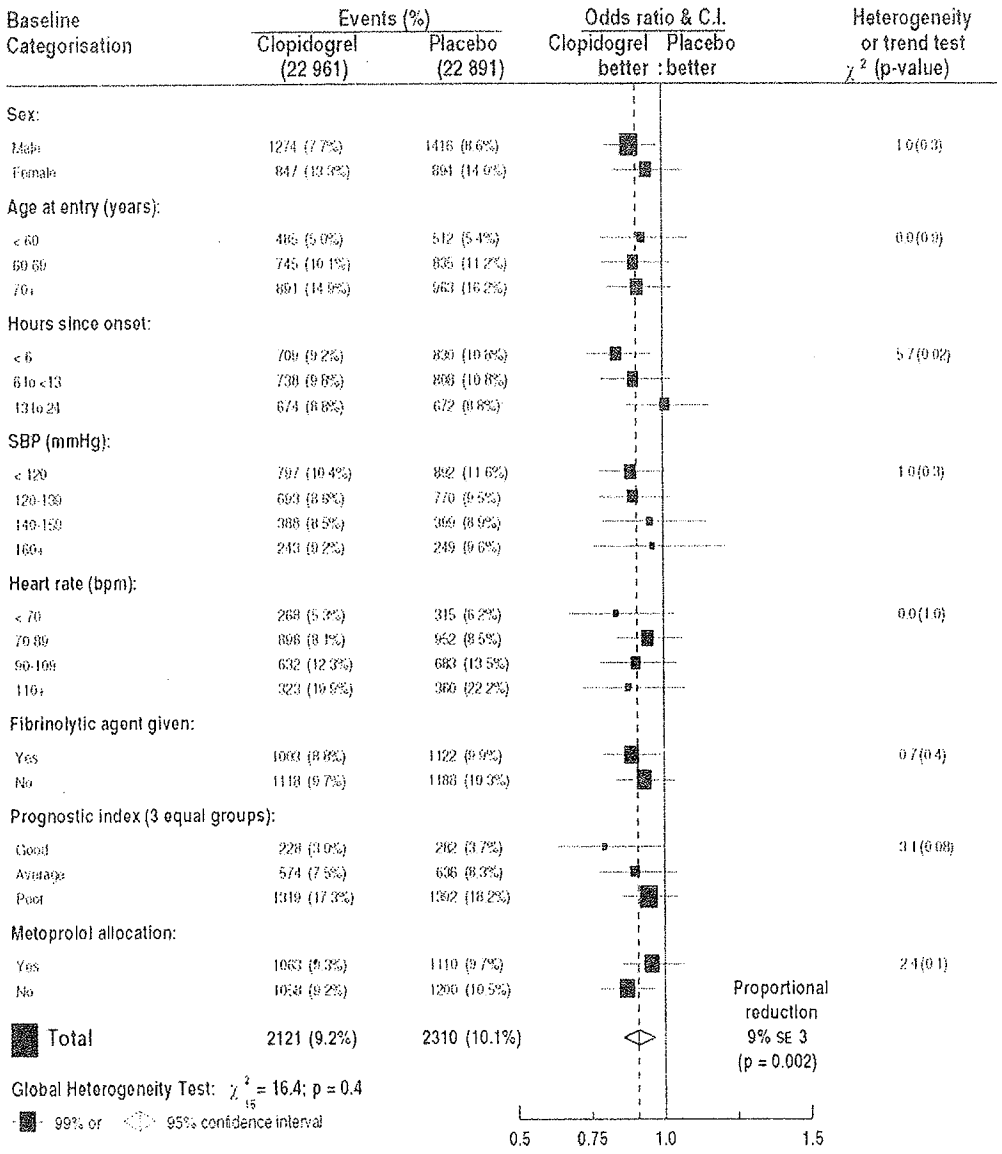
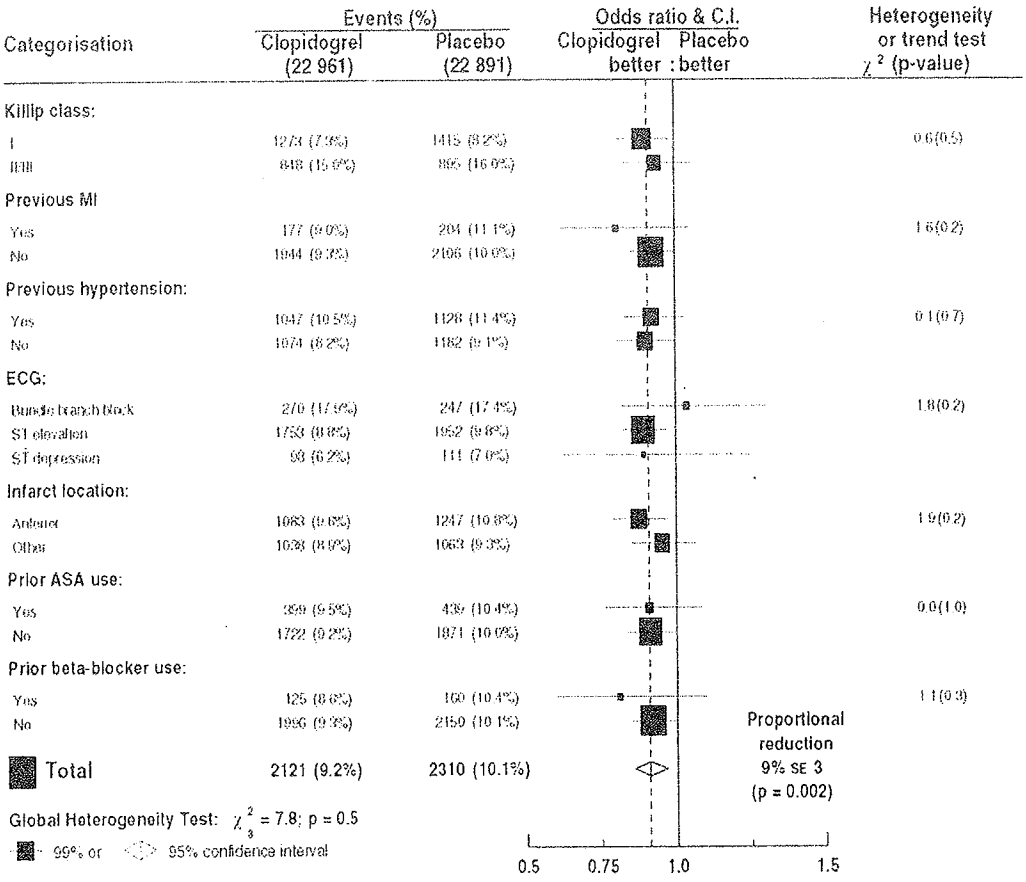


Figure 6. Composite endpoint by additional subgroups of baseline characteristics in COMMIT



As can be seen above, all subgroups trended in the right direction except for subjects whose randomization was delayed by 13 hours post beginning of symptoms and subjects with bundle branch block.

1.3.2.2 Discussion of COMMIT findings

These findings were driven by a prominent effect in subjects who were randomized within 13 hours of the beginning of symptoms. No effect was observed in the subgroup (N=15328) where randomization to study drug occurred more than 13 hours since beginning of symptoms (Figure 5 page 17).

Clopidogrel and ASA were expected to act through the inhibition of platelet aggregation and the subsequent formation of new thromboemboli, but the findings discussed above limiting the effectiveness to the subgroup randomized within 13 hours is not supportive of this mechanism, and rather mimics the effect of thrombolysis in STEMI which ceases to have an effect after the first few hours. Also of note, two thirds of the subjects with delayed study therapy (> 13 hours) were not given fibrinolytics.

Most of the effect in this study was observed in subjects with anterior MI, and since this is usually more severe than non-anterior MI, the lack of effect past 13 hours post-randomization could be explained by the postponement of randomization in non-severe cases.

Also, the observed waning and disappearance of the effect of clopidogrel on both co-primary endpoints (Figure 3 page 16 and Figure 4 page 16) around the time that clopidogrel was expected to reach steady state and optimal pharmacodynamic effect, is interesting.

1.3.2.2 CLARITY findings

Table 2. Odds ratio of the primary composite endpoint (occurrence of an occluded IRA on the predischarge angiogram, or death or recurrent MI) in CLARITY

Primary efficacy endpoint	Clopidogrel N = 1752	Placebo N = 1739	p value	OR	95% CI
Number (%) of patients reporting the endpoint	262 (15.0%)	377 (21.7%)	0.00000036	0.64	0.53,0.76

Table 3. Odds ratio of the primary composite endpoint in CLARITY by PTCA (Analysis by Dr. Zhang)

	Angioplasty prior to angiography				No angioplasty prior angiography			
	Clopidogrel N=964	Placebo N=966	OR	p-value	Clopidogrel N=788	Placebo N=773	OR	p-value
Number (%) reporting endpoint	147	222	0.66	<0.001	115	155	0.73	0.007

Table 4. Individual components of the composite endpoint in CLARITY

	Clopidogrel 1752	Placebo 1739	OR
Occluded IRA			
N (subjects undergoing angiography)	1640	1634	
n (%) patients reporting endpoint	192 (11.7%)	301 (18.4%)	0.64
Death			
n (%) patients reporting endpoint	45 (2.6%)	38 (2.2%)	1.18
Recurrent MI			
n (%) patients reporting endpoint	44 (2.5%)	62 (3.6%)	0.69

Figure 7. Kaplan-Meir curve for death or recurrent MI up to day 30 in CLARITY (note: study drug was taken for a maximum of 8 days)

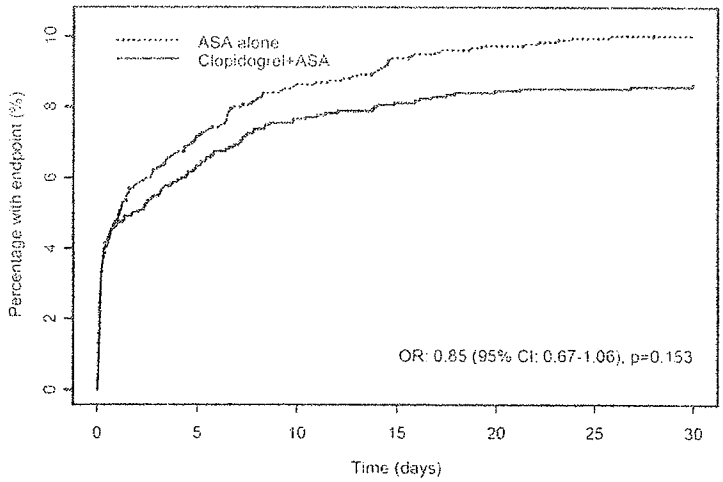


Table 5. Secondary endpoint analyses in CLARITY

Secondary efficacy endpoint	Clopidogrel	Placebo	p value	Mean difference	95% CI
Adjusted mean ST segment resolution of an ECG at 180 minutes after the first dose of study drug	N = 1068 53.01	N = 1021 55.12	0.223b	-2.11	-5.50,1.28
	Clopidogrel	**Placebo**	**p value**	**OR**	**95% CI**
Number (%) of patients with occluded IRA on pre-discharge angiogram	N = 1640 192 (11.7%)	N = 1634 301 (18.4%)	<0.001b	0.59	0.48,0.72
Number (%) of patients with death, recurrent MI, or recurrent myocardial ischemia (severe or leading to revascularization) by the time of the start of pre-discharge angiography	N = 1752 145 (8.3%)	N = 1739 162 (9.3%)	0.274b	0.88	0.69,1.11

Since the first secondary endpoint (ST segment resolution) was not statistically significant, testing of other secondary endpoints is not relevant because of the hierarchy testing procedure.

Figure 8. Primary analysis by baseline characteristic subgroups in CLARITY

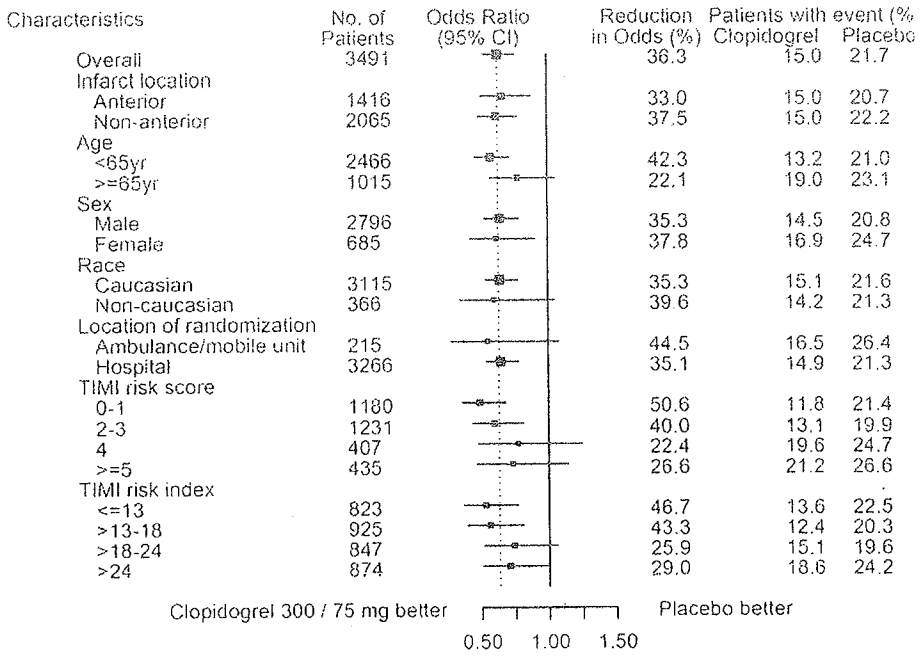
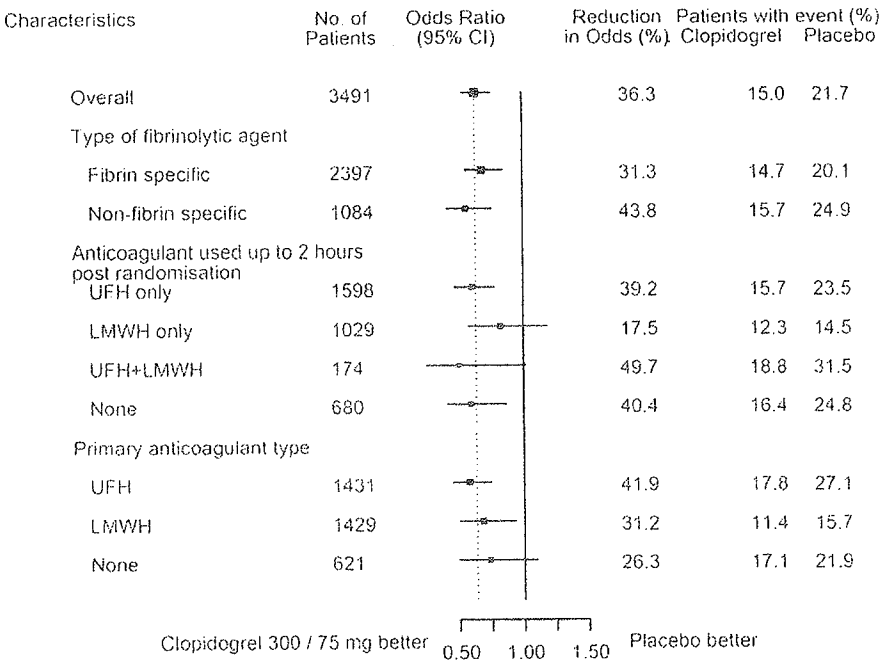


Figure 9. Primary analysis by the use of other concomitant therapy subgroups in CLARITY



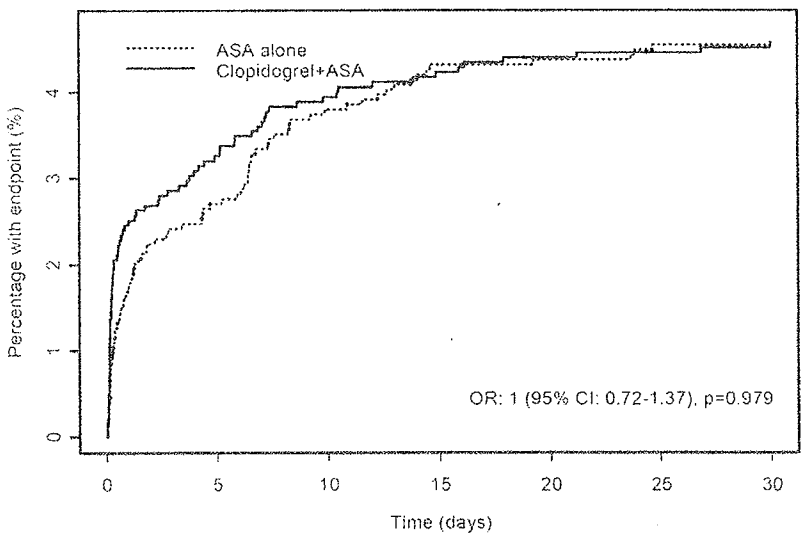
1.3.2.2 Discussion of CLARITY findings

CLARITY met its primary objective of a statistically significant difference between the treatment arms in the primary composite outcome (Table 2 page 19), occlusion of the infarct-related artery (IRA) or death or re-infarction. The difference in the primary outcome was robust and consistent across all subgroup categories (Figure 8 page 21 and Figure 9 page 21). This difference in effect was driven by the effect on the component of occluded IRA (Table 4 page19). Total number of events from the other two components constituted less than one third of the overall number of events.

The secondary objective outcome of a difference in ST segment resolution at 180 minutes after the first dose of study drug intake was not met.

Mortality a component of the composite outcome trended in the wrong direction ((45 (2.6%) and 38 (2.2%) see Figure 10 below) for clopidogrel and placebo respectively), and the degree of ST segment resolution at 180 minutes post first dose of study drug (a secondary endpoint) was not different between the two treatment arms. These findings led to the question of whether the degree of patency of the infarct related artery is a good marker of a beneficial outcome in the general STEMI population represented by the study population.

Figure 10. Kaplan Meir curve for death in CLARITY (note: subjects received study drug for a maximum of 8 days)



1.3.3 Safety

Clopidogrel has been marketed for years and millions of subjects have been exposed to this drug, but its interaction with other anticoagulants and antithrombotics and fibrinolytics that are commonly used for the management of STEMI with regard to the risk of bleeding has not been investigated.

Data collection in COMMIT was limited because this study was focused on the evaluation of efficacy rather than safety. The report of serious adverse events was left to the discretion of the interpretation of the investigator which was based on their

judgment of the relatedness to the study drug. The protocol specified that only serious adverse events judged by the investigator to be study drug related were to be reported. The findings from this study should be interpreted cautiously with regard to the conclusion on the safety of clopidogrel in the STEMI population.

1.3.3.1 Bleeding

Bleeding is an important side effect of clopidogrel and it is the focus of this safety review. The COMMIT study by design collected limited information on bleeding. Information on major and other non-cerebral bleeding was collected under "Possible side-effects of trial treatment"; and information on stroke of probable hemorrhagic origin was collected under "Major events after randomization in hospital".

CLARITY on the other hand was more comprehensive in the collection of adverse events than COMMIT.

Bleeding was reported as a cause of death in COMMIT in 19 (0.1%) subjects on clopidogrel and 18 (0.1%) subjects on placebo; and in CLARITY in 13 (0.8%) subjects on clopidogrel and 10 (0.6%) subjects on placebo.

Bleeding was reported as a serious adverse event in CLARITY in 58 (3.4%) on clopidogrel and in 37 (2.2%) on placebo with 8 (0.4%) intracranial on clopidogrel compared to 12 (0.7%) on placebo; and 12 (0.7%) hemopericardium on clopidogrel compared to 3 (0.2%) on placebo;

Bleeding as a cause of study discontinuation was reported in COMMIT in 429 (1.9%) subjects on clopidogrel compared to 364 (1.6%) subjects on placebo with the majority of discontinuations due to non-cerebral hemorrhage (87% and 90% on clopidogrel and placebo respectively); around 6% (in each group) due to cerebral hemorrhage and the remaining (26 (6%) on clopidogrel and 14 (4%) on placebo) due to "high risk of bleeding".

In CLARITY, bleeding led to discontinuation in 29 (1.8%) subjects on clopidogrel compared to 27 (1.6%) subjects on placebo.

Except for intracranial hemorrhage where an excess was observed on placebo compared to clopidogrel, all bleeds were higher on clopidogrel compared to placebo.

The most common bleeds in CLARITY were gastrointestinal ((18 (1.0%) vs. 10 (0.6%)), followed by catheter site ((13 (0.8%) vs. 6 (0.4%)) and pericardial ((12 (0.7%) vs. 3 (0.2%)). Bleeding in subjects 70 years of age or older was more than 3 times higher on clopidogrel compared to placebo (23 (1.3%) vs. 7 (0.4%) respectively).

1.3.3.1 Other adverse events

COMMIT had the statistical power to possibly quantify the risk of TTP, liver failure and aplastic anemia, but COMMIT was not focused on hypotheses testing. Besides when the study started, TTP was not yet determined to be an adverse event of clopidogrel.

No cases of thrombotic thrombocytopenic purpura were reported in either study and the numbers of subjects with thrombocytopenia in CLARITY were similar on both treatment arms.

1.3.4 Dosing Regimen and Administration

Per the CURE trial findings optimal inhibition of platelet aggregation by clopidogrel is accomplished by delivering the 300 mg loading dose before initiation of the 75 mg maintenance dose.

1.3.5 Drug-Drug Interactions

NA

1.3.6 Special Populations

The findings of CURE showed that elderly patients (75 years of age and older) benefited less and were at a higher risk of bleeding than younger patients.

1.4 Generalizability of the Efficacy Findings

1.4.1 Factors that might affect the generalizability of the findings of COMMIT to a non-Chinese population and a US-type medical standards and practice

Table 6. Comparison of selected demographics and other baseline characteristics in COMMIT and CLARITY

	COMMIT	CLARITY
Ethnicity		
Caucasian	0%	90%
Asian	100%	2%
Other	0%	10%
Gender		
Male	72%	80%
Female	28%	20%
Age (yrs)		
Mean (SD)	61.3 (11.8)	57.4 (10.3)
Range	15.4-100.3	18-79
Mean SBP (SD) mmHg	128 (22.5)	135 (22.7)
Mean DBP (SD) mmHg	81 (14.5)	81 (14.3)
HR mean (SD) bpm	82 (17.2)	75 (17.3)
Prior MI	8%	9%
History of hypertension	43%	43%
Infarct location		
Anterior	54	41%
Non-anterior	46	59%
Duration of hospitalization		
Mean (SD) (days)	14.9 (7.8)	

Table 7. Comparison of selected medical characteristics in COMMIT and CLARITY

	COMMIT[1]	CLARITY
Randomization within 6 hours	34%	91%

	COMMIT[1]	CLARITY
Randomization > 13 hours	33.4%	NA
Mean (SD) hours since onset	10.3 (6.7)	2.8 (2.1)
Use of nitrates	94%	72%
Fibrinolytics	55%	100%
Antiarrhythmics	22.3	9%
Diuretics	23%	18%
ACE-I	68%	55%
CCB	11.8	5%
Need for PTCA	3%[2]	56%
PTCA during index hospitalization[3]	0%	56%

[1] Urokinase, a fibrinolytic is commonly used in China while streptokinase is more commonly used in this country.
[2]These were discontinued from the protocol;
[3]Other cases of revascularizations such as those performed during a subsequent period of hospitalization (5%), as a scheduled day case (3%) and other (0.6%) are not included.

As can be seen from the table above, there are some substantial differences between the medical management of STEMI in the Chinese population and the Western population.

For the applicability of the findings of COMMIT in the US two questions remain unanswered:

1. Quantification of the added harm or benefit of the loading dose on the objectives targeted by COMMIT in a STEMI population medically managed per US medical standards;
2. Interaction and the quantification of interaction between clopidogrel and angioplasty;

1.4.2 Relevance of the Findings of CLARITY to a STEMI population

The findings of CLARITY are not conclusive with regard to how much clinical benefit is gained by reinstituting epicardial blood flow, especially in the context of an absence of a difference in the other components of the composite endpoint.

2 INTRODUCTION AND BACKGROUND

Dose-dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses and 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 Days 3 and 7. At steady state, the average inhibition level observed with a dose of 75 mg 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.

Early use of ASA has become routine for a wide range of patients admitted to hospital with suspected or definite acute MI as a result of the findings of the Second International Study of Infarct Survival (ISIS-2), where one month of daily ASA (162 mg) reduced the risk of early death by approximately 25% and the risks of nonfatal reinfarction and stroke by approximately 50% in 17000 patients with suspected acute MI.

Both clopidogrel and ASA are approved for the reduction of cardiovascular events in acute coronary syndrome patients. It is believed by the sponsor that unstable angina and acute MI (with or without ST-segment elevation) are believed to share a common underlying pathophysiology and represent different degrees of the same disease. Therefore, it was hypothesized that the combination clopidogrel/ASA would have an effect in STEMI as it did in ACS.

2.1 Product Information

NA

2.2 Currently Available Treatment for Indications

ASA is the only other anti-platelet indicated in the treatment of acute ST elevation MI. Other non-platelet-targeted therapies include fibrinolytics, GP IIb/IIIa and anti-coagulants.

2.3 Availability of Proposed Active Ingredient in the United States

Clopidogrel is currently marketed in the US and many other countries including China for the indication of acute coronary syndrome with unstable angina and NSTEMI.

2.4 Important Issues with Pharmacologically Related Products

NA

2.5 Presubmission Regulatory Activity

COMMIT was not under IND, but when the study was completed the Sponsor proposed the submission of this study for the support of an indication in acute ST elevation MI. The results of COMMIT were presented to the Agency in a meeting and it was recommended that a supplemental NDA be submitted containing the findings of COMMIT.

In the minutes of the pre-NDA meeting in July of 2005, the Agency commented that COMMIT was the only outcome study and it was conducted in a non-U.S. population. Therefore, Agency needs to be convinced that it is relevant despite differences in clinical practice and, consequently, will predict benefit to the U.S. population. The agency required that this argument be addressed clearly and in detail.

2.6 Other Relevant Background Information

NA

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

NA

3.2 Animal Pharmacology/Toxicology

NA

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Sources of efficacy review depended on the pivotal studies, CLARITY and COMMIT. One of these studies, COMMIT, was conducted solely in China.

Sources for safety review relied mostly on the two pivotal studies, but findings published from other studies not submitted with this application, CHARISMA and MATCH, were also used especially with regard to bleeding.

4.2 Tables of Clinical Studies

Table 8. List of (submitted) clinical studies in acute ST elevation MI

Study	Study drug	Design	Objective	Duration	Population
COMMIT	Clopidogrel 75 mg + ASA	R, DB, PC	1. Death or re-infarction or stroke; 2. all deaths	Discharge up to Day 28	45852 Acute MI with ECG abnormalities
CLARITY	Clopidogrel 300 mg (loading dose), and 75 mg thereafter	R, DB, PC	Occluded infarct related artery or death or recurrent MI	Angiography, discharge up to Day 8	3491 STEMI treated with fibrinolytics

Table 9. Other studies used for safety review

Study	Study drug	Design	Objective	Duration	Population
MATCH	ASA 75 mg or placebo + Clopidogrel 75 mg	R, DB, PC	Ischemic stroke or MI or Vascular death or re-hospitalization for acute ischemic events	18 months	7599 recent IS or TIA + at least one vascular risk factor
CHARISMA	+ ASA 75-162 mg	R, DB, PC	MI or stroke or CV death	30 months	15603 at high risk of atherothrombotic events

IS: ischemic stroke

TIA: transient ischemic attack

4.3 Review Strategy

Safety from the pivotal studies was summarized for each study separately for a number of reasons including the omission of the loading dose in the COMMIT trial, differences in concomitant use of products that affect the outcome of bleeding and other differences that are inherent to a different study population.

Adverse events were blindedly re-coded by the reviewer and safety summary tables were generated.

Additional safety data from literature regarding bleeding was also summarized.

4.4 Data Quality and Integrity

Five investigation centers in China, for COMMIT, were audited by Dr. Gan of DSI. Centers were selected based on the number of subjects enrolled and on the observed effect of treatment. The comments from the audit were that there was sufficient documentation to assure that study subjects existed, eligibility criteria were fulfilled, assigned study medication was received and adverse events were adequately reported.

4.5 Compliance with Good Clinical Practices

In COMMIT, the informed consent method was left to the discretion of the study investigator to be obtained either in writing or orally from patients or their relatives. Per the following language, it seems that the consent was not obtained from some patients in certain circumstances: "since any delays starting treatment may lead to lives being lost, it may not be considered appropriate to discuss the various treatment options in prolonged detail. The degree and timing of consent is, therefore, left tot individual doctors to decide of individual patients, in the light of local requirements and advice from any relevant local ethical committee".

Per the submission report, data from two centers were omitted from analyses because major GCP violations were detected.

4.6 Financial Disclosures

Sanofi-Synthelabo stated that they have not entered into any financial arrangement with any clinical investigators as defined in 21 CFR 54.

Some investigators did not provide financial equity ownership disclosure despite many attempts on the part of the Sponsor.

5 CLINICAL PHARMACOLOGY

NA

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

6.1.1 Methods

6.1.2 General Discussion of Endpoints

A. COMMIT

The primary endpoints for the clopidogrel treatment comparison were two: the composite of death, reinfarction or stroke; and death.

B. CLARITY

The primary endpoint was the composite of death or recurrent MI (by the time of the start of predischarge angiogram) or occlusion (TIMI Flow Grade 0 or 1) of the infarct related artery on the predischarge angiogram.

6.1.3 Study Design

A. COMMIT

COMMIT/CCS-2 "A randomized trial of clopidogrel plus aspirin (ASA) versus ASA alone and of metoprolol versus placebo, among patients with suspected acute myocardial infarction (MI)"

First patient was enrolled on July 30 1999 and last patient was completed on February 28 2005.

It was stated[1] that the trial was set jointly by the Clinical Trial Service Unit (Clinical Trial Service Unit) at the University of Oxford and the Beijing coordinating center based at the Fuwai Hospital, Chinese Academy of Medical Sciences, and that the general structure of the study was planned independently of the companies funding the study (Astra-Zeneca and Sanofi) who had no representatives in its organization and who were to remain blinded to the results as they accumulated.

This study was not conducted under an IND, therefore, the protocol was not submitted for review before initiation of the study. The protocol was published during the first year of randomization by the Second Chinese Cardiac Study (CCS-2) Collaborative Group[1].

This was a randomized, double-blind, placebo-controlled, 2 x 2 factorial trial investigating two active treatments, clopidogrel and metoprolol in the prevention of death, reinfarction and/or stroke in subject admitted to the hospital for acute MI confirmed with ECG abnormalities. The study was conducted solely in China. Subjects were randomized within 24 hour of the beginning of their symptoms in a 2 x 2 factorial design to clopidogrel or placebo, and metoprolol or placebo.

After randomization, subjects were to first receive their daily ASA 162 mg and clopidogrel 75 mg or ASA 162 mg and placebo, followed by three IV injections two to three minutes apart of either metoprolol 5 mg or placebo. The injections could be halted or stopped all together if blood pressure and/or heart rate were affected adversely.

Metoprolol 50 mg tablet or placebo was to be started 15 minutes after the last injection and given every 6 hours for the remaining of first day and the second day.

From the third day on, metoprolol 200 mg or placebo was to be given qd until Day 28 or discharge or death whichever came first.

All other patient management was at the discretion of the treating physician except that non-trial antiplatelets and betablockers were to be avoided during the 4-week trial duration.

At discharge or death a single page discharge form was to be filled with brief detail on compliance with study treatment, other treatment received during hospitalization, possible trial treatment side effects, major clinical events and cause of death if patient died. No post-hospital follow-up was required.

Subjects presenting within 24 hours of symptoms of suspected AMI with ECG abnormalities (ST elevation, ST depression or BBB) were considered for inclusion, provided that the treating doctor considered that there was no clear indication or contraindication to the trial therapy.

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[1] Second Chinese Cardiac Study (CCS-2) Collaborative Group; Journal of Cardiovascular Risk 2000, 7:435-441

Reasons for exclusion from the trial were not pre-specified by the protocol but were at the discretion of the physician. Examples were given such as low benefit in subjects at low risk of death, or anticipated high risk of adverse events including previous allergy to aspirin, active bleeding or active hemostatic disorder, SBP < 100 mmHg, heart rate < 50 bpm, third degree heart block or cardiogenic shock.

Random allocation and blinding of the study treatment at each participating center seem to have been conducted adequately by using pre-packed, sequentially numbered trial drug packs that had been prepared and sealed, in cases of 8 packs each, centrally. The physician responsible removed the next available randomization pack, completed the one-page entry form attached to the outside of the randomization pack before removing the box of trial treatments from the pack. A copy of the form was to be returned together with a copy of the most recent pre-entry ECG sheet on the day of study entry to the coordinating center in Beijing.

The choice of the clopidogrel dose, 75 mg, was based on the experience with the CAPRIE trial. By the time results of CURE became available showing the benefit of clopidogrel as a loading dose of 300 mg plus a 75 mg maintenance dose, 15000 subjects had already been enrolled in COMMIT, and the decision was not to amend the protocol.

The choice of ASA dose was based on the ISIS-2 study, where ASA at a dose of 162 mg daily was shown to be highly effective in the emergency treatment of acute MI[2].

Patients and investigators, the Clinical Trial Service Unit, both companies (Sanofi-Synthelabo Research and AstrZeneca) and all committees except the DSMB and statistician who performed interim analyses were blinded to the study drug identity for individual patients.

Concomitant fibrinolytic therapy, where indicated, was strongly encouraged. All other aspects of patient management were entirely at the discretion of the patient's own physician, except that nontrial beta-blocker and antiplatelet therapy were to be avoided during the scheduled treatment period (i.e., up to 4 weeks in the hospital) unless they were considered to be clearly indicated.

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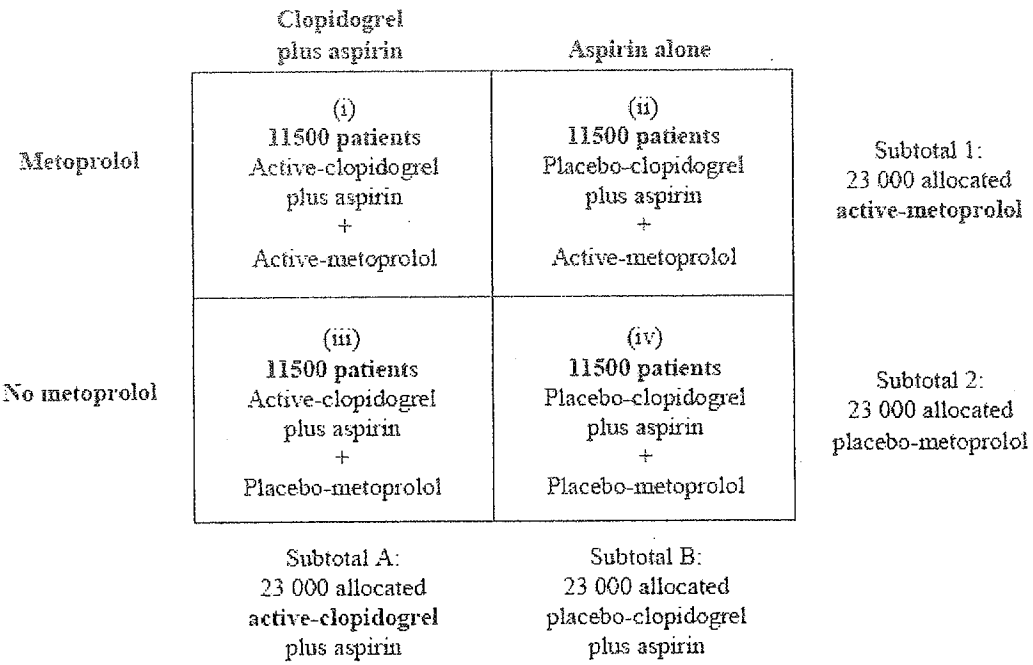
[2] ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction. ISIS-2. Lancet 1988;2(8607):349-60.

Figure 11. Schema of study design



I. Efficacy evaluation

1. Primary efficacy variables

Primary efficacy was assessed based on the occurrence of two coprimary endpoints during the scheduled trial treatment period defined as randomization through Day 28, hospital discharge or death, and these endpoints were the composite of death, reinfarction or stroke; and all-cause mortality.

2. Secondary efficacy variables

The other planned efficacy outcomes included:

-any reinfarction (fatal and nonfatal);

-any stroke;

-any pulmonary embolism;

-other major clinical events in hospital during the scheduled treatment period that were explicitly recorded (i.e., cardiogenic shock, heart failure requiring persistent treatment, presumed cardiac rupture, ventricular fibrillation/other cardiac arrest);

II. Safety evaluation

Safety was assessed based on the incidence of bleeding and other adverse events.

All bleeding events were recorded as 1 of 3 types:

a. -major noncerebral bleeding (fatal or nonfatal requiring transfusion);

b. -other noncerebral bleeding;

c. -hemorrhagic stroke;

Other adverse events collected are:

d. -persistent hypotension (SBP <90 mmHg);

e. -bradycardia (heart rate persistently <40 beats/minute);

f. - "volunteered AEs";

Only SAEs that were both unexpected (unexpected AEs were defined as those that would not be expected among patients given antiplatelet therapy[3] or beta-blocker for suspected acute MI) and believed with a reasonable probability to be due to study treatment were to be reported. Per this definition and per the timing of COMMIT, many of the adverse events that were determined to be caused by clopidogrel in the post-marketing phase, e.g., TTP would have been missed.

III. Statistical analyses

It was stated that the statistical analysis plan has been revised blind to the specific treatment results.

1. Sample size

Original sample size calculation was based on the findings of the first Chinese cardiac study where an in-hospital death rate among subjects with acute MI was expected to be around 10% even in the presence of antiplatelet and/or fibrinolytic therapy.

If clopidogrel plus ASA produced a 10% reduction in mortality, then 15000 subjects in each treatment arm would be needed with a mortality rate of 9% (1350 out of 15000) on clopidogrel vs. 10% (1500) on placebo to show a statistically significant difference between the treatment groups (two-sided p-value = 0.003).

A further 4% of the patients were expected to experience non-fatal events including MI or stroke. It was then hypothesized that an overall risk reduction of 11% of the composite of death, reinfarction or stroke would be observed if active treatment with clopidogrel reduced major non-fatal events by 15%.

Later on, it was decided that the sample size needed to be increased. Table below shows numbers of anticipated major events in a population of 46000 patients with suspected acute infarction.

Table 10. Anticipated major efficacy events in the COMMIT population

Event	Proportional Risk Reduction	Active (23000)	Control (23000)	Two-sided p-values
Death	10%	2070 (9.0%)	2300 (10.0%)	0.003
Nonfatal re-infarction or stroke/arrest	15%	782 (3.4%)	920 (4.0%)	0.006
Total: death, re-infarction or stroke/arrest	11%	2530 (12.4%)	3220 (14.0%)	<0.0001

[3] Based on findings of trials that studied non-thionopyridin antiplatelets;

2. Data analyses

Although patients in COMMIT/CCS-2 were randomized between four treatment groups in a 2 x 2 factorial design with placebo control, it was assumed that the intake of metoprolol by half of the subjects on clopidogrel would not interfere with the accurate assessment of the effect of clopidogrel on the study outcomes. Therefore, a two-way instead of a four-way comparison was planned for the evaluation of efficacy.

Information would be provided about whether the combined proportional effects of clopidogrel and metoprolol are approximately multiplicative.

All analyses were to be based on the ITT (randomly allocated study treatments), irrespective of adherence. For each particular outcome or group of outcomes, the analysis would be of the number of patients suffering such an outcome at least once during the scheduled trial treatment period (randomization to whichever comes first of death in hospital, first discharge alive from hospital or day 28).

For the primary analyses, the comparisons would involve comparing the survival curves for the two treatment using "logrank" analyses of the two co-primary end-points, and all time-to-event analyses would be based on the first relevant event. If a patient is discharged alive before day 28 without a relevant event, the logrank analysis would treat this patient as if he were event-free up to day 28 (rather than censoring on the day of discharge) even if he/she had an event after discharge and before Day 28. If the time of an event is unknown for a particular patient, then it would be assumed to have been as early as possible given whatever information is available.

The effect of treatment was to be presented as odds ratio (clopidogrel vs. placebo) and absolute benefit per 1000 subjects (placebo minus clopidogrel).

No adjustment for multiplicity was to be made to the first co-primary endpoint. If the p-value of the second co-primary endpoint were more extreme than that for the first co-primary, the p-value for the latter was to be used in discussing the significance of the effects of treatment on it.

3. Interim analyses

It was stated that interim analyses of the primary endpoint (and other information such as serious adverse events believed by the physician responsible to be due to the trial treatment) were to be performed at regular intervals during the trial period and reviewed by an independent Data Monitoring Committee.

4. Subsidiary comparisons

The principal subsidiary comparisons were, as specified in the published protocol, the effects of clopidogrel on the combined end-point and on death, during days 0-1, days 2-7 and days 8-28 of the scheduled treatment period.

Other subsidiary outcomes analyzed using log-rank analysis (as for the primary endpoints) were MI (separating fatal and non-fatal); and stroke (separating ischemic versus hemorrhagic; with and without CT/MRI confirmation; with and without residual handicap).

Other subsidiary outcomes (where time to event was not collected or used) analyzed using ordinary odds ratio calculations and (95% CIs) were persistent hypotension; bradycardia; cardiogenic shock;

heart failure requiring persistent treatment; presumed cardiac rupture; ventricular fibrillation; other cardiac arrest; and pulmonary embolus.

5. Subgroup analyses

Additional analyses of the effect of clopidogrel on the composite endpoint in population subgroups including:

-age: <60, 60-69, 70+;
-hours since onset of symptoms: <6, 6 to <13, 13 to 24;
-systolic blood pressure: <120, 120-139, 140-159, 160+;
-heart rate <70, 70-89, 90-109, 110+ bpm;
-Fibrinolytic therapy intake;
-Randomization to metoprolol;
-Prognosis defined as good, average and poor (three similar sized groups based on absolute risk) constructed using the prognostic index based on baseline characteristics using Cox regression analyses to identify and find the best fit for predictive variables (of the overall risk of death, reinfarction or stroke) and derive the coefficient of prediction.

Other non-prespecified subgroups of interest (defined according to baseline characteristics) included Killip class: I, II/III; previous MI: yes, no; history of hypertension: yes, no; ECG change including bundle branch block (BBB), ST elevation, ST depression; infarct location: anterior vs. other; prior ASA: yes, no; prior beta-blocker: yes, no.

B. CLARITY

CLARITY-TIMI 28 – "Clopidogrel as Adjunctive Reperfusion Therapy – Thrombolysis in Myocardial Infarction - 28: A randomized, double-blind, placebo-controlled trial comparing clopidogrel plus ASA versus ASA alone in patients with acute STEMI treated with fibrinolytic therapy"

This was an international, multicenter, randomized, double-blind, placebo-controlled clinical trial comparing clopidogrel plus ASA with ASA alone in subjects with STEMI treated with fibrinolysis.

Within 6 hours of the onset of a qualifying STEMI, subjects were to be randomized in a 1:1 ratio to receive either clopidogrel or placebo. All subjects were also to receive daily aspirin for the duration of the study.

Subjects were to receive study drug up to and including the day of angiography. For subjects who do not undergo angiography, administration of study drug was to continue up to and including day 8 or discharge from the hospital, whichever came first.

Coronary angiography was to be performed during the index hospitalization between 48 and 192 hours after the start of study medication to determine late patency of the infarct related artery. Also, 12-lead ECGs were to be obtained at baseline and at 90 and 180 minutes after administration of the loading dose of study drug to assess early reperfusion.

The loading dose (300 mg) was to be administered with the start of fibrinolysis, and subjects were to take 1 tablet (clopidogrel 75 mg or placebo) daily thereafter.

The dose of ASA depended on previous intake. If no ASA was taken within the previous 24 hours, 150-325 mg was to be given and if ASA was taken within 24 hours, 150-162 mg was to be given. This initial dose was to be chewed or given IV, and 75-162 mg was to be given daily thereafter.

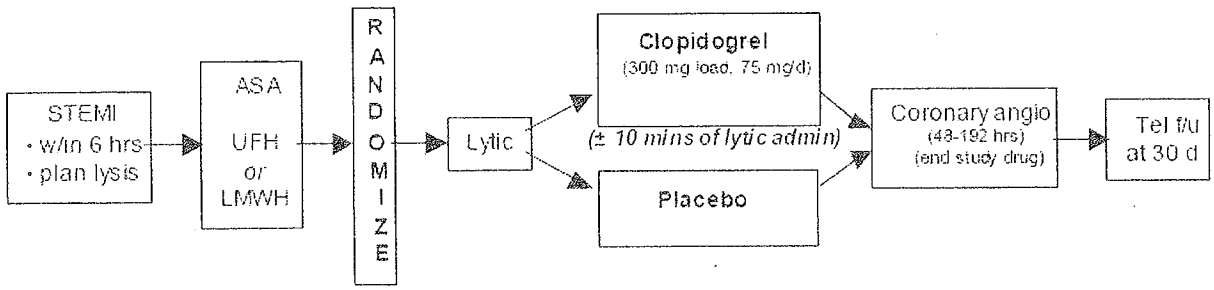
For subjects who undergo coronary stenting at the time of their initial angiogram, it is recommended that blinded study drug be discontinued and open-label clopidogrel be administered after the initial angiogram with a loading dose of 300 mg, followed by 75 mg daily.

Study drug was to be discontinued after angiography. In subjects who did not undergo angiography, it was to be discontinued after Day 8 or hospital discharge, whichever came first.

Other circumstances in which study drug was to be discontinued included CABG where study medication was to be withheld 5 days prior the procedure; need for chronic oral anticoagulation; major and unprovoked minor bleeding; and evidence of neutropenia (neutrophil count <1500/mm3), thrombocytopenia (platelet count <100,000/mm3) or thrombotic thrombocytopenic purpura (TTP).

All subjects were to be followed for 30 days through telephone contact regardless of whether or not they continued on the study drug.

Figure 12. Schema of study design



To be included were subjects 18 to 75 years of age with onset of ischemic discomfort at rest within 12 hours of randomization; symptoms of prolonged (>20 minutes) ischemic discomfort at rest associated with electrocardiographic evidence of new ST segment elevation ≥0.10 mV (80 msec after the J point) in at least 2 contiguous limb leads or ≥0.20 mV in at least 2 contiguous precordial (chest) leads, or left bundle branch block not known to be old; with a fibrinolytic agent (alteplase, reteplase, tenecteplase, or streptokinase), an anticoagulant (if receiving a fibrin-specific fibrinolytic), and ASA as planned treatment;

To be excluded were subjects with the intention of performing early coronary angiography (within 48 hours of fibrinolysis); treatment within 7 days prior to enrollment or planned treatment with clopidogrel or ticlopidine; contraindication to fibrinolysis; treatment with >4000 U bolus of UFH in patients ≤ 67 kg or treatment with 5000 U bolus of UFH in patients > 67 kg within 6 hours; treatment with >30 mg IV or >1.1 mg/kg SC of enoxaparin within 8 hours; or treatment with >130 U/kg of dalteparin within 8 hours; planned use of a glycoprotein IIb/IIIa

inhibitor as part of the initial pharmacologic reperfusion therapy; anticipated use of urokinase as fibrinolytic; prior CABG; evidence of cardiogenic shock or acute pulmonary edema requiring intubation or an intra-aortic balloon pump; known serum creatinine >2.5 mg/dL; known hepatic insufficiency; platelet count <100,000 / mm^3; prior hypersensitivity (i.e., allergic reaction) to ASA, ticlopidine, or clopidogrel, prior neutropenia or heparin-induced thrombocytopenia; pregnancy or women of child-bearing potential who are not using an acceptable contraceptive method; previous enrollment in CLARITY-TIMI 28;

Protocol-specific major clinical events, including non-fatal recurrent myocardial infarction, stroke, and major hemorrhagic events were to be adjudicated by the trial's clinical event committee.

Use of non-study drug clopidogrel or ticlopdine was prohibited, except following coronary stenting.

Use of GP IIb/IIIa inhibitors (e.g., abciximab, eptifibatide, and tirofiban) was permitted only after the initial coronary angiogram is obtained;

All subjects were to be treated with one of the standard, approved fibrinolytic regimens at the discretion of the treating physician (e.g. alteplase, reteplase, tenecteplase, streptokinase).

All subjects receiving a fibrin-specific fibrinolytic (i.e., alteplase, reteplase, tenecteplase) were to be treated with a heparin regimen.

Subjects were to have three 12-lead study ECGs performed at pre-randomization and 90 and 180 minutes after administration of the study drug loading dose. These ECGs were to be sent to a blinded-TIMI ECG Core Laboratory for analysis.

The following laboratory parameters were to be evaluated at local clinical laboratories:
-complete blood count (CBC) with differential at baseline;
-coagulation parameters (PT, aPTT) at baseline and aPTT at 3 hours after the initiation of fibrinolysis;
-ACT (activated clotting time) to be measured (not in subjects receiving LMWH) prior to anticoagulation at the start of catheterization for angiography;
-CK-MB and troponin after the initiation of fibrinolysis: five times over 48 hours (i.e., approximately every 8 hours); post-revascularization: three times over the subsequent 24 hours (i.e., approximately every 8 hours); in suspected recurrent ischemia or reinfarction: 3 times over the subsequent 24 hours following onset of symptoms;

Interim clinical endpoints and adverse events were to be collected via a 30-day follow-up phone call, and medical records were to be retrieved and reviewed for events that resulted in hospitalization.

Subjects were to undergo coronary angiography during the index hospitalization between 48 and 192 hours after the start of study medication. TIMI Flow Grade (TFG) in the infarct-related artery was to be read by the TIMI Angiographic Core Laboratory, which was to be blinded to treatment assignment and clinical endpoints.

Cardiac catheterization before 48 hours will be permitted in subjects who develop cardiogenic shock or persistent hemodynamic instability, manifest clear clinical evidence of failed reperfusion (e.g., persistent severe chest pain and <50% resolution of ST segment elevation), or

develop recurrent ischemia as documented by recurrent ischemic ECG changes and ischemic chest pain.

Table 11. CLARITY-Study flow-chart

Evaluation/Procedure	Baseline	Time 0	90 min	180 min	24-48 hrs	Daily	Angiogram (Day 3-8)	Discharge	Day 30 Tele FU
Screening	x								
Informed Consent	x								
Medical History	x								
Physical Exam	x								
12-lead ECG	x		x	x					
Continuous ECG (selected sites)		x	x	x	x	x	x		
Hematology	x								
Coagulation parameters	x			x	x				
Myonecrosis markers	x				x		x		
Ischemia, myonecrosis, hemostatic, inflammatory, and neurohormonal markers (selected sites)	x						x		
ASA	x					x	x	x	x
Anticoagulant	x	x	x	x	x				
Randomization	x								
Fibrinolytic	x								
Study Drug		x				x	x		
Angiography							x		
Clinical events		x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x
Pharmacogenomic Informed Consent/Blood sample (selected sites)	x								

I. Efficacy Objectives

The primary objective of this study was to demonstrate in subjects with acute STEMI treated with fibrinolytic therapy that the combination of clopidogrel plus ASA would reduce the proportion of subjects who have an occluded infarct-related artery (defined as TIMI Flow Grade 0 or 1) on the pre-discharge angiogram, who die or have a recurrent MI by the end of the calendar day following angiography or by hospital discharge, whichever comes first[4].

The secondary objectives of this study were to demonstrate that clopidogrel plus ASA would reduce the proportion of subjects with an occluded infarct-related artery on the pre-discharge angiogram; improve early reperfusion as indicated by the degree of ST segment resolution on a 12-lead ECG at 180 minutes after study drug loading dose as compared to baseline; and that proportion of subjects who survive without recurrent MI or severe recurrent myocardial ischemia were higher with the combination of clopidogrel/ASA by the end of the calendar day following angiography or by hospital discharge, whichever came first[4].

[4] For subjects who do not undergo angiography, day 8 or hospital discharge, whichever comes first, was to be used;

Other objectives were of scientific interest and were to be examined as exploratory analyses, see 10.4 Other endpoints to be explored in CLARITY page 102.

II. Safety Objectives

The primary safety objective was to compare the treatment groups with regard to the rate of TIMI major bleeding;

The secondary safety objective was to evaluate the rate of intracranial hemorrhage, all stroke, all bleeding, or thrombocytopenia;

III. Statistical analyses

1. Sample size

A sample size of 1100 subjects per arm (or a total of 2200 subjects) would afford 82% power to detect a 5% absolute reduction (24% relative reduction) from 21% to 16% in the rate of the primary efficacy endpoint using a two-sided p=0.05 level test. This power calculation incorporated a continuity correction and assumed a dropout rate of 5%.

The event rate of death, recurrent MI, or TFG 0/1 in placebo was approximated from STEMI trials using UFH in which angiography revealed that approximately 20% of the subjects would be found to have TFG of 0/1 in the infarct-related artery (IRA), both at 60-90 minutes and at 5-7 days after randomization in these trials.

Populations considered for analyses included:

-ITT population in which subjects would be analyzed according to the study medication to which they were randomized irrespective of whether they received it;

-Angiographic endpoints were to be assessed in subjects who were randomized and underwent angiography;

-Secondary analyses were to be performed in the ITT population in which a closed infarct-related artery was to be imputed for subjects who die prior to angiography.

-treated population was to consist of all subjects randomized who have received at least one dose of study medication. Safety analyses were to be conducted according to the study medication received;

-per-protocol population was to consist of the treated population excluding subjects who had major protocol violations (defined as those that interfere with the evaluation of the primary efficacy parameter). Major protocol violations were to be defined prior to unblinding of the study database. Secondary efficacy analyses were to be performed in this population to assess the robustness of the treatment effect;

2. Primary Efficacy Endpoints

The primary endpoint of this trial is the composite of an occluded infarct-related artery (defined as TIMI Flow Grade 0 or 1) on the pre-discharge angiogram or death or recurrent MI by the end of the calendar day following angiography[5].

Secondary Efficacy Endpoints

-TIMI Flow Grade 0 or 1 in the IRA on the pre-discharge angiogram;

-Death, recurrent MI, or recurrent myocardial ischemia (severe or leading to urgent revascularization) by the end of the calendar day following angiography[5];

-Degree of ST segment resolution at 180 minutes after study drug loading dose;

3. Efficacy Analyses

a. Primary Analyses

The primary endpoint was to be analyzed using logistic regression analysis with adjustment for type of fibrinolytic (fibrin-specific vs. non-fibrin specific), type of anticoagulant (UFH vs. LMWH vs. none) and infarct location (anterior vs. non-anterior), and tested at a significance level of <0.05. Additional analyses were to be conducted adjusting for any differences in baseline characteristics deemed clinically significant using a covariate-adjusted logistic regression model.

b. Secondary Analyses

-Angiographic (TFG 0/1 in the IRA) and clinical (death, MI, or recurrent myocardial ischemia) secondary efficacy endpoints were to be analyzed using the logistic regression model described in the primary analysis.

-Electrocardiographic secondary endpoint (degree of ST segment resolution at 180 minutes after study drug loading dose) were to be analyzed using a linear regression model with adjustment for type of fibrinolytic, type of anticoagulant, and infarct location.

-Additional analyses, if appropriate, were to be conducted adjusting for any additional differences in baseline characteristics deemed clinically significant using a covariate-adjusted regression model.

c. Subgroup Analyses

Analyses computing rates of the primary and secondary endpoints and point estimates with 95% confidence intervals for the effect of clopidogrel were to be conducted by type of fibrinolytic, type of anticoagulant, infarct location, randomization in ambulance/mobile care vs. in hospital, and by age and sex.

4. Safety analyses

Safety analyses were to be performed for major bleeding, all bleeding, stroke, intracranial hemorrhage, and thrombocytopenia. Additional analyses were to evaluate procedure- and non-procedure-related bleeding events. Incidence of AEs and SAEs were to be summarized by treatment group.

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[5] For subjects who do not undergo angiography, day 8 or by hospital discharge, whichever comes first, was to be used;

5. Interim analyses

An interim safety evaluation was performed by the DSMB on 14 April 2004. Partially blinded (treatment groups coded as Drug X and Drug Y) tabular summaries of stroke/ICH (total, hemorrhagic, and non-hemorrhagic), bleeding events (TIMI major and TIMI minor), and death for 1628 patients prepared by a [redacted] statistician not involved in the day-to-day activities of the study were reviewed and the recommendation was that the study should continue as planned. b(4)

6.1.4 Efficacy Findings

See 1.3 Summary of Clinical Findings page 14.

6.1.5 Clinical Microbiology

NA

6.1.6 Efficacy Conclusions

Both CLARITY and COMMIT despite significantly meeting their primary objectives did not demonstrate that clopidogrel is clinically beneficial in ST elevation acute myocardial infarction in subjects optimally managed by the state of the art treatment regimens.

There is no data that support that late patency of the infarct-related artery as is shown by CLARITY is correlated with a beneficial clinical outcome.

Extrapolating the findings of COMMIT to a STEMI population that is managed more aggressively and with all available treatment modalities as is the case with patients in the US would be unwise since it is not known whether clopidogrel would add anything to the state of the art treatment modalities applied in this country. Also, it is not known how the interaction between a strong antiplatelet such as clopidogrel with its loading dose regimen and clothing/coagulation inhibitors would manifest.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Table 12. Proportion of patients with treatment-emergent AEs leading to death, any treatment-emergent SAEs, or AEs leading to permanent discontinuation (treated population) in CLARITY

	Clopidogrel N = 1733	Placebo N = 1719
Patients with TEAEs		
Angiography[1]	817 (47.1)	821 (47.8)
End of follow-up	983 (56.7)	981 (57.1)
Patients with TESAE		
Angiography1	306 (17.7)	314 (18.3)
End of follow-up2	431 (24.9)	452 (26.3)
Patients with TEAEs with an outcome of death by end of follow-up[2]	78 (4.5)	79 (4.6)
Patients with AEs leading to permanent discontinuation by end of follow-up[2]	119 (6.9)	147 (8.6)

[1] Events from the time of first dose of study drug until the calendar day following pre-discharge angiography, or by Day 8 or hospital discharge, whichever came first, for patients who did not undergo an angiography;

[2] Events from the time of first dose of study drug until end of follow-up, Day 30;

7.1.1 Deaths

A. COMMIT

Table 13. Death by cause in COMMIT

Event	Clopidogrel (N = 22961)	Placebo (N = 22891)
All death[1]	1726 (7.5)	1845 (8.1)
Arrhythmia	432 (1.9)	454 (2.0)
Asystole	642 (2.8)	697 (3.0)
Cardiac rupture	188 (0.8)	210 (0.9)
Cardiogenic shock	503 (2.2)	562 (2.5)
Reinfarction	113 (0.5)	101 (0.4)
Stroke	72 (0.3)	87 (0.4)
Pulmonary embolus	26 (0.1)	18 (0.1)
Severe bleeding	19 (0.1)	14 (0.1)
Other cardiac	21 (0.1)	18 (0.1)
Other noncardiac (see Table 45 page 96)	26 (0.1)	53 (0.2)

[1] Some deaths had more than one cause reported

B. CLARITY

Table 14. Death by cause in CLARITY

Preferred term of AEs leading to death	Clopidogrel 1733 N (%)	Placebo 1719 N (%)
All adverse events leading to death	78 (4.5)	79 (4.6)
Bleeding	13 (0.8)	10 (0.6)

Preferred term of AEs leading to death	Clopidogrel 1733 N (%)	Placebo 1719 N (%)
Non-bleeding	75 (4.3)	71 (4.1)
Cardiovascular disorders	34 (2.0)	34 (2.0)
Cardiac failure	32 (1.8)	32 (1.9)
Cardiac failure left	1 (0.1)	3 (0.2)
Ventricular septal defect	5 (0.3)	2 (0.1)
Heart rate and rhythm	42 (2.4)	41 (2.4)
Arrhythmia	2 (0.1)	4 (0.2)
Arrhythmia ventricular	0 (0.0)	1 (0.1)
AV block	0 (0.0)	2 (0.1)
AV block complete	6 (0.3)	4 (0.2)
Cardiac arrest	30 (1.7)	28 (1.6)
Fibrillation atrial	1 (0.1)	0 (0.0)
Fibrillation ventricular	13 (0.8)	13 (0.8)
Tachycardia ventricular	9 (0.5)	4 (0.2)
Myo-, endo-, pericardial and valve disorders	24 (1.4)	21 (1.2)
Myocardial rupture (post infarct)	16 (0.9)	9 (0.5)
Myocardial infarction	6 (0.3)	8 (0.5)
Pericardial effusion	2 (0.1)	3 (0.2)
Angina pectoris	1 (0.1)	4 (0.2)
Coronary artery disorder	1 (0.1)	0 (0.0)
Resistance mechanism disorders	1 (0.1)	1 (0.1)
Sepsis	1 (0.1)	1 (0.1)
Vascular (extracardiac) disorders	4 (0.2)	2 (0.1)
Cerebrovascular disorder	2 (0.1)	2 (0.1)
Vascular disorder	2 (0.1)	0 (0.0)
Platelet, bleeding and clotting disorders	13 (0.8)	11 (0.6)
Hemopericardium	9 (0.5)	3 (0.2)
Cerebral hemorrhage	1 (0.1)	7 (0.4)
Embolism pulmonary	1 (0.1)	0 (0.0)
GI hemorrhage	1 (0.1)	0 (0.0)
Haematemesis	1 (0.1)	0 (0.0)
Hemorrhage intracranial	1 (0.1)	0 (0.0)
Thrombosis coronary	0 (0.0)	1 (0.1)
Body as a whole - general disorders	1 (0.1)	2 (0.1)
Death	0 (0.0)	2 (0.1)
Sudden death	1 (0.1)	0 (0.0)
CNS disorders	0 (0.0)	1 (0.1)
Convulsions grand mal	0 (0.0)	1 (0.1)
Respiratory system disorders	2 (0.1)	4 (0.2)
Hypoxia	0 (0.0)	1 (0.1)
Pneumonia	1 (0.1)	0 (0.0)
Pneumonitis	0 (0.0)	1 (0.1)
Respiratory insufficiency	1 (0.1)	2 (0.1)
Urinary system disorders	0 (0.0)	1 (0.1)
Renal failure acute	0 (0.0)	1 (0.1)

-Myocardial rupture and expectedly hemopericardium caused more deaths on clopidogrel than on placebo.

-VT caused twice as many deaths on clopidogrel;

7.1.2 Other Serious Adverse Events

A. COMMIT

Serious adverse events were not collected in the COMMIT trial. Only those SAEs that were both "unexpected" (defined as those that would not be expected among patients given antiplatelet therapy[6] or beta-blocker for suspected acute MI) and believed with a reasonable probability to be due to study treatment were to be reported.

At the time of design of COMMIT, a number of adverse events that became later known to be associated with clopidogrel were not taken into account and thus were not investigated.

B. CLARITY

Table 15. Serious adverse events observed up to the end of the day following angiography, or Day 8 or hospital discharge whichever came first in CLARITY

SOC Preferred term	Clopidogrel 1733 N (%)	Placebo 1719 N (%)
All treated patients	1733	1719
All adverse events	306 (17.7)	314 (18.3)
Application Site Disorders	1 (0.1)	0 (0.0)
Injection site bleeding	1 (0.1)	0 (0.0)
Autonomic Nervous System Disorders	1 (0.1)	0 (0.0)
Syncope	1 (0.1)	0 (0.0)
Body as a Whole - General Disorders	3 (0.2)	1 (0.1)
Allergic reaction	1 (0.1)	0 (0.0)
Chest pain	2 (0.1)	0 (0.0)
Death	0 (0.0)	1 (0.1)
Cardiovascular Disorders General,	55 (3.2)	67 (3.9)
Cardiac failure	45 (2.6)	60 (3.5)
Cardiac failure left	3 (0.2)	4 (0.2)
Heart disorder	1 (0.1)	0 (0.0)
Hypertension aggravated	3 (0.2)	1 (0.1)
Hypotension	5 (0.3)	2 (0.1)
Ventricular septal defect	5 (0.3)	2 (0.1)
CNS Disorders	3 (0.2)	1 (0.1)
Convulsions	1 (0.1)	0 (0.0)
Convulsions grand mal	0 (0.0)	1 (0.1)
Encephalopathy	2 (0.1)	0 (0.0)
Gastro-Intestinal System Disorders	3 (0.2)	2 (0.1)
Duodenal ulcer hemorrhagic	1 (0.1)	0 (0.0)
Gastric ulcer hemorrhagic	0 (0.0)	1 (0.1)
Gastritis hemorrhagic	2 (0.1)	1 (0.1)
Heart Rate and Rhythm Disorders	82 (4.7)	90 (5.2)
Arrhythmia	1 (0.1)	1 (0.1)
Arrhythmia nodal	0 (0.0)	1 (0.1)

[6] Based on findings of trials that studied non-thionopyridin antiplatelets;

SOC Preferred term	Clopidogrel 1733 N (%)	Placebo 1719 N (%)
Arrhythmia ventricular	0 (0.0)	1 (0.1)
AV block	3 (0.2)	4 (0.2)
AV block complete	10 (0.6)	11 (0.6)
Bradycardia	4 (0.2)	1 (0.1)
Cardiac arrest	29 (1.7)	29 (1.7)
Fibrillation atrial	6 (0.3)	5 (0.3)
Fibrillation ventricular	39 (2.3)	42 (2.4)
Tachycardia ventricular	19 (1.1)	16 (0.9)
Liver and Biliary System Disorders	0 (0.0)	1 (0.1)
Cholelithiasis	0 (0.0)	1 (0.1)
Metabolic and Nutritional Disorders	1 (0.1)	0 (0.0)
Diabetes mellitus	1 (0.1)	0 (0.0)
Myo-, Endo-, Pericardial and Valve Disorders	152 (8.8)	180 (10.5)
Angina pectoris	63 (3.6)	68 (4.0)
Angina pectoris aggravated	7 (0.4)	9 (0.5)
Coronary artery disorder	0 (0.0)	1 (0.1)
Myocardial infarction	49 (2.8)	79 (4.6)
Myocardial ischemia	12 (0.7)	13 (0.8)
Myocardial rupture (post infarct)	15 (0.9)	8 (0.5)
Pericardial effusion	4 (0.2)	3 (0.2)
Pericarditis	5 (0.3)	7 (0.4)
Neoplasms	4 (0.2)	2 (0.1)
Carcinoma	1 (0.1)	0 (0.0)
Colon carcinoma	0 (0.0)	1 (0.1)
GI neoplasm malignant	2 (0.1)	0 (0.0)
Neoplasm malignant	1 (0.1)	1 (0.1)
Rectal carcinoma	0 (0.0)	1 (0.1)
Platelet, Bleeding and Clotting Disorders	56 (3.2)	37 (2.2)
Cerebral hemorrhage	6 (0.3)	13 (0.8)
Embolism limb	1 (0.1)	1 (0.1)
Epistaxis	2 (0.1)	1 (0.1)
GI hemorrhage	6 (0.3)	4 (0.2)
Gingival bleeding	0 (0.0)	1 (0.1)
Haemarthrosis	0 (0.0)	1 (0.1)
Haematemesis	4 (0.2)	1 (0.1)
Haematoma	2 (0.1)	1 (0.1)
Haematuria	3 (0.2)	0 (0.0)
Hemorrhage intracranial	2 (0.1)	0 (0.0)
Hemorrhage NOS	2 (0.1)	0 (0.0)
Hemorrhage rectum	2 (0.1)	1 (0.1)
Hemopericardium	10 (0.6)	3 (0.2)
Hemorrhage of operative wound	15 (0.9)	4 (0.2)
Oral hemorrhage	1 (0.1)	0 (0.0)
Thrombocytopenia	6 (0.3)	6 (0.3)
Thrombosis coronary	0 (0.0)	1 (0.1)
Psychiatric Disorders	1 (0.1)	0 (0.0)
Dementia	1 (0.1)	0 (0.0)
Red Blood Cell Disorders	1 (0.1)	4 (0.2)
Anemia	1 (0.1)	4 (0.2)

SOC Preferred term	Clopidogrel 1733 N (%)	Placebo 1719 N (%)
Reproductive Disorders, Female	0 (0.0)	1 (0.1)
Endometrial hyperplasia	0 (0.0)	1 (0.1)
Resistance Mechanism Disorders	3 (0.2)	1 (0.1)
Sepsis	3 (0.2)	1 (0.1)
Respiratory System Disorders	9 (0.5)	7 (0.4)
Apnea	1 (0.1)	0 (0.0)
Bronchitis	1 (0.1)	0 (0.0)
Chest x-ray abnormal	1 (0.1)	0 (0.0)
Hemothorax	1 (0.1)	1 (0.1)
Hypoxia	0 (0.0)	1 (0.1)
Pneumonia	0 (0.0)	2 (0.1)
Pneumonia lobar	1 (0.1)	1 (0.1)
Pneumonitis	0 (0.0)	1 (0.1)
Pulmonary edema	3 (0.2)	0 (0.0)
Respiratory insufficiency	2 (0.1)	1 (0.1)
Secondary Terms	1 (0.1)	1 (0.1)
Alcohol problem	1 (0.1)	0 (0.0)
Post-operative wound infection	0 (0.0)	1 (0.1)
Skin and Appendage Disorders	1 (0.1)	0 (0.0)
Angioedema	1 (0.1)	0 (0.0)
Urinary System Disorders	0 (0.0)	2 (0.1)
Renal failure acute	0 (0.0)	2 (0.1)
Vascular (Extracardiac) Disorders	6 (0.3)	7 (0.4)
Cerebrovascular disorder	3 (0.2)	7 (0.4)
Peripheral ischemia	1 (0.1)	0 (0.0)
Vascular disorder	2 (0.1)	0 (0.0)

-Hemopericardium was reported as SAE in (10 vs. 3) three as many times reported on clopidogrel as on placebo;
-Hemorrhage of operative wound and hematemesis were reported as SAEs in (15 vs. 4) four as many subjects on clopidogrel;
-Ventricular septal defect was reported as SAE in (5 vs. 2) twice and a half as many subjects on clopidogrel;
-Myocardial rupture was reported as SAE in (15 vs. 8) almost twice as many subjects on clopidogrel;
-Other hemorrhages including GI, hematuria were reported as SAEs more commonly on clopidogrel;

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

A. COMMIT

Table 16. Treatment compliance and main reasons for stopping study drug prematurely in COMMIT

Category	Clopidogrel	Placebo
Randomized	N = 22961	N = 22891
Treatment not started	109 (0.5)	116 (0.5)
Treatment completed	21241 (92.5)	21210 (92.7)
Completed follow-up	22959	22891
Unknown	2	0

Category	Clopidogrel	Placebo
Treatment discontinued	1609 (7.0)	1565 (6.8)
Reason for discontinuation		
PTCA or stent	684 (3.0)	713 (3.1)
Adverse event	549 (2.4)	494 (2.2)
MI not confirmed	103 (0.4)	90 (0.4)
Patient refusal	40 (0.2)	35 (0.2)
Other	233 (1.0)	233 (1.0)

The main reason for discontinuation in COMMIT was PTCA or need for a stent, followed by adverse events;

B. CLARITY

Table 17. Disposition of CLARITY study population

	Clopidogrel	Placebo
Patients Randomized	1752	1739
Patients Randomized and treated	1729 (98.7)	1723 (99.1)
Patients Randomized and not treated	23 (1.3)	16 (0.9)
Up to Angiography, Day 8 or hospital discharge (whichever comes first) when no angiogram date available		
Patients completing treatment	1622 (93.8)	1623 (94.2)
Death up to angiography	45 (2.6)	38 (2.2)
Patients permanently discontinuing study drug	69 (4.0)	64 (3.7)
Reason for discontinuation		
AE/SAE	35 (50.7)	31 (48.4)
Subject no longer meets study criteria	4 (5.8)	6 (9.4)
Subject withdrew consent	8 (11.6)	4 (6.3)
Administrative	22 (31.9)	22 (34.4)
Other	0 (0.0)	1 (1.6)
Randomization up to Day 30 assessment date		
Patients completing follow-up	1669 (95.3)	1658 (95.3)
Patients not completing follow-up but not reported dead	3 (0.2)	1 (0.1)
Death during follow-up	80 (4.6)	80 (4.6)

7.1.3.2 Adverse events associated with dropouts

A. COMMIT

Table 18. Discontinuations due to adverse events by reason in the COMMIT study (analysis completed by reviewer)

	Clopidogrel N=22961	Placebo N=22891	OR
Non-cerebral bleeding	375 (1.63)	326 (1.42)	1.15
Non-MI/suspected non-MI	103 (0.45)	90 (0.39)	1.14
Non-specific symptoms (nausea,cough,pain)	85 (0.37)	79 (0.35)	1.07
Cannot swallow(coma,vomiting,psychiatric disorder)	45 (0.2)	47 (0.21)	0.95
No use of study drug due to serious complications including death	30 (0.13)	40 (0.17)	0.75
Hemorrhagic or mixed stroke	27 (0.12)	24 (0.1)	1.12
High risk of bleeding (easy bruising,etc)	26 (0.11)	14 (0.06)	1.85
Risk factor for bleeding(Ulcer, aneurysm; etc)	23 (0.1)	24 (0.1)	0.96
Allergy/skin pruritus	21 (0.09)	24 (0.1)	0.87

	Clopidogrel N=22961	Placebo N=22891	OR
Low WBC and/or Low PCT	17 (0.07)	15 (0.07)	1.13
Cardiac failure/cardiac failure aggravation/reduced cardiac function	16 (0.07)	13 (0.06)	1.23
Acute.GI (appendicitis; pancreatitis, gastric perforation, etc)	5 (0.02)	5 (0.02)	1.00
Cardiac arrest	3 (0.01)	2 (0.01)	1.50
Cerebral infarction	3 (0.01)	2 (0.01)	1.50
Pericarditis/Pericarditic fluid	3 (0.01)	2 (0.01)	1.50
Prolonged coagulating time	3 (0.01)	5 (0.02)	0.60
Thrombolytic therapy/heparin	3 (0.01)	5 (0.02)	0.60
Abnormal liver function (Hepatitis)	2 (0.01)	6 (0.03)	0.33
Acute pancreatitis	2 (0.01)	0 (0)	-
Hemolytic anemia/Hb Urine/drug-induced haemolysis	2 (0.01)	1 (0)	1.99
Renal failure	1 (0)	4 (0.02)	0.25
cerebral tumor (bleeding)	1 (0)	0 (0)	-
Re-infarct	0 (0)	7 (0.03)	0.00
gout	0 (0)	1 (0)	0.00

B. CLARITY

Table 19. Adverse events leading to permanent discontinuation of study drug in CLARITY

SOC Preferred term	Clopidogrel 1733		Placebo 1719	
	No. of reports	No. of pts (%)	No. of reports	No. of pts (%)
All adverse events	140	119 (6.9)	172	147 (8.6)
Bleeding	26	25 (1.4)	24	23 (1.3)
Non-bleeding	114	100 (5.8)	148	126 (7.3)
Chest pain	0	0 (0.0)	1	1 (0.1)
Chest pain precordial	0	0 (0.0)	1	1 (0.1)
Cardiac failure	6	6 (0.3)	20	17 (1.0)
Cardiac failure left	1	1 (0.1)	1	1 (0.1)
Hypertension aggravated	0	0 (0.0)	1	1 (0.1)
Hypotension	2	2 (0.1)	1	1 (0.1)
Ventricular septal defect	1	1 (0.1)	2	2 (0.1)
Duodenal ulcer hemorrhagic	1	1 (0.1)	0	0 (0.0)
Duodenitis	1	1 (0.1)	0	0 (0.0)
Dyspepsia	1	1 (0.1)	0	0 (0.0)
Gastric ulcer hemorrhagic	0	0 (0.0)	1	1 (0.1)
Gastritis hemorrhagic	1	1 (0.1)	0	0 (0.0)
Gastroesophageal reflux	1	1 (0.1)	0	0 (0.0)
AV block complete	1	1 (0.1)	1	1 (0.1)
Cardiac arrest	2	2 (0.1)	3	3 (0.2)
Fibrillation atrial	0	0 (0.0)	1	1 (0.1)
Fibrillation ventricular	5	5 (0.3)	7	7 (0.4)
Tachycardia ventricular	4	4 (0.2)	2	2 (0.1)
Hepatic enzymes increased	2	2 (0.1)	0	0 (0.0)
Back pain	1	1 (0.1)	0	0 (0.0)
Angina pectoris	31	31 (1.8)	31	31 (1.8)
Angina pectoris aggravated	4	4 (0.2)	4	4 (0.2)

SOC Preferred term	Clopidogrel 1733		Placebo 1719	
	No. of reports	No. of pts (%)	No. of reports	No. of pts (%)
Coronary artery disorder	0	0 (0.0)	1	1 (0.1)
Myocardial infarction	34	34 (2.0)	55	55 (3.2)
Myocardial ischemia	6	6 (0.3)	10	10 (0.6)
Pericardial effusion	0	0 (0.0)	1	1 (0.1)
Pericarditis	2	2 (0.1)	1	1 (0.1)
GI neoplasm malignant	1	1 (0.1)	0	0 (0.0)
Neoplasm malignant	1	1 (0.1)	0	0 (0.0)
Cerebral hemorrhage	6	6 (0.3)	11	11 (0.6)
Epistaxis	1	1 (0.1)	0	0 (0.0)
GI hemorrhage	4	4 (0.2)	4	4 (0.2)
Haematemesis	2	2 (0.1)	1	1 (0.1)
Haematoma	2	2 (0.1)	0	0 (0.0)
Haematuria	0	0 (0.0)	2	2 (0.1)
Hemorrhage intracranial	1	1 (0.1)	0	0 (0.0)
Hemorrhage NOS	1	1 (0.1)	0	0 (0.0)
Hemorrhage rectum	0	0 (0.0)	1	1 (0.1)
Hemopericardium	2	2 (0.1)	0	0 (0.0)
Hemorrhage of operative wound	4	4 (0.2)	1	1 (0.1)
Oral hemorrhage	0	0 (0.0)	1	1 (0.1)
Thrombocytopenia	0	0 (0.0)	1	1 (0.1)
Depression	0	0 (0.0)	1	1 (0.1)
Anemia	1	1 (0.1)	1	1 (0.1)
Hemothorax	0	0 (0.0)	1	1 (0.1)
Respiratory insufficiency	1	1 (0.1)	1	1 (0.1)
Angioedema	2	2 (0.1)	0	0 (0.0)
Oliguria	1	1 (0.1)	0	0 (0.0)
Renal failure acute	0	0 (0.0)	1	1 (0.1)
Cerebrovascular disorder	1	1 (0.1)	0	0 (0.0)
Vascular disorder	2	2 (0.1)	0	0 (0.0)

7.1.3.3 Other significant adverse events

1. Bleeding

A. Bleeding in CLARITY

Table 20. Adjudicated TIMI bleeding in CLARITY

Safety endpoint	Clopidogrel N = 1733	Placebo N = 1719	OR	p value	95 CI
N (%) of patients reporting any bleeding	302 (17.4)	221 (12.9)	1.43	<0.001	1.19,1.73
Adjudicated bleeding	67 (3.9)	44 (2.6)	1.51	-	-
Major	23 (1.3)	19 (1.1)	1.20	-	-
Minor	17 (1.0)	9 (0.5)	1.87	-	-
Minimal	28 (1.6)	16 (0.9)	1.74	-	-
None	1 (0.1)	1 (0.1)	0.99	-	-
Non-adjudicated bleeding	246 (14.2)	185 (10.8)	1.32	-	-

Table 21. Adjudicated stroke

Event (%)	Clopidogrel N = 1733	Placebo N = 1719	p value	OR	95% CI
Stroke/ICH	10 (0.6)	21 (1.2)	0.048	0.47	0.20,1.05
ICH	8 (0.5)	12 (0.7)	0.380	0.66	0.23,1.76

Table 22. Bleeding in CLARITY by site (of bleeding)

Site of bleeding	Clopidogrel 1733	Placebo 1719	OR
Catheter site	13 (0.75)	6 (0.35)	2.15
Gastrointestinal	18 (1.04)	10 (0.58)	1.79
Genitourinary	6 (0.35)	4 (0.23)	1.49
Intracranial	8 (0.46)	12 (0.7)	0.66
Other	11 (0.63)	8 (0.47)	1.36
Pericardial	12 (0.69)	3 (0.17)	3.97
Retroperitoneal	0 (0)	1 (0.06)	0.00
Subcutaneous	3 (0.17)	1 (0.06)	2.98

Except for intracranial bleeding, the risk of bleeding in all other sites especially pericardial, catheter and gastrointestinal was higher on clopidogrel;

Table 23. Bleeding by intensity and seriousness in CLARITY (reviewer's analysis)

Intensity	Clopidogrel 1733	Placebo 1719	OR
Mild	5 (0.29)	9 (0.52)	0.55
moderate	35 (2.02)	16 (0.93)	2.17
Severe	27 (1.56)	20 (1.16)	1.34
Not serious	9 (0.52)	8 (0.47)	1.12
Serious	58 (3.35)	37 (2.15)	1.55

A slight in crease in serious bleeding on clopidogrel compared to placebo

Table 24. Bleeding by age quartiles in CLARITY (reviewer's analysis)

Age	Clopidogrel 1733	Placebo 1719	OR
<60	19 (1.1)	10 (0.58)	1.88
60-65	9 (0.52)	11 (0.64)	0.81
66-70	16 (0.92)	16 (0.93)	0.99
>=70	23 (1.33)	7 (0.41)	3.26

Bleeding risk is greater in the oldest subjects of the study population and this is consistent with CURE findings;

Table 25. Bleeding by weight quartiles in CLARITY (reviewer's analysis)

Weight in Kg	Clopidogrel 1733	Placebo 1719	OR
< 68	14 (0.81)	12 (0.7)	1.16
>= 68 and <76.4	16 (0.92)	11 (0.64)	1.44
>=76.4 and <85	15 (0.87)	9 (0.52)	1.65
>=85	21 (1.21)	9 (0.52)	2.31

As body weight increased, the risk of bleeding increased; this could be explained by the interaction with concomitant bleed-promoting medications that are adjusted by weight;

B. Bleeding in COMMIT

Table 26. Bleeding (cerebral vs. non-cerebral) in COMMIT (reviewer's analysis)

	Clopidogrel N=22999	Placebo N=23065	OR
Any bleeding	927 (4.0)	819 (3.6)	1.13
Major noncerebral bleed	71 (0.31)	66 (0.29)	1.07
Other noncerebral bleed	843 (3.7)	722 (3.1)	1.16
Stroke, probably hemorrhagic	56 (0.24)	56 (0.24)	1.0

Table 27. Bleeding by age quartiles in COMMIT (reviewer's analysis)

Any bleed[1] by age in years	Placebo	Clopidogrel	OR
All ages N	22999	23065	
Bleeding	819 (3.6)	927 (4.0)	1.13
<=52.73 N	5699	5811	
Bleeding	150 (2.63)	143 (2.46)	0.93
>52.73 <=62.92 N	5810	5711	
Bleeding	173(2.98)	233 (4.08)	1.37
>62.92 <=70.2 N	5732	5785	
Bleeding	228 (3.98)	271 (4.68)	1.18
>70.2 N	5754	5755	
Bleeding	268 (4.66)	280 (4.87)	1.04

[1]Includes major and other non-cerebral + hemorrhagic stroke

No difference in the risk of bleeding was observed between the difference age groups in the COMMIT population. This could be explained by the omission of the loading dose in this study.

Table 28. Major non-cerebral bleeding by age quartiles (reviewer's analysis)

Major non-cerebral bleed	Clopidogrel N=22999	Placebo N=23065	OR
All ages	71 (0.31)	66 (0.29)	1.07
Age <=52.73	5 (0.09)	7 (0.12)	0.75
52.73< age <=62.92	12 (0.21)	17 (0.29)	0.72

62.92< age <=70.2	24 (0.41)	23 (0.4)	1.03
Age > 70.2	30 (0.52)	19 (0.33)	1.58

C. Bleeding in other studies

Summarized safety from published findings of MATCH and CHARISMA follow:

Table 29. Bleeding in the MATCH study[7]

Bleeding Events	Clopidogrel + ASA N (%)	Clopidogrel + placebo N (%)	Diff. bet treatments [CI]	p
Life-threatening	96 (3)	49 (1)	2.6% [0.64,1.88]	<0.0001
Fatal	16 (<1)	11 (<1)	0.13% [-0.14,0.40]	
Non-fatal	81 (2)	38 (1)	1.15% [0.59,1.79]	
Symptomatic intracranial	40 (1)	25 (1)	0.40% [-0.01,0.82]	
Major	73 (2)	22 (1)	1.36% [0.86,1.86]	<0.0001
Minor	120 (3)	39 (1)	2.16% [1.51,2.81]	<0.0001

Table 30. Bleeding (adjudicated) in the CHARISMA study[8]

Bleeding Events N (%)	Clopidogrel (n=1659)	Placebo (n=1625)	RR (95% CI)	p
Fatal	7 (0.4)	5 (0.2)	1.71 (0.50,5.84)	0.38
Primary ICH	7 (0.4)	6 (0.4)	1.14 (0.38,3.39)	0.81
GUSTO severe bleeding	34 (2.0)	20 (1.2)	1.67 (0.96,2.88)	0.07
GUSTO moderate bleeding	36 (2.2)	22 (1.4)	1.60 (0.95,2.71)	0.08

2. Thrombocytopenia

Table 31. Incidence of thrombocytopenia in the CLARITY trial

	Clopidogrel	Placebo
Total number of patients	1733	1719
Number of patients reporting endpoint	6 (0.3%)	6 (0.3%)
Number of patients reporting severe thrombocytopenia	1 (0.1%)	2 (0.1%)
Number of patients reporting profound thrombocytopenia	1 (0.1%)	0 (0.0%)

7.1.4 Other Search Strategies

Other search strategies used included literature reporting of findings from other studies conducted for marketing purposes[7,8].

[7] Hans-Christoph Diener; Lancet 2004:364:331-37
[8] Bhatt DL, Fox KA, Hacke W, et al. 2006, in press

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

The methods of eliciting adverse events in the two pivotal studies were different which led to separate summarization of their safety.

COMMIT had an abbreviated CRF, the protocol did not specify that other adverse events be collected beside those that were serious (believed to be unexpected and related to the study), leading to death or discontinuation, and was not organized to deal with the multitude of common adverse events to which the study population was predisposed.

Very few adverse events were reported spontaneously (volunteered), summarized in table below, and these are non-informative because they do not reflect the incidence of common adverse event in the whole study population.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

All reported adverse events in CLARITY were re-coded by the reviewer, blinded to treatment allocation, into preferred-term categories.

7.1.5.3 Incidence of common adverse events

See 7.1.5.4 Common adverse event tables below.

7.1.5.4 Common adverse event tables

A. COMMIT

Table 32. Volunteered adverse events in COMMIT

Event Class	Clopidogrel (N = 22961)	Placebo (N = 22891)
Any	542(2.4)	509 (2.2)
AV Block	372 (1.6)	355 (1.6)
Other Vascular	90 (0.4)	83 (0.4)
Hematological	3 (0.0)	5 (0.0)
Respiratory	30 (0.1)	28 (0.1)
Gastrointestinal	2 (0.0)	1 (0.0)
Allergic	13 (0.1)	11 (0.0)
Other	32 (0.1)	26 (0.1)

B. CLARITY

Table 33. Number of patients who reported TEAEs (≥1.0%) in CLARITY (per reviewer's recoding of AEs)

	Clopidogrel	Placebo	OR
VT/VF	131 (7.56)	121 (7.04)	1.07
Cardiac/circulatory failure	112 (6.46)	126 (7.33)	0.88
Hypotension	106 (6.12)	88 (5.12)	1.19
Angina pectoris	96 (5.5)	118 (6.9)	0.78

	Clopidogrel	Placebo	OR
Headache/cephalgia	86 (4.96)	80 (4.65)	1.07
Nausea/vomiting	81 (4.67)	73 (4.25)	1.10
Chest pain (all kinds)	74 (4.27)	73 (4.25)	1.01
Myocardial infarction/ischemia	63 (3.64)	94 (5.47)	0.66
Bradycardia	55 (3.17)	44 (2.56)	1.24
Fever	53 (3.06)	53 (3.08)	0.99
Fibrillation atrial	37 (2.14)	44 (2.56)	0.83
Heart block (all kinds)	37 (2.14)	48 (2.79)	0.76
Cardiac arrest	36 (2.08)	31 (1.8)	1.15
Agitation/Panic attack/Restlessness/Anxiety	23 (1.33)	27 (1.57)	0.84
Back pain	23 (1.33)	22 (1.28)	1.04
Ventricular extrasystoles	22 (1.27)	18 (1.05)	1.21
Pericarditis/pericardial effusion	21 (1.21)	31 (1.8)	0.67
Hypertension/+aggravated	20 (1.15)	24 (1.4)	0.83
Hypokalaemia	20 (1.15)	14 (0.81)	1.42
Respiratory disorder	20 (1.15)	21 (1.22)	0.94
Cardiac aneurysm/cardiac rupture	19 (1.1)	14 (0.81)	1.35
DM/+aggravated	19 (1.1)	8 (0.47)	2.36
Hemorrhage of operative wound	19 (1.1)	7 (0.41)	2.69
Arrhythmia (all kinds)	18 (1.04)	26 (1.51)	0.69
Insomnia	18 (1.04)	7 (0.41)	2.55
Anuria/oliguria/Renal failure/BUN or Creatinine increased	17 (0.98)	10 (0.58)	1.69

Events that occurred with a slight increase on clopidogrel were hemorrhage of the operative wound, cardiac rupture, diabetes + aggravated diabetes, hypokalemia, insomnia and compromise of the renal function;

7.1.5.5 Identifying common and drug-related adverse events

Bleeding is a common adverse event of clopidogrel especially in elderly subjects, but the CLARITY (the more reliable of the two studies with regard to adverse event ascertainment) did not show a big difference between the treatment arms. The CLARITY population was exposed to a number of anti-clothing, antithrombotic and anti-coagulation drugs and was closely observed and monitored for bleeding, also exposure to the study drug was short with a maximum of eight day which could explain the absence of a difference in bleeding between the two treatment arms.

7.1.5.6 Additional analyses and explorations

As was shown by age analyses of CURE data, elderly subjects in CLARITY bled more than younger subjects.

7.1.6 Less Common Adverse Events

The adverse events that are observed rarely on clopidogrel and that were identified in its postmarketing phase include the following:

-thrombocytopenia: was ascertained in CLARITY only and the incidence was similar in both active and control treatment groups;

-TTP: none was reported in the CLARITY study population, and it is not sure whether it was ascertained in the COMMIT study population;

-hepatic failure: only one case reported in the CLARITY study population, and none in the COMMIT study population;

7.1.7 Laboratory Findings

No laboratory data were collected for COMMIT or CLARITY.

7.1.8 Vital Signs

NA

7.1.9 Electrocardiograms (ECGs)

NA

7.1.10 Immunogenicity

NA

7.1.11 Human Carcinogenicity

NA

7.1.12 Special Safety Studies

NA

7.1.13 Withdrawal Phenomena and/or Abuse Potential

NA

7.1.14 Human Reproduction and Pregnancy Data

NA

7.1.15 Assessment of Effect on Growth

b(4)

7.1.16 Overdose Experience

NA

7.1.17 Postmarketing Experience

b(4)

7.2 Adequacy of Patient Exposure and Safety Assessments

Clopidogrel has been approved for ACS and there is ample experience with its safety profile, and as a result, the two studies that were submitted for this sNDA focused mostly on efficacy.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

In reviewing safety, data from submitted studies CLARITY and COMMIT and from post marketing studies, MATCH[9] and CHARISMA[10], and known post marketing experience were used to draw conclusions on safety.

7.2.1.1 Study type and design/patient enumeration

See Table 8. List of (submitted) clinical studies in acute ST elevation MI, page 27; and Table 9. Other studies used for safety review page 27.

7.2.1.2 Demographics

A. COMMIT

Table 34. Demographic and other baseline characteristics of the COMMIT study population

Characteristic	Clopidogrel 75 mg* (N = 22961)	Placebo (N = 22891)	All patients
Sex - n (%)			
Female	6366 (27.7)	6393 (27.9)	12759 (27.8)
Male	16595 (72,3)	16498 (72.1)	33093 (72.2)
Age at entry (yr) - n (%)			
< 60	9624 (41.9)	9463 (41.3)	19087 (41.6)
60-69	7361 (32.1)	7470 (32.6)	14831 (32.3)
70 +	5976 (26.0)	5958 (26.0)	11934 (26.0)
Age at entry (yr)			
Mean (SD)	61.3 (11.9)	61.4 (11.8)	61.3 (11.8)
Range	15.4-100.3	15.4-99.3	15.4-100.3
SBP (mmHg) - n (%)			
< 120	7690 (33.5)	7709 (33.7)	15399 (33.6)
120-139	8092 (35.2)	8108 (35.4)	16200 (35.3)
140-159	4549 (19.8)	4471 (19.5)	9020 (19.7)
160+	2630 (11.5)	2603 (11.4)	5233 (11.4)
SBP (mmHg)			
Mean (SD)	128.2 (22.6)	128.2 (22.5)	128.2 (22.5)
Range	60.0-250.0	60.0-250.0	60.0-250.0
DBP (mmHg) - n (%)			
< 70	3584 (15.6)	3535 (15.4)	7119 (15.5)
70-79	6194 (27.0)	6190 (27.0)	12384 (27.0)
80-89	6002 (26.1)	6070 (26.5)	12072 (26.3)
90+	7181 (31.3)	7096 (31.0)	14277 (31.1)
DBP (mmHg)			
Mean (SD)	81.0 (14.6)	80.9 (14.4)	81.0 (14.5)

[9] Hans-Christoph Diener; Lancet 2004:364:331-37;
[10] Bhatt DL, Fox KA, Hacke W, et al. 2006, in press;

Characteristic	Clopidogrel 75 mg* (N = 22961)	Placebo (N = 22891)	All patients
Range	40.0-177.0	40.0-180.0	40.0-180.0
HR (bpm) - n (%)			
< 70	5094 (22.2)	5043 (22.0)	10137 (22.1)
70-89	11101 (48.3)	11161 (48.8)	22262 (48.6)
90-109	5140 (22.4)	5069 (22.1)	10209 (22.3)
110+	1626 (7.1)	1618 (7.1)	3244 (7.1)
Heart rate (bpm)			
Mean (SD)	82.2 (17.2)	82.1 (17.2)	82.1 (17.2)
Range	40-228	40-225	40-228
Killip class - n (%)			
I	17320 (75.4)	17283 (75.5)	34603 (75.5)
II	4601 (20.0)	4504 (19.7)	9105 (19.9)
III	1040 (4.5)	1104 (4.8)	2144 (4.7)
Disease history			
Prior MI	1972 (8.6)	1846 (8.1)	3818 (8.3)
History of hypertension	9935 (43.3)	9903 (43.3)	19838 (43.3)

B. CLARITY

Table 35. Baseline demographic characteristics in the CLARITY, ITT population

	Clopidogrel N=1752	Placebo N=1739
Age (yrs)		
n with data	1752	1739
<65	1219 (69.6)	1252 (72.0)
>= 65	533 (30.4)	487 (28.0)
Mean	57.7	57.2
Median	58	57
sd	10.3	10.3
Range	28-78	18-79
Gender		
n with data	1752	1739
Female	352 (20.1)	336 (19.3)
Male	1400 (79.9)	1403 (80.7)
Race		
n with data	1752	1739
Asian/oriental	43 (2.5)	30 (1.7)
Black	28 (1.6)	35 (2.0)
Caucasian	1569 (89.6)	1556 (89.5)
Other	112 (6.4)	118 (6.8)
BMI (kg/m2)		
n with data	1658	1648
Normal (<= 25)	489 (29.5)	487 (29.6)
Overweight (>25-30)	775 (46.7)	774 (47.0)
Obese (>30)	394 (23.8)	387 (23.5)
Mean	27.5	27.4
Median	26.9	26.8
sd	4.3	4.4
Range	16.3-53.2	15.4-66.7
SBP		
Mean (sd)	133.9 (23.48)	135.4 (23.21)
Range	60,210	65,215
DBP		

	Clopidogrel N=1752	Placebo N=1739
Mean (sd)	80.3 (14.95)	81.3 (14.54)
Range	15,130	40, 125
HR		
Mean (sd)	75.49 (18.26)	75.25 (17.78)
Range	30,160	30,161
Killip class		
I	1376 (78.5)	1348 (77.5)
II	129 (7.4)	134 (7.7)
III	3 (0.2)	2 (0.1)

7.2.1.3 Extent of exposure (dose/duration)

Table 36. Extent of exposure to study drug (treated population)

Extent of exposure	Clopidogrel N= 1733	Placebo N=1719	Overall N=3452
Number of days			
1	283 (16.3)	329 (19.1)	612 (17.7)
2	74 (4.3)	76 (4.4)	150 (4.3)
3	210 (12.1)	203 (11.8)	413 (12.0)
4	334 (19.3)	286 (16.6)	620 (18.0)
5	263 (15.2)	253 (14.7)	516 (14.9)
6	205 (11.8)	218 (12.7)	423 (12.3)
7	184 (10.6)	177 (10.3)	361 (10.5)
8	123 (7.1)	116 (6.7)	239 (6.9)
>=9	57 (3.3)	61 (3.5)	118 (3.4)
Mean	4.5	4.4	4.4
Median (SD)	4 (2.3)	4 (2.4)	4 (2.3)
Range	1.0-13.0	1.0-13.0	1.0-13.0

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Safety findings, especially bleeding, from two other studies were summarized in this review, and these are described briefly below. These were not integrated with the primary source data because they were conducted in populations that are slightly different from the ones studied for the indication under review. Also these studies were conducted for postmarketing purposes and can stand on their own especially with regard to bleeding.

7.2.2.1 Other studies

MATCH (Management of ATherothrombosis with Clopidogrel in High-risk patients with recent transient ischemic attack or ischemic stroke) study randomized, double-blind placebo-controlled trial that was conducted in high-risk cerebrovascular patients receiving clopidogrel 75 mg. Included were subjects with either recent TIA or ischemic stroke plus at least one cardiovascular risk factors.

The primary endpoint was the composite of MI or ischemic stroke, or vascular death or re-hospitalization for an acute ischemic event. The study enrolled 7599 subjects and followed them for an average of 17.5 months.

CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) was a randomized, double-blind, placebo-controlled trial that was conducted in subjects with at least one of the following: documented coronary disease and/or documented cerebrovascular disease and/or documented symptomatic PAD and/or two major or one major and two minor or three minor risk factors.

Subjects with requirement for clopidogrel, need for chronic therapy with high dose (162 mg/day) ASA or non-steroidal anti-inflammatory drug, current use of oral anti-thrombotic medications with intention for long-term treatment, planned revascularization procedure were excluded.

The primary endpoint was the composite of first occurrence of MI, stroke or cardiovascular death. The study enrolled 16603 subjects and followed them for an average of 30 months.

7.2.2.2 Postmarketing experience

Post-marketing experience established an association between clopidogrel and TTP; liver failure; pancreatitis; agranulocytosis; autoimmune-type disorders including vasculitis, lichen planus, toxic epidermal necrolysis and interstitial pneumonitis; and glomerulopathy and increased creatinine.

In the postmarketing phase it was shown (MATCH data) that the addition of ASA to clopidogrel added no benefit to subjects with recent TIA and stroke; instead, it increased their risk of fatal and major bleeding.

Clopidogrel was shown (CHARISMA data) to be associated with increased risk of all cause mortality and cardiovascular mortality (RR=1.41, CI: [1.02,1.95]) and RR=1.74, CI: [1.16, 2.62]) respectively) in subjects characterized as having multiple risk factors but no ACS or STEMI.

7.2.2.3 Literature

7.2.3 Adequacy of Overall Clinical Experience

COMMIT, the largest clopidogrel clinical trial to have been conducted and the only study that could have evaluated the incidence and possibly confirmed the risk of at least some of the adverse events that were observed in its postmarketing-phase, failed to accomplish this goal. Except for bleeding adverse events and efficacy parameters, COMMIT is practically useless in answering some of the safety questions that were not answered by previous less powered trials.

CLARITY adequately assessed some of the adverse events that were experienced by its study population, but was underpowered for testing causality associations.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

NA

7.4.2.2 Explorations for time dependency for adverse findings

COMMIT exposed subjects for an average of less than a month and CLARITY for an average of less than one week, and the difference in exposure between subjects in each study was not big enough to explore the effect of duration on the risk of adverse events in the STEMI population.

7.4.2.3 Explorations for drug-demographic interactions

Per findings of CURE, subjects 75 years of age and older bled more often and experienced more severe bleeding than younger subjects. Similarly an age dose-response was observed for bleeding in the CLARITY population.

7.4.2.4 Explorations for drug-disease interactions

NA

7.4.2.5 Explorations for drug-drug interactions

All subjects randomized into COMMIT and CLARITY were suspected for an acute MI which dictate medical conducts and procedures that could magnify the risk and severity of bleeding.

7.4.3 Causality Determination

NA

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The current label says: Plasma concentrations of the main circulating metabolite are significantly higher in elderly (≥75 years) compared to young healthy volunteers but these higher plasma levels were not associated with differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.

b(4)

Per the findings of CURE, the risk of bleeding increased with age, and the label was modified to reflect this risk as an added footnotes to Table /: CURE Incidence of bleeding complications (% patients) of the label.

Clopidogrel was investigated and is indicated in ACS as a loading dose of 300 mg and a maintenance dose of 75 mg. No dose formulation lower than 75 mg was investigated, and the investigation of omitting the loading dose, especially in patients at high risk of bleeding events, including the elderly, was not investigated.

8.2 Drug-Drug Interactions

NA

8.3 Special Populations

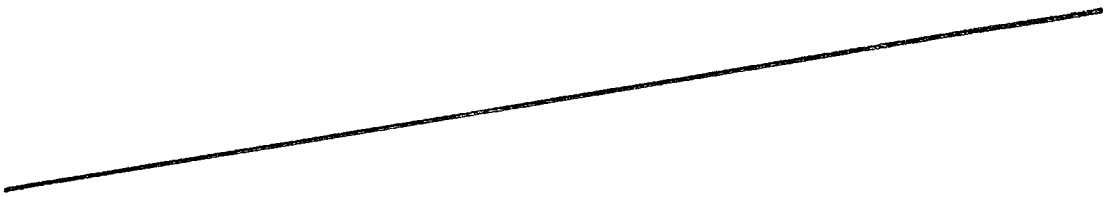
Per the label, plasma concentrations were studied in the elderly and even if the main circulating metabolites were higher, the effect of Plavix on coagulation parameters was

not different from those in young healthy volunteers. However, in CURE there was excess bleeding, including major, in elderly subjects and these findings were not volunteered by the sponsor.

Of interest, especially in the light of what we know from CURE and the findings of MATCH and CHARISMA, is the bleeding safety of clopidogrel in elderly and women.

8.4 Pediatrics

For its current indication, reduction of atherothrombotic events, a waver was granted for studying clopidogrel in pediatrics.



b(4)

8.5 Advisory Committee Meeting

NA

8.6 Literature Review

List the articles read to validate the timing of angiography, ST segment resolution and others

8.7 Postmarketing Risk Management Plan

NA

8.8 Other Relevant Materials

Two studies (MATCH and CHARISMA) that are relevant especially to safety have been conducted, their findings have been published, and findings on bleeding are summarized in this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

COMMIT has shown that clopidogrel reduced mortality and re-infarction following ST segment elevation acute myocardial infarction in a Chinese population that was not managed optimally by US medical-care standards which raises the question of whether clopidogrel would add any benefit to a STEMI population treated in the US.

CLARITY showed that clopidogrel reduced the rate of TIMI flow grade 0/1 occlusion in the infarct related artery, but the question remains whether a late x patent infarct-related artery would translate to a clinical benefit.

9.2 Recommendation on Regulatory Action

See 1 EXECUTIVE SUMMARY page 13.

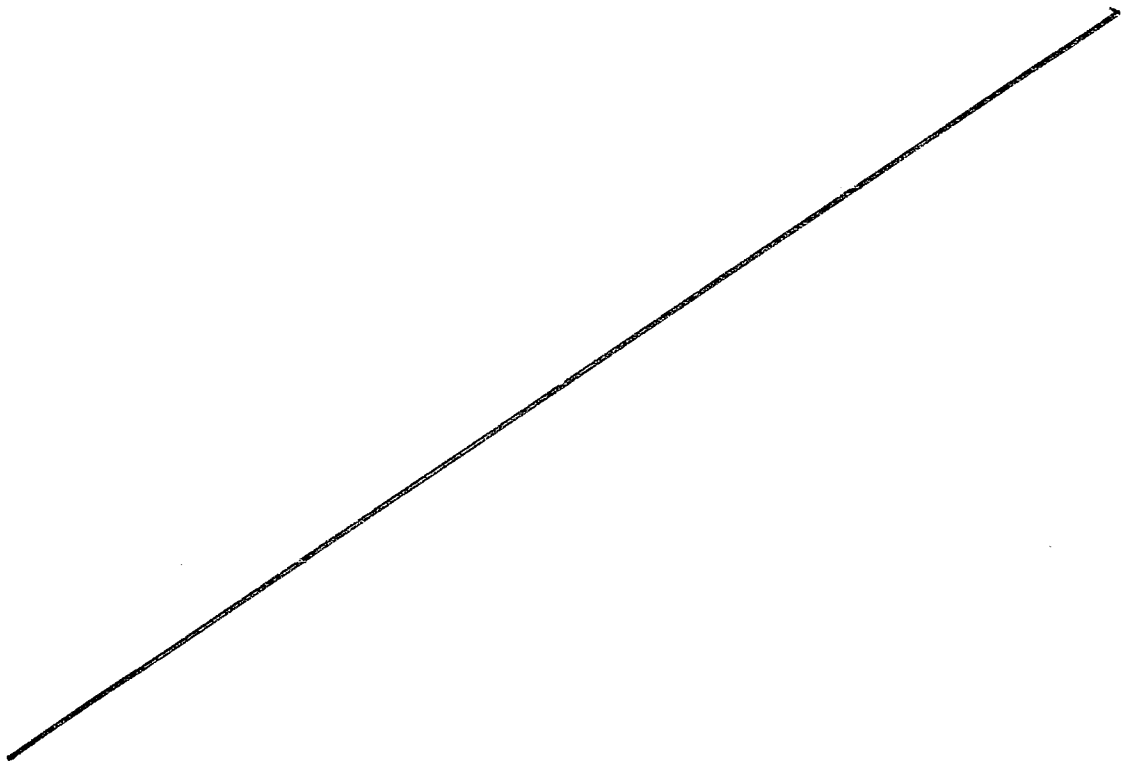
9.4 Recommendation on Postmarketing Action

NA

9.4 Labeling Review

Only sections changed are included here.

CLINICAL STUDIES



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30 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__√__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical-__2__

10 APPENDICES

10.1 General findings

10.1.1 General findings in COMMIT

Table 38. Qualifying events of entry in the study

Qualifying Event	Clopidogrel (N = 22961)	Placebo (N = 22891)	All patients (N = 45852)
Hours since onset			
Mean (SD)	10.3 (6.7)	10.3 (6.7)	10.3 (6.7)
Range	0.2-24.0	0.1-24.0	0.1-24.0
Hours since onset - n (%)			
< 6	7745 (33.7%)	7707 (33.7%)	15452 (33.7%)
6 to < 13	7567 (33.0%)	7505 (32.8%)	15072 (32.9%)
13 to 24	7649 (33.3%)	7679 (33.5%)	15328 (33.4%)
Final diagnosis of initial MI - n (%)			
Confirmed MI	22002 (95.8%)	21946 (95.9%)	43948 (95.8%)
Suspected MI	410 (1.8%)	404 (1.8%)	814 (1.8%)
Unstable angina	288 (1.3%)	308 (1.3%)	596 (1.3%)
Other	261a (1.1%)	233 (1.0%)	494 (1.1%)

Table 39. Baseline ECG characteristics in COMMIT

ECG Abnormality	Clopidogrel 75 mg* (N = 22961)	Placebo* (N = 22891)	Overall (N = 45852)
Bundle branch block	1505 (6.6)	1423 (6.2)	2928 (6.4)
ST elevation: Anterior alone	11314 (49.3)	11515 (50.3)	22829 (49.8)
ST elevation: Inferior alone	6570 (28.6)	6386 (27.9)	12956 (28.3)
ST elevation: Anterior and Inferior	941 (4.1)	873 (3.8)	1814 (4.0)
ST elevation: Other	1052 (4.6)	1104 (4.8)	2156 (4.7)
ST depression, without ST elevation	1579 (6.9)	1590 (6.9)	3169 (6.9)

Table 40. Patient and other baseline characteristics by use of anticoagulants in COMMIT

Category	Prior Lytics Use		(N = 45852)
	Yes (N = 22794)	No (N = 23058)	
Sex - n (%)			
Female	5249 (23.0%)	7510 (32.6%)	12759 (27.8%)
Male	17545 (77.0%)	15548 (67.4%)	33093 (72.2%)
Age at entry (yr) - n (%)			
< 60	10951 (48.0%)	8136 (35.3%)	19087 (41.6%)
60-69	7495 (32.9%)	7336 (31.8%)	14831 (32.3%)
70 +	4348 (19.1%)	7586 (32.9%)	11934 (26.0%)
Age at entry (yr)			
Mean (SD)	59.3 (11.5)	63.3 (11.8)	61.3 (11.8)
Range	15.4-99.9	20.2-100.3	15.4-100.3
SBP (mmHg) - n (%)			
< 120	8424 (37.0%)	6975 (30.2%)	15399 (33.6%)

Category	Prior Lytics Use		(N = 45852)
	Yes (N = 22794)	No (N = 23058)	
120-139	8094 (35.5%)	8106 (35.2%)	16200 (35.3%)
140-159	4246 (18.6%)	4774 (20.7%)	9020 (19.7%)
160+	2030 (8.9%)	3203 (13.9%)	5233 (11.4%)
SBP (mmHg)			
Mean (SD)	125.9 (21.1)	130.5 (23.6)	128.2 (22.5)
Range	60.0-250.0	60.0-250.0	60.0-250.0
DBP (mmHg) - n (%)			
< 70	3792 (16.6%)	3327 (14.4%)	7119 (15.5%)
70-79	6310 (27.7%)	6074 (26.3%)	12384 (27.0%)
80-89	5924 (26.0%)	6148 (26.7%)	12072 (26.3%)
90+	6768 (29.7%)	7509 (32.6%)	14277 (31.1%)
DBP (mmHg)			
Mean (SD)	80.3 (14.2)	81.6 (14.8)	81.0 (14.5)
Range	40.0-170.0	40.0-180.0	40.0-180.0
HR (bpm) - n (%)			
< 70	5442 (23.9%)	4695 (20.4%)	10137 (22.1%)
70-89	11244 (49.3%)	11018 (47.8%)	22262 (48.6%)
90-109	4762 (20.9%)	5447 (23.6%)	10209 (22.3%)
110+	1346 (5.9%)	1898 (8.2%)	3244 (7.1%)
Heart rate (bpm)			
Mean (SD)	81.0 (16.5)	83.3 (17.8)	82.1 (17.2)
Range	40.0-228.0	40.0-220.0	40.0-228.0
Killip class - n (%)			
I	17775 (78.0%)	16828 (73.0%)	34603 (75.5%)
II	4128 (18.1%)	4977 (21.6%)	9105 (19.9%)
III	891 (3.9%)	1253 (5.4%)	2144 (4.7%)
Disease history			
Prior MI	1652 (7.2%)	2166 (9.4%)	3818 (8.3%)
History of hypertension	9588 (42.1%)	10250 (44.5%)	19838 (43.3%)
Neither MI nor hypertension	12392 (54.4%)	11752 (51.0%)	24144 (52.7%)
Hours since onset			
Mean (SD)	8.6 (6.2)	12.0 (6.8)	10.3 (6.7)
Range	0.1-24.0	0.2-24.0	0.1-24.0
Hours since onset - n (%)			
< 6	9954 (43.7%)	5498 (23.8%)	15452 (33.7%)
6 to < 13	7622 (33.4%)	7450 (32.3%)	15072 (32.9%)
13 to 24	5218 (22.9%)	10110 (43.8%)	15328 (33.4%)
Final diagnosis of initial MI - n (%)			
Confirmed MI	22428 (98.4%)	21520 (93.3%)	43948 (95.8%)
Suspected MI	176 (0.8%)	638 (2.8%)	814 (1.8%)
Other	190 (0.8%)	900 (3.9%)	1090 (2.4%)
ECG abnormality			
Bundle branch block	1307 (5.7%)	1621 (7.0%)	2928 (6.4%)
ST elevation: Anterior alone	12033 (52.8%)	10796 (46.8%)	22829 (49.8%)
ST elevation: Inferior alone	7250 (31.8%)	5706 (24.7%)	12956 (28.3%)
ST elevation: Anterior	951 (4.2%)	863 (3.7%)	1814 (4.0%)

Category	Prior Lytics Use		(N = 45852)
	Yes (N = 22794)	No (N = 23058)	
and Inferior			
ST elevation: Other	874 (3.8%)	1282 (5.6%)	2156 (4.7%)
ST depression, without ST elevation	379 (1.7%)	2790 (12.1%)	3169 (6.9%)

Table 41. Use of non-trial anti-platelets and beta-blockers in the hospital in COMMIT

Medication	Clopidogrel 75 mg* (N = 22961)	Placebo* (N = 22891)	Overall (N = 45852)
Nontrial antiplatelet agents	2305 (10.0%)	2280 (10.0%)	4585 (10.0%)
Nontrial beta-blockers	2464 (10.7%)	2538 (11.1%)	5002 (10.9%)

Table 42. Selected medication use prior to randomization in COMMIT

Medication	Clopidogrel 75 mg* (N = 22961)	Placebo* (N = 22891)
ASA	4214 (18.4%)	4230 (18.5%)
Beta-blocker	1457 (6.3%)	1533 (6.7%)
Fibrinolytic agent in all patients	11407 (49.7%)	11387 (49.7%)
Fibrinolytic agent in patients randomized < 13 hours after onset of MI	8780 (38.2%)	8796 (38.4%)
Fibrinolytic agent in patients randomized ≥ 13 hours after onset of MI	2627 (11.4%)	2591 (11.3%)

Table 43. Use of other therapies in the hospital in COMMIT

Medication	Clopidogrel 75 mg*	Placebo*	Overall (N = 45852)
All patients	22961	22891	
Fibrinolytic agents before/after entry	12468 (54.3)	12499 (54.6)	24967 (54.5)
Patients randomized < 13 hours after onset of MI	15312	15212	
Fibrinolytic agents before/after entry	9548 (62.4)	9631 (63.3)	19179 (62.8)
Patients randomized ≥ 13 hours after onset of MI	7649	7679	
Fibrinolytic agents before/after entry	2920 (38.2)	2868 (37.3)	5788 (37.8)
Anticoagulants	17022 (74.1)	17157 (75.0)	34179 (74.5)
Anti-arrhythmics	5150 (22.4)	5093 (22.2)	10243 (22.3)
ACE inhibitors	15649 (68.2)	15638 (68.3)	31287 (68.2)
Nitrates (oral or i.v.)	21615 (94.1)	21590 (94.3)	43205 (94.2)
Diuretics	5344 (23.3)	5344 (23.3)	10688 (23.3)
Calcium antagonists	2701 (11.8)	2705 (11.8)	5406 (11.8)

Table 44. Duration of hospitalization for patients still alive at Day 28

Duration (days)	Clopidogrel (N = 22961)	Placebo (N = 22891)	Overall (N = 45852)
Mean (SD)	14.9 (7.9)	14.9 (7.8)	14.9 (7.8)
Median	14.0	14.0	14.0

Days: number of days from admission to discharge for those discharged alive at or before Day 28; otherwise 28 days

Table 45. Cause of deaths "Other noncardiac" in COMMIT

Subject ID	Treatment	Cause of Death
05003-043	Clopidogrel 75 mg	unexpected accidents
10017-020	Clopidogrel 75 mg	anoxic encephalopathy
10027-001	Clopidogrel 75 mg	Severe anemia
10027-007	Clopidogrel 75 mg	Renal failure
11011-048	Clopidogrel 75 mg	Multi-organ failure
11012-028	Clopidogrel 75 mg	Renal failure
11026-033	Clopidogrel 75 mg	Transfusion reaction
11047-005	Clopidogrel 75 mg	Ketoacidosis
11061-048	Clopidogrel 75 mg	Ketoacidosis
11061-061	Clopidogrel 75 mg	Ketoacidosis
13004-016	Clopidogrel 75 mg	Renal failure
21005-054	Clopidogrel 75 mg	Tumor metalease
21068-002	Clopidogrel 75 mg	Renal failure
25004-029	Clopidogrel 75 mg	Tumor metalease
25016-102	Clopidogrel 75 mg	Ketoacidosis
25086-001	Clopidogrel 75 mg	Septicaemia
45028-015	Clopidogrel 75 mg	Transfusion reaction
45028-267	Clopidogrel 75 mg	epilepsy seizure
51006-104	Clopidogrel 75 mg	Renal failure
57004-038	Clopidogrel 75 mg	Renal failure
61034-008	Clopidogrel 75 mg	Tumor metalease
71013-009	Clopidogrel 75 mg	Infection/shock
81004-003	Clopidogrel 75 mg	Ketoacidosis
83002-037	Clopidogrel 75 mg	Infection/shock
83008-018	Clopidogrel 75 mg	Giving up treatment(relative/patient)
83008-063	Clopidogrel 75 mg	Multi-organ failure
03030-007	Placebo	Phosphate poisoning
05010-030	Placebo	Renal failure
05031-009	Placebo	Infection/shock
05099-014	Placebo	Renal failure
05111-015	Placebo	unexpected accidents
10006-043	Placebo	ARDS
10032-006	Placebo	Tumor metalease
10046-145	Placebo	Renal failure
10053-030	Placebo	anoxic encephalopathy
11023-135	Placebo	Tumor metalease
11033-063	Placebo	Multi-organ failure
11038-010	Placebo	unexpected accidents
11042-023	Placebo	Septicaemia
11054-223	Placebo	Renal failure
13021-081	Placebo	Unknown
15025-027	Placebo	overdose
15034-030	Placebo	Multi-organ failure

Subject ID	Treatment	Cause of Death
15042-034	Placebo	Multi-organ failure
21006-124	Placebo	Multi-organ failure
21016-006	Placebo	Multi-organ failure
25009-158	Placebo	Severe anemia
25039-029	Placebo	Tumor metalease
25039-056	Placebo	Infection/shock
25071-013	Placebo	Ketoacidosis
25100-015	Placebo	Ketoacidosis
25123-498	Placebo	Renal failure
25129-201	Placebo	Renal failure
25136-011	Placebo	Ketoacidosis
25144-004	Placebo	Renal failure
25159-013	Placebo	Tumor metalease
31010-181	Placebo	Renal failure
35012-014	Placebo	anoxic encephalopathy
40001-024	Placebo	Tumor metalease
41010-005	Placebo	Acute pancreatitis
43030-035	Placebo	Renal failure
45011-002	Placebo	Tumor metalease
45035-084	Placebo	Tumor metalease
45040-008	Placebo	Multi-organ failure
45046-024	Placebo	Renal failure
45047-015	Placebo	Infection/shock
45047-070	Placebo	Emotional disturbance
61001-005	Placebo	Renal failure
61007-004	Placebo	Renal failure
61013-001	Placebo	hyperkalemia
61016-006	Placebo	Multi-organ failure
61044-010	Placebo	Renal failure
71002-016	Placebo	Intracranial tumours
73014-071	Placebo	Multi-organ failure
73020-008	Placebo	Tumor metalease
81002-012	Placebo	Multi-organ failure
81004-054	Placebo	Renal failure
83002-014	Placebo	Multi-organ failure
83002-016	Placebo	Suicide

10.1.2 CLARITY General findings

Table 46. Cardiovascular medical history (ITT population) in CLARITY

Total number of patients	**Clopidogrel** 1752	**Placebo** 1739	**Overall** 3491
Number of patients who reported at least one medical abnormality	1384 (79.0)	1402 (80.6)	2786 (79.8)
History of hypertension			
Previous documented MI	159 (9.1)	159 (9.1)	318 (9.1)

Total number of patients	Clopidogrel 1752	Placebo 1739	Overall 3491
Angina pectoris	402 (22.9)	402 (23.1)	804 (23.0)
Prior congestive heart failure	28 (1.6)	26 (1.5)	54 (1.5)
Atrial fibrillation	24 (1.4)	30 (1.7)	54 (1.5)
Peripheral arterial disease	69 (3.9)	81 (4.7)	150 (4.3)
Venous thromboembolic disease	18 (1.0)	22 (1.3)	40 (1.1)
Hypertension	750 (42.8)	764 (43.9)	1514 (43.4)
Hyperlipidemia	564 (32.2)	574 (33.0)	1138 (32.6)
Family history of CAD	665 (38.0)	594 (34.2)	1259 (36.1)
Diabetes mellitus	289 (16.5)	286 (16.4)	575 (16.5)
Prior coronary angiography	143 (8.2)	148 (8.5)	291 (8.3)
Percutaneous coronary intervention	84 (4.8)	85 (4.9)	169 (4.8)

Table 47. Summary of qualifying events (ITT population) in CLARITY

Total number of patients	Clopidogrel 1752	Placebo 1739	Overall 3491
Hours since onset of ischemic symptoms to randomization			
n with data	1751	1739	3490
<2	491 (28.0)	533 (30.6)	1024 (29.3)
2 to <4	775 (44.3)	746 (42.9)	1521 (43.6)
4 to <6	331 (18.9)	309 (17.8)	640 (18.3)
6 to <9	111 (6.3)	113 (6.5)	224 (6.4)
9 to <12	42 (2.4)	31 (1.8)	73 (2.1)
>=12	1 (0.1)	7 (0.4)	8 (0.2)
Mean	3.3	3.3	3.3
Median	2.8	2.7	2.8
sd	2.0	2.1	2.1
Range	0.0-18.3	0.0-23.2	0.0-23.2
Number (%) of patients admitted to hospital prior to symptom onset	39 (2.2)	45 (2.6)	84 (2.4)

Table 48. Baseline distribution of factors used in the efficacy analyses (ITT population) in CLARITY

Total number of patients	Clopidogrel 1752	Placebo 1739
Type of fibrinolytic used		
n with data	1752	1739
Fibrin specific	1206 (68.8)	1191 (68.5)
Non-fibrin specific	542 (30.9)	542 (31.2)
None	4 (0.2)	6 (0.3)
Anticoagulant used up to two hours post-randomization		
n with data	1752	1739
UFH	808 (46.1)	792 (45.5)
LMWH	528 (30.1)	506 (29.1)
UFH+LMWH	85 (4.9)	90 (5.2)
None	331 (18.9)	351 (20.2)
Infarct location		
n with data	1752	1739
Anterior	722 (41.2)	697 (40.1)
Non-anterior	1030 (58.8)	1042 (59.9)

Table 49. Baseline ST deviation in CLARITY

	Clopidogrel	Placebo
Baseline sum of ST deviation		
n with data	1540	1501
Mean	12.9	13.2
Median	10.8	10.8
sd	8.7	8.6
Range	0.5-77.9	2.0-65.5

Table 50. Medications taken concomitantly with the study drug (treated population) in CLARITY

	Clopidogrel	Placebo
Beta blockers	1371 (79.2)	1345 (78.3)
Nitrates	1253 (72.4)	1238 (72.1)
Calcium channel blockers	88 (5.1)	76 (4.4)
Antiarrhythmics	126 (7.3)	142 (8.3)
Statins	1105 (63.8)	1067 (62.1)
Other lipid lowering agents	49 (2.8)	42 (2.4)
ACE inhibitors	969 (56.0)	917 (53.4)
Angiotensin receptor blockers	26 (1.5)	29 (1.7)
Diuretics	316 (18.3)	291 (16.9)
Cardiac glycoside and/or other inotropes	80 (4.6)	71 (4.1)
NSAIDs	86 (5.0)	97 (5.6)
Anti-diabetic medications (not mutually exclusive)	309 (17.9)	297 (17.3)
Ticlopidine	10 (0.6)	4 (0.2)
Open label clopidogrel	61 (3.5)	62 (3.6)

Table 51. Compliance with study drug (treated population) in CLARITY

Total number of patients	Clopidogrel 1733	Placebo 1719
When was study medication stopped compared to the earliest of angiography/Day 8/hospital discharge/death		
Same calendar day	1331 (76.8)	1355 (78.8)
Day before, <= 24 hours	243 (14.0)	221 (12.9)
Day before, >24 hours	92 (5.3)	79 (4.6)
More than 1 day before	67 (3.9)	64 (3.7)

10.1.3 Other study general findings

Table 52. MATCH baseline characteristics

	clopidogrel + Placebo N=3802	clopidogrel + ASA N=3797
Age (mean)	66.1	66.5
Female	37.0%	37.0%
Qualifying event		
TIA	21.0	21.0
Stroke	79	79
Hypertension	78.2	78.3

	clopidogrel + Placebo N=3802	clopidogrel + ASA N=3797
Diabetes	68.4	68.4
Hypercholesterolemia	57.0	56.0
Smoking	47.0	48.0
Previous TIA	19.0	19.0
Angina pectoris	12.0	12.7
Symptomatic PAD	10.2	10.2
Previous MI	5.0	4.6

Table 53. CHARISMA baseline characteristics

	clopidogrel N=7802	Placebo N=7801
Age (median)	64.0	64.0
Female	29.7	29.8
Ethnicity		
Caucasian	80.4	79.9
Hispanic	10.0	10.7
Asian	5.0	5.0
Black	3.2	3.0
Other	1.5	1.4
Inclusion group		
Documented CVD	77.7	78.1
Multiple risk factor	21.3	20.8
Smoking		
Current	20.1	20.3
Former	48.8	48.7

10.2 Study Committees

10.2.1 COMMIT study committees

The Steering Committee was co-chaired by Professor Li-Sheng Liu and Professor Rory Collins and also included one principal study coordinator/international liaison representative (Zheng-Ming Chen), 2 clinical coordinators, 1 administrative coordinator, 2 statisticians, and other members from the People's Republic of China. This Committee was responsible for the major organizational and policy decisions and provided the scientific and strategic direction of the trial and met about once a year. Additional statistical advice was obtained from Sir Richard Peto (Oxford University, United Kingdom).

COMMIT Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) composed of 2 members (Peter Sandercock and T.H. Lam) and co-chaired by Drs. Peter Sleight and Stephen MacMahon was responsible for monitoring safety. About once a year during the study, an independent Clinical Trial Service Unit statistician prepared interim reports for the DSMB that included analyses of the primary endpoints and other information, if available, such as unexpected serious adverse events (SAEs)

believed by the physician to be related to the trial treatments (as defined in the protocol). In light of these analyses, the DSMB provided advice to the Chairmen of the Steering Committee.

COMMIT DSMB minutes

-12/06/2001, 11785 subjects had been recruited and no modifications were recommended;

-04/30/2002, 20056 subjects had been recruited and it was agreed that the trial should continue to its planned sample size;

-9/11/2003, no safety concerns were observed;

-11/07/2004, data from 42217 discharge forms were considered, the decision for the study to continue unchanged was unanimous, and it was stated that the study was going to closeout in the Spring of 2005;

Of interest is the absence of a mention of the sample size amendment in the minutes of the DSMB.

10.2.1 CLARITY study committees

10.3 Study amendments

10.3.1 COMMIT study amendments

Sample size

It is not known who conducted the data analyses and who interpreted the findings that determined that the sample size had to be increased. The minutes of the DSMB mention nothing about these analyses/findings and the requirement to increase the sample size.

The planned sample size was increased during the course of the study to be at least 45,000 because the overall, blinded, event rate observed in the study (8% for mortality and 10% for the combined outcome of death, reinfarction or stroke) was lower than that anticipated (10% for mortality and 14% for the combined outcome) in the published study protocol.

In a letter dated 14 February 2003 from the cochairman of the Steering Committee to the Principal Investigator, it was recommended to recruit as many as 48000 patients, up to a fixed closure date for the study at the time of the Chinese spring festival in 2005 (09 February 2005).

10.3.2 CLARITY study amendments

Table 54. Protocol amendments of CLARITY

Reasons for Amendment
28 February 2003
• Increased sample size from 2200 to 3000 randomized patients and number of sites from 220 to 290;
• Adjusted power calculations based on increase in sample size;
• Redefined primary and secondary efficacy objectives and outcomes to include patients who died or had a recurrent MI by the time of the start of coronary angiography instead of by the end of the calendar day following angiography;
• Added exclusion criterion of anticipated use of urokinase for fibrinolysis;

• Specified that aPTT determination was required only for those patients receiving UFH;
• Specified that serial CK-MB and/or troponin measurements were required for patients with suspected recurrent ischemia or reinfarction;
• Specified that blinded study drug therapy could be initiated before all baseline laboratory results were obtained, and if these results were subsequently found to be abnormal, study drug could be suspended;
• Changed the dosing regimen for ASA to an initial dose of 150-500 mg (instead of 150-325 mg) for patients not receiving ASA within the previous 24 hours and oral or IV administration;
• Redefined stroke to also include any event that resulted in death within 24 hours and was due to a cerebral lesion of vascular origin;
• Clarified the requirement that Investigators report all clinical events and SAEs, using the Alert Report Booklet;
• Added ability to randomize a patient in an ambulance or mobile care unit and defined the place of randomization as an element for subgroup analysis;
• Provided additional guidelines for dosing with dalteparin and nadroparin.
30 December 2003
• Changed the primary inclusion criterion to include patients with new LBBB in addition to those with new ST segment elevation on their ECG;
• Specified that patients were to be randomized within 12 hours (instead of 6 hours) after the onset of symptoms;
• Changed the guideline for the timing for administration of the loading dose of blinded study drug to be from within 10 to 45 minutes of the start of fibrinolysis;
• Changed exclusion criterion #2 to treatment with clopidogrel or ticlopidine within 7 days (instead of within 10 days) prior to enrollment;
• Changed exclusion criterion #4 with regard to UFH dosing to be consistent with most recent STEMI guidelines, making dosing based on weight, and added restriction concerning treatment with >90 anti-Xa IU/kg nadroparin;
• Deleted exclusion criteria for PCI within prior 3 months, LBBB or paced rhythm precluding identification of MI location, history of drug or alcohol abuse, and hemodynamically significant valvular heart disease, endocarditis, hypertrophic cardiomyopathy, restrictive cardiomyopathy, or complex or cyanotic congenital heart disease;
• Changed exclusion criterion #9 to specify evidence of cardiogenic shock or acute pulmonary edema requiring intubation or an IABP (instead of diuretic use);
• Changed exclusion criterion #11 to reflect a known serum creatinine >2.5 mg/dL (instead of >2 mg/dL);
• Clarified that a unique Patient Number was to be assigned at the time of randomization instead of at the time written informed consent was obtained;
• Updated dosing regimen for ASA to be consistent with most recent STEMI guidelines;
• Clarified that only SAEs were to be reported using the Alert Report Booklet;
• Specified maintenance of a separate database for continuous ECG, serum biomarkers, static ECG (for exploratory analysis), and genomics, with analysis and reporting of data from these substudies separated from the main study;
28 July 2004
• Increased total expected number of randomized patients from 3000 to 3500;
• Adjusted power calculations based on increase in sample size.

10.4 Other endpoints to be explored in CLARITY

-Any reinfarction (separating fatal and non-fatal);

-Any stroke (separating ischemic or not; with and without CT/MRI confirmation; with and without residual handicap);

-Any pulmonary embolus (separating fatal and non-fatal);

-Any "major" (i.e. fatal or non-fatal transfused) non-cerebral bleed;

-Any non-cerebral bleed (including the previously analyzed major bleeds);

-Other major clinical events in hospital during the scheduled treatment period that were explicitly recorded (i.e. cardiogenic shock, heart failure requiring persistent treatment, presumed cardiac rupture, VF/other cardiac arrest);

10.5 Substudies

Planned substudies included assessments of silent ischemia using continuous ECG monitoring and exploratory evaluation of various serum biomarkers. The analyses and reporting of these substudies would be separate from the main study analyses.

Blood samples from baseline and at the start of angiography were to be collected for the assessment of existing cardiac biomarkers including CK-MB, total cardiac troponin I and T, troponin TIC complex, myoglobin, B-type natriuretic peptide, C-reactive protein, IL-6, CD40L, and potentially other novel biomarkers characterized during or after completion of this study. All blood samples for the biomarker substudy were to be sent to the core laboratory for analysis.

For sites participating in the continuous ECG monitoring substudy, a blood sample for markers of ischemia was to be obtained at the end of the monitoring period and sent to the TIMI Biomarker Core Laboratory for analysis.

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/s/

Salma Lemtouni
5/5/2006 09:34:08 AM
MEDICAL OFFICER
COMMIT-CLARITY

Division of Cardio-Renal Drug Products (HFD-110)

Medical Officer Review of IND Protocol

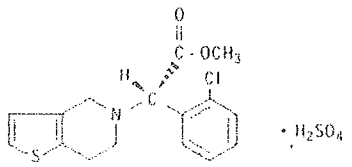
TABLE OF CONTENT

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-839 / S-034

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW #1	1. ORGANIZATION ONDQA/DPE/Branch IV	2. NDA NUMBER 20-839	
3. NAME AND ADDRESS OF APPLICANT (*City and State*) Sanofi-Aventis Inc. 300 Somerset Corporate Boulevard P.O. Box 6977 Bridgewater, NJ 08807.		4. AF NUMBER 5. SUPPLEMENT (S) NUMBER(S) DATES(S)	
6. NAME OF DRUG PLAVIX	7. NONPROPRIETARY NAME Clopidogrel bisulfate	SE1-034	11-17-2005
8. SUPPLEMENT PROVIDES FOR: the use of Plavix in the treatment of patients with acute myocardial infarction.		9. AMENDMENTS DATES	
10. PHARMACOLOGICAL CATEGORY Acute Myocardial Infarction	11. HOW DISPENSED RX ✓ OTC	12. RELATED IND/NDA/DMF	
13. DOSAGE FORM(S) Tablets	14. POTENCY 75 mg Tablets		
15. CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA AND MOLECULAR WEIGHT Methyl (+)-(S)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate sulfate (1:1) $C_{16}H_{16}ClNO_2S \cdot H_2SO_4$ MW: 419.9 		16. RECORDS AND REPORTS CURRENT YES__ NO REVIEWED YES__ NO	

17. COMMENTS

This efficacy supplement provides for the use of Plavix in the treatment of patients with acute myocardial infarction. There are no changes to the chemistry, manufacturing and controls section. There are no changes proposed to the description, dosage and administration and how supplied section of labeling. An environmental assessment document was submitted for the proposed increase in use of clopidogrel. A consult request was submitted to OPS to evaluate the EA document. The review of the EA document was completed and found acceptable by Dr. Ruth Gannunis, a contract reviewer and was signed off by Dr. Nguyen Bai, Supervisor for this project in OPS/IO on August 28, 2006, and by Dr. Raanan Bloom and Dr. Moheb Nasr on August 30, 2006 respectively. Based on the above, the applicant's calculation of [redacted] that is estimated to enter into the aquatic environment is found to be acceptable. b(4)

18. CONCLUSIONS AND RECOMMENDATIONS

This supplement is recommended for approval from the standpoint of chemistry, manufacturing and controls.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Nallaperumal Chidambaram, Ph.D.		08-30-2006

DISTRIBUTION	ORIGINAL NDA	DIVISION FILE	Reviewer: N. Chidambaram Ph.D.	CSO: Meg Pease-Fye HFD-110	Division Director: Eric P. Duffy Ph.D.

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

/s/

Nallaperumal Chidambaram
8/30/2006 04:20:00 PM
CHEMIST

Eric Duffy
8/30/2006 04:30:35 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-839 / S-034

ENVIRONMENTAL ASSESSMENT

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drugs Evaluation and Research

Memorandum

Date: August 28, 2006

From: Bai Nguyen, Chemist, OPS, CDER, FDA, HFD-354

To: Administrative Files: NDA 20-839/S-034

Subject: Finding of No Significant Impact (FONSI) for Plavix Tablets (97.86 mg clopidogrel bisulfate equivalent to 75 mg clopidogrel free base)

The following FONSI was completed after reviewing the corresponding environmental assessment, by a contract reviewer, Dr. Ruth Ganunis (reference number: 1007548). As a chemist reviewer from Office of Pharmaceutical Science/IO and a supervisor for this project, I am responsible for technical content as well as entering of this FONSI into Division File System. If you have questions regarding this review, please feel free to contact me directly.

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NDA 20-839 / S-034

Plavix® Tablets

(97.86 mg clopidogrel bisulfate equivalent to 75 mg clopidogrel free base)

Food and Drug Administration
Center for Drug Evaluation and Research

Office of New Drug Quality Assessment

Date Completed: August 20, 2006

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-839 / S-034

75-mg Plavix® Tablets
(97.86 mg clopidogrel bisulfate equivalent to 75 mg clopidogrel free base)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement, therefore, will not be prepared.

In support of its supplemental new drug application for Plavix® Tablets, Sanofi-Synthelabo Inc. prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impact of the use and disposal from use of clopidogrel bisulfate. This supplement provides for the use of Plavix® (clopidogrel bisulfate) Tablets, a previously approved product, for the treatment of acute coronary syndrome for patients with ST segment elevation acute myocardial infarction.

Clopidogrel bisulfate and its metabolites are expected to enter the aquatic environment. They are not volatile and are not expected to adsorb strongly to soil or sediment. Clopidogrel bisulfate is susceptible to slow hydrolysis and aerobic biodegradation. The results of toxicity studies indicate that clopidogrel bisulfate and its metabolites are not expected to be toxic to aquatic organisms at expected environmental concentrations.

Plavix® Tablets will be used by patients in their homes and in hospitals and clinics throughout the United States. Hospitals and clinics will dispose empty or partially empty packages according to their standard operating procedures. Typically, a community solid waste management system will be used for drugs administered at home. The community solid waste management system may include landfills, incineration and recycling. Minimal quantities of unused drug may be disposed in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be used and disposed without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

PREPARED BY
Ruth Ganunis
Chemist, Center for Drug Evaluation and Research

CONCURRED BY
Bai Nguyen
Environmental Officer, Center for Drug Evaluation and Research

CONCURRED BY
Jon Clark
Associate Director for Policy, Office of Pharmaceutical Science, Center for Drug Evaluation and Research

CONCURRED BY
Moheb Nasr.
Director, Office of New Drug Chemistry, Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Appended Electronic Signature Page

PLAVIX

Environmental Assessment

10 October 2005

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LIST OF ABBREVIATIONS

clopidogrel: clopidogrel bisulfate Form II, clopidogrel hydrogensulfate Form II.
EA: Environmental Assessment.
EC: Effects Concentration.
EEC: Expected Environmental Concentration.
EIC: Expected Introduction Concentration.
FDA: US Food and Drug Administration.
FDA EA Document: FDA Guidance for Industry Environmental Assessment of Human Drugs and Biologics Applications, July, 1998, CMC 6 Revision 1.
GRAS: Generally recognized as safe.
MEEC: Maximum Expected Environmental Concentration.
NOEC: No Observed Effect Concentration.
OECD: Organisation for Economic Co-operation and Development.
POTW: Publicly Owned Treatment Works.
TAD: USFDA Environmental Assessment Technical Assistance Handbook Document.

1.1 Environmental Assessment

This Environmental Assessment was written to address the environmental impact of PLAVIX® and its drug substance clopidogrel bisulfate Form II (clopidogrel). The Chemistry, Manufacturing, and Controls (CMC) data for clopidogrel was described in NDA 20-839 (submitted to IND 34,663, Serial No. 170, 14 March 1997) and in the NDA 20-839/S-009. Significant portions of this Environmental Assessment (EA) were previously submitted in sNDA 20-839/S019, dated August 21, 2001 (1). The applicant is providing a full version of the EA in this submission to simplify review.

Increased use of clopidogrel is predicted as a result of projected increased sales of PLAVIX®, a previously approved drug, upon approval of the new indication described in this submission. Estimates of maximum forecasted annual production of the drug in the next five years and an estimate of Maximum Expected Environmental Concentration (MEEC) are provided in the Environmental Assessment appendices, Confidential Appendix-MEEC calculations, (Section 1.1.12.2).

1.1.1 Date

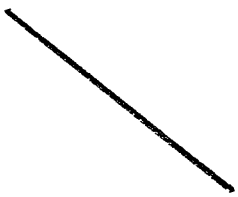
September 26, 2005

1.1.2 Name of applicant

Sanofi-Synthelabo Inc.

1.1.3 Address

DMF Holder: Sanofi Chimie
9 Rue Du President Allende
94256 Gentilly Cedex
France b(4)



Contact for FDA: Ms. Nancy Kribbs
Sanofi-Synthelabo Inc.
9 Great Valley Parkway
Malvern, PA 19355
USA

1.1.4 Description of the proposed action

1.1.4.1 Description of the requested approval

Sanofi-Synthelabo Inc. is requesting approval per section 505(b) of the Food, Drug and Cosmetic Act for the use of clopidogrel (clopidogrel bisulfate) for the treatment of acute coronary syndrome for patients with ST segment elevation acute myocardial infarction. PLAVIX® is produced as tablets which contain 97.875 mg of clopidogrel bisulfate (corresponding to 75 mg of clopidogrel base). PLAVIX® tablets are packaged in white, high-density polyethylene (HDPE) bottles or clear [redacted] blister packs. An Environmental Assessment (EA) is submitted pursuant to 21 CFR, part 25 and the FDA Guidance for Industry Environmental Assessment of Human Drugs and Biologics Applications, July 1998 CMC 6 Revision 1 (FDA EA Document) (2).

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1.1.4.2 Need for the proposed action

Clopidogrel, the active ingredient in PLAVIX® inhibits platelet aggregation to reduce atherothrombotic events in patients presenting with acute coronary syndrome. Clopidogrel appears to have an antiplatelet aggregation mode of action by modification of the platelet adenosine diphosphate (ADP) receptor.

1.1.4.3 Location where the product will be used

The drug product is intended for use in, and will be distributed to hospitals, pharmacies, and clinics for use by patients in their homes throughout the United States.

Empty or partially empty packages generated at U.S. hospitals, pharmacies or clinics will be disposed of according to site waste disposal procedures either by the user or after return to Bristol-Myers Squibb or Sanofi-Synthelabo facilities.

Out-of-specification, unused or outdated clopidogrel drug product returned for disposal to Bristol-Myers Squibb or Sanofi-Synthelabo will be packaged, shipped, and incinerated as industrial, non-hazardous wastes according to applicable environmental regulations.

Hospitals, pharmacies, clinics, and individual patients in the home may also dispose of empty or partially empty containers of drug product as part of their community waste management system, which may include landfills, incineration, or recycling. Minimal quantities of unused drug waste generated in the home could be disposed via the sewer system.

1.1.5 Identification of chemical substance that is the subject of the proposed action

This Environmental Assessment was written using preclinical data and environmental fate and effects testing on clopidogrel and its drug substance clopidogrel. Clopidogrel is described in NDA 20-839 (submitted to IND 34,663, Serial No. 170; Information Amendment: Chemistry, Manufacturing, and Controls) in the NDA 20-839/S-009.

1.1.5.1 Nomenclature

Product Trade name: PLAVIX®

- **For the drug substance Clopidogrel:**

Established Name (USAN) for Drug Substance: Clopidogrel bisulfate

CAS Number: 120202-66-6 (clopidogrel)
113665-84-2 (clopidogrel base)

USAN: methyl (*S*)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4*H*)-acetate sulfate (1:1)
methyl (+)-(*S*)-α-(o-chlorophenyl)-6,7-dihydrothieno[3,2-c] pyridine- 5-(4*H*)-acetate, sulfate (1:1)

CAS Name (clopidogrel):
Thieno [3,2-c] pyridine-5 (4*H*)-acetic acid, alpha-(2-chlorphenyl)-6,7-dihydro-, methyl ester, (*S*)-,sulfate (1:1)

IUPAC Name: (*S*)-(2-chlorophenyl)-(6,7-dihydro-4*H*-thieno[3,2-c]pyridin-5yl)-acetic acid methyl ester

Non-proprietary names:

INN, BAN: Clopidogrel
USAN: Clopidogrel bisulfate

Synonyms: Clopidogrel, clopidogrel bisulfate, clopidogrel bisulfate [redacted]
clopidogrel hydrogen sulfate, clopidogrel hydrogen sulfate [redacted] b(4)

Company code: SR25990C (clopidogrel bisulfate [redacted])
SR25990 (clopidogrel base)

1.1.5.2 Molecular formula

$C_{16}H_{16}Cl\ NO_2S \cdot H_2SO_4$ (clopidogrel)
$C_{16}H_{16}Cl\ NO_2S$ (clopidogrel base)

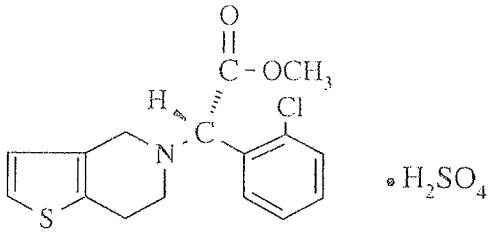
1.1.5.3 Molecular weight

419.9 (clopidogrel)
321.8 (clopidogrel base)

1.1.5.4 Physical and chemical data

- **For the drug substance Clopidogrel:**

Structural formula:



Appearance: White to off-white powder

Bulk density (1): about 0.40 g/mL untapped
about 0.53 g/mL tapped

Melting point (determined by differential scanning calorimetry) (1): 176.8°C

Vapor pressure at 25°C (3): $< 1.33 \times 10^{-5}$ Pascals ($< 1.0 \times 10^{-7}$ Torr)

Solubility in water (1):

6.8 g/L at pH = 2.6
3.0 g/L at pH = 3
0.05 g/L at pH = 4
0.01 g/L at pH = 6
0.01 g/L at pH = 8

Solubility in solvents:

Table (1.1.5.4) 1 - Solvent solubility of clopidogrel (1)

Solvent	Solubility at Saturation Point (g/L at 25°C)	Instantaneous Solubility Descriptive Term (USP and Ph. Eur.)
Methanol	459	Freely soluble
Ethanol	52	Soluble
Methylene chloride	15	Slightly soluble
Acetone	3.2	Slightly soluble
Dioxane	2.4	Very slightly soluble
Ethyl ether	0.01	Practically insoluble

Partition coefficient octanol/water (1):
(K_{ow} at pH = 7.4) 3.89
Log K_{ow} at pH = 7.4: 0.59

UV visible absorption (4):
195, 270, and 277 nm (buffer pH = 3)
193 nm (buffer pH = 7)
198 nm (buffer pH = 10)

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Dissociation constant (pKa) (5): 4.54

Hydrolysis rate (aqueous, 28 day) (6): 10% at pH of 7 and 9% at 25°C

Aerobic biodegradation in water (7) : 0% after 35 days

1.1.5.5 Health and safety data (clopidogrel)

Table (1.1.5.5) 1 - Clopidogrel Health and Safety

Assessment	Value
Sanofi-Synthelabo exposure limit band	0.02- 0.1 mg/m^3
Dust explosion minimum ignition energy	10-25 mJ
Minimum dust cloud ignition temperature	440-460°C
A/B dust flammability classification	Group A (Flammable)

1.1.5.6 Toxicity data (clopidogrel)(1)

- **Acute exposure**

Table (1.1.5.6) 1 - Toxicology data (clopidogrel)

Route	Test	Species	Results
Oral	LD_{50}	Rat	≥ 2 g/kg
Oral	LD_{50}	Mouse	≥ 2 g/kg
Oral	LD_{50}	Baboon	> 2 g/kg
Intravenous	LD_{50}	Rat	110 mg/kg
Intravenous	LD_{50}	Mouse	160 mg/kg

- **Effects of repeated\chronic exposure**

PLAVIX® is known to prolong bleeding time and inhibit platelet aggregation in the clinic. Exposure may increase risk of bleeding from trauma, surgery or other pathological conditions. At higher dose levels, increased plasma cholesterol, liver effects and gastrointestinal intolerance were observed.

- **Developmental and reproductive toxicity**

Reproduction studies in rats and rabbits at 65 and 78 times the recommended human dose of 75 mg/day showed no evidence of impaired fertility or fetal toxicity.

In another study, clopidogrel was found to have no effect on fertility of male and female rats at up to 52 times the recommended human dose (75 mg/day).

- **Genotoxicity**

Table (1.1.5.6) 2 - Genotoxicity (clopidogrel)

Test	Test System	Results
Ames	*Salmonella typhimurium* *E.Coli*	Negative
DNA repair test	Rat hepatocyctes	Negative
Forward gene mutation	(CHO/HGPRT)	Negative
Chromosomal aberration	(CHO cells)	Negative
Mouse micronucleus test	Mouse micronucleus	Negative

- **Carcinogenicity**

There was no evidence of tumorigenicity in 78-week rat and 104-week mouse studies with plasma exposures 25 times that in humans at the recommended dose of 75 mg/day clopidogrel.

1.1.5.7 Environmental data

- **Oxygen demand (clopidogrel)** (1)

COD: 1,260 g O_2/kg clopidogrel bisulfate
ThOD: 1,520 g O_2/kg clopidogrel bisulfate
BOD: Not determined because of low water solubility at test pH (7.0)

- **Aerobic biodegradation** (7)

Aerobic biodegradation in water:
clopidogrel: 0 % after 35 days (Results indicated that the 46%·degradation at day 35 was caused by physical, not biological processes.)

:

- **Environmental effects**

Table (1.1.5.7) 1 - Clopidogrel environmental effects test summary

Test and Test Organism	Toxicity Concentration
Microbial Growth Inhibition (USFDA 4.02) (8)	
Bacillus subtilis	800 ppm
Nostoc muscorum	200 ppm
Aspergillus niger	> 1000 ppm
Trichoderma viride	> 1000 ppm
Clostridium perfringens	> 1000 ppm
Algal Toxicity (OECD 201, biomass) (9)	
Pseudokirchneriella subcapitata 72 hour EC_{50}	4.40 ppm
Pseudokirchneriella subcapitata 72 hour NOEC	0.850 ppm
Daphnia Acute Toxicity (USFDA 4.08) (10)	
Daphnia magna 24 hour EC_{50}	16 ppm
Daphnia magna 48 hour EC_{50}	8.3 ppm
Daphnia magna 48 hour NOEC	6.2 ppm
Fish Acute Toxicity (OECD 203, USFDA 4.11) (11)	
Oncorhynchus mykiss 96 hour LC_{50}	4.00 ppm
Oncorhynchus mykiss 96 hour NOEC	1.01 ppm

- **Additives**

A listing of additives to the drug substance to formulate drug product is described in the Environmental Assessment appendices, Confidential Appendix – Composition of Drug Product (Section 1.1.12). The physical/chemical properties and environmental data for the additives are also detailed in the Environmental Assessment appendices, Confidential Appendix – Composition of Drug Product (Section 1.1.12).

1.1.6 Environmental Issues

The CDER Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications, July 1998 (FDA EA Document) (2), was used to develop strategies for evaluating the environmental fate and effects of the proposed action.

- **Identification of substance of interest**

A table of formulation constituents of PLAVIX/ISCOVER® and a description of the properties of the excipients to formulate drug product are described in Section 1.1.12. The pharmaceutical excipients (mannitol, Macrogol 6000, microcrystalline cellulose, hydrogenated castor oil, ——— hydroxypropyl cellulose, carnauba wax and the constituents of ——— ———, are commonly used and considered by the applicant to be pharmacologically inactive with very low toxicity (see Section 1.1.12) and do not present a significant environmental toxicity risk. In addition, all of the formulation excipients are permitted for direct addition to food for human consumption in the US by the Food and Drug Administration (21 CFR parts 172 and 180) and are therefore Generally Recognized As Safe (GRAS) (12). Evaluation of the environmental risk was therefore limited to the pharmaceutical active in the formulation, clopidogrel. Environmental fate and effects studies have been performed on clopidogrel as described in Sections 1.1.6.1 through 1.1.6.6.

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1.1.6.1 Environmental fate of the released substance

- **Clopidogrel metabolism** (1)

Pharmacokinetic studies have demonstrated that clopidogrel is extensively metabolized. Following repeated administration of clopidogrel (10 to 150 mg/day for 14 to 16 days), the concentration of unmetabolized clopidogrel was below the limit of detection at doses up to 100 mg/day. Clopidogrel is inactive *in vitro* and is considered a bioprecursor since it needs metabolic activation to express activity.

Human and animal studies indicated 20 metabolites of clopidogrel. The principal circulating metabolite is SR26334, a carboxylic acid derivative of clopidogrel. SR26334 is inactive in humans when dosed orally or IV. After administration of 400 mg of clopidogrel in humans, about 4% of SR26334 was excreted in urine.

No metabolites were identified which are excreted in concentrations greater than 10% of dose. The primary identified metabolites have a similar and simpler chemical structure to clopidogrel. As such, they are likely to exhibit a similar or more rapid environmental depletion rate than the parent. The metabolites are or are likely to be pharmacologically inactive and are therefore likely to exhibit lower environmental toxicity than the parent. Because of these considerations, to be conservative, fate and effects testing was performed on the parent compound clopidogrel.

- **Physical and chemical properties of clopidogrel**

Physical and chemical properties were determined for clopidogrel. They are summarized (Environmental Assessment appendices, Non-confidential Appendix – Data Summary Table for Clopidogrel, Section 1.1.10) and discussed in detail below.

- Solubility

Clopidogrel showed moderately low solubility in water in the environmental pH range (1). The solubility of anhydrous clopidogrel in various solvents was also determined (1). Upon consideration of these and other other physical and chemical data indicative of fate such as the octanol/water partition coefficient (1), it is apparent that clopidogrel will migrate to the water compartment despite its decreasing water solubility with increased pH.

- Dissociation constant

The dissociation constants were determined using potentiometry methods (5). The compound dissociated at one dissociation constant; 4.55 (pk_1), indicating an ionized species will exist within the environmental pH range.

- Partition coefficient

The partition coefficient log K_{ow} = 0.59 was determined by potentiometry methods (1). This value indicates little or no tendency to bioconcentrate or sorb significantly into organic materials such as soils, aquatic or terrestrial life forms.

- Vapor pressure

The vapor pressure was measured at 25°C by the gas saturation method at $< 1.33 \times 10^{-5}$ Pascal ($< 1.0 \times 10^{-7}$ Torr) (3). This negligible value indicates that clopidogrel is not likely to volatilize from water or as a solid.

- UV/visible absorption spectrum

The UV spectrum performed in aqueous buffer media over a wavelength range of [redacted] nm (4) showed an absorption band with the following maximum absorption wavelengths:

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[redacted] nm (pH = [redacted] buffer)
[redacted] nm (pH = [redacted] buffer)
[redacted] nm (pH = [redacted] buffer)

This indicates light absorption occurs outside of the spectral range associated with daylight, thus photodegradation does not offer a likely mechanism for degradation.

- **Environmental depletion mechanisms of clopidogrel**

Abiotic and aerobic biodegradation studies were conducted to evaluate the biodegradation depletion mechanism for the drug substance in the environment. They included the Hydrolysis Rate, Aerobic Biodegradation, and Chemical Oxygen Demand (COD).

- Hydrolysis rate

The hydrolysis rate of the drug substance was investigated in aqueous media at a pH of 7 and 9 at 25°C and 50°C (6). Ten percent hydrolysis was observed after 28 days at pH = 7 and 9 at 25°C, indicating that hydrolysis in the environmental temperature and pH range is not a rapid depletion mechanism.

- Aerobic biodegradation

The aerobic biodegradation in water study indicated no biodegradation occurring after 35 days (7). The test report indicates that the 46 % measured degradation at day 35 may be related to the changing solubility of clopidogrel in the test system caused by physical processes rather than biodegradation.

- Biochemical, chemical and theoretical oxygen demand (1)

The biochemical oxygen demand could not be determined because the water solubility of clopidogrel was lower than the test protocol requirement.

The chemical oxygen demand and theoretical oxygen demand are listed below.

COD = 1,260 g O_2/kg clopidogrel bisulfate
ThOD = 1,520 g O_2/kg clopidogrel bisulfate

- **Summary of environmental depletion mechanisms of clopidogrel**

Fate data do not show a rapid depletion mechanism for clopidogrel in the environment. These data indicate that the drug substance will migrate into the aquatic compartment in the undegraded form. After entry into the aquatic compartment, fate studies indicate non-rapid degradation by hydrolysis and possibly aerobic biodegradation.

- **Expected environmental concentration for clopidogrel**

The expected environmental concentration (EEC) and the Expected Introduction Concentration (EIC) are described in Section 1.1.6.5. The EIC and EEC are not expected to differ significantly, except from dilution in the aquatic environment since no rapid depletion mechanism was identified and sorption and bioaccumulation are not indicated in the environment.

The Maximum Expected Environmental Concentration (MEEC) value for clopidogrel was calculated using the estimated highest annual quantity of production for all indications in any of the first five years of clopidogrel marketing. See Environmental Assessment appendices, Confidential Appendix - MEEC Calculation (Section 1.1.12.2).

- **Summary of environmental fate of clopidogrel**

Based on the water solubility and low vapor pressure, clopidogrel exhibits no discernible tendency to volatilize and migrate into the atmospheric compartment from the solid state or while diluted in aqueous solutions. Water and solvent solubility, vapor pressure, partition coefficient and dissociation constant data indicate that the drug substance will migrate to the aquatic compartment. Based on the low partition coefficient ($\log K_{ow} = 0.59$), the drug substance exhibits no discernible tendency to bioconcentrate in aquatic or terrestrial life forms.

After entry into the aquatic compartment, fate studies indicate non-rapid degradation by hydrolysis and aerobic biodegradation.

1.1.6.2 Environmental effects of the released substance

Studies summarized below have been conducted to identify the effects of the drug substance clopidogrel into the environment.

- **Human and mammalian effects of clopidogrel** (1)

- Acute toxicity

The estimated LD_{50} for an oral dose of clopidogrel was the same for rats, mice, and baboons (> 2 g/kg). For intravenous administration, the estimated LD_{50} values were similar in both rats (110 mg/kg) and mice (160 mg/kg).

- **Chronic toxicity**

Carcinogenicity studies - Clopidogrel is considered to be non-tumorogenic based upon a 78-week mouse study and a 104-week rat study.

Reproductive toxicity - Clopidogrel showed no effect on fertility in a rat study. No evidence of impaired fertility or fetal toxicity was shown in other studies in rats and rabbits.

Genotoxicity - Clopidogrel was negative in all genotoxicity tests including the Ames/*Salmonella typhimurium/E. coli* mutagenicity assay, an *in vivo* mouse micronucleus assay, a forward gene mutation assay (CHO/HGPRT), a DNA repair test (rat hepatocytes) and a chromosomal aberration assay (CHO cells).

- **Environmental effects studies of clopidogrel**

The available fate data indicate that the drug substance will migrate to the aquatic compartment. Consequently, all toxicity studies were performed in the water compartment. The tiered approach in the FDA EA Document (2) was used to direct study of the effects of the drug substance on life forms in the aquatic compartment. Fate data indicates that microbial inhibition test was recommended. The log K_{ow} value indicated that Tier 1 testing (acute toxicity, one species) should be performed. As explained in Section 1.1.6.5, the Algal, *Daphnia* acute and Fish acute toxicity tests were performed at the Tier 2 testing level described in the FDA EA document. The environmental effects test data for clopidogrel are summarized below.

- **Microbial inhibition**

The microbial inhibition study per the USFDA Environmental Assessment Technical Assistance Handbook (TAD) (13) protocol 4.02 produced a threshold inhibition level of 200 ppm for *Nostoc sp.* (8). This is an indication that the drug substance has a low tendency to inhibit the activity of microbes in the aquatic environment.

- **Algal toxicity**

Algal toxicity was tested by measuring cell growth as biomass and growth rate of *Pseudokirchneriella subcapitata* for 72 hours per the OECD 201 method (9). The results indicated mean EC_{50} values of 4.4 ppm (biomass) and >6.92 ppm (growth rate). The no observed effect concentration (NOEC) was determined to be 0.850 ppm for both study endpoints.

- ***Daphnia* acute toxicity**

The *Daphnia* acute toxicity study per the USFDA TAD 4.08 protocol produced an EC_{50} (median effective concentration at 24 hours) of 16 ppm, an EC_{50} at 48 hours of 8.3 ppm and a No Observed Effect Concentration (NOEC) of 6.2 ppm (10).

- **Fish acute toxicity**

Rainbow trout (*Oncorhynchus mykiss)* acute toxicity was studied in a 96 hour test according to the USFDA TAD 4.11 and OECD 203 protocol (11). A mean LC_{50} of 4.00 ppm and a NOEC of 1.01 ppm was reported. The LC_{50} of 4.00 ppm represents the lowest acute toxicity value determined for clopidogrel and is used in the determination of the LC_{50} / MEEC concentration ratio described in Section 1.1.6.5 .

1.1.6.3 Use of resources

- **Materials**

All materials used in the drug substance/product manufacturing and distribution are readily available and will not cause depletion of any natural resources that are in short supply.

- **Effects upon endangered species and historic places**

The production, distribution and use of clopidogrel substance, PLAVIX® product, and the disposal of associated wastes will have no impact on threatened or endangered species.

Property listed in or eligible for listing in the National Register of Historic Places will not be impacted by the clopidogrel or PLAVIX® production or distribution activity or any related waste disposal.

1.1.6.4 Summary of fate and effects of emissions in the production and distribution cycles

The expected emissions from the clopidogrel, and PLAVIX® chemical and pharmaceutical manufacturing and distribution processes will be in compliance with the measures to protect the environment as defined by local, regional and national environmental laws and regulations.

It is predicted that the atmospheric, aquatic and terrestrial ecosystems, and human health will not be affected deleteriously by clopidogrel manufacturing or distribution. This is based upon consideration of regulatory compliance, manufacturing process controls, fate and effect studies, waste and materials management, safe work practices, hazard communication, and other procedures.

As described in Section 1.1.4.3, all returned goods wastes are disposed at off-site permitted facilities, in accordance with existing environmental regulations. Hospitals and offices may also dispose of unused drug product as a part of their medical waste disposal procedures according to environmental regulations.

1.1.6.5 Summary of fate and effects of emissions during patient use

The drug product PLAVIX® is intended to be distributed to hospitals, clinics and pharmacies for use by patients in their homes throughout the United States. The primary route of entry of clopidogrel into the environment will be via human excretions from use.

- **Clopidogrel fate and effects summary**

Pharmacokinetic studies indicate significant evidence of clopidogrel transformation in humans to pharmacologically inactive species generally of a simpler chemical structure expected to be more rapidly depleted. However, calculations were made assuming that clopidogrel will be untransformed in humans and enter into and be discharged from Publicly Owned Treatment Works (POTW) unchanged. The calculations were made despite the likelihood that these factors support the assumption that clopidogrel's excreted metabolites are likely to have a lower environmental toxicity than the parent.

The low vapor pressure and octanol/water partition coefficient (K_{ow}) and the solubility characteristics of the drug substance indicate that it will remain in the water compartment with no migration to the atmospheric compartment. The drug substance exhibits no discernible tendency to partition to sewage sludge or aquatic sediments or to bioconcentrate in aquatic or terrestrial life forms based on the low partition coefficient ($\log K_{ow} = 0.59$) and water solubility data.

Fate data do not indicate a rapid depletion mechanism for clopidogrel in the environment. However, non-rapid degradation was indicated in hydrolysis and aerobic biodegradation studies.

The Maximum Expected Environmental Concentration (MEEC) value for clopidogrel base was calculated using the estimated highest annual quantity of production for all indications in any of the next five years. The aquatic compartment expected introduction concentration (EIC) formula is described in the FDA EA Document. The MEEC is the EIC or the expected environmental concentration (EEC), which ever is greater. In this case, the EIC is the greater value, since it does not account for dilution after discharge from a POTW. The MEEC was calculated as shown in the Environmental Assessment appendices, Confidential Appendix - MEEC Calculation (Section 1.1.12.2).

The tiered toxicity testing approach recommended in the FDA EA document (2) employs assessment factors to determine whether the numbers and types of tests employed have adequately characterized potential environmental effects. When a single acute toxicity test using an organism from the recommended base set of three aquatic organisms (Tier 1) is employed to characterize potential environmental effects, the FDA EA document

recommends that an LC_{50}/MEEC ratio (assessment factor) of at least 1000 be attained. If the LC_{50}/MEEC ratio attained is less than 1000, then effects testing using the entire base set (Tier 2) is recommended to more precisely characterize potential effects.

In order to more accurately assess clopidogrel's effects and in anticipation that continually increasing clopidogrel sales might trigger need for Tier 2 effects testing, clopidogrel acute aquatic toxicity was performed using the entire base set of three organisms described in the FDA EA document. The test results indicated that trout are the most sensitive base set organism, with a 96-hour LC_{50} of 4.00 ppm.

The LC_{50}/MEEC ratio for clopidogrel base (using the lowest LC_{50} result) exceeds 1000, indicating that testing using the entire base set of three organisms has more than adequately characterized its potential environmental effects. Although Tier 1 testing would have adequately characterized potential clopidogrel environmental effects in accordance with the FDA EA document recommendations, the high LC_{50}/MEEC ratio demonstrated using the LC50 obtained from the most sensitive organism (as determined using Tier 2 testing) provides strong assurance that there will be no significant environmental impact from clopidogrel at the maximum concentration at which it could occur in the environment due to use by patients (assuming no human metabolism or environmental depletion). In summary, this assessment indicates that there will be no significant environmental impact from clopidogrel at the concentration at which it will appear in the environment.

1.1.6.6 Summary of the fate and effects of emissions from disposal

Since wastes from patient use are disposed at incineration, landfill, or other facilities regulated by the EPA or State agencies which consider environmental impacts from waste disposal, the Expected Introduction Concentration (EIC) for disposal does not need to be calculated and further evaluation of environmental fate and effects of emissions from disposal does not need to be made.

1.1.7 Mitigation Measures

Environmental impacts associated with the manufacturing, shipment, distribution, use, and waste disposal of the drug substance clopidogrel and drug product PLAVIX® will be made negligible through the use of appropriate control measures as required by permitting and other procedures and regulatory requirements.

1.1.8 Alternative to the Proposed Action

No potential adverse environmental impacts have been identified for the proposed action. The only alternative to the proposed action is that of no action, thus depriving patients an important therapy. The approval of the proposed action will provide an important benefit to patients in need of treatment for acute coronary syndrome with no significant environmental risk.

1.1.9 List of Contributors and Preparers

Peter Wilson
Master of Environmental Pollution Control
Manager, Environment

Sanofi-Synthelabo Inc.
9 Great Valley Parkway
Malvern, Pennsylvania 19355

1.1.10 Non-confidential appendix - data summary tables for clopidogrel

Table (1.1.10) 1 - Data summary table for clopidogrel

Physical/ Chemical Characterization	
Water solubility (1)	6.8 g/L at pH = 2.6 3.0 g/L at pH = 3 0.05 g/L at pH = 4 0.01 g/L at pH = 6 0.01 g/L at pH = 8
Solvent solubility at saturation point (g/l @ 25°C) (1)	
Methanol	459
Ethanol	52
Methylene chloride	15
Acetone	3.2
Dioxane	2.4
Ethyl ether	0.01
Dissociation constant (pK_a) (5)	4.54
Octanol/Water partition coefficient (Log K_{ow}) (1)	0.59 at pH= 7.4
Vapor pressure at 25°C (Pascals) (3)	$< 1.33 \times 10^{-5}$
Bulk density (1):	about 0.40 g/ml untapped about 0.53 g/ml tapped
Depletion Mechanisms	
UV visible absorption peaks (nm) (4)	195, 270, and 277 nm (buffer pH = 3) 193 nm (buffer pH = 7) 198 nm (buffer pH = 10)
Hydrolysis rate (aqueous, 28 day) (6)	10% at pH of 7 and 9 at 25°C
Aerobic biodegradation in water (7)	none after 35 days

Table (1.1.10) 1 - Data summary table for clopidogrel (continued)

Environmental Effects	
Microbial Growth Inhibition (USFDA 4.02) (8)	
Bacillus subtilis	800 ppm
Nostoc muscorum	200 ppm
Aspergillus niger	> 1000 ppm
Trichoderma viride	> 1000 ppm
Clostridium perfringens	> 1000 ppm
Algal Toxicity (OECD 201) (9)	
Pseudokirchneriella subcapitata - 72 hour EC_{50} biomass	4.40 ppm
Pseudokirchneriella subcapitata - 72 hour NOEC biomass	0.850 ppm
Daphnia Acute Toxicity (USFDA 4.08) (10)	
Daphnia magna 24 hour EC_{50}	16 ppm
Daphnia magna 48 hour EC_{50}	8.3 ppm
Daphnia magna 48 hour NOEC	6.2 ppm
Rainbow Trout Acute Toxicity (11)	
(OECD 203 / USFDA 4.11)	
Oncorhynchus mykiss 96 hour LC_{50}	4.00 ppm
Oncorhynchus mykiss 96 hour NOEC	1.01 ppm

1.1.11 References

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(18) Registry of Toxic Effects of Chemical Substances (RTECS)

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Bai Nguyen
8/28/2006 11:18:08 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-839 / S-034

STATISTICAL REVIEW(S)

Statistical Review and Evaluation (Addendum)

NDA/Serial Number:	20-839 / S_034
Drug Name:	Plavix (clopidogrel bisulfate)
Indication(s):	Acute Myocardial Infarction
Applicant:	Sanofi Aventis
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Jialu Zhang, Ph.D.
Concurring Reviewers:	John Lawrence, Ph.D. James Hung, Ph. D.
Medical Division:	Division of Cardio-Renal Drug Products, HFD-110
Clinical Team:	Salma Lemtouni, M.D.
Project Manager:	Meg Pease-Fye, Pharm.D.
Keywords:	Drug interaction, sample size increase

The reference is made to the sponsor's submission on May 16, 2006 in response to the Agency's questions. The submission is considered as a major amendment.

The sponsor responded to the three questions that the Division raised. Specifically, the response to Question 2 is to explain the COMMIT results in patients who received or did not receive metoprolol. The response to Question 3 is to clarify when and how the sample size increase decision was made.

The patients who had metoprolol only have a lower event rate compared to the patients who had placebo. The patients who had metoprolol and clopidogrel, on the other hand, have a similar event rate compared to the patients who had clopidogrel only. The observed difference may or may not be purely due to random chance in this study. The statistical interaction test for the possible difference between metoprolol versus placebo and the combo versus clopidogrel is inconclusive. That is, this study does not provide sufficient evidence to support either that there is an interaction or that there is no interaction.

On December 5 of 2000, a letter signed by Drs. Zhengming Chen (Clinical Trial Service Unit principal investigator), Rory Collins (co-chairman of steering committee) and Richard Peto (statistician) requested to increase sample size from 30000 to 40000. By the time the request was made, the sponsor estimated approximately 8,000 patients were randomized. Apparently, the decision of increasing sample size was made before the outcome or enrollment of the first 30,000

patients and thus probably independently from the insignificant results based on the first 30,000 patients.

Jialu Zhang, Ph.D.
Mathematical Statistician

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/s/

Jialu Zhang
7/12/2006 11:01:34 AM
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James Hung
7/12/2006 03:06:24 PM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	20-839 / S_034
Drug Name:	Plavix (clopidogrel bisulfate)
Indication(s):	Acute Myocardial Infarction
Applicant:	Sanofi Aventis
Date(s):	Date of Document: November 17, 2005 PDUFA due date: May 17, 2006
Review Priority:	Priority
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Jialu Zhang, Ph.D.
Concurring Reviewers:	John Lawrence, Ph.D. James Hung, Ph. D.
Medical Division:	Division of Cardio-Renal Drug Products, HFD-110
Clinical Team:	Salma Lemtouni, M.D.
Project Manager:	Meg Pease-Fye, Pharm.D.
Keywords:	Hazard rate, sample size increase

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The two trials (CLARITY and COMMIT) showed significant results on primary efficacy endpoints using clopidogrel in treating patients with ST-elevation myocardial infarction.

The treatment effect seems most significant in the first two days in COMMIT study. The primary endpoints in COMMIT are statistically significant. However, the study may be overpowered and the sample size increase during the trial is a concern to the reviewer. Specifically, the initial planned 30000 patient population is noticeably different from the patients recruited later in hazard ratio and the analyses of primary endpoints showed no statistical significance between the treatment groups for the first 30000 patients. It is also noted that the DSMB was unblinded to the primary endpoints.

The primary efficacy result of CLARITY appears to be driven by occluded IRA events. It is uncertain whether CLARITY provides enough evidence and whether the nominal p-values in COMMIT support the efficacy claim.

1.2 Brief Overview of Clinical Studies

The objective of the two trials is to support the extension of clopidogrel use in patients with ST-elevation myocardial infarction (STEMI). EFC5133 (CLARITY) is a multinational, randomized, double-blind, placebo-controlled, 2 parallel group study comparing clopidogrel plus acetylsalicylic acid (ASA) versus ASA alone. 300 mg loading dose of clopidogrel was given to the patients in clopidogrel group in CLARITY on the day of randomization and followed by 75 mg daily doses. EFC7018 (COMMIT) is a multi-center, randomized, double-blind, placebo-controlled, 2 x 2 factorial design study in patients with suspected acute MI receiving daily ASA (162 mg) or 75 mg/day clopidogrel with ASA. No loading dose of clopidogrel was given.

1.3 Statistical Issues and Findings

The hazard rate in COMMIT study is not constant over the time. Instead the hazard functions show that the risk of patients in both clopidogrel and control groups decrease greatly after two or three days in the trial. Patients in COMMIT were not given any loading dose. Also the treatment effect seems most significant in the first two days and it appears to be the driving force of the efficacy results in COMMIT study.

The COMMIT study has two co-primary endpoints, but the protocol and SAP did not pre-specify the hypothesis. In other words, it is unknown whether the sponsor would claim the efficacy of clopidogrel only when both composite endpoint and all cause mortality are significant. If not, there are multiple procedures available to control the type I error, which would lead to different

conclusions. Therefore, it is not possible to say whether both endpoints are statistically significant.

COMMIT may potentially be overpowered. A total of 46000 patients will provide 95% power to detect 10% relative risk reduction based on event rate of 8% in control group at α level of 0.01.

Both the CLARITY and COMMIT trials increased sample size during the trial. There is some concern on the potential type I error inflation since DSMB of both trials were either partially unblinded or completely unblinded to the primary endpoints. No interim analysis result was reported in the clinical study report.

Since the p-value of the primary composite endpoint in CLARITY is extremely small, the adverse impact of the sample size increase at this level on the type I error rate is not expected to be large enough to make the statistical significance of this p-value go away. The exploratory analyses using original sample size (2200 patients) showed statistical significance in the primary composite endpoint. Thus in my view, the primary efficacy endpoint is statistically significant.

The sample size increase in COMMIT trial is worrisome. The hazard ratio of the initial planned 30000 patient population is noticeably different from the hazard ratio of the patients recruited later and the analyses of primary endpoints showed no statistical significance between the treatment groups for the first 30000 patients (Table 11 and Table 12).

The primary efficacy result of CLARITY appears to be driven by occluded IRA events. Death and recurrent MI only count for a small portion of the composite events. In addition, death events in the two treatment groups show the opposite direction of the primary efficacy results.

2. INTRODUCTION

2.1 Overview

Plavix (clopidogrel) is currently approved in treating patients with recent myocardial infarction (MI), recent stroke or established peripheral arterial disease (PAD) for the reduction of atherothrombotic events. To support the extension of clopidogrel use in patients with ST-elevation myocardial infarction (STEMI), two trials were conducted: EFC5133 (CLARITY-TIMI 28, Clopidogrel as Adjunctive ReperfusIon TherapY – Thrombolysis in Myocardial Infarction – 28) and EFC7018 (COMMIT/CCS-2, ClOpidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study).

EFC5133 (also referred as CLARITY) involved 319 study centers in 23 countries. A total of 3491 patients were randomized to a double-blinded treatment and included in the efficacy analysis. Eligible patients were randomized in a double-blind manner to receive either clopidogrel or matching placebo. All patients were also to receive fibrinolytic therapy initially and also daily ASA for the duration of the study. The primary efficacy endpoint was analyzed using a logistic regression analysis with terms included for treatment group, type of fibrinolytic, type of anticoagulant used up to 2 hours post-randomization, and infarct location. Sample size was increased twice due to lower than expected event rate.

EFC7018 (also referred as COMMIT) was 2 x 2 factorial design study in patients with suspected acute MI receiving daily ASA (162 mg). A total of 45852 patients were randomized. Patients presenting within 24 hours of the onset of the symptoms of suspected acute MI were randomized among 4 possible treatment combinations. Sample size was increased once during the trial due to the lower than expected event rate.

2.2 Data Sources

The sponsor's electronic submission is stored under the directory of \\CDSESUB1\N20839\S_034 in the center's electronic document room.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 STUDY EFC 5133 - CLARITY

CLARITY is a multinational, randomized, double-blind, placebo-controlled, 2 parallel group study comparing clopidogrel plus acetylsalicylic acid (ASA) versus ASA alone in patients with acute ST elevation myocardial infarction (STEMI) treated with fibrinolytic therapy.

3.1.1.1 Study Objectives

The primary objective is to demonstrate that, in patients with STEMI treated with background ASA and initial fibrinolytic therapy, clopidogrel (300 mg loading dose followed by 75 mg/day) reduced the proportion of patients who had an occluded infarct-related artery (IRA) compared with placebo.

3.1.1.2 Study Design

Patient were randomized within 12 hours of the onset of symptoms of STEMI to receive either clopidogrel or placebo up to and including the day of angiography or Day 8 or hospital discharge, whichever came first. Eligible patients were randomized in a double-blind manner to receive either clopidogrel (300 mg loading dose followed by 75 mg/day) or matching placebo. All patients were to receive fibrinolytic therapy initially and also daily ASA (150 to 325 mg) for the duration of the study.

3.1.1.3 Sample Size Determination and Interim Analyses

The sample size for CLARITY TIMI-28 as planned in the original protocol was 2200 patients. Assuming 5% dropout rate, this sample size of 1100 patients per group would have afforded 82% power to detect a 24% relative risk reduction from 21% to 16% in the rate of the primary composite efficacy endpoint, using a 2-sided significance level of 0.05.

Due to a concern that the projected event rate might be lower than originally predicted, the sample size for the trial was increased to 3000 patients in Protocol Amendment 2 (Feb 2003) and was increased again to 3500 patients in Protocol Amendment 4. The sponsor stated that 3000 patients would have provided 80% power to detect a 20% relative risk reduction (from 21.0% to 16.8% by clopidogrel versus placebo) in the rate of the primary efficacy endpoint using a 2-sided significance level of 0.05. The final sample size provided 95% power to detect a 24% relative risk reduction from 19% to 14.4% in the rate of the primary endpoint between clopidogrel and placebo. Sample size re-estimation should be based on the same relative risk reduction in order to control the type I error.

An interim safety evaluation was performed by the DSMB when data regarding death, stroke, and bleeding were available for 50% of patients. Partially blinded (treatment groups coded as Drug X and Drug Y) tabular summaries of stroke/ICH, bleeding events and death were prepared for the DSMB by a statistician not involved in the day-to-day activities of the study. No specific statistical stopping rules were provided, and no stopping rule for efficacy was applied.

3.1.1.4 Efficacy Measures

(1) Primary Efficacy Endpoint

The primary efficacy assessment was based on the composite endpoint of an occluded IRA (TIMI flow grade 0 or 1) on the predischarge angiogram or death or recurrent MI by the time of start of angiography or Day 8 or hospital discharge, whichever came first.

Per the clinical study report, the primary efficacy endpoint was analyzed using a logistic regression analysis with terms included for treatment group, type of fibrinolytic, type of anticoagulant used up to 2 hours post-randomization, and infarct location.

(2) Secondary Efficacy Endpoints

Secondary efficacy assessments were based on the following endpoints analyzed in a hierarchical order: degree of ST segment resolution at 180 minutes after first dose of study drug; occluded IRA on predischarge angiogram; and composite outcome of death, recurrent MI, or recurrent myocardial ischemia by the time of start of angiography or Day 8 or hospital discharge, whichever came first.

The degree of ST segment resolution was analyzed using ANCOVA model with baseline ST segment deviation as the covariate. The other two secondary endpoints were analyzed using a similar model to the model in the primary efficacy analysis.

3.1.1.5 Patient Disposition, Demographic and Baseline Characteristics

The study involved 319 study centers in 23 countries. A total of 3491 patients were randomized to a double-blinded treatment and included in the efficacy analysis. Of the randomized patients, 153 were from sites in the United States of America (USA), 260 were from sites in Canada, 2261 were from sites in Europe, and 817 were from sites in other regions (Argentina, Australia, Brazil, Israel, Mexico, South Africa, and Turkey).

The clopidogrel and placebo treatment groups are similar with regard to cardiovascular and non-cardiac medical history. Majority of patients (80.3%) in the study are males. The study population is composed of 89.5% Caucasians. A total of 52.7% of patients have non-cardiac medical history. The key characteristics of the qualifying ischemic event are comparable between the clopidogrel and placebo groups.

47.7% patients in the clopidogrel group and 49.8% in the placebo group received medications during the 2 weeks prior to study entry. The most commonly received medication is ASA (15.7%). A total of 76.8% of the clopidogrel group patients and 78.8% of the placebo group patients received blinded study drug through the day of angiography, or through Day 8 or hospital discharge for those who did not undergo angiography.

A total of 4 patients in the clopidogrel group and 8 patients in the placebo group received incorrect study drug. These patients were randomized to one group and received the medication for the other group.

3.1.1.6 Sponsor's Primary Efficacy Results

The sponsor concluded that the rate of occurrence of the composite primary outcome were significantly lower for the clopidogrel group compared with the placebo group (p-value<0.0001). Among the individual components of the primary endpoint, clopidogrel has the greatest effect on the rate of an occluded IRA (Table 2).

Table 1. Primary Efficacy Analysis in EFC5133

Primary efficacy endpoint	Clopidogrel 300/75 mg[a] N = 1752	Placebo[a] N = 1739	p value	OR	95% CI
Number (%) of patients reporting the endpoint	262 (15.0%)	377 (21.7%)	0.00000036	0.64	0.53,0.76

a. With background ASA and initial fibrinolytic therapy

[Source: sponsor's clinical study report eff5133.pdf Table(11.1.1) 1]

Table 2. Summary on Individual Components of the Primary Endpoint

Clopidogrel 300/75 mg[a]		Placebo[a]	Overall
Occluded IRA			
N	1640	1634	3274
n (%) of patients reporting endpoint	192 (11.7%)	301 (18.4%)	493 (15.1%)
Death			
N	1752	1739	3491
n (%) of patients reporting endpoint	45 (2.6%)	38 (2.2%)	83 (2.4%)
Recurrent MI			
N	1752	1739	3491
n (%) of patients reporting endpoint	44 (2.5%)	62 (3.6%)	106 (3.0%)

a. With background ASA and initial fibrinolytic therapy
[Source: sponsor's clinical study report eff5133.pdf Table(11.1.1) 2]

In Table 2, patients were counted under each component of the primary endpoint experienced. The analysis of occluded IRAs on the pre-discharge angiograms included patients from the ITT population who underwent angiography before discharge. No attempt was made to impute a value to missing TIMI Flow Grade. Patients with no TIMI Flow Grade available were not included in the analysis. Therefore the total number of patients in comparing the rate of occluded IRA is smaller than the ITT population.

3.1.1.7 Sponsor's Secondary Efficacy Results

The sponsor specified a hierarchy procedure in the protocol to test secondary efficacy endpoints. The treatment effect on the adjusted mean ST segment resolution at 180 minutes after the first dose of clopidogrel is not statistically significant. As this is the first endpoint to be tested in the hierarchy procedure, no claim can be made on these secondary endpoints.

Table 3. Secondary Efficacy Endpoint Analyses

Secondary efficacy endpoint	Clopidogrel 300/75 mg[a]	Placebo[a]	p value	Mean difference	95% CI
Adjusted mean ST segment resolution of an ECG at 180 minutes after the first dose of study drug	N = 1068 53.01	N = 1021 55.12	0.223	-2.11	-5.50,1.28
Secondary efficacy endpoint	**Clopidogrel 300/75 mg**	**Placebo**	**p value**	**OR**	**95% CI**
Number (%) of patients with occluded IRA on pre-discharge angiogram	N = 1640 192 (11.7%)	N = 1634 301(18.4%)	<0.001	0.59	0.48,0.72
Number (%) of patients with death, recurrent MI, or recurrent myocardial ischemia (severe or leading to revascularization) by the time of the start of pre-discharge angiography	N = 1752 145 (8.3%)	N = 1739 162 (9.3%)	0.274	0.88	0.69,1.11

a With background ASA and initial fibrinolytic therapy.
[Source: sponsor's clinical study report eff5133.pdf Table(11.1.2) 1]

3.1.1.8 Reviewer's Results

According to the clinical study report, the sample size was increased twice. The relative risk reduction changed from 24% to 20% in the first increase with the same power. The second re-estimation showed the same relative risk reduction, however, the power changed from 82% to 95%. The changes of sample size may inflate type I error. In addition, mortality is part of the composite primary endpoint and DSMB is partially unblinded (treatment groups coded as Drug X and Drug Y) to the mortality events, sample size increase in this case is somewhat worrisome. However, since the p-value of the primary composite endpoint is extremely small, the adverse impact of the sample size increase at this level on the type I error rate is not expected to be large enough to make the statistical significance of this p-value go away. The exploratory analyses using original sample size (2200 patients) also showed statistical significance in the primary composite endpoint. Thus in my view, the primary efficacy endpoint is statistically significant (Table 4). It is also noticed that patients recruited later have higher event rate (18.9% in clopidogrel group and 27.2% in placebo group) although the odds ratio (0.62) is similar to the patients who were recruited earlier.

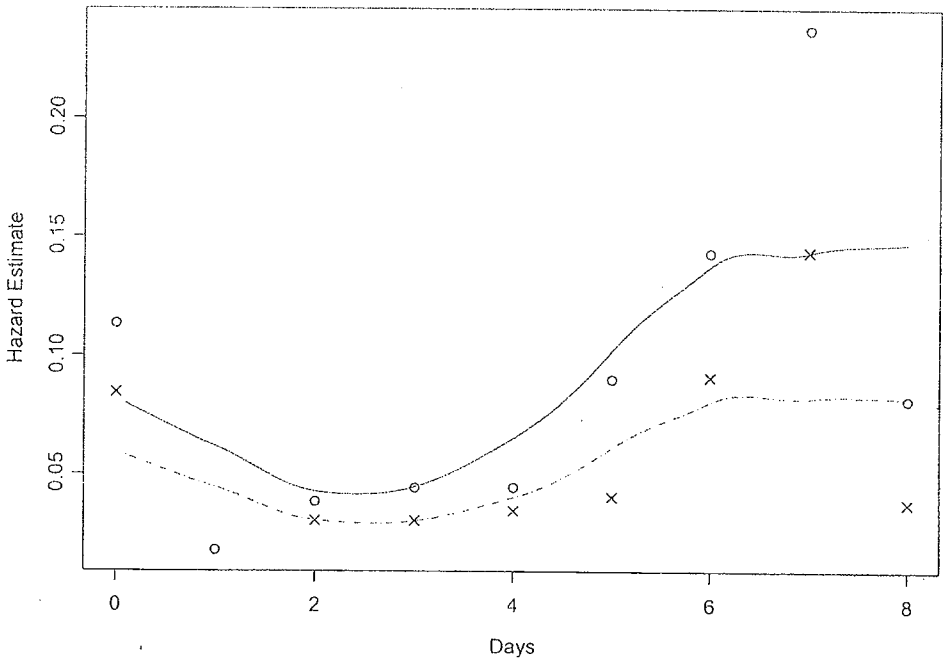
Table 4. Analyses of the First 2200 Patients

	Clopidogrel 300/75 mg		Placebo				
Primary efficacy endpoint Number (%) of patients reporting the endpoint	**N**	**# of patients reporting events**	**N**	**# of patients reporting events**	**p value**	**OR**	**95% CI**
Final Sample Size of 3491	1752	262 (15.0%)	1739	377 (21.7%)	<0.001	0.64	0.53,0.76
Initial planned Sample Size of 2200	1107	140 (12.7%)	1093	201 (18.4%)	<0.001	0.64	0.41, 0.88

The sponsor specified a hierarchy procedure in the protocol to test secondary efficacy endpoints. The treatment effect on the adjusted mean ST segment resolution at 180 minutes after the first dose of clopidogrel is not statistically significant. As this is the first endpoint to be tested in the hierarchy procedure, no claim should be made on any of these secondary endpoints.

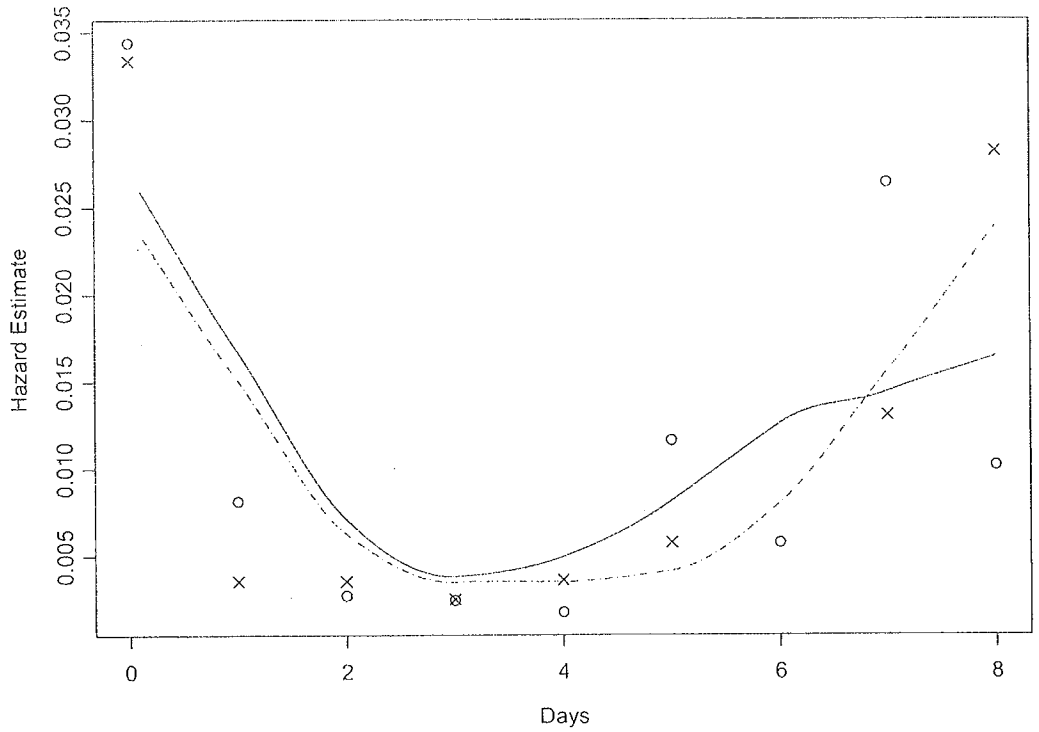
Hazard functions are plotted for the primary composite endpoint in clopidogrel and control groups. Patients in clopidogrel group appear to have lower risk than patients in control group throughout the 8 days of trial period (Figure 1). Since the primary composite endpoint includes death or recurrent MI or an occluded IRA on the predischarge angiogram, the rising of the hazard rates in both groups may be interpreted by more angiograms conducted as time approached Day 8. As showed in Table 5, the number of death and MI events decreased dramatically in the first few days. This is similar to the hazard function in COMMIT.

Figure 1. Hazard Functions of Composite Endpoint in CLARITY



* Red solid line is hazard function for control group, blue dotted line is hazard function for clopidogrel group. Circles are the point estimates of hazard rates in control group, 'x's are point estimates of hazard rates in clopidogrel group (see Appendix A).

Figure 2. Hazard Functions of Death and MI Events in CLARITY



* Red solid line is hazard function for control group, blue dotted line is hazard function for clopidogrel group. Circles are the point estimates of hazard rates in control group, 'x's are point estimates of hazard rates in clopidogrel group (see Appendix A).

Table 5. Hazard Rate Estimate of Death and MI Events in CLARITY

	Placebo			Clopidogrel		
Day	Hazard Rate	# of Events	Patient Time	Hazard Rate	# of Events	Patient Time
0	0.0344	51	1483.5	0.0333	51	1529.5
1	0.0081	11	1353.9	0.0035	5	1410.0
2	0.0027	3	1098.6	0.0036	4	1125.0
3	0.0024	2	816.5	0.0025	2	794.3
4	0.0018	1	565.2	0.0036	2	552.8
5	0.0116	4	344.9	0.0058	2	347.5
6	0.0057	1	174.8	0.0000	0	176.3
7	0.0264	2	75.9	0.0131	1	76.6
8	0.0102	1	98.4	0.0281	3	106.6

If excluding patients who had angioplasty before angiography, 181 out of 1577 patients in placebo and 288 out of 1575 patients in clopidogrel had occluded IRA.

3.1.1.9 Conclusions

The reviewer is able to replicate the primary endpoint efficacy results and confirm secondary efficacy results in study 5133.

Sample size increase in this case is somewhat worrisome. However, since the p-value of the primary composite endpoint is extremely small, the adverse impact of the sample size increase at this level on the type I error rate is not expected to be large enough to make the statistical significance of this p-value go away. The exploratory analyses using original sample size (2200 patients) showed statistical significance in the primary composite endpoint. Thus in my view, the primary efficacy endpoint is statistically significant.

The primary efficacy result appears to be driven by occluded IRA events. Death and recurrent MI only count for a small portion of the composite events. In addition, deaths seem to show an opposite direction. It is uncertain whether CLARITY provides sufficient evidence to support the efficacy claim.

3.1.2 STUDY EFC 7018 - COMMIT

3.1.2.1 Study Objectives

The primary objective of this study was to determine whether the addition of clopidogrel to ASA for up to 4 weeks in hospital in patients with suspected acute MI can reduce mortality and the risk of major vascular events compared to ASA alone.

3.1.2.2 Study Design

This was a multi-center, randomized, double-blind, placebo-controlled, 2 x 2 factorial design study in patients with suspected acute MI receiving daily ASA (162 mg). Patients presenting within 24 hours of the onset of the symptoms of suspected acute MI were randomized in a 2 x 2 factorial design among 4 possible treatment combinations [75 mg clopidogrel versus placebo once daily (QD), and metoprolol versus placebo QD], and treated for up to 4 weeks in hospital or until prior discharge. The 2x2 factorial design is to support the efficacy results of two drugs (clopidogrel and metoprolol) from two different sponsors. Since metoprolol is not the drug of interest for this submission, the primary analysis in this trial pooled the 4 treatment groups into two groups (clopidogrel versus control). The effect of clopidogrel compared with control was also analyzed by metoprolol strata to ensure the consistency.

3.1.2.3 Sample Size Determination and Interim Analyses

The protocol of COMMIT study proposed to enroll 20000-30000 patients. The sample size was calculated by separating relative risk reduction by the mortality events and events of

reinfarction/stroke. Assuming control group has 10% mortality rate and 4% reinfarction/stroke rate, the relative risk reduction is 10% for each category, the number of events can be computed separately for mortality and reinfarction/stroke (Table 6) and the trial would have 98% power. A sample size of 20000 to 30000 was recommended in the protocol. On December 5 of 2000, a letter signed by Drs. Zhengming Chen (Clinical Trial Service Unit principal investigator), Rory Collins (co-chairman of steering committee) and Richard Peto (statistician) requested to increase sample size from 30000 to 40000 with a note stating that the target of 40,000 patients was clearly foreseen before the first patient was randomized and the request was stated clearly at the first meeting of potential collaborators as well as several subsequent meetings. The difference of maximum number of patients enrolled (30000 versus 40000) is not mentioned in the clinical study report.

Table 6. Major Events among 30,000 Patients with Suspected Acute MI

Event	Proportional risk reduction	Active (15,000)	Control (15,000)	Two-sided p values
Death	10%	1350 (9.0%)	1500 (10.0%)	0.003
Non-fatal reinfarction or stroke/arrest*	15%	510 (3.4%)	600 (4.0%)	0.006
Total: Death, reinfarction or stroke/arrest*	**11%**	**1860 (12.4%)**	**2100 (14.0%)**	**<0.0001**

** The combined outcome for the antiplatelet comparison is to be death, non-fatal reinfarction or stroke, whereas for the beta-blocker comparison it is to be death, non-fatal reinfarction or cardiac arrest.*

During the course of the study, however, tracking of the blinded event rates revealed a lower in-hospital mortality rate than was originally assumed (8% as opposed to 10%). In a letter dated 14 February 2003, the Steering Committee recommended to recruit as many as 48000 patients, up to a fixed closure date for the study. In order to have at least 95% statistical power to detect a 10% relative risk reduction with a two-sided p-value < 0.05, it was considered necessary to recruit at least 45000 patients.

At regular intervals during the trial period, interim analyses of the primary endpoints (and of other information where available, such as SAEs believed to be due to the trial treatments) were performed. Interim analyses of the primary endpoints were to provide information to the independent Data Monitoring Committee confidentially to decide whether to modify intake to the study or increase sample size. It is not clear how many interim analyses were performed. The sponsor stated that given the extremeness of the stopping rule (a difference of at least 3 standard deviations), the exact number of interim analyses is of little importance and does not affect the determination of the final significance level for the co-primary outcomes. No interim analyses results were reported in the clinical study report.

3.1.2.4 Efficacy Measures

(1) Primary Efficacy Endpoint

The study has two co-primary endpoints: a composite endpoint of death, reinfarction or stroke and all cause mortality. The two co-primary endpoints were pre-specified in the protocol. No primary efficacy endpoint analysis method was specified in protocol or statistical analysis plan. The protocol briefly mentioned that main analyses would compare all patients who allocated active-clopidogrel plus aspirin with all those allocated placebo-clopidogrel plus aspirin. This is not clear how the α was adjusted for the two co-primary endpoints.

(2) Secondary Efficacy Endpoints

No secondary endpoints or corresponding analyses were pre-specified. The protocol only stated that the principle subsidiary comparisons would be of the effects of adding clopidogrel to aspirin on death during days 0-1, days 2-7 and day 8 to the end of the scheduled treatment period. Subgroup analyses in regard to age, systolic blood pressure (SBP), heart rate, delay from symptom onset to randomization and use of fibrinolytic therapy were planned to be conducted.

3.1.2.5 Patient Disposition, Demographic and Baseline Characteristics

A total of 45852 patients were randomly assigned to receive either clopidogrel (22961) or placebo (22891). Of these 45852 patients, 45627 (22852 for clopidogrel, 22775 for placebo) received at least one dose of study drug. The majority of the patients were male (72.2%). The mean (SD) age was 61.3 (11.8) years with 11934 (26%) patients aged 70 years or older at entry and 785 (1.71%) patients aged below 35. Almost 25% of the patients were Killip class II or III.

Table 7. Demographic and Baseline Data of Patients in COMMIT Study

Characteristic	Treatment		Overall
	Clopidogrel 75 mg (N = 22961)	Placebo (N = 22891)	(N = 45852)
Sex - n (%)			
Female	6366 (27.7%)	6393 (27.9%)	12759 (27.8%)
Male	16595 (72.3%)	16498 (72.1%)	33093 (72.2%)
Age at entry (yr)			
Mean (SD)	61.3 (11.9)	61.4 (11.8)	61.3 (11.8)
Range	15.4-100.3	15.4-99.3	15.4-100.3
SBP (mmHg)			
Mean (SD)	128.2 (22.6)	128.2 (22.5)	128.2 (22.5)
Range	60.0-250.0	60.0-250.0	60.0-250.0
DBP (mmHg)			
Mean (SD)	81.0 (14.6)	80.9 (14.4)	81.0 (14.5)
Range	40.0-177.0	40.0-180.0	40.0-180.0
Heart rate (bpm)			
Mean (SD)	82.2 (17.2)	82.1 (17.2)	82.1 (17.2)
Range	40-228	40-225	40-228
Killip class - n (%)			
I	17320 (75.4%)	17283 (75.5%)	34603 (75.5%)
II	4601 (20.0%)	4504 (19.7%)	9105 (19.9%)
III	1040 (4.5%)	1104 (4.8%)	2144 (4.7%)

[Source: sponsor's clinical study report eff7018.pdf Table(10.5.1) 1]

The reviewer found out that two patients in placebo group had missing age record and two patients in placebo group had age 0.31 and 0.00. This is not reflected in the baseline data reported by the sponsor.

Table 8. Summary of Percentages of Patients in Different Age Strata

Age	Frequency	Percent
<=35	785	1.71
36-40	1417	3.09
41-45	2344	5.11
46-50	4199	9.16
51-55	5014	10.94
56-60	5348	11.66
61-65	6823	14.88
66-70	8005	17.46
>70	11917	25.99
Total	45852	100

The percentage of patients with a confirmed MI was similar for the 2 treatment groups. The mean (SD) time from onset of symptoms to randomization was 10.3 (6.7) hours, with 33.7% of patients

randomized within 6 hours. 261 (1.1%) patients in the clopidogrel group and 233 (1.0%) patients in the placebo group were not confirmed with an ACS diagnosis.

Table 9. Summary of Qualifying Event Data

Qualifying Event	Treatment		Overall
	Clopidogrel 75 mg* (N = 22961)	Placebo (N = 22891)	(N = 45852)
Hours since onset			
Mean (SD)	10.3 (6.7)	10.3 (6.7)	10.3 (6.7)
Range	0.2-24.0	0.1-24.0	0.1-24.0
Hours since onset - n (%)			
< 6	7745 (33.7%)	7707 (33.7%)	15452 (33.7%)
6 to < 13	7567 (33.0%)	7505 (32.8%)	15072 (32.9%)
13 to 24	7649 (33.3%)	7679 (33.5%)	15328 (33.4%)
Final diagnosis of initial MI - n (%)			
Confirmed MI	22002 (95.8%)	21946 (95.9%)	43948 (95.8%)
Suspected MI	410 (1.8%)	404 (1.8%)	814 (1.8%)
Unstable angina	288 (1.3%)	308 (1.3%)	596 (1.3%)
Other	261 (1.1%)	233 (1.0%)	494 (1.1%)

[Source: sponsor's clinical study report eff7018.pdf Table(10.5.3) 1]

3.1.2.6 Sponsor's Primary Efficacy Results

No primary efficacy endpoint analysis method was specified in protocol or statistical analysis plan. The p-values reported in the clinical study report are based on log-rank test.

Clopidogrel produced a significant 9% (95% CI 3, 14; p = 0.002) proportional risk reduction in the primary combined endpoint of death, reinfarction or stroke compared with placebo, both given in combination with ASA. Similarly, clopidogrel significantly reduced by 7% (95% CI 1, 13; p = 0.03) the proportional risk of death from any cause compared with placebo, both given in combination with ASA.

Table 10. Primary Efficacy Results in COMMIT Study

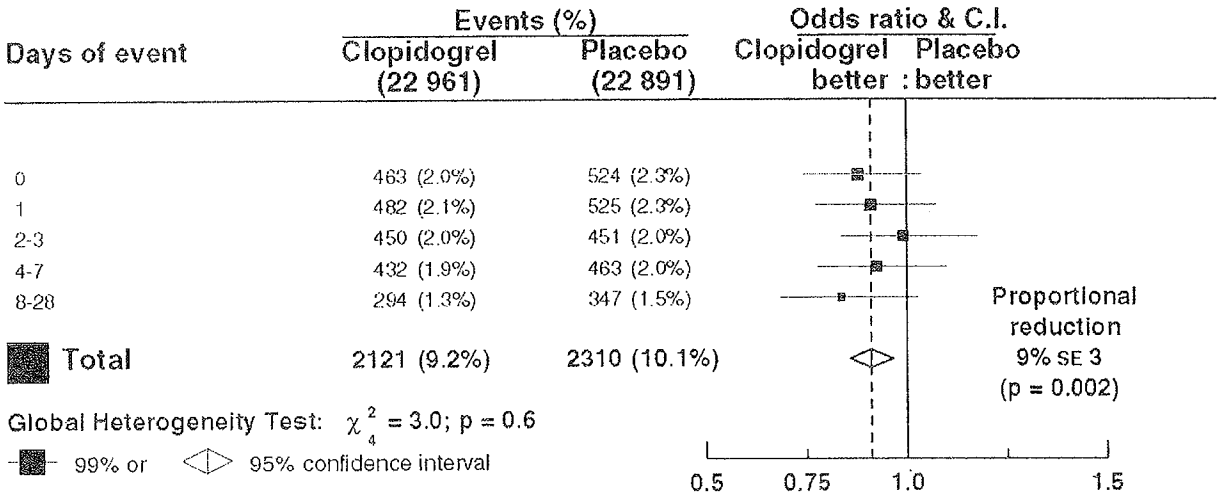
Event	No. (%) With Event		Odds Ratio (95% CI)	Absolute Benefit /1000 (SE)	Two-sided p-value
	Clopidogrel 75 mg (N = 22961)	Placebo (N = 22891)			
Composite endpoint: Death, re-MI or Stroke	2121 (9.2%)	2310 (10.1%)	0.91 (0.86, 0.97)	8.5 (2.8)	0.002
Death	1726 (7.5%)	1845 (8.1%)	0.93 (0.87, 0.99)	5.4 (2.5)	0.029
Nonfatal re-MI[c]	270 (1.2%)	330 (1.4%)	0.81 (0.69, 0.95)	2.7 (1.1)	0.011
Nonfatal stroke[c]	127 (0.6%)	142 (0.6%)	0.89 (0.70, 1.13)	0.7 (0.7)	0.333

[Source: sponsor's clinical study report eff7018.pdf Table(11.1.1) 1]

3.1.2.7 Sponsor's Secondary Efficacy Results

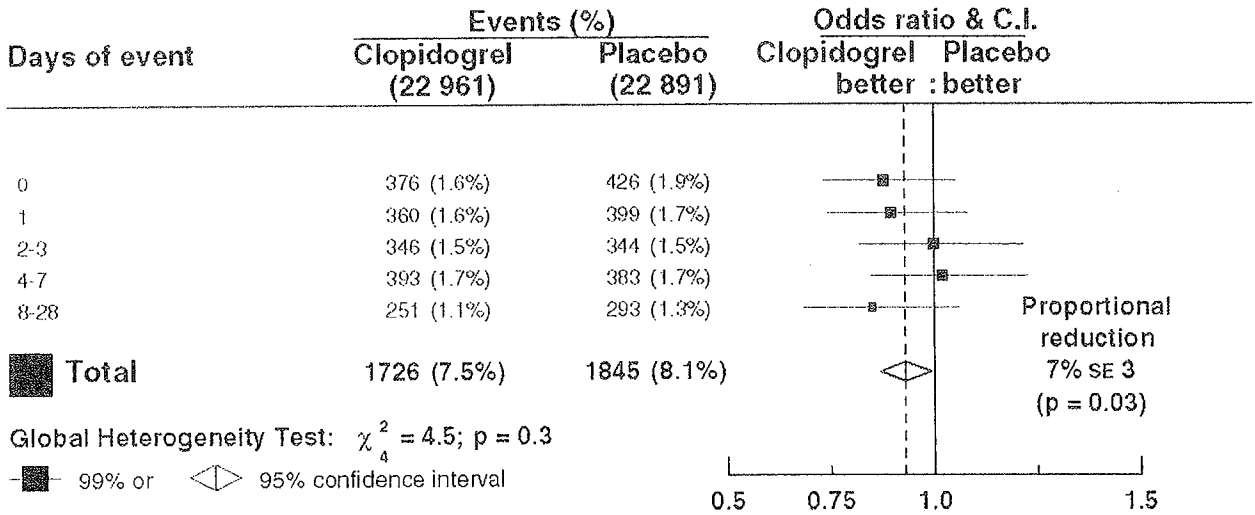
The benefit of clopidogrel 75 mg daily on the primary combined endpoint of death, reinfarction or stroke appeared to emerge rapidly, with a 12% (p = 0.05) proportional reduction on the day of randomization (Day 0 corresponding to an average of 12 hours) (Figure 3). Similar results were observed for the death from any cause co-primary endpoint (
Figure 4). The sponsor stated that the rapidly emerging clopidogrel effect did not differ significantly over the time and it yielded a significant reduction in both co-primary endpoints for an average of about two weeks of treatment.

Figure 3. Summary of Combined Co-primary Endpoint by Day of Event



[Source: the Sponsor's Clinical Study Report on study EFC7018, page 42]

Figure 4. Summary of Co-primary Endpoint of Death from Any Cause by Day of Event



[Source: the Sponsor's Clinical Study Report on study EFC7018, page 43]

3.1.2.8 Reviewer's Results

The reviewer can replicate most of the sponsor's primary efficacy results. The estimate of hazard ratio on composite endpoint is 0.910 with 95% CI (0.858, 0.966). This corresponds to the 9% risk reduction. The Kaplan-Meier estimate of composite event rate at day 28 is 10.9% (95% CI 10.4% — 11.4%) in clopidogrel group and 11.8% (95% CI 11.4% — 12.4%) in control. The estimate of the hazard ratio on all-cause death events is 0.927 with 95% CI (0.868, 0.990), which means 7.3% risk reduction. The Kaplan-Meier estimate of all-cause death rate at day 28 is 9.1% (95% CI 8.6% - 9.6%) in clopidogrel group and 9.7% (95% CI 9.2% -10.2%) in control group. The reviewer obtained p-value of 0.023 in all-cause death events using the log-rank test, which is slightly smaller than the sponsor's result.

The sample size was increased twice from originally planned maximum of 30000 to 40000 then to 48000. There is concern that the study may potentially overpowered. A total of 46000 patients will provide 95% power to detect 10% relative risk reduction based on event rate of 8% in control group at α level of 0.01. In the letter dated on December 5 of 2000, the steering committee requested for a sample size increase. The letter stated "With 40,000 patients, 20,000 allocated active treatment and 20,000 allocated control, these assumptions would lead us to expect about 200-300 fewer deaths with active than with control treatment (e.g. 1800 vs 2000, 2p<0.001, or 1700 vs 2000, 2p<0.0001). Even if the observed difference in mortality was 'only' 150 deaths, it would still be significant (1850 vs 2000, 2p<0.01)."

In addition, even though the sponsor claimed that the decision of sample size increase was based on lower in-hospital mortality by tracking of the blinded event rates, the reviewer is concerned about the potential type I error inflation due to the sample size increase under the condition that the DSMB was unblinded to examine primary endpoints.

To investigate possible inconsistency, this reviewer performed the same primary analyses on the composite endpoint and all-cause mortality for the first 30000 patients recruited and for the added 15852 patients (Table 11 and Table 12). For the composite endpoint, the p-value of log rank test is 0.0558. The Kaplan-Meier estimate of event rates at day 28 are 11.4% (95% CI, 10.8% - 12.0%) for clopidogrel group and 12.0% (95% CI, 11.4% - 12.7%) for control group. Log rank test on all cause mortality shows no statistical significance (p=0.167). On the other hand, the patients recruited later show a significant treatment difference between two groups. The p-value of composite endpoint in log rank test is 0.0054. This means the 15852 patients who were recruited later after sample size increase demonstrated significance between treatment groups by themselves. The hazard ratio of the initial 30000 patient population is noticeably different from the hazard ratio of the 15852 patients recruited later. This is a concern to the reviewer since the sample size increase during the trial also involves DSMB's capability of accessing results of unblinded primary endpoints.

Table 11. Analysis of the Composite Endpoint Based on the First 30000 Patients in COMMIT

Primary efficacy composite endpoint: death, re-MI or stroke	Clopidogrel 300/75 mg N	# of patients reporting events	Placebo N	# of patients reporting events	p value	HR (95% CI)
Final Sample Size of 45852	22961	2121 (9.2%)	22891	2310 (10.1%)	0.002	0.91 (0.86, 0.97)
Initial planned Sample Size of 30000	15029	1474 (9.8%)	14971	1568 (10.5%)	0.056	0.933 (0.869,1.002)
Added 15852 patients	7932	647 (8.2%)	7920	742 (9.4%)	0.005	0.862 (0.772,0.958)

Table 12. Analysis of All-Cause Mortality Based on the First 30000 Patients in COMMIT

Primary efficacy composite endpoint: death, re-MI or stroke	Clopidogrel 300/75 mg N	# of patients reporting events	Placebo N	# of patients reporting events	p value	HR (95% CI)
Final Sample Size of 45852	22961	1726 (7.5%)	22891	1845 (8.1%)	0.029	0.93 (0.87, 0.99)
Initial planned Sample Size of 30000	15029	1171 (7.8%)	14971	1229 (8.2%)	0.167	0.95 (0.87, 1.02)
Added 15852 patients	7932	555 (7.0%)	7920	616 (7.8%)	0.047	0.891 (0.794,0.999)

No significant clopidogrel-metoprolol interaction is found based on the Cox proportional hazards model (p=0.140).

Table 13. Hazard Ratio by Metoprolol

		N	Hazard Ratio	95% CI	p-value
Metoprolol	Yes	22929	0.952	(0.875, 1.036)	0.256
	No	22923	0.871	(0.802, 0.947)	0.001

The summaries of endpoints by day of events provided by the sponsor (Figure 3 and Figure 4) are somewhat inaccurate in the sense that the percentage of events in each period is computed by dividing the total number of events in that period by the total number of patients assigned in each group. The percentages computed this way fail to take the censored patients into account. The correct way of computing the percentages should be dividing the total number of events in the period by the amount of patient exposure.

The hazard functions for clopidogrel and control groups are not constant over time (Figure 6) and the plot seems to suggest that the treatment effect is mostly significant in the first two days (day 0 and day 1). If excluding the patients who censored or had any of the composite events in the first two days, the hazard ratio of clopidogrel group over control group on composite endpoint is

0.923 with 95% CI (0.853, 1.00). The p-value of log-rank test is 0.0484 and p-value of likelihood ratio test in Cox proportional hazards model is 0.0493.

Figure 5. Kaplan-Meier Curve for COMMIT study

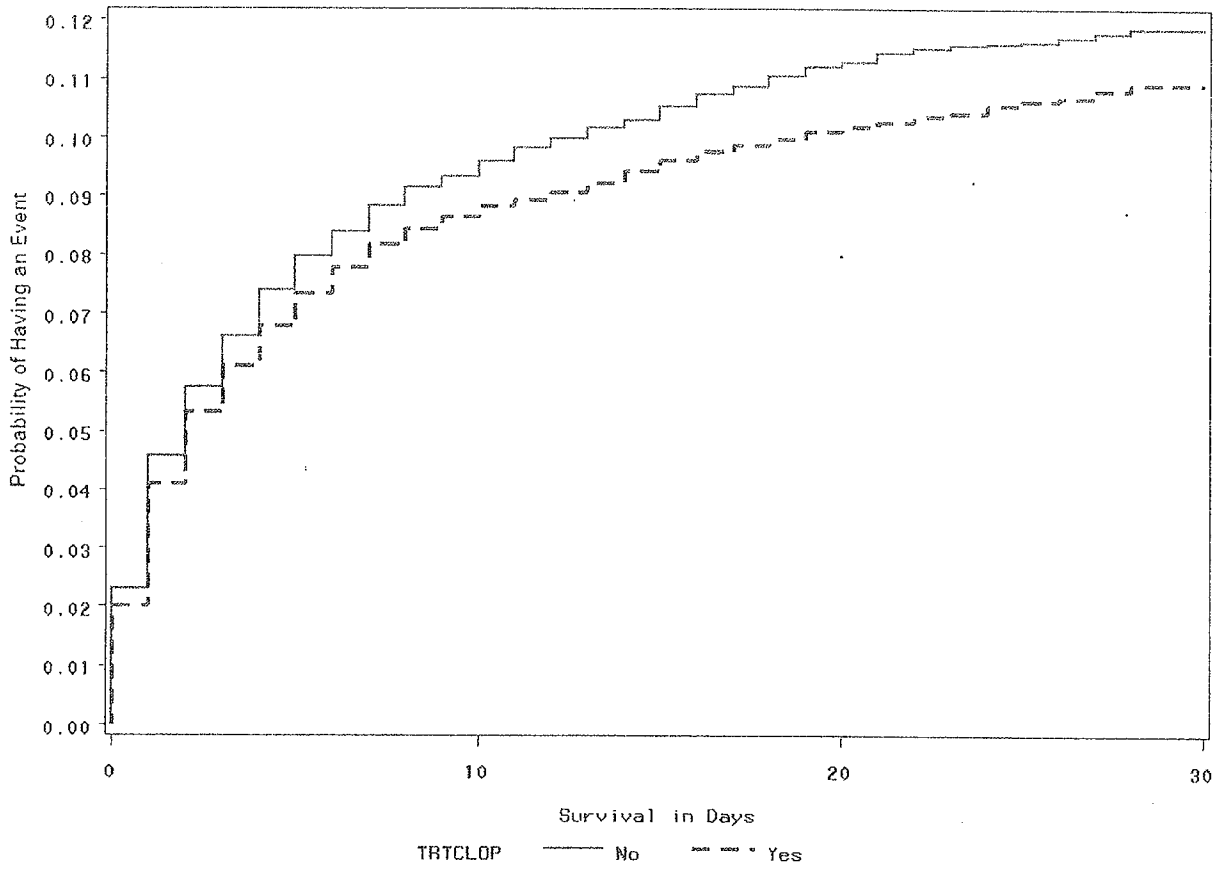
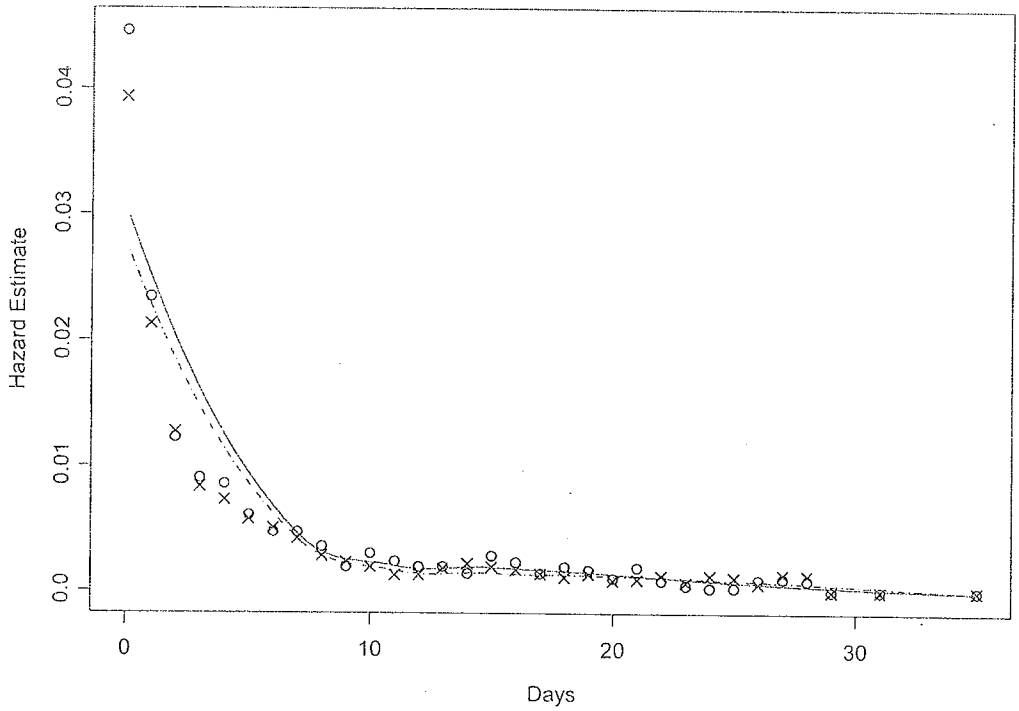


Figure 6. Hazard functions for clopidogrel and placebo groups in COMMIT study



* Red solid line is hazard function for control group, blue dotted line is hazard function for clopidogrel group. Circles are the point estimates of hazard rates in control group, 'x's are point estimates of hazard rates in clopidogrel group (see Appendix A).

Table 14. Summary on Individual Components of the Primary Endpoint in COMMIT

	Plavix (N=22961)	Control (N=22891)	Odds Ratio	95% CI
all MI*	465	538	0.859	(0.734, 0.984)
all stroke*	214	246	0.866	(0.682, 1.050)

* Counts all patients who had MI or stroke events

The p-values in Table 10 are nominal p-values. The protocol and SAP did not pre-specify the hypothesis. In other words, it is unknown whether the sponsor would claim the efficacy of clopidogrel only when both composite endpoint and all cause mortality are significant. If not, there are multiple procedures to control the type I error, which would lead to different conclusions. For example, if Bonferroni test were used, each hypothesis will be tested at alpha level of 0.025 and all-cause mortality will not be considered statistically significant. If sequential gatekeeper procedure or Hochberg procedure were used, both co-primary endpoints will win. Therefore, it is not possible to say whether both endpoints are statistically significant.

3.1.2.9 Conclusions

The reviewer is able to verify the efficacy results of COMMIT study. It is found that the effect of clopidogrel is most significant within the first two days. The hazard functions show that the risk of patients in both clopidogrel and control groups decrease greatly after two or three days in the trial. It is noteworthy that patients in COMMIT were not given any loading dose. Since the primary endpoints in COMMIT are different from the one in CLARITY, the hazard functions are not comparable.

There is potential type I error inflation due to sample size increase under the situation that the DSMB was unblinded on primary endpoints. It is even more worrisome that the hazard ratio of the initial planned 30000 patient population is noticeably different from the hazard ratio of the patients recruited later and the analyses of primary endpoints showed no statistically significance between the treatment groups for the first 30000 patients. The study may also potentially overpowered. A total of 46000 patients will provide 95% power to detect 10% relative risk reduction based on event rate of 8% in control group at α level of 0.01.

The protocol and SAP did not pre-specify the hypothesis. In other words, it is unknown whether the sponsor would claim the efficacy of clopidogrel only when both composite endpoint and all cause mortality are significant. If not, there are multiple procedures to control the type I error, which would lead to different conclusions. Therefore, it is not possible to say whether both endpoints are statistically significant.

No significant clopidogrel-metoprolol interaction is found based on the Cox proportional hazards model.

3.2 Evaluation of Safety

Please see medical reviewer's comments for safety information.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender and Ethnic group

Clopidogrel effect in Study 5133 (CLARITY) is consistent across different race, gender and age subgroups (Table 15, Table 16 and Table 17)

Table 15. Subgroup Analysis in Race on Primary Endpoint Event Rate in CLARITY Study

Treatment	Race	N	Total	Percentage (%)
Clopidogrel	White	1569	236	15.04
	Black	28	3	10.71
	Asian	43	1	2.33
	Other	112	22	19.64
Control	White	1556	338	21.72
	Black	35	6	17.14
	Asian	30	3	10.00
	Other	118	30	25.42

Table 16. Subgroup Analysis in Gender on Primary Endpoint Event Rate in CLARITY Study

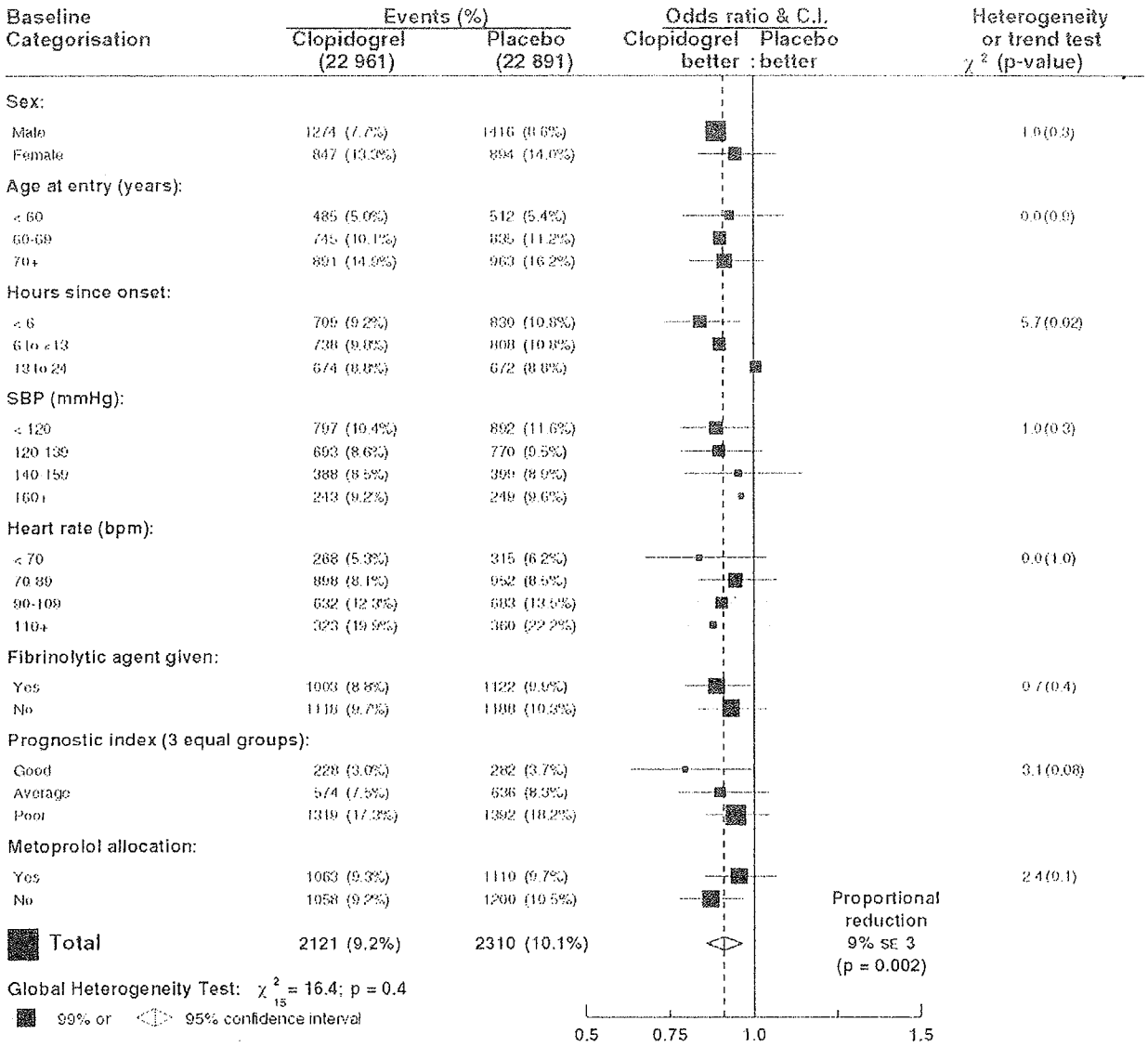
Treatment	Sex	N	Total	Percentage (%)
Clopidogrel	Female	352	59	16.76
	Male	1400	203	14.50
Control	Female	336	83	24.70
	Male	1403	294	20.96

Table 17. Subgroup Analysis in Age on Primary Endpoint Event Rate in CLARITY Study

Treatment	Age	N	Total	Percentage (%)
Clopidogrel	<65	1219	161	13.21
	>=65	533	101	18.95
Control	<65	1252	264	21.09
	>=65	487	113	23.20

Clopidogrel also shows consistent treatment effect across age and gender subgroups in COMMIT study (Figure 7). Due to the fact that the study was conducted in China, no subgroup analysis is conducted on race. It appears that clopidogrel is more effective when patients take the medicine within 13 hours after the onset of acute myocardial infarction. Also clopidogrel appears to show a smaller or no effect on patients with high systolic blood pressure (SBP>140).

Figure 7. Summary of Subgroup Analyses on Combined Coprimary Endpoint in COMMIT Study



[Source: Sponsor's clinical study report eff7018.pdf Figure (11.1.3) 1]

Table 18. Subgroup Analyses on Age and Gender in COMMIT

		Treatment		Placebo	
		N	Total events	N	Total events
Age	<65	13009	769	12921	865
	>65	9952	1352	9970	1445
Gender	male	16595	1274	16498	1416
	female	6366	847	6393	894

4.2 Other Subgroup Populations

About 56% patients in CLARITY went through Percutaneous transluminal coronary angioplasty (PTCA). Subgroup analysis was conducted to examine the consistency of primary efficacy results in patients who had PTCA versus patients who had not (Table 19).

Table 19. Subgroup Analysis on Patients Who Had PTCA versus Patients Who Had Not in CLARITY

	Clopidogrel		Placebo			
	N	Patients Reporting Endpoint	N	Patients Reporting Endpoint	p-value	OR
With Angioplasty	964	147	966	222	<0.001	0.66
No Angioplasty	788	115	773	155	0.007	0.73
Total	1752	262	1739	377	<0.001	0.64

A total of 132 patients are considered to have angioplasty before angiography. Out of the 132 patients, 90 patients had angioplasty in the same day of angiography but with missing time of angioplasty and therefore were assumed to receive angioplasty before angiography. If excluding the patients who received angioplasty before angiography, 288 out of 1571 patients in control group had occluded IRA from angiography and 181 out of 1572 patients in clopidogrel group had occluded IRA. The result is consistent with the ITT population.

Regional analysis in CLARITY shows that most countries except Canada and Austria in the study have consistent treatment effect (Table 20).

Table 20. Regional Analysis in CLARITY

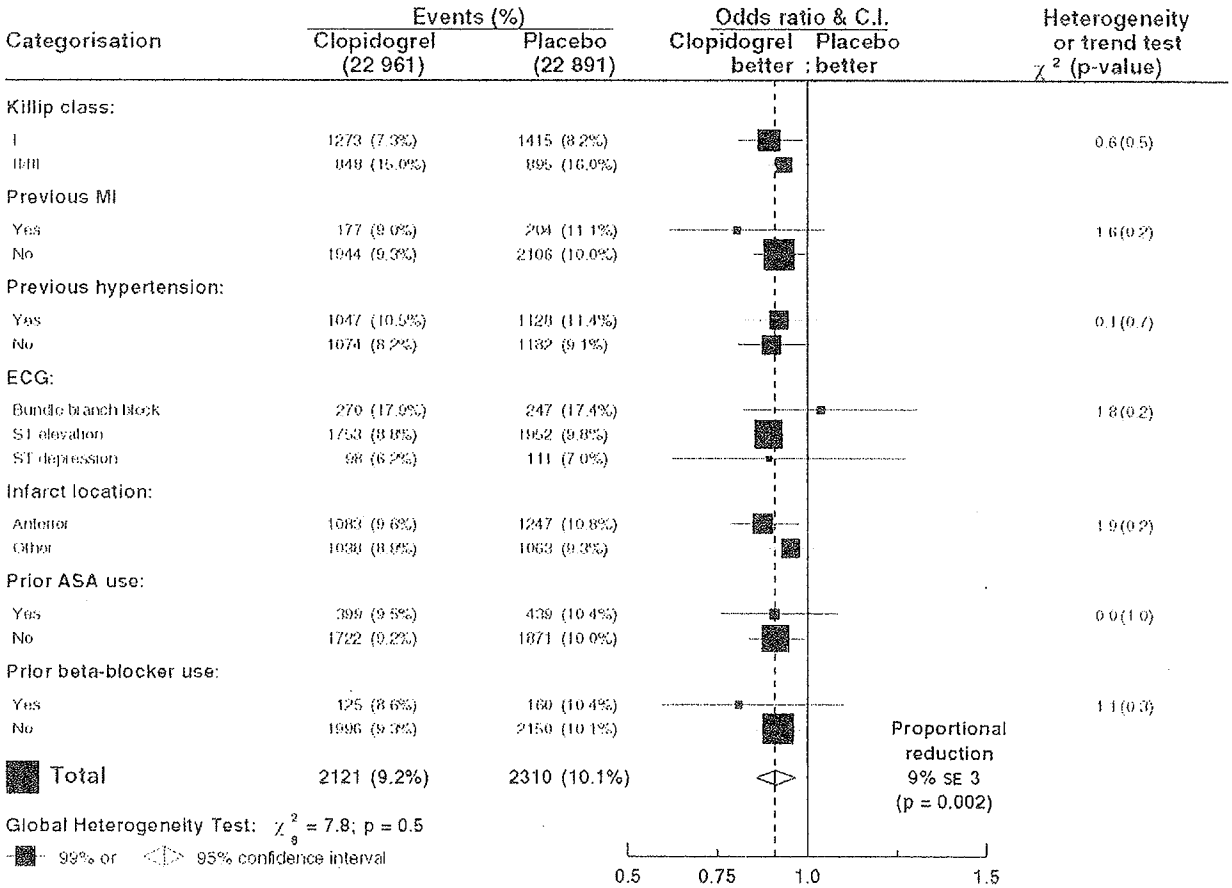
Country	Treatment	N	Total Events
Argentina	Clopidogrel	67	12
Argentina	Placebo	68	20
Australia	Clopidogrel	28	2
Australia	Placebo	30	8
Austria	Clopidogrel	39	9
Austria	Placebo	39	6
Belgium	Clopidogrel	121	21
Belgium	Placebo	120	23
Brazil	Clopidogrel	97	14
Brazil	Placebo	99	27
Canada	Clopidogrel	133	19
Canada	Placebo	127	18
France	Clopidogrel	131	24
France	Placebo	133	31
Germany	Clopidogrel	105	19
Germany	Placebo	106	25
Hungary	Clopidogrel	29	3
Hungary	Placebo	28	4

Country	Treatment	N	Total Events
Ireland	Clopidogrel	23	3
Ireland	Placebo	25	4
Israel	Clopidogrel	99	11
Israel	Placebo	99	20
Italy	Clopidogrel	66	7
Italy	Placebo	62	13
Mexico	Clopidogrel	72	14
Mexico	Placebo	68	21
Netherlands	Clopidogrel	88	12
Netherlands	Placebo	86	21
Poland	Clopidogrel	52	8
Poland	Placebo	50	12
Portugal	Clopidogrel	11	1
Portugal	Placebo	9	2
Russia	Clopidogrel	116	24
Russia	Placebo	121	32
South Africa	Clopidogrel	34	3
South Africa	Placebo	33	5
Spain	Clopidogrel	179	25
Spain	Placebo	185	39
Sweden	Clopidogrel	65	7
Sweden	Placebo	67	12
Turkey	Clopidogrel	11	0
Turkey	Placebo	12	2
United Kingdom	Clopidogrel	104	13
United Kingdom	Placebo	101	18
United States	Clopidogrel	82	11
United States	Placebo	71	14

COMMIT was conducted in China with 100% population of Chinese. Therefore, no regional analysis was performed in COMMIT.

Figure 8 summarizes some additional exploratory subgroup analyses on the combined coprimary endpoint.

Figure 8. Summary of Additional Subgroup Analyses on the Combined Coprimary Endpoint in COMMIT Study



[Source: Sponsor's clinical study report eff7018.pdf Figure (11.1.3) 2]

The sponsor reported about 10% patients in both clopidogrel and placebo groups who took non-trial antiplatelet agents. These patients should not be included in the analysis. If those patients are excluded from the analysis, the estimate of the hazard ratio on the composite endpoint is 0.893 with 95% CI (0.840, 0.951). The result is consistent with the primary efficacy results.

Clopidogrel also shows a significant treatment effect when patients with no confirmed MI are excluded from the analysis (p-value=0.002). The estimate of the hazard ratio on the composite endpoint is 0.910 with 95% confidence interval of (0.857, 0.966).

Compared to CLARITY study, a much lower percentage of patients (54.5%) took a fibrinolytic agent in COMMIT. The subgroup analysis conducted by the sponsor shows that clopidogrel has no significant treatment effect among patients who did not take a fibrinolytic agent (Table 21). Reviewer has similar results in some additional subgroup analyses listed in Table 21. It is noted that the primary composite event rate showed consistent numeric trend across subgroups (Figure 7 and Figure 8). Clopidogrel appears to be less effective when given more than 12 hours after the onset of symptoms and appears to have a smaller than additive effect on top of metoprolol.

Table 21. Additional Subgroup Analyses in COMMIT

		N	Hazard Ratio	95% CI	p-value
Fibrinolytic Agent	Yes	22794	0.887	(0.814, 0.966)	0.006
	No	23058	0.933	(0.859, 1.012)	0.094
Hypertension	Yes	19838	0.923	(0.848, 1.004)	0.061
	No	26014	0.899	(0.828, 0.977)	0.012
hours since onset	<6 hour	15459	0.843	(0.762, 0.931)	<0.001
	6 hour - <13 hour	15065	0.902	(0.816, 0.997)	0.043
	>=13 hour	15328	1.004	(0.902, 1.118)	0.938
Location of MI	Anterior alone	22829	0.875	(0.806, 0.949)	0.001
	Inferior alone	12956	0.97	(0.854, 1.103)	0.645
	Other	10067	0.942	(0.839, 1.057)	0.306
Metoprolol	Yes	22929	0.952	(0.875, 1.036)	0.256
	No	22923	0.871	(0.802, 0.947)	0.001

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The hazard rate in COMMIT study is not constant over the time. Instead the hazard functions show that the risk of patients in both clopidogrel and control groups decrease greatly after two or three days in the trial. Patients in COMMIT were not given any loading dose. Also the treatment effect seems most significant in the first two days and it appears to be the driving force of the efficacy results in COMMIT study.

The COMMIT study has two co-primary endpoints, but the protocol and SAP did not pre-specify the hypothesis. In other words, it is unknown whether the sponsor would claim the efficacy of clopidogrel only when both composite endpoint and all cause mortality are significant. If not, there are multiple procedures available to control the type I error, which would lead to different conclusions. Therefore, it is not possible to say whether both endpoints are statistically significant.

COMMIT may potentially be overpowered. A total of 46000 patients will provide 95% power to detect 10% relative risk reduction based on event rate of 8% in control group at α level of 0.01.

Both the CLARITY and COMMIT trials increased sample size during the trial. There is some concern on the potential type I error inflation since DSMB of both trials were either partially unblinded or completely unblinded to the primary endpoints. No interim analysis result was reported in the clinical study report.

Since the p-value of the primary composite endpoint in CLARITY is extremely small, the adverse impact of the sample size increase at this level on the type I error rate is not expected to be large enough to make the statistical significance of this p-value go away. The exploratory analyses using original sample size (2200 patients) showed statistical significance in the primary composite endpoint. Thus in my view, the primary efficacy endpoint is statistically significant.

The sample size increase in COMMIT trial is worrisome. The hazard ratio of the initial planned 30000 patient population is noticeably different from the hazard ratio of the patients recruited later and the analyses of primary endpoints showed no statistical significance between the treatment groups for the first 30000 patients.

The primary efficacy result of CLARITY appears to be driven by occluded IRA events. Death and recurrent MI only count for a small portion of the composite events. In addition, death events in the two treatment groups go to the opposite direction of the primary efficacy results.

5.2 Conclusions and Recommendations

The two trials (CLARITY and COMMIT) showed significant results on primary efficacy endpoints using clopidogrel in treating patients with ST-elevation myocardial infarction.

The treatment effect seems most significant in the first two days in COMMIT study. The primary endpoints in COMMIT are statistically significant. However, the study may be overpowered and the sample size increase during the trial is a concern to the reviewer. Specifically, the initial planned 30000 patient population is noticeably different from the patients recruited later in hazard ratio and the analyses of primary endpoints showed no statistical significance between the treatment groups for the first 30000 patients. It is also noted that the DSMB was unblinded to the primary endpoints.

The primary efficacy result of CLARITY appears to be driven by occluded IRA events. It is uncertain whether CLARITY provides enough evidence and whether the nominal p-values in COMMIT support the efficacy claim.

Appendix A

The hazard function plot Figure 1 are made as follows: The estimate of the hazard rate for treatment/placebo group is calculated as the number of composite primary events occurring in the treatment/placebo group in each day divided by the total patient time in that day. The plot was made in Splus. The hazard functions are plotted by fitting a local regression model.

Figure 2 and Figure 6 are plotted similarly except that the number of events in each day includes death and MI events in Figure 2 and the number of composite events in each day counts death, reinfarction or stroke and all cause mortality in Figure 6.

```
# dot for placebo, cross for treatment
plot(data0$day, data0$hazardest, xlab="Months", ylab="Hazard Estimate")
predP<-predict.loess(loess(hazardest~day, data0,
   degree=1),newdata=data.frame(day=c(1:350)/10))
lines(c(1:350)/10,predP,type="l", col=3)
for (i in 1:length(data1$day))
{
   points(data1$day[i],data1$hazardest[i],pch=4)
}
predT<-predict.loess(loess(hazardest~day, data1, degree=1),
   newdata=data.frame(day=c(1:350)/10))
lines(c(1:350)/10,predT,type="l", col=2)
```

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

/s/

Jialu Zhang
4/27/2006 09:45:12 AM
BIOMETRICS

John Lawrence
4/27/2006 09:48:27 AM
BIOMETRICS

James Hung
4/27/2006 09:50:53 AM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-839 / S-034

OTHER REVIEW(S)

MEMORANDUM

To: Meg Pease-Fye, MS
Division of Cardiovascular and Renal Products

From: Iris Masucci, PharmD, BCPS
DDMAC

Date: April 4, 2006

Re: Comments on draft labeling for Plavix (clopidogrel) tablets
NDA 20-839/S-034

I have reviewed the proposed label for Plavix for the new indication of ST-elevation MI and offer the following comments.

Clinical Studies

1. Figure 4

   This figure presents results only for the composite endpoint. When composite endpoints are used, all components of the composite should be presented, as is recommended in the newly finalized guidance on the Clinical Studies section of labeling. We suggest that a table be used, instead of the histogram, which presents all components of the composite.

2. [redacted] b(4)

   Is this statement on the subgroup analyses adequately supported? If not, we recommend deletion.

3. *"As shown in Table 3 and Figures 5 and 6 below, PLAVIX significantly reduced the relative risk of death from any cause by 7% (p = 0.029), and the relative risk of the combination of reinfarction, stroke or death by 9% (p = 0.002)."*

   As recommended in the guidance, the absolute risk reductions (0.9% and 0.6%) should be presented along with the relative risk reductions. Relative risk reductions alone can be misleading and overstate the drug's benefits.

4. Table 3

The presentation of the composite endpoint and its components is somewhat confusing. It appears that the two co-primary endpoints are in bolded type, and the three composite components are listed in the second row of the table. For clarity, we suggest a presentation that more clearly identifies the components of the composite and that easily identifies the main outcome measures of the study, e.g.:

*Composite endpoint: Death, MI, or Stroke
*Death
Non-fatal MI
Non-fatal Stroke
* denotes co-primary endpoints

This table presents p-values for all three components of the composite endpoint. Does the study design and analysis plan allow for the presentation of p-values for all of these? If not, we recommend deletion of the p-values for non-fatal MI and stroke.

5. Figures 5 and 6

Are these figures presenting cumulative event rates truly additive to the main presentation of the study results? If not, we recommend deletion.

6. [redacted] b(4)

Is the statement about benefits being evident as early as [redacted] adequately supported by the data? If not, we recommend deletion.

7. Figure 7

This figure on subgroups includes a column for [redacted] b(4)
[redacted] Is the inclusion of these values appropriate here? We note that Figure 3 for the CURE study does not include them.

Indications and Usage

1. *"For patients with ST-segment elevation acute myocardial infarction, PLAVIX has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction or stroke."*

Does this statement accurately capture all the results from both studies? It appears to reflect specifically the endpoints from the COMMIT study. Are the CLARITY results adequately reflected here?

Are we comfortable with the "death from any cause" portion of the indication? It is also somewhat confused by the introductory statement for all the indications saying that "Plavix is indicated for the reduction of atherothrombotic events as follows:" Does "death from any cause" accurately fall under this heading?

Is it important to note in the indication that patients in the studies also may have received thrombolytics, e.g., "For patients with ST-segment elevation acute MI, including those receiving thrombolytics, Plavix has been shown..."?

Precautions – Drug Interactions

1. *"In addition to the above specific interaction studies, patients entered into clinical trials with PLAVIX received a variety of concomitant medications including* ***diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents*** *(including* ***insulin),*** ***thrombolytics, heparins*** *(unfractionated and LMWH),* ***GPIIb/IIIa antagonists, antiepileptic agents*** *and* ***hormone replacement therapy*** *without evidence of clinically significant adverse interactions."*

We recommend changing "hormone replacement therapy" to "estrogen and estrogen/progestin products." The Division of Reproductive and Urologic Products no longer uses the term "hormone replacement therapy" when describing these drugs (see the January 31, 2003 Federal Register announcement of the draft guidance on the clinical evaluation of estrogen and estrogen/progestin products for details).

Adverse Reactions

1. *"The overall rate of noncerebral major bleeding or cerebral bleeding in COMMIT was low and similar in both groups as shown in Table 5 below."*

To say that the rate of bleeding was "low and similar in both groups" is promotional in tone. We recommend deletion. The sentence can be rewritten to say simply that the results are presented below.

2. Table 5

We recommend deletion of the p-values presented in this table for each bleeding category in the COMMIT study. In general, p-values are not presented with adverse event rates unless they were pre-specified endpoints in a study specifically designed to evaluate safety.

3. Neutropenia, GI, and Rash subsections

We note the deletion of the sections describing these adverse events. Are they adequately captured elsewhere in this section?

4. *"No additional clinically relevant events to those observed in CAPRIE with a frequency*

≥2.5%, have been reported during the CURE, CLARITY and COMMIT controlled studies."

Is this statement adequately supported? If not, we recommend deletion.

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

/s/

Iris Masucci
4/6/2006 02:30:04 PM
DDMAC REVIEWER

RHPM Overview
NDA 20-839/SE-1-034
Plavix (clopidogrel bisulfate) 75 mg Tablets

Sponsor:	Sanofi-Aventis
Classification:	Priority
Submission Date:	November 17, 2005
Receipt Date:	November 17, 2005
User Fee Goal Date:	May 17, 2006, extended to August 17, 2006

Background
Plavix was originally approved on November 17, 1997, based on the CAPRIE study, for the reduction of atherosclerotic events (myocardial infarction, stroke, and vascular death) in patients with atherosclerosis documented by recent stroke, recent myocardial infarction, or established peripheral arterial disease. On February 27, 2002, Plavix was approved for Acute Coronary Syndrome (ACS) based on the findings of the CURE study. This supplemental application proposes a new indication for Plavix in patients with ST-elevation myocardial infarction (STEMI), based on the findings of the COMMIT and CLARITY studies.

A teleconference was held with Sanofi on May 11, 2006 (prior to the original PDUFA goal date) to alert them to the following issues:

- CLARITY contributes little support for the proposed indication, since its success was mostly attributable to effects on the patency of the infarct-related artery, which is not an accepted surrogate.
- COMMIT is of questionable relevance to the U.S. patient care setting. The major differences in medical practice between these countries are the prevalence of PCI, choice of thrombolytics, and use of anti-lipid drugs. The Agency requested additional information and relevant literature to summarize why these aspects of care are not relevant to the effectiveness of clopidogrel in other settings.
- An interaction between clopidogrel and metoprolol was noted in the COMMIT study. Additional information was requested.
- The results of COMMIT appear to be different in the first 30,000 subjects (initial planned enrollment) and the last 15,000.

The Division requested additional information to address these issues. The Division and Sanofi agreed that this information would constitute a major amendment and would extend the PDUFA goal date until August 17, 2006.

User Fee
The user fee for this application was paid in full prior to the submission of the application.

Labeling
The original submission contains proposed draft labeling revised to include the new indication as well as changes to other sections of the package insert that reflect the findings of the COMMIT and CLARITY studies.

Correspondence and meetings

1. July 21, 2005 meeting - Format and content of the sNDA were discussed
2. May 11, 2006 teleconference – Issues leading to a Major Amendment to extend the PDUFA date were discussed
3. August 17, 2006 Action Letter – approval letter was issued to Sanofi
4. August 17, 2006 General advice letter – issued to explain that another action letter would be issued due to an error in the labeling attached to the first approval letter
5. August 17, 2006 2nd Action Letter – issued with correct wording in the label

Divisional Memo

In his memo dated August 28, 2006, Dr. Stockbridge stated that because arterial patency does not necessarily predict clinical benefit, CLARITY results are supportive, but that COMMIT was the primary basis for the regulatory decision. He noted that the major question with COMMIT was whether the effects were likely to apply to the US setting. He concluded that the data were persuasive that the effects seen in COMMIT, supported by CLARITY, were relevant to the US, in a setting of STEMI when PCI is not imminent.

Medical Review

In her initial review dated May 5, 2006, Dr. Lemtouni noted that neither COMMIT nor CLARITY supported Sanofi's claim that clopidogrel reduces risk of negative outcomes of STEMI in optimally treated population. The addition of clopidogrel would not add clinical benefit on top of other medical management practices in the US. Further, the CLARITY study was inconclusive because the primary composite endpoint was driven by arterial patency, and there was no significant difference between clopidogrel and placebo in death or recurrent MI. Although COMMIT met its primary endpoint (composite of death, recurrent MI, stroke and all-cause mortality), the study was performed in a 100% Chinese population and in China. Dr. Lemtouni questioned the medical setting and the similarity of results to the US setting.

In her subsequent review, dated July 12, 2006, Dr. Lemtouni concluded that clopidogrel does seem to have an extra benefit even in patients who are optimally treated with "state of the art" management therapies. She still found the results of CLARITY to be inconclusive with regard to clinical benefit for patients with STEMI and noted adverse trends for death, myocardial rupture and hemopericardium, although there does seem to be a beneficial trend on mortality and re-infarction. Pertinent to COMMIT, Dr. Lemtouni noted differences in medical management in this setting between the US and Chinese populations; timing of the study drug intake relative to the beginning of symptoms, rate of PTCA implementation, and the omission of loading dose in China.

Statistical Review

In her review dated April 27, 2006, Dr. Zhang summarized the submitted studies:

> CLARITY involved 319 study centers in 23 countries. A total of 3491 patients were randomized to a double-blinded treatment and included in the efficacy analysis. Eligible patients were randomized in a double-blind manner to receive either clopidogrel or matching placebo. All patients were also to receive fibrinolytic therapy initially and also daily ASA for the duration of the study. The primary efficacy endpoint was analyzed using a logistic regression analysis with terms included for treatment group, type of fibrinolytic, type of anticoagulant used up to 2 hours

post-randomization, and infarct location. Sample size was increased twice due to lower than expected event rate.

The objective of the two trials is to support the extension of clopidogrel use in patients with ST-elevation myocardial infarction (STEMI). CLARITY is a multinational, randomized, double-blind, placebo-controlled, 2 parallel group study comparing clopidogrel plus acetylsalicylic acid (ASA) versus ASA alone. 300 mg loading dose of clopidogrel was given to the patients in clopidogrel group in CLARITY on the day of randomization and followed by 75 mg daily doses.

COMMIT is a multi-center, randomized, double-blind, placebo-controlled, 2 x 2 factorial design study in patients with suspected acute MI receiving daily ASA (162 mg) or 75 mg/day clopidogrel with ASA. No loading dose of clopidogrel was given.

She made the following conclusions:

The two trials (CLARITY and COMMIT) showed significant results on primary efficacy endpoints using clopidogrel in treating patients with ST-elevation myocardial infarction.

The treatment effect seems most significant in the first two days in COMMIT study. The primary endpoints in COMMIT are statistically significant; however, the study may be overpowered and the sample size increase during the trial is of concern. Specifically, the initial planned 30000 patient population is noticeably different from the patients recruited later in hazard ratio and the analyses of primary endpoints showed no statistical significance between the treatment groups for the first 30000 patients. It is also noted that the DSMB was unblinded to the primary endpoints.

The primary efficacy result of CLARITY appears to be driven by occluded IRA events. It is uncertain whether CLARITY provides enough evidence and whether the nominal p-values in COMMIT support the efficacy claim.

Dr. Lemtouni also reviewed the submitted financial disclosure statement and found it acceptable.

Environmental Assessment
Drs. Ganunis, Bguyen and Chidambaram reviewed the submitted environmental assessment and found it acceptable.

Division of Scientific Investigations
Investigation of five sites in China was performed and FDA 483s were issued to all sites. Dr. Gan noted all deviations and findings in his review dated May 5, 2006. He concluded that there was sufficient documentation to assure that audited patients did exist, study eligibility criteria were fulfilled, participant received assigned study drugs, adverse events were reported properly, and primary endpoints were captured according to the protocol. He also noted concerns about possible sample size manipulations but found no evidence.

Pediatrics
The Division granted a full waiver of pediatric studies in the indication of ST-segment elevation Acute Myocardial Infarction in a letter dated October 24, 2005.

Labeling
The Sponsor submitted annotated proposed labeling and was reviewed by DDMAC on April 6, 2006. Comments were provided.

CSO Summary
An approval letter was drafted for Dr. Stockbridge's signature.

Meg Pease-Fye, M.S.
Regulatory Health Project Manager
August 28, 2006

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

/s/

Margaret Pease-Fye
9/5/2006 01:48:28 PM
CSO

77 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

___√___ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-839 / S-034

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Because health matters

Patent Department

Central Document Room
Center for Drug Evaluation and Research
Food & Drug Administration
5901-B Ammendale Rd.,
Beltsville, MD 20705-1266

November 17, 2005
CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Dear Sirs,

PATENT INFORMATION

Re: NDA 20-839 Supplement – Acute Myocardial Infarction; Submission of Patent Information for PLAVIX™

The undersigned submits Patent Information including completed Forms FDA 3542a for three patents. These forms relate to U.S. Patents Nos. 4,847,265, 6,429,210, and 6,504,030.

Pursuant to 21 C.F.R. § 314.53(d)(4), two complete copies are attached: one for the Chemistry, Manufacturing and Controls section of the review copy of the supplemental NDA, and one to be used as an archival copy. This Patent Information is submitted pursuant to 21 C.F.R. § 314.53(c) and (d)(2).

If you should have any questions, please contact me.

Best Regards,

Lee Caffin
Aventis Pharmaceuticals, Inc.
1041 Route 202-206, P.O. Box 6800
Bridgewater, NJ 08807-0800
Telephone: 908-541-5460
Fax: 908-231-2626
Encl. (6)

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-839 Supplement: Acute Myocardial Infarction

NAME OF APPLICANT / NDA HOLDER
Sanofi-Synthelabo Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
PLAVIX

ACTIVE INGREDIENT(S)	STRENGTH(S)
clopidogrel bisulfate	75 mg

DOSAGE FORM
Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
4,847,265	7/11/1989	11/17/2011

d. Name of Patent Owner	Address *(of Patent Owner)*	
Sanofi-Aventis	174 Avenue de France	
	City/State: 75013 Paris	
	ZIP Code: FRANCE	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
Gerald V. Dahling Vice President, Global Patent Litigation	1041 Route 202-206 – P.O. Box 6800	
	City/State: Bridgewater, NJ	
	ZIP Code: 08807-0800	FAX Number *(if available)*: 908-231-4738
	Telephone Number: 908-231-4562	E-Mail Address *(if available)*: gerald.dahling@sanofi-aventis.com

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Lee Caffin	11/17/2005

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Lee Caffin	
Address Aventis Pharmaceuticals Inc. 1041 Route 202-206 – P.O. Box 6800	City/State Bridgewater, New Jersey
ZIP Code 08807-0800	Telephone Number 908-541-5460
FAX Number *(if available)* 908-231-2626	E-Mail Address *(if available)* lee.caffin@sanofi-aventis.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.htm*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Notes to Form FDA 3542a for U.S. Patent 4,847,265 submitted for NDA 20-839 (PLAVIX®) (Supplemental – Acute Myocardial Infarction)

Note to Question 2.2: U.S. Patent No. 4,847,265 claims the active ingredient of the drug product PLAVIX® as a compound, and these claims are not limited to specific polymorphic forms. However, the patent does not specifically claim any particular polymorph of the active ingredient, and therefore the answer to Question 2.2 is "no".

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER
20-839 Supplement: Acute Myocardial Infarction

NAME OF APPLICANT / NDA HOLDER
Sanofi-Synthelabo Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
PLAVIX

ACTIVE INGREDIENT(S)	STRENGTH(S)
clopidogrel bisulfate	75 mg

DOSAGE FORM
Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,429,210	8/6/2002	6/10/2019

d. Name of Patent Owner
Sanofi-Aventis

Address *(of Patent Owner)*
174 Avenue de France

City/State
75013 Paris

ZIP Code
FRANCE

FAX Number *(if available)*

Telephone Number

E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

☞ Gerald V. Dahling
Vice President, Global Patent Litigation

Address *(of agent or representative named in 1.e.)*
1041 Route 202-206 – P.O. Box 6800

City/State
Bridgewater, NJ

ZIP Code
08807-0800

FAX Number *(if available)*
908-231-4738

Telephone Number
908-231-4526

E-Mail Address *(if available)*
gerald.dahling@sanofi-aventis.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Lee Caffin	11/17/2005

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Lee Caffin	
Address Aventis Pharmaceuticals Inc. 1041 Route 202-206 – P.O. Box 6800	City/State Bridgewater, New Jersey
ZIP Code 08807-0800	Telephone Number 908-541-5460
FAX Number *(if available)* 908-231-2626	E-Mail Address *(if available)* lee.caffin@sanofi-aventis.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.htm*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER
20-839 Supplement: Acute Myocardial Infarction

NAME OF APPLICANT / NDA HOLDER
Sanofi-Synthelabo Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
PLAVIX

ACTIVE INGREDIENT(S)	STRENGTH(S)
clopidogrel bisulfate	75 mg

DOSAGE FORM
Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,504,030	1/7/2003	6/10/2019

d. Name of Patent Owner
Sanofi-Aventis

Address *(of Patent Owner)*
174 Avenue de France

City/State
75013 Paris

ZIP Code
FRANCE

FAX Number *(if available)*

Telephone Number

E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Gerald V. Dahling
Vice President, Global Patent Litigation

Address *(of agent or representative named in 1.e.)*
1041 Route 202-206 – P.O. Box 6800

City/State
Bridgewater, NJ

ZIP Code
08807-0800

FAX Number *(if available)*
908-231-4738

Telephone Number
908-231-4526

E-Mail Address *(if available)*
gerald.dahling@sanofi-aventis.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☒ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

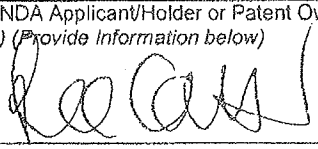
5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	11/17/2005

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Lee Caffin	
Address Aventis Pharmaceuticals Inc. 1041 Route 202-206 – P.O. Box 6800	City/State Bridgewater, New Jersey
ZIP Code 08807-0800	Telephone Number 908-541-5460
FAX Number *(if available)* 908-231-2626	E-Mail Address *(if available)* lee.caffin@sanofi-aventis.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-839 Supplement: Acute Myocardial Infarction

NAME OF APPLICANT / NDA HOLDER
Sanofi-Synthelabo Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
PLAVIX

ACTIVE INGREDIENT(S)	STRENGTH(S)
clopidogrel bisulfate	75 mg

DOSAGE FORM
Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
4,847,265	7/11/1989	11/17/2011

d. Name of Patent Owner
Sanofi-Aventis

Address *(of Patent Owner)*
174 Avenue de France

City/State
75013 Paris

ZIP Code
FRANCE

FAX Number *(if available)*

Telephone Number

E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Gerald V. Dahling
Vice President, Global Patent Litigation

Address *(of agent or representative named in 1.e.)*
1041 Route 202-206 – P.O. Box 6800

City/State
Bridgewater, NJ

ZIP Code
08807-0800

FAX Number *(if available)*
908-231-4738

Telephone Number
908-231-4562

E-Mail Address *(if available)*
gerald.dahling@sanofi-aventis.com

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

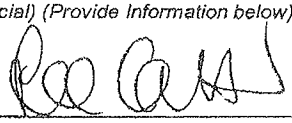
5. No Relevant Patents

	For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	11/17/2005

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Lee Caffin	
Address Aventis Pharmaceuticals Inc. 1041 Route 202-206 – P.O. Box 6800	City/State Bridgewater, New Jersey
ZIP Code 08807-0800	Telephone Number 908-541-5460
FAX Number *(if available)* 908-231-2626	E-Mail Address *(if available)* lee.caffin@sanofi-aventis.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Notes to Form FDA 3542a for U.S. Patent 4,847,265 submitted for NDA 20-839 (PLAVIX®) (Supplemental – Acute Myocardial Infarction)

Note to Question 2.2: U.S. Patent No. 4,847,265 claims the active ingredient of the drug product PLAVIX® as a compound, and these claims are not limited to specific polymorphic forms. However, the patent does not specifically claim any particular polymorph of the active ingredient, and therefore the answer to Question 2.2 is "no".

PATENT INFORMATION

Pursuant to 21 CFR 314.53(d)(4) the patent information for this supplement is being submitted concurrently herewith by separate letter addressed to the Central Document Room.

REQUEST FOR EXCLUSIVITY

Pursuant to 21 U.S.C. 355(c)(3)(D)(iv) and (j)(4)(D)(iv), and under the provisions of 21 CFR 314.108(b)(5), applicant hereby claims a period of exclusivity of three years from the date of approval of this supplemental application (sNDA) for the use of clopidogrel bisulfate for the reduction of atherothrombotic events in patients with Acute MI ST-segment elevation.

In support of the instant sNDA, applicant has conducted two clinical investigations (the CLARITY and COMMIT studies) under investigational new drug application IND 34,663 and certifies that, to the best of its knowledge, said clinical investigation is a new clinical investigation, the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by FDA to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product.

Applicant further certifies that a thorough search of the scientific literature has been conducted for all published studies or publicly available reports of clinical investigations relevant to the use of clopidogrel bisulfate for the reduction of atherothrombotic events in patients with Acute MI ST-segment elevation.and that no relevant studies or reports were found. Accordingly, in applicant's opinion and to the best of its knowledge no publicly available information exists to support the approval of the use of clopidogrel bisulfate in the indication for which applicant is seeking approval except for the new clinical investigation included in the instant sNDA. The new clinical investigation is therefore essential to approval of this sNDA.

EXCLUSIVITY SUMMARY

NDA # 20-839 SUPPL # 034 HFD # 110

Trade Name Plavix

Generic Name clopidogrel bisulfate

Applicant Name Sanofi-Aventis

Approval Date, If Known August 17, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE-1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

EFC5133 CLARITY-TIMI 28
EFC7018 COMMIT/CCS-2

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

Not Applicable

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

EFC5133 CLARITY-TIMI 28
EFC7018 COMMIT/CCS-2

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 34,663	YES ☒	! NO ☐
		! Explain:
Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:
Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Meg Pease-Fye, M.S.
Title: Regulatory Health Project Manager
Date: August 29, 2006

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.
Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Margaret Pease-Fye
8/29/2006 12:17:54 PM

Norman Stockbridge
8/29/2006 01:04:57 PM

PEDIATRIC DEFERRAL STATEMENT

The Sponsor has submitted a request to IND 34,663 for a full waiver (all pediatric age groups) of the pediatric study requirements as specified in 21 CFR 314.55(c) for Plavix (clopidogrel bisulfate) in the indication of ST-segment elevation Acute Myocardial Infarction (14 October 2005; SN 0589).

The Division responded on 24 October 2005 to the sponsor's request and agreed that a waiver is justified for Plavix for the reduction of atherothrombotic events (death, re-infarction, or stroke) in patients with ST segment elevation acute myocardial infarction for the entire pediatric population. A copy of the waiver approval is included in the current submission. (Item 20 Other).

NDA 20-839/S-034

Pediatric Page

PEDIATRIC DEFERRAL STATEMENT

Sanofi submitted a request to IND 34,663 for a full waiver (all pediatric age groups) of the pediatric study requirements as specified in 21 CFR 314.55(c) for Plavix (clopidogrel bisulfate) in the indication of ST-segment elevation Acute Myocardial Infarction (14 October 2005; SN 0589).

The Division responded on 24 October 2005 to the Sanofi's request and agreed that a waiver is justified for Plavix for the reduction of atherothrombotic events (death, re-infarction, or stroke) in patients with ST segment elevation acute myocardial infarction for the entire pediatric population.

Debarment Certification

Sanofi-Synthelabo hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmic Act in connection with this application.

Nancy Barone Kribbs, Ph.D.
Senior Director Drug Regulatory Affairs
Sanofi-Synthelabo Inc.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-839/S-034

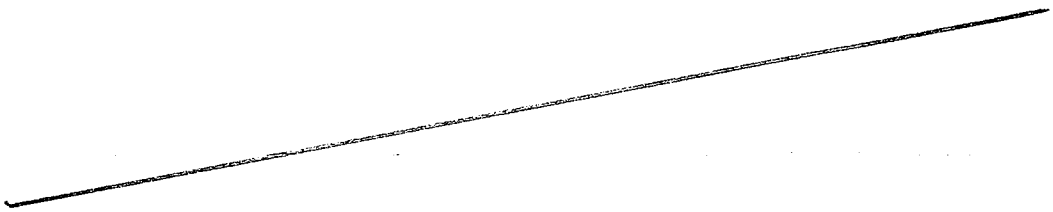
Sanofi-Aventis Inc.
Attention: Mr. Christopher Graham
300 Somerset Corporate Boulevard
P.O. Box 6977
Bridgewater, NJ 08807

Dear Mr. Graham:

Please refer to your supplemental new drug application(s) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) 75 mg Tablets.

We also refer to the approval letter for this supplement dated August 17, 2006 containing the agreed upon labeling text. We note an error in this text under the **CLINICAL STUDIES** section. You will receive a replacement action letter revising the **CLINICAL STUDIES** section as follows:

From:



b(4)

To read as follows:

> "The clinical evidence for the efficacy of Plavix is derived from four double-blind trials involving 81,090 patients: the CAPRIE study (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events), a comparison of Plavix to aspirin, and the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events), the COMMIT/CCS-2 (Clopidogrel and Metoprolol in Myocardial Infarction Trial / Second Chinese Cardiac Study) studies comparing Plavix to placebo, both given in combination with aspirin and other standard therapy and CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy – Thrombolysis in Myocardial Infarction)."

All other labeling will remain the same.

The date of the action will remain unchanged; however, the signature time will be one minute later in order to allow differentiation between letters

If you have any questions, please call:

Meg Pease-Fye, M.S.
Regulatory Health Project Manager
(301) 796 -1130

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Norman Stockbridge
8/18/2006 02:21:08 PM

MEMORANDUM

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

DATE: May 30, 2006

SUBJECT: **Issues leading to Major Amendment**
NDA 20-839/S-034, Plavix (clopidogrel) 75 mg Tablets

This supplemental new drug application proposed a new indication for Plavix in patients with ST-elevation myocardial infarction (STEMI), based on the findings of the COMMIT and CLARITY studies. Prior approvals for Plavix indications include:

- Acute Coronary Syndrome approved on February 27, 2002 based on CURE study
- the original approval based on the CAPRIE study for reduction of atherosclerotic events (myocardial infarction stroke, and vascular death) in patients with atherosclerosis documented by recent stroke, recent myocardial infarction, or established peripheral arterial disease on November 17, 1997.

A teleconference was held on May 11, 2006 between and Norman Stockbridge, Edward Fromm and Meg Pease-Fye from the Division of Cardiovascular and Renal Products and the following applicant representatives:

Sanofi-aventis
- Regulatory
  - Jon Villaume
  - Marjorie Christie
  - Nancy Kribbs
  - Lydie Baret-Cormel
- Statistics
  - Alex Boddy
  - Debbie Dukovic
- Medical
  - Christophe Gaudin
- Project Direction
  - Ghislaine Pisapia

Bristol-Meyers Squibb
- Regulatory
  - Nic Scalfarotto
- Medical
  - Mel Blumenthal
  - Brian Gavin
- Statistics
  - Harry Goyvaerts

This teleconference took place in order to alert the applicant to the following review issues affecting approval for these indications:

- CLARITY contributes little support for the proposed indication, since its success was mostly attributable to effects on the patency of the infarct-related artery, which is not an accepted surrogate.
- COMMIT is of questionable relevance to the U.S. patient care setting. The major differences in medical practice between these countries are the prevalence of PCI, choice of thrombolytics, and use of anti-lipid drugs. The Agency requested additional information and relevant literature to summarize why these aspects of care are not relevant to the effectiveness of clopidogrel in other settings.
- An interaction between clopidogrel and metoprolol was noted in the COMMIT study. Additional information was requested.
- The results of COMMIT appear to be different in the first 30,000 subjects (initial planned enrollment) and the last 15,000.

Meg Pease-Fye, M.S.
Regulatory Health Project Manager
Division of Cardiovascular and Renal Products

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

/s/

Margaret Pease-Fye
5/31/2006 11:23:16 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PDUFA GOAL DATE EXTENSION

NDA 20-839/S-034

Sanofi-Synthelabo Inc.
Attention: Marjorie Christie, Ph.D.
300 Somerset Corporate Boulevard
Bridgewater, New Jersey 08807

Dear Dr. Christie:

Please refer to your supplemental new drug application dated November 17, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) 75 mg Tablets.

On May 16, 2006, we received your major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is August 17, 2006.

If you have any questions, please call:

Ms. Meg Pease-Fye, M.S.
Regulatory Health Project Manager
(301) 796-1130

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Edward Fromm
5/22/2006 01:51:25 PM

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: April 7, 2006

TO: Meg Pease-Fye, M.S., Regulatory Project Manager, OND/OND I/DCRP
Salma Lemtouni, M.D., Medical Officer, OND/OND I/DCRP
Thomas Marciniak, M.D., Medical Team Leader, OND/OND I/DCRP
Norman Stockbridge, M.D., Division Director, OND/OND I/DCRP

THROUGH: Leslie Ball, M.D., Branch Chief, Good Clinical Practice Branch II (HFD-47)
Division of Scientific Investigations

FROM: David Gan, M.D., Dr.PH, MPH, Good Clinical Practice Branch II (HFD-47)
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: NDA 20839/S-034

APPLICANT: Sanofi-Aventis

DRUG: Plavix (clopidogrel Bisulfate) 75 mg Tablets

CHEMICAL CLASSIFICATION:

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Reduction in the occurrence of major vascular events including death, reinfarction and stroke following acute myocardial infarction

CONSULTATION REQUEST DATE: January 19, 2006

GOAL DATE TO PROVIDE CLINICAL INSPECTION SUMMARY: April 7, 2006

ACTION GOAL DATE: May 1, 2006

I. BACKGROUND

Sanofi-Aventis submitted a supplement to a New Drug Application for Plavix (clopidogrel bisulfate), for a new indication of acute myocardial infarction. Plavix is currently approved for reducing the combined rate of ischemic strokes, myocardial infarction (MI) or death in patients with a history of recent MI, stroke, established peripheral arterial disease or patients with acute coronary syndrome (unstable angina/non-Q-wave MI). Plavix is an anti-platelet agent that inhibits adenosine diphosphate (ADP) induced aggregation. Sanofi-Aventis is seeking to add a new indication to Plavix in reducing the combined risks of death, stroke,

and re-infraction associated with individuals who recently had acute MI.

Major vascular events such as re-infarction, stroke or vascular death can occur following an initial acute MI attack. One pathway that leads to production of these major vascular events is through aggregation of platelets and drugs that can inhibit the enzymatic pathways that lead to platelet aggregation can therefore be effective in reducing the major vascular events that follow an acute MI attack. Aspirin and β-blockers such as metoprolol have been shown in clinical studies to reduce the major vascular events that follow acute MI in patients. Aspirin inhibits platelet cyclo-oxygenase and prevents the formation of platelet aggregating agent thromboxane A_2. While β-blockers have been shown to reduce vascular events following acute MI, many physicians are hesitant to use β -blockers due to possible hypotension. As Plavix has been shown to have anti-platelet aggregation properties, it was postulated that Plavix could prevent the major vascular events associated with acute MI.

In support of the use of Plavix in patients with acute myocardial infarction, the sponsor conducted two large scale clinical trials: Commit CCS-2 (EFC7018) and Clarity TIMI28 (EFC5133). The two studies were randomized, double-blind, placebo-controlled trials that examined whether Plavix alone or in combination with Aspirin, reduced the risk major vascular events associated with acute MI. The results of the studies showed that Plavix taken alone or in combination with Aspirin provided a significantly reduced risk of combined death, re-infarction or stroke in patients with acute MI.

The primary focus of this inspection was the Commit CCS-2 (EFC7018) study.

(EFC7018 CCS-2) study:

The primary objective of the study is to determine whether the addition of Plavix to Aspirin with or without metoprolol for up to 4 weeks, can reduce mortality and the risk of combined major vascular events (i.e. death, re-infarction or stroke) that occur after the initial acute MI attack. Two primary efficacy endpoints were examined in this study. The first compared the combined endpoint of death, reinfarction or stroke in acute MI subjects treated with Plavix plus aspirin versus aspirin alone. The second primary efficacy endpoint examined whether Plavix reduced the risk of death from any cause. The sponsor was noted to be only submitting data concerning Plavix and Aspirin in support of this NDA supplement as metoprolol belongs to a different sponsor. The original study recruited 20-30,000 patients but was amended to recruit a total of 45-46,000 patients.

The study is a 2 X 2 factorial design comparing Plavix plus Aspirin with or without metoprolol or Aspirin alone with or without metoprolol. Patients who entered the hospital with signs or symptoms of suspected acute MI were initially screened. Eligibility for inclusion into the study required that the acute MI be confirmed by some diagnostic ECG abnormality (i.e. ST elevation and/or depression, BBB) and that the subjects entered the study within 24 hours of onset of the acute MI attack. It was noted that the protocol does not specify specific exclusion criteria and the judgment to not include a patient in the study was left to the responsible physician. Also, it was noted that due to the urgent need for treatments for patients that entered the hospital after an attack of acute MI, the degree, timing of consent, and method of consent (formal written consent or verbal discussion of study medication with patient or relatives) was left to individual doctors to decide for individual patients.

Patients were randomized into the study using the next available sequentially-numbered randomization envelope. After completion of the one-page entry form attached to the outside of the randomization envelope, the subjects were immediately given two antiplatelet tablets (75mg Plavix plus 162 mg Aspirin or placebo plus 162 mg Aspirin). Subjects were then sequentially given 3, 5 mg ampoules of metoprolol or placebo intravenously. Two minutes after each ampoule is given, the subject's heart rate and Systolic

blood Pressure (SBP) were measured. If the heart rate fell below 50 beats per minute or SBP fell below 90 mmHg or the patient developed cold sweats, the rest of the ampoules were not given. Fifteen minutes after completion of the IV injections, the subjects were given a 50 mg tablet of metoprolol or placebo by mouth and measured again for their heart rate and SBP. The subjects are then given one 50 mg tablet of metoprolol or placebo every six hours through the rest of the day, unless the patient entered during the night (i.e 18:00 – 23:59).

On Day 1, the subjects were given two antiplatelet tablets (75mg Plavix plus 162 mg Aspirin or placebo plus 162 mg Aspirin) once daily and 50 mg of metoprolol or placebo 4 times per day at approximately once very six hours.

On Day 2 through up to 4 weeks in the hospital, subjects were given two antiplatelet tablets (75mg Plavix plus 162 mg Aspirin or placebo plus 162 mg Aspirin) once daily for up to 4 weeks or until discharged or until death and one 200 mg controlled-release metoprolol or placebo once daily. Discharge forms were filled out upon either hospital discharge or death of the subject.
The study began on July 30, 1999, and concluded on February 28, 2005.

Basis for site selection

Domestic data did not include the mortality, stroke and reinfarction as the end points. The large simple trial conducted in China provided data for the indication of reduction of death, reinfarction and stroke. The review division has limited experience with data from China and requested DSI to check the validity of the findings.

The sites for inspection were chosen by the review team. Five sites in China were chosen initially. Two sites, the Liaoning Provincial People's Hospital and the Baotou Central Hospital, were chosen due to their large enrollment. Two sites, the Jilin Chemical Corporation Second General Hospital and the Shenyang Military 208 hospital were chosen due to their large enrollment and their location being close to Beijing. The review division requested that one of the sites investigated be the coordinating center in Beijing, China as all of the data funneled through the center and any changes or alterations to the data would occur at that site.

The review division added an additional site, the Mei County hospital system after consulting with DSI. The Mei county hospitals were rural hospitals with high mortalities. The CI at this site stopped recruiting study subjects three years ago.

The trial is a large sample size and simple trial. The protocol is very simple and easy to follow.

II. RESULTS (by site)

Table 1: Inspection results

Site # (Name and Address)	Country	Protocol	Inspection Date	EIR Date	Class
01020 Dr. Ruiping Zhao Baotou Central Hospital No. 61 Ring Road West Hedong district, Baotou City Inner Mongolia Postal code: 014040 Phone: 0472-6955377	China	EFC7018	3/13 to 3/17, 2006		VAI
11004 Dr. Zhanquan Li Liaoning Provincial People's Hospital No. 33 Wenyi Road, Shenhe district, Shenyang City, Liaoning Province Postal code: 110016 Phone: 024-24114377 or 024-24147900-8419 or 024-81635259	China	EFC7018	3/20 to 3/24, 2006		VAI
13041 Dr. Fengde Wang Jilin Chemical Corporation Second General Hospital No. 32 Datong Road Tiedong area, Longtian district, Jilin Province Postal code: 132022 Phone: 0432-3968926-8005	China	EFC7018	3/27 to 3/28, 2006		VAI
13043 Dr. Liwen Zheng Shenyang Military 208 hospital Changchun City, Jilin province Postal code: 130062 Phone: 0431-7973941-67013 or 0431-6988013	China	EFC7018	3/29 to 3/30, 2006		VAI
51006 Dr. J Zhong Mei County Guangdong Province	China	EFC7018	4/3, 2006		VAI
Dr. Lixin Jiang Fuwai hospital (coordinating center for this trial) 167 Beilishi Road Beijing, China Phone: 86-10-88365200 Fax: 86-10-88365201 email: fwoxford@yahoo.com.cn	China	EFC7018	3/9 to 3/10, 2006		Not Apply

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAIr= Deviation(s) form regulations, response requested. Data acceptable
OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection/Report not completed

Study Protocol:

EFC7018: A randomized trial of clopidogrel plus aspirin (ASA) versus ASA alone, and of metoprolol versus placebo, among patients with suspected acute myocardial infarction (MI) (COMMIT/CCS-2)

(1). Site 01020

Dr. Ruiping Zhao
Baotou Central Hospital
No. 61 Ring Road West
Hedong district, Baotou City
Inner Mongolia
Postal code: 014040

Inspection dates: 3/13 to 3/17, 2006

Methodology: Inspection assignments were issued to the field office. A DSI reviewer also participated in the inspection.

a. What was inspected?

Eighty two subjects of the 544 study subjects at this site were selected for a detail audit. We selected all study subjects with positive primary end points and all subjects age 45 or younger.

b. Limitations of inspection: None

c. General observations/commentary:

The following are the observations listed on the FDA 483 issued to the Clinical Investigator.

1. You did not always prepare or maintain accurate case histories with respect to observation and data pertinent to the investigation and informed consent. Specifically,

   a. Subject 01020-483. You recorded the discharge date of this subject as September 10 2004 on the case report form while the subject was actually discharged on [redacted].

   b. Subject 01020-406. You recorded the date of death of this subject as March 25, 2004 on the case report form while the subject died on [redacted] per source documents.

b(6)

c. Subject 01020-319. You recorded the date of death of this subject as October 16, 2003 on the case report form while the subject died on [redacted] per source documents.

d. Subject 01020-004. You recorded the discharge date of this subject as February 14, 2000 on the case report form while the actual discharge date was [redacted].

b(6)

e. Subject 01020-013. You did not report stopping the beta blocker (study medication) before discharge as required in the Case Report Form. Your records show that you stopped administering the beta blocker on March 9, 2000, and the subject was discharged on [redacted]

2. You did not keep a record of disposition of the unused supplies of the investigational drugs. Investigational drug disposition records are not adequate with respect to use by subjects. For example,

a. Subject 01020-013. Study drugs were started on February 14, 2000 and ended on March 9, 2000. Also, there is no documentation showing the disposition of the remaining test articles.

b. Subject 01020-204. Study drugs aspirin and clopidogrel were started on August 28, 2002. However, the source documents, medical records, only show the beginning dates of administration. They do not show each administration, or the end date of the treatments. Also, there is no documentation showing the disposition of the remaining test articles.

Item 2 b. was not a valid observation. The clinical investigator showed us the physician orders and the starting dates and stopping dates were recorded as a long term physician order for hospitalized patients.

Recommendation: The observations do not have significant impact the validity of the data submitted. Data from this site are acceptable.

(2) **Site** 11004

Dr. Zhanquan Li
Liaoning Provincial People's Hospital
No. 33 Wenyi Road,
Shenhe district, Shenyang City, Liaoning Province
Postal code: 110016

Inspection dates: 3/20 to 3/24, 2006

Methodology: Inspection assignments were issued to the field office. A DSI reviewer also participated in the inspection.

d. What was inspected?

Ninety eight study subjects of the 544 study subjects at this site were selected for detail review. All subjects with primary end points and subjects age 45 or younger were selected for the detail reviewing. The CI is very knowledgeable and the study was well conducted. The following were the Items listed on

the FDA 483.

e. Limitations of inspection: None

f. General observations/commentary:

The following were the Items listed on the FDA 483 issued to the Clinical Investigator.

1. You did not always prepare or maintain accurate case histories with respect to observation and data pertinent to the investigation and informed consent. Specifically,
   a. Subject 11004-030. You recorded the discharge date of this subject as April 13, 2000 on the case report form, while the subject was actually discharged on [redacted].
   b. Subject 11004-199. You stopped administering study medications on August 5, 2002 (source records) and did not report it on the Case Report Form. Discharge date was [redacted] (date of death).
   c. Subject 11004-495. You stopped administering study drug clopidogrel on August 25, 2004 (source records) and did not report it on the Case Report Form. Discharge date was [redacted]. b(6)
   d. Subject 11004-309. You recorded the discharge date of this subject as September 30, 2003 on the case report form, while the subject was actually discharged on [redacted], according to the source records.
2. You did not keep a record of disposition of the unused supplies of the investigational drugs. For example,
   a. Subject 11004-027. Subject was randomized on March 4, 2000; the patient was discontinued on March 9, 2000. There are no records of disposition of unused study drugs for the patient.

Recommendation: Data from site are acceptable.

(3) Site 13041

Fengde Dr. Wang
Jilin Chemical Corporation
Second General Hospital
No. 32 Datong Road
Tiedong area, Longtian district, Jilin Province
Postal code: 132022

Inspection Dates: 3/27 to 3/28, 2006.

Methodology: Inspection assignments were issued to the field office. A DSI reviewer participated in the inspection.

a. What was inspected?

We reviewed 28 of 208 study subjects at this site. All study subjects with primary end points were reviewed.

b. Limitations of inspection: The hospital administrators instructed the clinical investigator not to record any information concerning the study on the medical charts. The clinical investigator recorded all information include informed consent on a separate research record and stored at the drug box provided by the sponsor. Upon completing the study, the sponsor and the Fuwai central coordinator instructed all clinical investigators to destroy all remaining drugs. The clinical investigator at this site destroyed the remaining drug along with the research records. ECG with names and dates attached to the medical records are reviewed. Medical case histories, cardiac enzymes were reviewed.

c. General observations/commentary:

The following is the observations on the FDA 483.

1. You did not always prepare or maintain accurate case histories with respect to observation and data pertinent to the investigation and informed consent. Specifically,

a. You did not maintain case histories with respect to study drug such as CCS-2 starting dates and ending dates for most study subjects we reviewed.

b. You did not maintain records for informed consent for all subjects we reviewed (28 out of 208 subjects).

c. Subject 13041-074. The subject was enrolled on October 24, 2002, per source documents, while you recorded October 29, 2002 as enrollment date for this subject on the CRF.

d. Subject 13041-080. The subject died on [redacted], per source documents. You recorded the death date as November 19, 2002 on the CRF.

b(6)

e. Subject 13041-024. The subject was enrolled on July 30, 2001, per source documents. You recorded July 27, 2001 as the enrollment date for the subject on the CRF.

f. Subject 13041-048. The subject was discharged on [redacted], per source documents. You recorded March 28, 2002 as the discharge date for the subject on the CRF.

g. Subject 13041-058. The subject was discharged on [redacted], per source documents. You recorded July 8, 2002 as the discharge date for the subject on the CRF.

2. You did not keep a record of disposition of the unused supplies of the investigational drugs.

The CI reported the hospital administration ordered the CI not to record any information concerning the CCS-2 study on the medical charts. The CI recorded the information on a separate research record. Upon completing the study, the coordination center instructed the CI to destroy the remaining study drug. The CI destroyed the remaining drug along with the record attached to the box (14 x 18 cm). For each subject, there was a box of study drug.

Affidavits were obtained from the hospital administrator and the clinical investigator stated that the hospital ordered the clinical investigator not to record any information concerning the clinical trial on the study subjects' medical records. The clinical investigator stated that this is the first clinical trial conducted in this hospital and the hospital administrator was anxious about possible litigations against the hospital.

The clinical investigator volunteered the information during the inspectional interview.

Recommendation: Data from this site may be acceptable. We verified all study subjects are existed. Diagnosis, treatment and follow up of the patients were adequate.

(4) Site 13043

Dr. Liwen Zheng
Shenyang Military 208 hospital
Changchun City, Jilin province
Postal code: 130062

Inspection Dates: 3/29 to 3/30, 2006.

Methodology: Inspection assignments were issued to the field office. A DSI reviewer participated in the inspection.

a. What was inspected?

Thirty of 145 records at this site were reviewed. All subjects with primary end points were reviewed.

b. Limitations of inspection: None.

c. General observations/commentary:

The following are the observations listed on the FDA 483 issued to the clinical investigator.

For the clinical study identified as CCS-2, the following was noted:

1. You did not always prepare or maintain adequate case histories with respect to informed consent. Specifically,

a. For Subjects 13043-005/015/035. The informed consent forms for these subjects are not available for review. There is no discussion in the medical files regarding obtaining informed consent.

2. You did not keep a record of disposition of the unused supplies of the investigational drugs for each of the subjects enrolled in the study.

Recommendation: Data from site are acceptable.

(5) Site 51006

Dr. J Zhong
Mei County
Guangdong Province

Methodology: Inspection assignments were issued to the field office A DSI reviewer participated in the inspection.

a. What was inspected?

Thirty case histories of 129 study subjects at this sites were reviewed. The Clinical investigator enrolled a total of 129 study subjects. Of which, 74 subjects were from Mei County Hospital and Fifty five were from Mei County second hospital. ECGs and Informed Consent of the 55 study subjects from Mei County Second Hospital were reviewed and verified.

b. Limitations of inspection: Medical histories (55 study subjects) except ECGs and Informed Consent from Mei County Second hospital were not available.

General observations/commentary:

The following are the observations listed on the FDA 483 issued to the Clinical Investigator.

For the clinical study identified as CCS-2, the following was noted:

1. You did not always prepare or maintain accurate case histories with respect to observation and data pertinent to the investigation and informed consent. Specifically,

a. You enrolled a total of 129 study subjects for the CCS-2 study, 74 at Mei County First Hospital and 55at Mei County Second Hospital. You did not maintain medical case histories (except for EKG and Informed Consent) for the 55 subjects enrolled at the Mei County Second hospital.

b. Subject 51006-040. There is no source documentation to verify that this subject received the test articles, while you recorded on the CRF that this subject received the test articles.

c. Subject 51006-085. The subject died on [redacted], per source documents. You recorded the death date as October 19, 2002 on the CRF. b(6)

d. Subject 51006-057. The subject died on [redacted], per source documents. You recorded the death date as April 23, 2002 on the CRF.

2. You did not keep a record of disposition of the unused supplies of the investigational drugs.

Recommendation: We verified that the 55 study subjects exist by reviewing ECG and informed Consent. Lack of complete medical records for the 55 study subjects appear to be serious and it may impact the validity of the data submitted. However, the magnitude of the impact of the overall study is minimum. There were six study subjects with primary end points (all deaths). Two (77, 85)are in the Clopidogrel group and 4 (51, 87, and 108) are at the placebo group. Data from this site may be acceptable.

(6). Dr. Lixin Jiang
Fuwai hospital (coordinating center for this trial)
167 Beilishi Road
Beijing, China

Dr. Lixin Jiang is the coordinator at Fuwai hospital, the coordinating center for this trial. We visited the coordinating center on March 9 and March 10. We reviewed Case Report Forms and correspondences concerning the trial at the center.

We interviewed Dr. Jiang and Dr. Zhenming Chen, sponsor representative from Oxford University concerning the data quality of the trial. Dr. Chen stated that quality control measures include routine monitoring, extensive computerized check and extensive test and validation of IT system. The center audited 344 (27%) hospitals participated in the trial. On-site audits were done at hospitals selected on the basis of either the large number recruited or central statistical monitoring. The center reviewed 3237 study subjects.

Dr. Jiang reported that two hospitals audited committed fraud. The central monitoring identified unusually low event rates and rapid increases in the recruitment rate, and these were found to have deliberately entered some non-cardiac patients or invented patients. The sponsor excluded the data from these two hospitals.

I asked Dr. Chen why he needed 45852 study subjects for the trial and if this sample size the initial sample size estimated. Dr. Chen stated that the initial sample size was 15000 to 30000 on the original protocol. The sample size was increased to 45852. I asked Dr. Zhenming Chen why the study sample size was increased. Dr. Chen stated that the initial estimate of sample size was based on estimated mortality of 10% and the actual mortality was lower. Dr. Chen said the data committee made the recommendation to increase sample size to 40000. I requested a copy of the original protocol Oxford (cosponsor) submitted to Sanofi. I further requested a data analysis of the first 30000 study subjects to compare incidence rates of treatment group and the placebo group. Sanofi-Aventis submitted documents concerning the increase of sample size. Sanofi-Aventis did not submit the results of the data analysis I requested.

During the inspection, I sent an email to Dr. Jialu Zhang of FDA requesting her to conduct a data analysis to compare the incidence rates of the treatment group and the placebo group. The following is the results of the analysis:

Table 2: Analysis of the Composite Endpoint Based on the First 30000 Patients in COMMIT

Primary efficacy composite endpoint: death, re-MI or stroke	**Clopidogrel 300/75 mg** N	**# of patients reporting events**	**Placebo** N	**# of patients reporting events**	**p value**	**HR (95% CI)**
Final Sample Size of 45852	22961	2121 (9.2%)	22891	2310 (10.1%)	0.002	0.91 (0.86, 0.97)
Initial planned Sample Size of 30000	15029	1474 (9.8%)	14971	1568 (10.5%)	0.056	0.933 (0.869,1.002)
Added 15852 subjects	7932	647 (8.2%)	7920	742 (9.4%)	0.005	0.862 (0.772,0.958)

As illustrated from table 2, with the initial planned sample size of 30000, there were no significant difference between treatment group and placebo group with Hazard ratio of 0.933 and a borderline significance (CI 0.869, 1.002). Both the total sample size of 45852 and the added sample size of 15852 reached statistical significance.

I asked the study coordinator, Dr. Jiang why the study results were different between the initial planned sample size and the final study sample size. Dr. Jiang stated that the added study subjects may be different from the initial study subjects. Dr. Jiang also stated the medical practice for heart disease has improved a lot over the study period of five years (1999 to 2004).

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Observations noted above are based on the Form FDA 483s, preliminary EIRs and my observation during the inspection. An inspection summary addendum will be generated if conclusions changes significantly upon receipt and review of each final EIR.

There were minimum financial incentives for the trial. The sponsor paid $12 per study subject.

In general, for the five study sites inspected, it appears that sufficient documentation to assure that study subjects audited at those five sites did exist, study eligibility criteria were fulfilled, participants received assigned study medications, and adverse events were adequately reported per protocol. Primary endpoints were captured in accordance with protocol requirements.

I have concern about the possible sample size manipulation. However, I do not have solid evidence. The review division should perform further analysis concerning the sample size issues.

David Gan, M.D., Dr.PH, MPH
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments:

Leslie K. Ball, M.D.
Branch Chief, Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

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HFD-110/MO Team Leader (Thomas Marciniak, M.D.)
HFD-110/RPM(Meg Pease-Fye)
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/s/

David Gan
5/5/2006 03:23:04 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 20-839/S-034

Sanofi-Synthelabo Inc.
Attention: Nancy Barone Kribbs, Ph.D.
300 Somerset Corporate Boulevard
Bridgewater, New Jersey 08807

Dear Dr. Kribbs:

Please refer to your November 17, 2005 supplemental new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) 75 mg Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on January 16, 2006 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, please call:

Meg Pease-Fye, M.S.
Regulatory Health Project Manager
(301) 796-1130

Sincerely,

[See appended electronic signature page]

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
1/24/2006 05:39:16 PM

DSI CONSULT: Request for Clinical Inspections

Date: January 19, 2006

To: Ni Aye Khin, M.D., Branch Chief, GCP1, HFD-476
Leslie Ball, M.D., Branch Chief, GCP2, HFD-47

cc: Joanne L. Rhoads, M.D., Director, DSI, HFD-45
Norman Stockbridge, M.D., Ph.D., Acting Director
Division of Cardiovascular and Renal Products

From: Meg Pease-Fye, M.S., Regulatory Health Project Manager
Division of Cardiovascular and Renal Products

Subject: **Request for Clinical Site Inspections**
NDA 20-839/S-034
Sanofi-Aventis
Plavix (clopidogrel bisulfate) 75 mg Tablets

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

This NDA provides data for the following: new indication to an approved product to include acute myocardial infarction.

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Liaining Province People's Hosptial Shenyang, Liaoning	COMMIT	544	Acute MI
Baotou Central Hospital Baotou, Inner Mongolia	COMMIT	544	
Jilin Chemical Corporation Second General Hospital Jilin, Jilin	COMMIT	208	
Shenyang Military 208 Hospital Changchun, Changchun	COMMIT	145	

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Fuwai Hospital Beijing	COMMIT	N/A This is the coordinating center for this trial	

Domestic Inspections:

We have requested inspections because (please check all that apply):

____ Enrollment of large numbers of study subjects

____ High treatment responders

____ Significant primary efficacy results pertinent to decision-making

____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.

____ Other: SPECIFY

International Inspections:

We have requested inspections because (please check all that apply):

____ There are insufficient domestic data

____ Only foreign data are submitted to support an application

__X__ Domestic and foreign data show conflicting results pertinent to decision-making

____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.

__X__ Other: Only foreign data to support a mortality claim. Domestic data did not show an effect on this outcome. It is a large trial and our experience with data from China is limited therefore it is important to check the validity of the findings.

Five or More Inspection Sites (delete this if it does not apply):

We have requested these sites for inspection (international and/or domestic) because of the following reasons: Only the foreign data supports a mortality claim. Domestic data did not show an effect on this outcome. It is a large trial and our experience with data from China is limited therefore it is important to check the validity of the findings.

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) April 7, 2006. We intend to issue an action letter on this application by (division action goal date) May 1, 2006. The PDUFA due date for this application is May 17, 2006.

Should you require any additional information, please contact Meg Pease-Fye.

Concurrence: (if necessary)

Thomas Marciniak, Medical Team Leader
Salma Lemtouni, Medical Reviewer
Norman Stockbridge, Acting Division Director (for foreign inspection requests only)

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

/s/

Salma Lemtouni
1/19/2006 10:06:58 AM

Thomas Marciniak
1/19/2006 10:34:52 AM

Norman Stockbridge
1/20/2006 06:02:28 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 20-839 Supplement # 034 Efficacy Supplement Type **SE-1**

Trade Name: **Plavix**
Established Name: **clopidogrel bisulfate**
Strengths: **75 mg Tablets**

Applicant: **Sanofi-Aventis**
Agent for Applicant: **Nancy Kribbs, Ph.D.**

Date of Application: **November 17, 2005**
Date of Receipt: **November 17, 2005**
Date of Filing Meeting: **January 4, 2006**
Filing Date: **January 16, 2006**
Action Goal Date (optional): User Fee Goal Date: May 17, 2006

Indication(s) requested: Acute myocardial infarction

Type of Supplement: (b)(1) ☒ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.
(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☒ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☐ P ☒
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) **6**
Other (orphan, OTC, etc.) **N/A**

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO ☒

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐
- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Documents requiring an original signature (debarment certification, form 356H, financial disclosure, cover letter, user fee sheet) were the only paper provided with this submission
- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☐ YES ☒ NO ☐
- Is it an electronic CTD (eCTD)? N/A ☐ YES ☒ NO ☐
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.
- Patent information submitted on form FDA 3542a? YES ☐ NO ☒
- Exclusivity requested? YES, 3 Years NO ☐
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*
- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☐ NO ☒
- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: **34,663**

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) **July 21, 2005** NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☒ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☒ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☐ NO ☒

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? **N/A X**
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☒ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☐

- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 4, 2006

BACKGROUND:
Plavix is currently indicated for the reduction of atherothrombotic events in the following populations:

- Patients with a history of recent MI, recent stroke, or established peripheral arterial disease.
- Patients with acute coronary syndrome (unstable angina/non-Q-wave MI) including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention.

This efficacy supplement is for a new indication of acute myocardial infarction based on results from COMMIT/CCS-2 trial conducted in China and from the CLARITY-TIMI study.

ATTENDEES:
Norman Stockbridge, M.D., Ph.D., Acting Director, Division of Cardiovascular and Renal Products
Thomas Marciniak, M.D., Team Leader, Medical Officers
Salma Lemtouni, M.D., M.P.H., Medical Officer
Jialu Zhang, Ph.D., Statisician
Elizabeth Hausner, D.V.M., Pharmacology
Edward Fromm, R.Ph., Chief, Project Management Staff
Meg Pease-Fye, M.S., Regulatory Health Project Manager
Lance McLeroy, Pharm.D., Reviewer, Division of Drug Marketing, Advertising and Communications
Sharon Gershon, Pharm.D., Division of Scientific Investigations

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline	Reviewer	Expected Review
Medical:	Dr. Lemtouni	April 7, 2006
Secondary Medical:		
Statistical:	Dr. Zhang	April 7, 2006
Pharmacology:	Dr. Hausner	N/A
Statistical Pharmacology:	N/A	
Chemistry:	Dr. Chidambaram	N/A
Environmental Assessment (if needed):		
Biopharmaceutical:	Dr. Velazquez	N/A
Microbiology, sterility:	N/A	
Microbiology, clinical (for antimicrobial products only):	N/A	
DSI:	Dr. Gershon	April 7, 2006
Regulatory Project Management:	Ms. Pease-Fye	
Other Consults:		

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☒ NO ☐
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY	N/A ☒	FILE ☐	REFUSE TO FILE ☐
STATISTICS	N/A ☐	FILE ☒	REFUSE TO FILE ☐
BIOPHARMACEUTICS		FILE ☒	REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO ☐

PHARMACOLOGY	N/A ☒	FILE ☐	REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☐

CHEMISTRY		FILE ☒	REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Microbiology YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

2. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3. ☐ Convey document filing issues/no filing issues to applicant by Day 74.

Ms. Meg Pease-Fye
Regulatory Project Manager, HFD-110

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/s/

Margaret Pease-Fye
1/19/2006 08:02:43 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-839/S-034

PRIOR APPROVAL SUPPLEMENT

Sanofi-Synthelabo Inc.
Attention: Nancy Barone Kribbs, Ph.D.
300 Somerset Corporate Boulevard
Bridgewater, New Jersey 08807

Dear Dr. Kribbs:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Plavix® (clopidogrel bisulfate) 75 mg Tablets
NDA Number:	20-839
Supplement number:	034
Review Priority Classification:	Priority (P)
Date of supplement:	November 17, 2005
Date of receipt:	November 17, 2005

This supplemental application proposes Plavix® (clopidogrel bisulfate) for the new indication of Acute Myocardial Infarction.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 16, 2006, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 17, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the waiver granted on October 24, 2005, for the pediatric study requirement for this application.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products, Room 4161
5901-B Ammendale Road
Beltsville, MD 20705-1266

Please note that this letter supersedes the previous (December 1, 2005) acknowledgement letter. If you have any questions, please call:

Meg Pease-Fye, MS
Regulatory Health Project Manager
(301) 796-1130

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
12/2/2005 10:40:01 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 34,663

Sanofi-Synthelabo Inc.
Attention: Nancy Barone Kribbs, Ph.D.
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Kribbs:

Please refer to your submission dated October 14, 2005, requesting a waiver for pediatric studies for Plavix (clopidogrel bisulfate).

We have reviewed your submission and agree that a waiver is justified for Plavix for the reduction of atherothrombotic events (death, re-infarction, or stroke) in patients with ST segment elevation acute myocardial infarction for the entire pediatric population because Plavix does not represent a meaningful therapeutic benefit over existing treatments, and it is not likely to be used in a substantial number of patients.

Accordingly, at this time, a waiver for pediatric studies for your application is granted under section 2 of the Pediatric Research Equity Act.

If you have questions, please contact:

Meg Pease-Fye, M.S.
Regulatory Project Manager
301.796.1130

Sincerely,

[See appended electronic signature page]

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
10/24/2005 12:26:05 PM

Minutes of a Meeting

Meeting Date:	**July 21, 2005**
Application:	IND 34,663 NDA 20-839 Plavix (clopidogrel bisulfate)
Sponsor:	Sanofi-Aventis/Bristol-Myers Squibb
Type of Meeting:	**Type B** **Pre sNDA**
Date requested:	April 19, 2005
Date Confirmed:	April 29, 2005
Date Package Received:	May 24, 2005
Meeting Chair:	Robert Temple, M.D.
Meeting Recorder:	Meg Pease-Fye, M.S.

FDA Participants:
Robert Temple, M.D., Director, Office of Drug Evaluation I, HFD-101
Norman Stockbridge, M.D., Ph.D., Acting Director, Division of Cardio-Renal Drug Products, HFD-110
Abraham Karkowsky, M.D., Ph.D., Acting Deputy, Division of Cardio-Renal Drug Products, HFD-110
Thomas Marciniak, M.D., Team Leader, Medical Officers, HFD-110
Salma Lemtouni, M.D., M.P.H., Medical Officer, HFD-110
Karen Hicks, M.D., Medical Officer, HFD-110
Mehul Desai, M.D., Medical Officer, HFD-110
Katharine Lillie, M.D, Medical Officer, HFD-110
James Hung, Ph.D., Team Leader, Biometrics, HFD-710
Charles Le, Ph.D., Reviewer, Biometrics, HFD-710
Meg Pease-Fye, M.S., Regulatory Health Project Manager, HFD-110

Sanofi-Aventis Participants:
Christophe Gaudin, M.D., Cardiovascular Clinical Development
Catherine Marchese, M.D., Cardiovascular Clinical Development
Nancy Kribbs, Ph.D., Regulatory Development
Ghislaine Pisapia, M.S., Regulatory Development
Jon Villaume, Ph.D., Regulatory Development
Catherine Baillis, M.Sc., Project Direction
Lewis Fountain, Programming
Alex Boddy, M.S., Biostatistics
Leigh Carter, Regulatory Operations

Bristol-Myers Squibb Participants:
Melvin Blumenthal, M.D., Clinical Research
Grace Heckman, Global Regulatory Strategy
Andrew Bodnar, M.D., Corporate Strategy
Placido Grino, M.D., Global Medical Affairs
Harry Goyvaerts, Ph.D., Biostatistics

Oxford University Participants:
Rory Collins, M.D., M.Sc., Clinical Trials Services Unit
Zhengming Chen, M.D., Ph.D., Clinical Trials Services Unit

Background:
This meeting was held to discuss the scientific and clinical content of the planned NDA supplement for an acute myocardial infarction indication for Plavix. The Sponsors requested Agency advice and agreement on the use of the COMMIT/CCS-2 trial conducted in China. Based on results from this study and from the CLARITY-TIMI study, the Sponsors intend to submit during the fourth quarter of 2005 a sNDA for an indication in patients with ST-elevation acute MI.

Plavix is currently indicated for the reduction of atherothrombotic events in the following populations:

- Patients with a history of recent MI, recent stroke, or established peripheral arterial disease.
- Patients with acute coronary syndrome (unstable angina/non-Q-wave MI) including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention.

Meeting:
The sponsors presented the Agency with background and results from both the CLARITY-TIMI and COMMIT trials.

COMMIT/CCS-2 was a double-blind, 2x2 factorial study (clopidogrel vs. placebo and metoprolol vs. placebo) on top of aspirin 162 mg in patients within 24 hours of onset of suspected MI. The study enrolled 45,852 patients at 1250 sites in China. The primary end points were all-cause mortality and the composite of all-cause mortality, stroke, and recurrent MI, both evaluated for to time of hospital discharge or 28 days. Clopidogrel 75 mg (with no loading dose) was associated with a relative risk reductions of 7% for all-cause mortality ($p=0.03$) and 9% for the composite ($p=0.002$). The sponsor described a sequential analysis plan to deal with the multiple primary end points.

CLARITY/TIMI-28 was a double-blind, multi-national study of clopidogrel (300 mg loading plus 75 mg/day) and placebo in patients with acute MI planned for fibrinolysis and receiving aspirin and heparin. The primary end point was death, MI, or occlusion of the infarct-related coronary artery by the time of coronary angiography, hospital discharge, or day 8. Total follow-up for mortality is through 30 days. Clopidogrel was associated with a 36% reduction in primary end point events ($p<0.001$).

Questions:
1. Does the Agency agree that COMMIT/CCS-2 and CLARITY-TIMI 28 could support the following draft labeling changes to the package insert?

   INDICATIONS AND USAGE section

For patients with ST-segment elevation acute MI, Plavix has been shown to reduce the rate of all-cause death and the rate of a combined endpoint of re-infarction, stroke or death.

DOSAGE and ADMINSTRATION section
For patients with ST-segment elevation acute MI, the recommended dose of Plavix is 75 mg once daily (initiated with or without a loading dose), administered in combination with aspirin, with or without thrombolytics (see **CLINICAL STUDIES**).

Agency response: The COMMIT/CCS-2 study appears to be the primary support for the new claim.

Dr. Temple noted that the only outcome study is not in a U.S. population and the Agency needs to be convinced that it is relevant despite differences in clinical practice and, consequently, will predict benefit to the U.S. population. This argument needs to be addressed clearly and in detail.

In response to a question from the Division, Sanofi/BMS noted that urokinase was the predominant thrombolytic agent used in the COMMIT/CCS-2 study.

2. Does the Agency agree with the proposed content and format of the dossier?

Agency response: This is acceptable. Dr. Stockbridge was interested in deliberations of the data safety monitoring committees, particularly the process by which the trial size may have been increased, and discussions pertaining to formal interim analyses. He added that the Agency would like for these to be submitted and any documentation pertaining to these types of decisions. The sponsor noted that the DSMB and the steering committees are both unblinded.

3. Are the analyses and presentations to be included in the clinical study reports adequate to support the review?

Agency response: The Agency noted the absence of analyses by gender. The sponsor stated that this was not pre-specified in the data analysis plan, although they have the data and are willing to submit it to the Division. The sponsor was concerned about using subset analysis on non pre-specified criteria, believing that data may be misleading due to a small number of events or death. Dr. Temple agreed about the hazards, but said we would want to look anyway. He also reminded the sponsor that the Agency regulations demand demographic subset analysis.

The Division noted that they would like to receive a representative sample of the case report forms (CRF), and proposed that it would select a representative subset of patient identification numbers and that selected set will be copied and submitted to the Division. Sanofi/BMS agreed. Further, the Agency requested that CRFs and narratives be submitted for all deaths, drop-outs, and serious adverse events, particularly bleeding events.

4. Does the Agency agree with the proposed preparation/presentation of the COMMIT/CCS-2 database?

Agency response: Dr. Stockbridge strongly encouraged the sponsor not to submit two versions of COMMIT results, with and without treatment codes. The suggestion was made that the sponsor

submit the supplement without the datasets and that the data coordinating center submit the datasets in an amendment to the supplement. The sponsor had in fact already decided to use a single submission.

Other Discussion Points:

- Dr. Stockbridge asked if the datasets will show which patients are on metropolol (another arm of the large COMMIT/CCS-2 study). Sanofi/BMS replied that this seems reasonable and agreed to discuss this with AstraZeneca. A suggestion was made to use a code for the use of clopidogrel (Y / N) or metropolol (Y / N).

- The Division requested clarification about the statement in the briefing package that said, "The listing of patients by batch number is not available." The sponsor responded that they are unable to tell which batch number of the drug was given based on the randomization. However, the assigned treatment package number was recorded on the CRF. The Division found this acceptable.

- The sponsor sketched out their monitoring plan: the sponsor has ensured that the drug is properly packaged, numbered and labeled. Random samples of the packs were regularly sampled to see if they were properly randomized. Forms were manually registered and checked for correct sequence. Data were double entered, confirmed and corrected. On-site audits occurred in top-enrolling centers to inspect randomization of patients. A central monitor looked for variability and some problems were detected in enrollment in some centers and these centers were suspended; fortunately, in these centers, there were no deaths and only one MI which was not included as part of the analysis.

- Sanofi/BMS asked about priority review. The Agency suggested they submit their rationale for consideration.

Conclusions:

- Sanofi/BMS needs to outline why the Chinese outcome study has relevance to a U.S. population
- Sanofi/BMS will discuss with AstraZeneca the inclusion of metropolol use in data collection

Date Minutes Drafted: July 29, 2005
Date Minutes Finalized: August 8, 2005

Signature minutes preparer: *{See appended electronic signature page}*
Meg Pease-Fye, M.S.

Concurrence, Chair: *{See appended electronic signature page}*
Robert Temple, M.D.

Reviewed:
R. Temple 8/08/05
N. Stockbridge 8/5/05

A. Karkowsky	8/4/05
K. Hicks	8.02.05
M. Desai	8.01.05
K. Lillie	8.01.05
C. Le	7.29.05
J. Jung	8.01.05

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/s/

Margaret Pease-Fye
8/8/05 09:25:15 AM

Robert Temple
8/10/05 06:59:34 PM

NDA 20-839/S-034

Periodic Safety Update

A 4-month (or other) safety update will not be submitted for this supplement because the safety content for the submission included only the COMMIT and CLARITY trials (as per pre-sNDA agreement). These trials are completed and final study reports were included in the supplement.

Therefore, by default, there will be no new safety information to include.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☑ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) 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). I also certify that each listed clinical investigator required to disclose to the sponsor 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. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	see Table (3.1) 1	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Mark Staudenmeier	VP, Finacne
FIRM/ORGANIZATION	
Sanofi-Synthelabo Inc.	
SIGNATURE	**DATE**
Mark L Staudenmeier	10/14/2005

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Created by: PSC Media Arts (301) 443-1090 EF

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☐ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) 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). I also certify that each listed clinical investigator required to disclose to the sponsor 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. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

☑ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Mark Staudenmeier	VP, Finance
FIRM/ORGANIZATION Sanofi-Synthelabo Inc.	
SIGNATURE Mark L Staudenmeier	DATE 10-28-05

Paperwork Reduction Act Statement

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Food and Drug Administration
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Rockville, MD 20857

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84 Page(s) Withheld

√ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 2

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 20-839	Efficacy Supplement Type SE-1	Supplement Number 034	
Drug: **Plavix (clopidogrel bisulfate)**		Applicant: **Sanofi-Aventis**	
RPM: **Meg Pease-Fye, M.S.**		HFD-**110**	Phone # **301.796.1130**
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):	

❖ Application Classifications:	
◦ Review priority	( ) Standard (X) Priority
◦ Chem class (NDAs only)	
◦ Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	**May 17, 2006 - initial** **August 17, 2006 - extension**
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
◦ User Fee	(X) Paid UF ID number **3006262**
◦ User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
◦ User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	
◦ Applicant is on the AIP	( ) Yes (X) No
◦ This application is on the AIP	( ) Yes (X) No
◦ Exception for review (Center Director's memo)	
◦ OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
◦ Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified

◦ Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. ◦ [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
◦ [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).* ◦ [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "Yes," skip to question (4) below. If "No," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "No," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its*	( ) N/A (no paragraph IV certification) ( ) Verified ( ) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?	( ) Yes ( ) No
*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No,**" continue with question (5).*	
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).	( ) Yes ( ) No
*If "**No,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes,**" a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	

❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	Yes
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	Project Management 8.10.06