CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number:	**20839**
Trade Name:	**Plavix**
Generic Name:	**Clopidogrel bisulfate**
Sponsor:	**Sanofi Pharmaceuticals**
Approval Date:	**November 17, 1997**
Indication:	**Reduction of atherosclerotic events**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 20839

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				X
Approvable Letter	X			
Final Printed Labeling	X			
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)	X			
Statistical Review(s)			X	
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				X
Administrative Document(s)	X			
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 20839

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-839

NOV 17 1997

Sanofi Pharmaceuticals, Inc.
Attention: George Clay, Ph.D.
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Clay:

Please refer to your April 28, 1997 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) Tablets, 75 mg.

We acknowledge receipt of your submissions dated October 28, 30 and 31, and November 4 and 6, 1997.

This new drug application provides for the use of Plavix 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.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed draft. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-839. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Please note that the approved expiry date for Plavix is 24 months in all containers.

We also note that you have agreed to investigate further possibilities for additional code imprint to the tablet so that it could be more easily identified.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In future morbidity/mortality trials, we recommend that you ensure the following:

Please submit one market package of the drug product when it is available.

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 contact:

Mr. David Roeder
Regulatory Health Project Manager
(301) 594-5313

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc:
Original NDA
HFD-110
HF-2/MedWatch (with draft/final labeling)
HFD-002/ORM (with draft/final labeling)
HFD-92/DDM-DIAB (with draft/final labeling)
HFD-101 (with draft/final labeling)
HFD-101/L.Carter
HFD-40/DDMAC (with draft/final labeling)
HFD-613/OGD (with draft/final labeling)
HFD-735/DPE (with draft/final labeling)
HFD-560/OTC (with draft/final labeling - OTC drugs only)
HFD-21/ACS (with draft/final labeling - for drugs discussed at advisory committee meeting)
DISTRICT OFFICE
HFD-810/ONDC Division Director
HFI-20/Press Office (with draft/final labeling)
HFD-110/DRoeder
sb/11/6/97;11/10/97
R/D: RWolters/11/7/97
ADeFelice/11/7/97
JHung/11/7/97
CGanley/11/7/97
NMorgenstern/11/7/97

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20839

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-839

OCT 27 1997

Sanofi Pharmaceuticals, Inc.
Attention: George Clay, Ph.D.
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Clay:

Please refer to your April 28, 1997 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 acknowledge receipt of your amendments and correspondence dated April 30, May 1, 13, 15, and 22, June 5, 11, 16, 27 and 30, July 2, 14, 23 and 24, August 1, 13, 14, 18, 20 and 28, September 3, 10, 15, 17, 18, 22, 23, 25 (two), and 26 (two), and October 1, 2, 3, 6 (two), 13, 15 and 22, 1997.

We have completed the review of this application as submitted with draft labeling and it is approvable. Before the application may be approved, however, satisfactory resolution is required regarding the issue of documentation of the follow-up of patients who were early permanent discontinuations. To that end, we strongly suggest that you meet with the Division of Cardio-Renal Drug Products to discuss this matter at the earliest mutually convenient time. In addition, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed marked-up draft. If additional information relating to the safety or effectiveness of this drug becomes available, revision of the FPL may be required.

Please submit sixteen copies of the printed labels and other labeling, ten of which are individually mounted on heavy weight paper or similar material.

Please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Mr. David Roeder
Regulatory Health Project Manager
Telephone: (301) 594-5313

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc:
Original NDA
HFD-2/MLumpkin
HFD-92
HFD-101
~~HFD-110~~
HFD-110/Project Manager
HFD-40 (with draft labeling)
HFD-560/DBowen (with draft labeling - OTC drugs only)
DISTRICT OFFICE
HFD-110/KBongiovanni
sb/9/11/97

APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20839

FINAL PRINTED LABELING

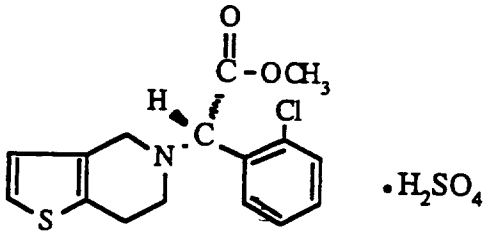
PLAVIX®

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 $C_{16}H_{16}Cl\,NO_2S \bullet H_2SO_4$ 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, engraved film-coated tablets containing 97.875 mg of clopidogrel bisulfate which is the molar equivalent of 75 mg of clopidogrel base.

Each tablet contains anhydrous lactose, hydrogenated castor oil, microcrystalline cellulose, polyethylene glycol 6000 and pregelatinized starch as inactive ingredients. The pink film coating contains ferric oxide (red), hydroxypropyl methylcellulose 2910, polyethylene glycol 6000 and titanium dioxide. 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 atherosclerotic cardiovascular disease as evidenced by stroke or transient ischemic attacks, myocardial infarction, or need for 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 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 in healthy volunteers receiving 75 mg of PLAVIX per day. No dosage adjustment is needed in renally impaired patients.

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 the CAPRIE (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events) trial. This 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).

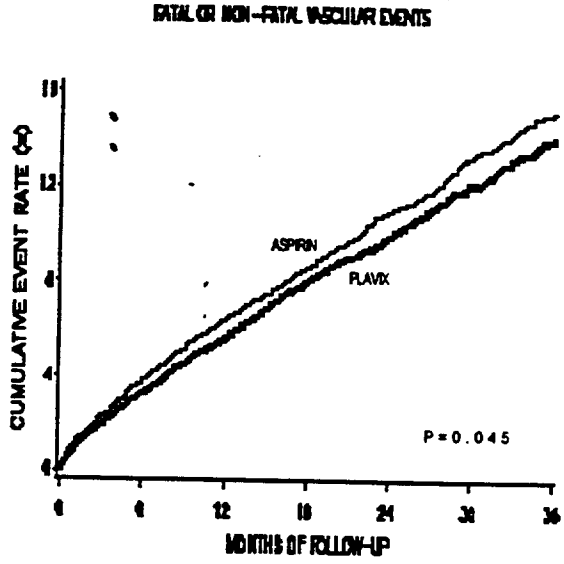
The trial's primary outcome was the time to first occurrence of new ischemic stroke (fatal or not), new myocardial infarction (fatal or not), or other vascular death. Deaths not easily attributable to nonvascular causes were all classified as vascular.

Outcome Events of the Primary Analysis

	PLAVIX	aspirin
Patients	9599	9586
IS (fatal or not)	438 (4.56%)	461 (4.81%)
MI (fatal or not)	275 (2.86%)	333 (3.47%)
Other vascular death	226 (2.35%)	226 (2.36%)
Total	939 (9.78%)	1020 (10.64%)

As shown in the table, PLAVIX was associated with a lower incidence of outcome events of every kind. The overall risk reduction (9.78% vs. 10.64%) 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 the figure. The event curves separated early and continued to diverge over the 3-year follow-up period.



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 atherothrombotic 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.

INDICATIONS AND USAGE

PLAVIX is indicated 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.

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

None.

PRECAUTIONS

General
As with other anti-platelet agents, PLAVIX should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions. If a patient is to undergo elective surgery and an antiplatelet effect is not desired, PLAVIX should be discontinued 7 days prior to surgery.

GI Bleeding: PLAVIX prolongs the bleeding time. In CAPRIE, PLAVIX was associated with a rate of gastrointestinal bleeding of 2.0%, vs. 2.7% on aspirin. 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 (such as aspirin and other nonsteroidal anti-inflammatory drugs [NSAIDs]) 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.

Information for Patients

Patients should be told that it may take them longer than usual to stop bleeding when they take PLAVIX, and that they should report any unusual bleeding to their physician. Patients should inform physicians and dentists that they are taking PLAVIX 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. The safety of chronic concomitant administration of aspirin and PLAVIX has not been established.

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. The safety of this combination has not been established, however, and concomitant use should be undertaken with caution.

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: The safety of the coadministration of PLAVIX with warfarin has not been established. Consequently, concomitant administration of these two agents 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.

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 CAPRIE received a variety of concomitant medications **including diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents, antiepileptic agents** and **hormone replacement therapy** without evidence of clinically significant adverse interactions.

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.

ADVERSE REACTIONS

PLAVIX has been evaluated for safety in more than 11,300 patients, including over 7,000 patients treated for 1 year or more. The overall tolerability of PLAVIX 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. The clinically important adverse events observed in CAPRIE are discussed below.

Hemorrhagic: In patients receiving PLAVIX in CAPRIE, 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.

Neutropenia/agranulocytosis: Ticlopidine, a drug chemically similar to PLAVIX, is associated with a 0.8% rate of severe neutropenia (less than 450 neutrophils/μL). Patients in CAPRIE (see Clinical Trials) were intensively monitored for neutropenia. Severe neutropenia was observed in six patients, four on PLAVIX and two on aspirin. Two of the 9599 patients who received PLAVIX and none of the 9586 patients who received aspirin had neutrophil counts of zero.

One of the four PLAVIX patients was receiving cytotoxic chemotherapy, and another recovered and returned to the trial after only temporarily interrupting treatment with PLAVIX.

Although the risk of myelotoxicity with PLAVIX thus appears to be quite low, this possibility should be considered when a patient receiving PLAVIX demonstrates fever or other sign of infection.

Gastrointestinal: Overall, the incidence of gastrointestinal events (e.g. abdominal pain, dyspepsia, gastritis and constipation) in patients receiving PLAVIX was 27.1%, compared to 29.8% in those receiving aspirin.

The incidence of peptic, gastric or duodenal ulcers was 0.7% for PLAVIX and 1.2% for aspirin.

Cases of diarrhea were reported in 4.5% of patients in the PLAVIX group compared to 3.4% in the aspirin group. However, these were rarely severe (PLAVIX=0.2% and aspirin= 0.1%).

The incidence of patients withdrawing from treatment because of gastrointestinal adverse reactions was 3.2% for PLAVIX and 4.0% for aspirin.

Rash and Other Skin Disorders: The incidence of skin and appendage disorders in patients receiving PLAVIX was 15.8% (0.7% serious); the corresponding rate in aspirin patients was 13.1% (0.5% serious).

The overall incidence of patients withdrawing from treatment because of skin and appendage disorders adverse reactions was 1.5% for PLAVIX and 0.8% for aspirin.

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 maximum of 3 years.

Adverse Events Occurring in ≥2.5% of PLAVIX Patients

	% Incidence (% Discontinuation)	
Body System Event	PLAVIX [n=9599]	Aspirin [n=9586]
Body as a Whole - general disorders		
Chest Pain	8.3 (0.2)	8.3 (0.3)
Accidental 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		
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	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		
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)

Incidence of discontinuation, regardless of relationship to therapy, is shown in parentheses.

Other adverse experiences of potential importance occurring in 1% to 2.5% of patients receiving PLAVIX in the CAPRIE controlled clinical trial are listed below regardless of relationship to PLAVIX. In general, the incidence of these events was similar in the aspirin-treated group.

Autonomic Nervous System Disorders: Syncope, Palpitation. *Body as a Whole - general disorders:* Asthenia, Hernia. *Cardiovascular disorders:* Cardiac failure. *Central and peripheral nervous system disorders:* Cramps legs, Hypoaesthesia, Neuralgia, Paraesthesia, Vertigo. *Gastro-intestinal 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 are listed below regardless of relationship to PLAVIX. In general, the incidence of these events was similar in the aspirin group.

Body as a whole: Allergic reaction, necrosis ischemic. *Cardiovascular disorders:* Edema generalized. *Gastrointestinal system disorders:* 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 maculo-papular, urticaria. *White cell and reticuloendothelial system disorders:* Agranulocytosis, granulocytopenia, leukemia, leukopenia, neutrophils decreased.

OVERDOSAGE

One case of deliberate overdosage with PLAVIX was reported in the large, controlled clinical study. A 34-year-old woman took a single 1,050-mg dose of PLAVIX (equivalent to 14 standard 75-mg tablets). There were no associated adverse events. No special therapy was instituted, and she recovered without sequelae.

No adverse events were reported after single oral administration of 600 mg (equivalent to 8 standard 75-mg tablets) of PLAVIX in healthy volunteers. The bleeding time was prolonged by a factor of 1.7, which is similar to that typically observed with the therapeutic dose of 75 mg of PLAVIX per day.

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

The recommended dose of PLAVIX is 75 mg once daily 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 is available as a pink, round, biconvex, film-coated tablet engraved with "75" on one side. Tablets are provided as follows:

NDC 63653-1171-4 bottles of 100
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]

Caution: Federal law prohibits dispensing without a prescription.

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

PLAVIX® is a registered trademark of Sanofi

Date of Labeling Approval

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20839

MEDICAL REVIEW(S)

Medical Review

NDA #: 20-839/BM
Drug Name: clopidogrel
Type of Document: Response to info request
Date Received: 10/31/97
Medical Reviewer: Charles J. Ganley, M.D.

NDA Volume:
Sponsor: Sanofi
Correspondence Date: 10/30/97
Date Completed: 11/04/97

This submission includes information from the case report forms of 10 patients[1] who were lost to follow-up for the greatest period of time prior to their completion of the trial. The information documents the communication between the investigator/center and the patient. All of the cases appear to adequately document non-fatal and fatal endpoint events with one exception. The notes provided for patient 714-002 are unintelligible.

Conclusion

This sample of patients provides some evidence of the adequacy of follow-up. No additional documentation is required for other patients lost to follow-up prior to final communication since it will have little impact on the approvability of the drug.

Other Issues

The CAPRIE Trial did not adhere to the protocol specified termination and follow-up of approximately 944 patients. Of these, 149 had less than one year of follow-up. There is no reason to force the sponsor to go out and find the status of these patients up to the time of their expected termination date because the outcome would have no impact on the approvability of clopidogrel.[2] In future morbidity/mortality trials, the sponsor should insure the following:

- All patients should have complete follow-up up to their expected termination date. Patients who do not have follow-up to their expected termination date should be classified as lost to follow-up rather than as having completed the study.
- If follow-up is to be performed by any method other than an office visit, there should be full documentation in the case report form of who made the contact, who was contacted, specific questions regarding the endpoint of interest and the method of communication (e.g. phone, letter).
- In many cases, protocol specific issues which were communicated as Bulletins to the investigators should have been submitted to the IND as amendments to the protocol.

Charles J. Ganley, M.D.

cc: orig.
HFD-110
HFD-110 / Project Manager / C. Ganley / R. Fenichel

[1] early permanent discontinuations lost to follow-up for > 1 year prior to final contact
[2] The labeling does not suggest superiority to aspirin. If it had, then further follow-up might be warranted.

NOV 3 1997

Medical Review

NDA #: 20-839/BM
Drug Name: clopidogrel
Type of Document: Response to info request
Date Received: 10/22/97
Medical Reviewer: Charles J. Ganley, M.D.

NDA Volume:
Sponsor: Sanofi
Correspondence Date: 10/22/97
Date Completed: 11/3/97

The sponsor, as per FDA request, provides information on the follow-up for 70 clopidogrel and 33 placebo patients who were lost to follow-up for > 1 year prior to their final visit. A listing for these patients is attached.

The majority of contacts were made by phone (85%), by the study coordinator (≈ 75 - 80 %), to the patient (≈ 65%) and specific questions were asked with regard to non-fatal outcomes (80 - 85%).

Regulatory Action

Documentation of follow-up has been requested for the ten clopidogrel patients with the greatest duration of lost to follow-up prior to the final visit.

Charles J. Ganley, M.D.

cc: orig.
HFD-110
HFD-110 / Project Manager / C. Ganley / R. Fenichel

ATTACHMENT 2: CAPRIE
CLOPIDOGREL PATIENTS
THAT WERE EARLY PERMANENT DISCONTINUATIONS,
WHOSE LAST VISIT PREVIOUS TO THE FINAL FOLLOW-UP VISIT WAS > 1 YEAR
AND WHO HAD NO PRIMARY OUTCOME EVENTS RECORDED

Site # (000)	Patient # (0000)	Who made contact?	Type of Contact:	Contact with:	Assessment of Vital Status	Specific Questions Asked About Non-Fatal OE	Assessment of OE From Time of Last Visit Visit until FFV
001	0017	study coord. or nurse	phone	patient	yes	yes	yes
001	0023	study coord. or nurse	phone	patient	yes	yes	yes
001	0035	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
002	0027	study coord. or nurse	phone	patient	yes	uncertain	yes
002	0031	study coord. or nurse	phone	patient	yes	yes	yes
006	0038	study coord. or nurse	written	patient	yes	yes	yes
008	0003	study coord. or nurse	phone	patient	yes	yes	yes
014	0015	study coord. or nurse	phone	patient	yes	yes	yes
020	0012	study coord. or nurse	phone	physician providing care	yes	yes	yes
023	0041	study coord. or nurse	home visit	patient	yes	yes	yes
024	0019	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
024	0033	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
027	0041	study coord. or nurse	written	patient	yes	yes	yes
028	0543	study coord. or nurse	written	patient	yes	yes	yes
032	0099	health professional[1]	phone	patient	yes	yes	yes
037	0011	study coord. or nurse	phone	health professional	yes	no	no[9]
037	0044	study coord. or nurse	phone	relative or caregiver	yes	no	uncertain
042	0030	study coord. or nurse	phone	patient	yes	yes	yes
046	0004	study coord. or nurse	phone	physician providing care	yes	yes	yes
049	0022	study coord. or nurse	phone	patient	yes	yes	yes
049	0042	study coord. or nurse	phone	patient	yes	yes	yes
049	0055	study coord. or nurse	phone	patient	yes	yes	yes
052	0027	study coord. or nurse	phone	relative or caregiver	yes	uncertain	uncertain
059	0041	study coord. or nurse	phone	relative or caregiver	yes	no	yes
071	0034	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
072	0015	study coord. or nurse	phone	patient	yes	yes	uncertain
078	0029	study coord. or nurse	phone	patient	yes	yes	yes
079	0033	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
081	0005	study coord. or nurse	phone	patient	yes	yes	yes
082	0019	health professional[2]	phone	patient	yes	no	no[10]
083	0029	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
084	0004	study coord. or nurse	phone	patient	yes	yes	yes
084	0008	study coord. or nurse	phone	patient	yes	yes	yes
090	0073	study coord. or nurse	other[4]	health professional	yes	yes	yes
092	0006	study coord. or nurse	phone	patient	yes	yes	yes
101	0012	study coord. or nurse	phone	patient	yes	yes	yes
101	0032	study coord. or nurse	phone	patient	yes	yes	yes
101	0040	study coord. or nurse	phone	patient	yes	yes	yes
104	0010	study coord. or nurse	phone	patient	yes	yes	yes
107	0020	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
112	0026	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
117	0007	study coord. or nurse	phone	patient	yes	yes	yes
118	0013	study coord. or nurse	phone	patient	yes	yes	yes
128	0037	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
128	0038	study coord. or nurse	phone	health professional	yes	yes	yes
129	0003	study coord. or nurse	phone	physician providing care	yes	yes	yes
133	0002	invest or subinvestigator	other[5]	physician providing care	yes	yes	yes
504	0006	invest or subinvestigator	other[6]	patient	yes	yes	yes
524	0016	health professional[3]	phone	patient	yes	yes	yes
611	0016	study coord. or nurse	phone	patient	yes	yes	yes
612	0086	study coord. or nurse	phone	patient	yes	yes	yes
612	0161	study coord. or nurse	phone	patient	yes	yes	yes
662	0028	invest or subinvestigator	phone	relative or caregiver	yes	yes	yes
663	0015	invest or subinvestigator	phone	patient	yes	yes	yes
663	0021	invest or subinvestigator	phone	patient	yes	yes	yes

ATTACHMENT 2: CAPRIE
CLOPIDOGREL PATIENTS
THAT WERE EARLY PERMANENT DISCONTINUATIONS,
WHOSE LAST VISIT PREVIOUS TO THE FINAL FOLLOW-UP VISIT WAS > 1 YEAR
AND WHO HAD NO PRIMARY OUTCOME EVENTS RECORDED

Site # (000)	Patient # (0000)	Who made contact?	Type of Contact:	Contact with:	Assessment of Vital Status	Specific Questions Asked About Non-Fatal OE	Assessment of OE From Time of Last Visit Visit until FFV
681	0005	invest or subinvestigator	phone	patient	yes	yes	yes
681	0013	invest or subinvestigator	phone	patient	yes	yes	yes
703	0049	study coord. or nurse	phone	physician providing care	yes	uncertain	uncertain
706	0039	study coord. or nurse	phone	patient	yes	yes	yes
706	0067	study coord. or nurse	phone	patient	yes	yes	yes
706	0199	study coord. or nurse	phone	patient	yes	yes	yes
706	0210	study coord. or nurse	home visit	patient	yes	yes	yes
708	0052	study coord. or nurse	phone	patient	yes	yes	yes
711	0065	study coord. or nurse	phone	patient	yes	uncertain	no
712	0100	study coord. or nurse	other[7]	patient	yes	uncertain	yes
714	0002	study coord. or nurse	written	physician providing care	yes	uncertain	yes
841	0088	invest or subinvestigator	phone	relative or caregiver	yes	yes	yes
845	0004	invest or subinvestigator	phone	patient	yes	yes	yes
881	0065	invest or subinvestigator	phone	patient	yes	uncertain	yes
881	0081	invest or subinvestigator	other[8]	patient	yes	uncertain	yes

[1] health professional = M.D. neurologist

[2] health professional = physician's assistant

[3] health professional = physician's medical secretary. In France, there is special training for a medical secretary.

[4] other = medical chart

[5] other = investigator's personal visit to the patient's internist

[6] other = patient's visit to a hospital

[7] other = patient seen in hospital clinic unrelated to CAPRIE study

[8] other = medical consultation

[9] Assessed only for vital status and this was assessed for the entire period from the visit previous to the FFV until the FFV.

[10] Assessed only for vital status and this was assessed for the entire period from the visit previous to the FFV until the FFV.

ATTACHMENT 3: CAPRIE
ASPIRIN PATIENTS
THAT WERE EARLY PERMANENT DISCONTINUATIONS,
WHOSE LAST VISIT PREVIOUS TO THE FINAL FOLLOW-UP VISIT WAS >1 YEAR
AND WHO HAD NO PRIMARY OUTCOME EVENTS REPORTED

Site # (000)	Patient # (0000)	Who made contact?	Type of Contact:	Contact with:	Assessment of Vital Status	Specific Questions Asked about Non-fatal OE	Assessment of OE From Time of Last Visit Visit until FFV
001	0011	study coord. or nurse	phone	patient	yes	yes	yes
001	0031	study coord. or nurse	phone	patient	yes	yes	yes
002	0039	study coord. or nurse	phone	patient	yes	yes	yes
037	0002	study coord. or nurse	phone	relative or caregiver	yes	yes	no
037	0042	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
049	0028	study coord. or nurse	phone	patient	yes	yes	yes
049	0035	study coord. or nurse	phone	patient	yes	yes	yes
049	0072	study coord. or nurse	phone	patient	yes	yes	yes
059	0025	study coord. or nurse	phone	physician providing care	yes	no	yes
071	0091	study coord. or nurse	phone	patient	yes	yes	yes
081	0058	study coord. or nurse	phone	patient	yes	yes	yes
082	0036	study coord. or nurse	phone	patient	yes	yes	yes
092	0036	study coord. or nurse	phone	patient	yes	yes	yes
101	0011	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
107	0009	study coord. or nurse	phone	patient	yes	yes	yes
107	0050	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
118	0009	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
128	0002	invest or subinvestigator	phone	health professional	yes	yes	yes
128	0052	invest or subinvestigator	phone	relative or caregiver	yes	uncertain	uncertain
612	0002	study coord. or nurse	phone	physician providing care	yes	yes	yes
612	0056	study coord. or nurse	written	physician providing care	yes	no	yes
662	0009	invest or subinvestigator	phone	patient	yes	yes	yes
663	0051	invest or subinvestigator	phone	patient	yes	yes	yes
706	0002	study coord. or nurse	phone	patient	yes	yes	yes
706	0019	study coord. or nurse	phone	patient	yes	yes	yes
706	0054	study coord. or nurse	phone	patient	yes	yes	yes
706	0059	study coord. or nurse	phone	patient	yes	yes	yes
706	0185	study coord. or nurse	phone	patient	yes	yes	yes
708	0053	study coord. or nurse	other[2]	patient	yes	yes	yes
841	0020	other[1]	phone	patient	yes	yes	yes
845	0078	invest or subinvestigator	phone	patient	yes	yes	yes
881	0023	invest or subinvestigator	phone	patient	yes	uncertain	yes
881	0039	invest or subinvestigator	phone	patient	yes	uncertain	yes

[1] other = At this European site, after the patient refused to speak with the investigator, and at the investigator's request, the medical monitor contacted the patient to elicit information.

[2] other = patient's visit to outpatient clinic

APPEARS THIS WAY
ON ORIGINAL

D. Rieder

OCT 17 1997

Memo to NDA Record

NDA #: 20-839
Drug Name: clopidogrel
Type of Document: response to information request

Medical Reviewer: Charles J. Ganley, M.D.

NDA Volume:
Sponsor: Sanofi
Correspondence Dates: 9/10, 9/17, 9/23, 9/25, 10/3 and 10/6/97
Date Completed: 10/14/97

The information included in this review was obtained from submissions to the NDA dated 9/10/97, 9/17/97, 9/23/97, 9/25/97, 10/3/97 and 10/6/97. All of these submissions were responses to FDA requests for additional information. This review will deal almost exclusively with validation of the final follow-up visit dates for the patients in the CAPRIE trial.

The termination of patients from CAPRIE differed in some respects from other morbidity and mortality trials previously reviewed by the Cardio-Renal Division[1]. The CAPRIE end date is not specified in the protocol but is outlined in Bulletin 10.1 (see attached). The end date for each patient was defined as the final scheduled follow-up visit just prior to the end date for the subgroup[2] (i.e. Prior MI, Prior Stroke, PAD) or 3 years after the date of randomization, whichever came first. Table 1. lists the study end dates for each subgroup. The end date for a subgroup was 1 year after the enrollment end date for the subgroup. Patient follow-up visits were not supposed to occur after the follow-up end date.

Table 1. Subgroup End Dates

Subgroup	Enrollment End Date*	Follow-up End Date
PAD	10/31/94	10/31/95
MI	12/31/94	1/31/96
Stroke	2/28/95	2/29/96

* no patients randomized into the subgroup after this date

For surviving patients with less than 3 years of follow-up, the Coordinating Methods Center for the CAPRIE study provided each investigator with theoretical final follow-up visit dates for their patients. The theoretical final follow-up visit date should be the patient end date. This date coincided with the scheduled follow-up visit.[3] Investigators were requested to perform any follow-up visit within ± 14 days of the scheduled visit date. As such, a patient could be evaluated [4] up to 14 days prior to their theoretical final follow-up visit date.

Validation of the Minimum One Year Follow-up in Surviving Patients

In the CAPRIE trial, patients were to be followed for a minimum of one year to a maximum of 3 years from their day of randomization. In an analysis of duration of follow-up, 1411 surviving patients had less than 365 days of follow-up. Table 2. lists the frequency distribution of the duration of follow-up for patients with less than 365 days of follow-up.

Table 2. Number of Patients with Less Than 365 Days of Follow-up

Duration of Follow-up (days)	N
358 - 364	1020
351 - 357	243
≤ 350	149

[1] Typically, morbidity/mortality trials have a study end date. The end date may be derived by the date a pre-specified number of endpoints is reached or it may reflect a pre-specified timepoint from the date the last patient was randomized. Generally, on this end date, the status of all randomized patients with regard to morbidity/mortality is known. The exception to this occurs when the duration of follow-up for patients is a set period of time (e.g. 2 years from their randomization date).
[2] the end date for each subgroup was 1 year from the enrollment end date for the subgroup (see Bulletin 10.1)
[3] from the CAPRIE Clinical Center Module page 26 (version 2.0) - All visits should be scheduled in relation to the date of randomization.
[4] by an office visit or contact by other means (e.g. letter, phone call)

The clinical center module of the Operations Manual[5] permitted the 4 month visits to occur within a window of ± 14 days. This would have permitted investigators to have a 14 day window around the 1 year follow-up visit date. Consequently, patients could have ≥ 351 days of follow-up and be considered to have fulfilled the one year of follow-up. One hundred and forty nine patients (78 aspirin, 71 clopidogrel; 77 PAD, 33 Prior Stroke, 39 Prior MI) had less than 351 days of follow-up. A complete list of these patients is included in the appendix. All of these patients were considered to have completed the study even though they did not complete 1 year of follow-up. A brief summary outlining the reason four patients (patient numbers: 052-0117, 300-0379, 308-0229, 309-0339) did not complete 365 days of follow-up are provided on appendix page vi. Based on this small sampling of patients, it is clear that follow-up should have been continued. Explanations for the remaining 145 patients has not been requested.

Completion Dates

The sponsor provided the FDA with a SAS program that determined the theoretical final follow-up visit date for each surviving patient with less than 3 years of follow-up. When this date is compared to the actual completion dates for each patient, 1009 patients had their final visit prior to the theoretical final follow-up date. If patients with a primary outcome event are excluded, 944 patients had visits prior to their theoretical final follow-up visit date. Table 2 lists the distribution among subgroups and treatment groups. Investigators in the PAD centers were less likely to adhere to the protocol with regard to evaluating patients on or after their scheduled termination visit.

Table 2. Number Of Patients Who Completed The Trial Prior To Their Scheduled Final Follow-Up Visit Date (excludes patients lost to follow-up and patients with outcome events)

	Stroke Subgroup	MI Subgroup	PAD Subgroup	Total
Clopidogrel	112	105	234	451
Aspirin	125	106	262	493
Total	237	211	495	944

Lost To Follow-Up

In the process of evaluating the completion dates of patients, the sponsor provided a brief summary for patient 020-0012 which outlined the circumstances surrounding the completion of this patient prior to their theoretical final follow-up visit date. Patient 020-0012 was randomized on 3/13/93 and was an early permanent discontinuation on 4/20/93. Subsequent follow-up visits showed that the patient was not contacted until the final follow-up visit of 9/22/95 (see attached follow-up form appendix page vii). The CRF simply documents that the patient was not seen at the center but was contacted by other means (e.g. by letter, by telephone, home visit or other) . The sponsor provided information that the investigator contacted the patient's General Practitioner who provided information regarding the patient's status. None of this information is documented in the case report form.

The case of patient 020-0012 raised some concerns because this patient was essentially lost to follow-up for over 2 years until the final follow-up visit. Because the primary endpoint involves the documentation of non-fatal events, questions were raised regarding the adequacy of follow-up[6] of patients who were early permanent discontinuations. The Steering Committee minutes of 3/24/95 allude to a problem with patients lost to follow-up (see appendix page viii) specifically among those who were early permanent discontinuations. The sponsor was asked to provide information on the number of patients who were early permanent discontinuations and who were lost to follow-up at the visit prior to their final follow-up visit or who had missed the visit prior to their final follow-up visit. Among patients who were early permanent discontinuations, 546 patients (264 aspirin, 282 clopidigrel; 154 stroke, 167 MI, 225 PAD) were lost to follow-up prior to their final follow-up visit and were not evaluated in person at the investigator's center. Table 3 lists the distribution among treatment and subgroups as a function of time lost to follow-up prior to the final visit.

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[5] page 26 of version 2.0

[6] particularly pertaining to the documentation of non-fatal events

Table 3. Number Of Early Permanent Discontinued Patients Lost To Follow-Up Prior To Their Final Follow-Up Visit.

	Treatment	Subgroup			
		Stroke	MI	PAD	Total
< 6 months	Aspirin	26	25	34	85
	Clopidigrel	27	16	34	77
	Total	53	41	68	162
6 - 12 months	Aspirin	19	44	53	116
	Clopidigrel	36	39	60	135
	Total	55	83	113	251
> 12 months	Aspirin	19	21	23	63
	Clopidigrel	27	22	21	70
	Total	46	43	44	133

Discussion

Adherence to the protocol, especially with respect to the termination of patients from the trial, is of paramount importance in morbidity/mortality studies. The failure to follow patients to their scheduled end date ultimately raises questions as to whether the early termination was deliberate (e.g. because of deterioration in clinical status or the presence of adverse experiences), by chance (e.g. simply a failure to adhere to the protocol) or a combination of both. The obvious concern is that endpoint events may not be documented. If the early termination of a patient is deliberate, one must determine if it was done with some knowledge of the patient's treatment assignment. Because of the inability of the Agency to adequately validate blinding of a study, it becomes important that the pre-specified procedures in the protocol be followed. When the findings are not robust, as is the case with CAPRIE with a marginally significant p value, a failure to capture a small number of events could have an impact of the statistical significance of the primary endpoint.

More than 5% of the survivors in CAPRIE had their final follow-up visit prior to their theoretical final follow-up visit date. The majority of these patients were from the PAD subgroup (495 of 944) and aspirin treatment group (493 of 944). Of these, 149 had less than the one year minimum follow-up. From the small sample of histories reviewed (see appendix page vi), it is clear that follow-up should have been continued for one year. ≠ 10,000

The cohort of patients who were early permanent discontinuations presented additional problem. In this group of patients, an office visit was not required for follow-up. As a consequence, 546 early permanent discontinued patients[7] were not evaluated in the office on their final visit and were lost to follow-up prior to that visit. Additional information will be required from the sponsor on a subgroup of these patients to document adequate follow-up with regard to the ascertainment of events.

Charles J. Ganley, M.D.

James Hung, Ph.D.

cc: orig.
HFD-110
HFD-110 / cso /ganley/fenichel/fredd
HFD-710/hung/mahjoob/chi

Concur: Dr. Mahjoob, Ph.D. 10/14/97

Dr. Chi, Ph.D. 10/17/97

appendix
List Of Patients With Less Than 1 Year Of Follow-Up
Bulletin 10.1
Summary of Four Surviving Patients with the Shortest Follow-up
Excerpt From Steering Committee Minutes March 24, 1995
Follow-Up Visit Form For Patient 020-0012

[7] these patients did not have a primary event

Patients with < 351 Days of Follow-up

Patient ID	Dose	Pre-existing Condition	Completion Date	Randomization Date	Duration (days)
01633 300 0379	clopidogrel	MINF	16-Oct-95	30-Jan-95	259
01633 309 0339	clopidogrel	PAD	1-Aug-95	6-Oct-94	299
01633 308 0229	Aspirin	MINF	18-Oct-95	21-Dec-94	301
01633 052 0117	clopidogrel	MINF	15-Nov-95	17-Jan-95	302
01633 706 0310	clopidogrel	PAD	23-Aug-95	14-Oct-94	313
01633 107 0083	Aspirin	MINF	11-Dec-95	30-Jan-95	315
01633 884 0047	Aspirin	MINF	29-Oct-95	15-Dec-94	318
01633 665 0056	Aspirin	PAD	4-Aug-95	20-Sep-94	318
01633 665 0053	Aspirin	PAD	18-Jul-95	2-Sep-94	319
01633 706 0330	Aspirin	PAD	15-Sep-95	31-Oct-94	319
01633 023 0115	Aspirin	PAD	12-Sep-95	26-Oct-94	321
01633 706 0276	clopidogrel	PAD	26-Jul-95	8-Sep-94	321
01633 023 0118	Aspirin	PAD	20-Sep-95	31-Oct-94	324
01633 706 0284	clopidogrel	PAD	4-Aug-95	12-Sep-94	326
01633 300 0631	Aspirin	PAD	21-Jun-95	28-Jul-94	328
01633 612 0277	Aspirin	PAD	21-Sep-95	28-Oct-94	328
01633 069 0053	Aspirin	ISTR	16-Jan-96	21-Feb-95	329
01633 307 0127	Aspirin	ISTR	23-Jan-96	28-Feb-95	329
01633 076 0072	clopidogrel	PAD	30-Aug-95	5-Oct-94	329
01633 706 0314	Aspirin	PAD	8-Sep-95	14-Oct-94	329
01633 517 0052	Aspirin	MINF	2-Nov-95	6-Dec-94	331
01633 681 0034	clopidogrel	PAD	2-Aug-95	5-Sep-94	331
01633 773 0205	clopidogrel	PAD	23-Aug-95	26-Sep-94	331
01633 131 0121	Aspirin	ISTR	19-Jan-96	21-Feb-95	332
01633 612 0275	clopidogrel	PAD	26-Sep-95	28-Oct-94	333
01633 612 0278	Aspirin	PAD	26-Sep-95	28-Oct-94	333
01633 618 0233	clopidogrel	PAD	4-Sep-95	6-Oct-94	333
01633 612 0276	Aspirin	PAD	27-Sep-95	28-Oct-94	334
01633 006 0113	clopidogrel	ISTR	24-Jan-96	22-Feb-95	336
01633 107 0071	clopidogrel	MINF	21-Sep-95	20-Oct-94	336
01633 612 0237	Aspirin	PAD	24-Jul-95	22-Aug-94	336
01633 612 0251	Aspirin	PAD	1-Aug-95	30-Aug-94	336
01633 612 0274	clopidogrel	PAD	28-Sep-95	27-Oct-94	336
01633 703 0068	clopidogrel	PAD	31-Aug-95	29-Sep-94	336
01633 131 0088	clopidogrel	ISTR	4-Oct-95	1-Nov-94	337
01633 612 0240	Aspirin	PAD	25-Jul-95	22-Aug-94	337
01633 684 0064	clopidogrel	PAD	26-Sep-95	24-Oct-94	337
01633 706 0294	Aspirin	PAD	26-Aug-95	23-Sep-94	337
01633 131 0099	Aspirin	ISTR	27-Oct-95	23-Nov-94	338
01633 634 0217	Aspirin	MINF	6-Dec-95	2-Jan-95	338
01633 706 0242	clopidogrel	PAD	27-Jul-95	23-Aug-94	338
01633 024 0079	clopidogrel	MINF	12-Oct-95	7-Nov-94	339
01633 706 0305	Aspirin	PAD	9-Sep-95	5-Oct-94	339
01633 023 0111	Aspirin	PAD	20-Aug-95	14-Sep-94	340
01633 006 0109	Aspirin	ISTR	3-Jan-96	27-Jan-95	341
01633 044 0068	Aspirin	ISTR	6-Nov-95	30-Nov-94	341

Patients with < 351 Days of Follow-up

Patient ID	Dose	Pre-existing Condition	Completion Date	Randomization Date	Duration (days)
01633 131 0107	Aspirin	ISTR	11-Dec-95	3-Jan-95	342
01633 579 0040	Aspirin	ISTR	29-Jan-96	21-Feb-95	342
01633 311 0060	clopidogrel	MINF	8-Jan-96	31-Jan-95	342
01633 788 0042	clopidogrel	MINF	21-Dec-95	13-Jan-95	342
01633 093 0057	clopidogrel	PAD	20-Jun-95	13-Jul-94	342
01633 706 0292	clopidogrel	PAD	27-Aug-95	19-Sep-94	342
01633 511 0023	Aspirin	ISTR	2-Feb-96	24-Feb-95	343
01633 848 0039	clopidogrel	ISTR	29-Jan-96	20-Feb-95	343
01633 034 0024	clopidogrel	MINF	10-Nov-95	2-Dec-94	343
01633 111 0036	Aspirin	MINF	12-Sep-95	4-Oct-94	343
01633 711 0171	Aspirin	MINF	19-Dec-95	10-Jan-95	343
01633 068 0082	clopidogrel	PAD	6-Sep-95	28-Sep-94	343
01633 577 0032	Aspirin	PAD	12-Sep-95	4-Oct-94	343
01633 706 0278	Aspirin	PAD	18-Aug-95	9-Sep-94	343
01633 706 0332	clopidogrel	PAD	9-Oct-95	31-Oct-94	343
01633 708 0119	Aspirin	PAD	18-Jul-95	9-Aug-94	343
01633 773 0236	Aspirin	PAD	5-Oct-95	27-Oct-94	343
01633 051 0066	Aspirin	PAD	7-Sep-95	28-Sep-94	344
01633 044 0075	clopidogrel	ISTR	2-Feb-96	22-Feb-95	345
01633 008 0088	clopidogrel	MINF	11-Jan-96	31-Jan-95	345
01633 115 0035	clopidogrel	MINF	10-Jan-96	30-Jan-95	345
01633 122 0050	clopidogrel	MINF	5-Jan-96	25-Jan-95	345
01633 093 0061	Aspirin	PAD	5-Oct-95	25-Oct-94	345
01633 053 0033	clopidogrel	ISTR	8-Feb-96	27-Feb-95	346
01633 018 0082	Aspirin	MINF	8-Dec-95	27-Dec-94	346
01633 028 0169	Aspirin	MINF	11-Jan-96	30-Jan-95	346
01633 052 0100	Aspirin	MINF	16-Oct-95	4-Nov-94	346
01633 665 0059	clopidogrel	PAD	25-Sep-95	14-Oct-94	346
01633 706 0241	Aspirin	PAD	22-Jul-95	10-Aug-94	346
01633 706 0324	clopidogrel	PAD	9-Oct-95	28-Oct-94	346
01633 023 0119	clopidogrel	ISTR	5-Dec-95	23-Dec-94	347
01633 511 0024	clopidogrel	ISTR	9-Feb-96	27-Feb-95	347
01633 013 0056	clopidogrel	MINF	1-Nov-95	19-Nov-94	347
01633 059 0050	Aspirin	MINF	8-Jan-96	26-Jan-95	347
01633 788 0040	clopidogrel	MINF	18-Dec-95	5-Jan-95	347
01633 773 0232	clopidogrel	PAD	3-Oct-95	21-Oct-94	347
01633 204 0033	Aspirin	ISTR	29-Nov-95	16-Dec-94	348
01633 309 0254	clopidogrel	MINF	4-Oct-95	21-Oct-94	348
01633 929 0013	Aspirin	MINF	2-Oct-95	19-Oct-94	348
01633 612 0269	clopidogrel	PAD	27-Sep-95	14-Oct-94	348
01633 706 0268	Aspirin	PAD	21-Aug-95	7-Sep-94	348
01633 008 0091	Aspirin	ISTR	17-Jan-96	2-Feb-95	349
01633 029 0050	clopidogrel	ISTR	12-Feb-96	28-Feb-95	349
01633 033 0069	Aspirin	ISTR	7-Feb-96	23-Feb-95	349
01633 313 0042	Aspirin	ISTR	8-Feb-96	24-Feb-95	349
01633 508 0045	Aspirin	ISTR	12-Dec-95	28-Dec-94	349
01633 607 0103	clopidogrel	ISTR	8-Feb-96	24-Feb-95	349

Patients with < 351 Days of Follow-up

Patient ID	Dose	Pre-existing Condition	Completion Date	Randomization Date	Duration (days)
01633 609 0162	Aspirin	ISTR	22-Nov-95	8-Dec-94	349
01633 011 0045	clopidogrel	MINF	4-Jan-96	20-Jan-95	349
01633 106 0047	clopidogrel	MINF	25-Sep-95	11-Oct-94	349
01633 200 0027	clopidogrel	MINF	28-Nov-95	14-Dec-94	349
01633 619 0049	Aspirin	MINF	18-Dec-95	3-Jan-95	349
01633 135 0023	clopidogrel	PAD	10-Oct-95	26-Oct-94	349
01633 612 0267	clopidogrel	PAD	28-Sep-95	14-Oct-94	349
01633 612 0268	clopidogrel	PAD	28-Sep-95	14-Oct-94	349
01633 612 0270	Aspirin	PAD	28-Sep-95	14-Oct-94	349
01633 706 0236	Aspirin	PAD	5-Jul-95	21-Jul-94	349
01633 706 0265	clopidogrel	PAD	15-Aug-95	31-Aug-94	349
01633 706 0321	Aspirin	PAD	11-Oct-95	27-Oct-94	349
01633 007 0045	clopidogrel	ISTR	11-Jan-96	26-Jan-95	350
01633 075 0052	Aspirin	ISTR	10-Jan-96	25-Jan-95	350
01633 131 0123	clopidogrel	ISTR	9-Feb-96	24-Feb-95	350
01633 305 0153	clopidogrel	ISTR	21-Dec-95	5-Jan-95	350
01633 604 0050	clopidogrel	ISTR	6-Nov-95	21-Nov-94	350
01633 771 0091	Aspirin	ISTR	12-Feb-96	27-Feb-95	350
01633 771 0092	Aspirin	ISTR	12-Feb-96	27-Feb-95	350
01633 844 0040	Aspirin	ISTR	30-Nov-95	15-Dec-94	350
01633 883 0131	clopidogrel	ISTR	30-Oct-95	14-Nov-94	350
01633 028 0167	Aspirin	MINF	10-Jan-96	25-Jan-95	350
01633 028 0168	Aspirin	MINF	11-Jan-96	26-Jan-95	350
01633 037 0073	Aspirin	MINF	4-Dec-95	19-Dec-94	350
01633 037 0074	clopidogrel	MINF	11-Jan-96	26-Jan-95	350
01633 065 0064	clopidogrel	MINF	15-Jan-96	30-Jan-95	350
01633 119 0038	clopidogrel	MINF	25-Oct-95	9-Nov-94	350
01633 624 0125	clopidogrel	MINF	24-Oct-95	8-Nov-94	350
01633 624 0127	Aspirin	MINF	19-Oct-95	3-Nov-94	350
01633 624 0174	clopidogrel	MINF	16-Jan-96	31-Jan-95	350
01633 624 0175	Aspirin	MINF	16-Jan-96	31-Jan-95	350
01633 049 0080	clopidogrel	PAD	13-Jul-95	28-Jul-94	350
01633 055 0087	Aspirin	PAD	8-Aug-95	23-Aug-94	350
01633 081 0080	Aspirin	PAD	11-Aug-95	26-Aug-94	350
01633 135 0015	clopidogrel	PAD	25-Jul-95	9-Aug-94	350
01633 135 0020	clopidogrel	PAD	10-Oct-95	25-Oct-94	350
01633 528 0207	clopidogrel	PAD	24-Jul-95	8-Aug-94	350
01633 577 0031	clopidogrel	PAD	5-Sep-95	20-Sep-94	350
01633 610 0079	Aspirin	PAD	10-Oct-95	25-Oct-94	350
01633 612 0230	Aspirin	PAD	29-Jun-95	14-Jul-94	350
01633 706 0231	clopidogrel	PAD	4-Jul-95	19-Jul-94	350
01633 706 0232	clopidogrel	PAD	3-Jul-95	18-Jul-94	350
01633 706 0233	Aspirin	PAD	14-Jul-95	29-Jul-94	350
01633 706 0235	Aspirin	PAD	26-Jul-95	10-Aug-94	350
01633 706 0240	Aspirin	PAD	3-Jul-95	18-Jul-94	350
01633 706 0245	Aspirin	PAD	21-Jul-95	5-Aug-94	350
01633 706 0252	Aspirin	PAD	7-Aug-95	22-Aug-94	350

Patients with < 351 Days of Follow-up

Patient ID	Dose	Pre-existing Condition	Completion Date	Randomization Date	Duration (days)
01633 706 0258	Aspirin	PAD	10-Aug-95	25-Aug-94	350
01633 706 0260	Aspirin	PAD	9-Aug-95	24-Aug-94	350
01633 706 0261	clopidogrel	PAD	9-Aug-95	24-Aug-94	350
01633 706 0267	Aspirin	PAD	18-Aug-95	2-Sep-94	350
01633 706 0269	clopidogrel	PAD	16-Aug-95	31-Aug-94	350
01633 706 0270	Aspirin	PAD	17-Aug-95	1-Sep-94	350
01633 706 0272	Aspirin	PAD	16-Aug-95	31-Aug-94	350
01633 706 0328	clopidogrel	PAD	16-Oct-95	31-Oct-94	350
01633 706 0331	clopidogrel	PAD	16-Oct-95	31-Oct-94	350

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

CAPRIE BULLETIN . . . . . .

STOPPING OF PATIENT FOLLOW-UP

In Bulletin No. 10 we provided the dates of stopping patient recruitment for each of the three clinical groups and promised to let you know later the corresponding dates for stopping follow-up. The Steering Committee and the Development Decision Committee, a group of senior representatives of the Sponsors, have now agreed that:

There will be no patient follow-up visits beyond:

31 October, 1995	**for PAD patients**
31 January, 1996	**for MI patients**
29 February, 1996	**for Stroke patients**

The Final Visit for each patient will occur at the time of a regularly scheduled visit as per protocol.

Listings of individual patient follow-up schedules are being prepared by the Coordinating and Methods Centre and will be distributed to Clinical Centres shortly. These should facilitate the timely close-out for each patient.

There will be no compassionate drug use following completion of follow-up for individual patients. As indicated in the protocol, open-label Clopidogrel will not be available for patients completing the study since the relative efficacy of Clopidogrel and aspirin will not be established until after the study is completed and analyzed.

When the study data base is finally closed, it is planned to provide each Clinical Investigator with a list of their patients and corresponding allocated treatment and it will be up to each investigator as to whether or not this treatment allocation is made known to individual patients.

Michael Gent

Please Direct Inquiries To:

CAPRIE Coordinating and Methods Centre
Hamilton Civic Hospitals Research Centre
Henderson General Division
711 Concession Street
Hamilton, Ontario, Canada
L8V 1C3

(905) 527-2299, Ext. 2626 (Telephone)
(905) 575-2639 (Facsimile)

February 27, 1995

Bulletin No. 10.1

Summary of Four Surviving Patients with the Shortest Follow-up

Patient 052-0117 (302 days of follow-up): *This patient was randomized on 17 January 1995. The drug was temporarily discontinued due to adverse events (unstable angina and pruritus). Drug was not restarted because the patient withdrew consent secondary. Accordingly, the patient was an early permanent discontinuation (EPD) after only 1 month in the trial. The final contact with the patient was on 15 November 1995 and the CRF contained no information on why this visit was early.*

Patient 300-0379 (259 days of follow-up): *This patient was randomized on 30 January 1995. The month 6 visit was conducted on 01 June 1995 and the patient was considered an early permanent discontinuation (EPD) due to an adverse event. The month 8 visit for EPD follow-up was conducted on 16 October 1995 and listed as study completion. The patient should have returned for the month 12 visit but apparently, due to a misunderstanding by the study coordinator, the patient did not return for the visit.*

Patient 308-0229 (301 days of follow-up): *This patient was randomized on 21 December 1994. In August 1995 the patient was hospitalized with chest pain. At that time the patient was advised that if he had further episodes of chest pain he should undergo coronary artery bypass grafting (CABG). The patient experienced further chest pain and underwent CABG. CAPRIE drug was stopped for the surgery but the patient's surgeon did not want the patient to recommence CAPRIE study drug and started the patient on aspirin. The patient withdrew consent to continue in the CAPRIE study in August 1995; however, the investigator was able to get information on the patient's status as of 18 October 1995, and this was considered the last visit.*

Patient 309-0339 (299 days of follow-up): *The patient was randomized on 06 October 1994. The study coordinator apparently misunderstood when the final visits for PAD patients were to be conducted and performed the final follow-up visit on 01 August 1995. A visit to follow-up an ongoing adverse event occurred on 14 September 1995, however, this was after the patient was considered to have completed the study.*

Follow-up Visit Form for Patient 020-0012

	Drug No. SR 25990C Protocol No. P1633	Center No.	Patient No.	Visit No.		Page No in Form 1/1
		020	012	110	SD4	
– Patient Initials –				Date of contact (D D M M M Y Y)	07 JUL 95 (20 JUL 95)	

EARLY PERMANENT DISCONTINUATION FOLLOW-UP

NOTE: **This form should only be completed if study drug has been PERMANENTLY DISCONTINUED:**

Please continue to follow the patient according to their original study schedule and associated visit numbers.

A) FOLLOW-UP CONTACT

Please tick (✓) one box for each question

	YES	NO
Has the patient attended for a scheduled follow-up visit?	☐	☑

If NO:

	YES	NO
Has successful contact been made with the patient (e.g. by letter, by telephone, a home visit, or other)?	☑	☐

B) OUTCOME EVENTS (See Outcome Events definitions)

Please tick (✓) one box

	YES	NO	DON'T KNOW
Has the patient had an outcome event since the last follow-up visit?	☐	☑	☐

NOTE: **If YES, please complete: OUTCOME EVENTS FORM.**

If event was fatal, also complete: STUDY COMPLETION FORM.

I have reviewed each page of this completed assessment and accept full responsibility for the contents.

SIGNATURE _____ DATE 04 JUL 95 (D D M M M Y Y)

V.1.1. (8-92

Excerpt from Steering Committee Minutes of 3/24/95

(6) Patients Lost to Follow-up:

R.S. Roberts presented data on patients for whom the number of days since last known contact was greater than 180 days. These data were of concern given that (1) such patients cannot be taking study drug, and (2) the primary analysis is based on an intention-to-treat. In view of the different methods of early reporting of complete visits among the RDCCs, the CMC and Data Management Group Executive are attempting to assess the reliability of these data. It was recommended that Investigators be advised of the importance of re-establishing contact with potentially lost-to-follow up patients and to re-institute study drug therapy whenever possible. It appeared that the follow-up of EPDSD patients is less diligent than for patients still on study drug. This needs to be investigated further.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20839

CHEMISTRY REVIEW(S)

D. Rueda

AUG 6 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-839 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 1 Aug 97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	28 Apr 97	28 Apr 97	1 May 97
AMENDMENT	16 Jun 97	17 Jun 97	18 Jun 97

NAME & ADDRESS OF APPLICANT: Sanofi Pharmaceuticals, Inc.
9 Great Valley Parkway
Malvern, PA 19355

DRUG PRODUCT NAME:

Proprietary:	Plavix
Nonproprietary/USAN:	Clopidogrel (INN, BAN) Clopidogrel Bisulfate (USAN)
Code Name/#:	SR25590C
Chem.Type/Ther.Class:	1 P

PATENT STATUS: US 4,529,596, Sanofi SA, exp 7/5/03, Drug, Drug Product, Method of Use
US 4,847,265, Sanofi, exp 2/12/08, Drug, Drug Product
US 5,576,328, Elf Sanofi, exp 1/31/14, Method of Use

PHARMACOL.CATEGORY/INDICATION: Prevention of vascular ischemia

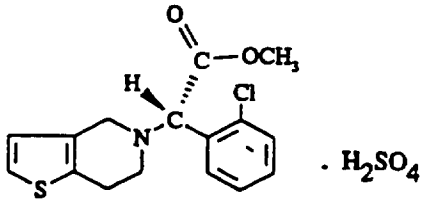
DOSAGE FORM: TCM

STRENGTHS: 75 mg

ROUTE OF ADMINISTRATION: Oral

DISPENSED: _x_ Rx ___ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Methyl (+)-(S)-α-(2-Chlorophenyl)-6,7-dihydrothieno(3,2-c)pyridine-5(4*H*)-acetate Hydrogen Sulfate

$C_{16}H_{16}ClNO_2S \cdot H_2SO_4$ Base: 321.83 Salt: 419.9

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable): None

CONSULTS: Environmental Assessment
Division of Biopharmaceutics

REMARKS/COMMENTS:

Most of the CMC information was submitted to IND IC170, on 14 Mar 97. All volume numbers not preceded by "N" refer to this submission (ie. v. 1, p.40). Where additional information was submitted to the NDA, the volume number is preceded by "N," ie. v. N1.3, p. 5.

A Request for Trademark Review, dated 11 Feb 97, was sent to the Labeling and Nomenclature Committee from HFD-530. A response was received from the Committee, dated 27 Mar 97, finding the proposed namae unaccepteble because of similarities to Flarex, Flavin and Lasix. The amendment of 16 Jun 97 is the applicant's response to the Agency's objections to their proposed Tradename.

CONCLUSIONS & RECOMMENDATIONS:

NOT APPROVABLE

The deficiencies noted during the review of this application are minor and should be easily corrected. None are of such a nature as to impede approval as far as the manufacturing and controls protion of the application is concerned.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/JShort/5/21/97
HFD-110/CSO
District
HFD-810/CHoiberg
R/D Init by: Rwolters/8/4/97

James H. Short, Ph.D., Review Chemist
filename: **N20-839.CR1**

SEP 12 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-839 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 11 Sep 97

SUBMISSION	TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL		28 Apr 97		
AMENDMENT	NC	28 Aug 97	2 Sep 97	4 Sep 97
AMENDMENT	BC	3 Sep 97	5 Sep 97	7 Sep 97

NAME & ADDRESS OF APPLICANT: Sanofi Pharmaceuticals, Inc.
9 Great Valley Parkway
Malvern, PA 19355

DRUG PRODUCT NAME:

Proprietary: Plavix
Nonproprietary/USAN: Clopidogrel (INN, BAN)
Clopidogrel Bisulfate (USAN)
Code Name/#: SR25590C
Chem.Type/Ther.Class: 1 P

PATENT STATUS: US 4,529,596, Sanofi SA, exp 7/5/03, Drug, Drug Product, Method of Use
US 4,847,265, Sanofi, exp 2/12/08, Drug, Drug Product
US 5,576,328, Elf Sanofi, exp 1/31/14, Method of Use

PHARMACOL.CATEGORY/INDICATION: Prevention of vascular ischemia

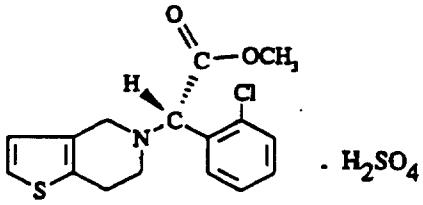
DOSAGE FORM: TCM

STRENGTHS: 75 mg

ROUTE OF ADMINISTRATION: Oral

DISPENSED: _x_ Rx ___ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Methyl (+)-(S)-α-(2-Chlorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridine-5(4*H*)-acetate Hydrogen Sulfate

$C_{16}H_{16}ClNO_2S \cdot H_2SO_4$ Base: 321.83 Salt: 419.9

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable): None

CONSULTS: Division of Biopharmaceutics

REMARKS/COMMENTS:

A Request for Trademark Review, dated 11 Feb 97, was sent to the Labeling and Nomenclature Committee from HFD-530. A response was received from the Committee, dated 27 Mar 97, finding the proposed name unacceptable because of similarities to Flarex, Flavin and Lasix.

Methods Validation will be requested as soon as the dissolution specification is set.

A request was sent to HFD-324 *via* the EES system on 3 Jun 97 requesting inspection of Sanofi's plant at Sisteron and plant at for manufacture of the drug substance; inspection of Sanofi's plant at Ambares for manufacture of the drug product; and inspection of 7 other facilities for packaging of the drug product. Decisions have not been made on the Mayaguez, PR facility, Sisteron, France facility and Ambares, France facility. The last inspection was scheduled for August 8, 1997.

The correspondence of 28 Aug 97 provides for withdrawl of the Environmental Assessment included in the original submission. The applicant requests a categorical exclusion for clopidogrel bisulfate from preparation of an Environmental Assessment based upon the fifth year marketing estimates and environmental fate data that the quantity of the substance expected to enter the aquatic environment is below The requested categorical is granted, based on the information provided..

The amendment of 3 Sep 97 provides the applicant's responses to the Agency's deficiency letter of 6 Aug 97.

CONCLUSIONS & RECOMMENDATIONS:

NOT APPROVABLE until the impurities specifications for the drug substance are properly aligned, the test is added to the specifications for the drug substance, and labeling issues are resolved.

The deficiencies noted below will be conveyed to the applicant.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/JShort/9/8/97
HFD-110/CSO
District
HFD-810/CHoiberg
R/D Init by: Rwolters/9/12/97

James H. Short, Ph.D., Review Chemist
filename: N20-839.CR2

OCT - 9 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-839 **CHEM.REVIEW #:** 3 **REVIEW DATE:** 7 Oct 97

SUBMISSION	TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL		28 Apr 97		
AMENDMENT	BC	22 Sep 97	23 Sep 97	25 Sep 97
AMENDMENT	BC	26 Sep 97	29 Sep 97	1 Oct 97
AMENDMENT	BC	1 Oct 97	3 Oct 97	7 Oct 97
AMENDMENT	BC	2 Oct 97	3 Oct 97	7 Oct 97
AMENDMENT	BC	6 Oct 97	7 Oct 97	10/9/97

NAME & ADDRESS OF APPLICANT:

Sanofi Pharmaceuticals, Inc.
9 Great Valley Parkway
Malvern, PA 19355

DRUG PRODUCT NAME:

Proprietary: Plavix
Nonproprietary/USAN: Clopidogrel (INN, BAN)
Clopidogrel Bisulfate (USAN)
Code Name/#: SR25590C
Chem.Type/Ther.Class: 1 P

PATENT STATUS:

US 4,529,596, Sanofi SA, exp 7/5/03,
Drug, Drug Product, Method of Use
US 4,847,265, Sanofi, exp 2/12/08,
Drug, Drug Product
US 5,576,328, Elf Sanofi, exp 1/31/14,
Method of Use

PHARMACOL.CATEGORY/INDICATION: Prevention of vascular ischemia

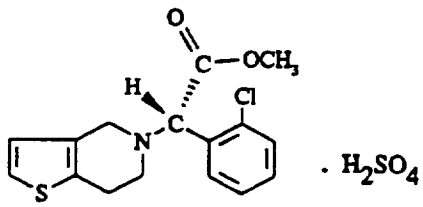
DOSAGE FORM: TCM

STRENGTHS: 75 mg

ROUTE OF ADMINISTRATION: Oral

DISPENSED: _x_ Rx ___ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



. H_2SO_4

Methyl (+)-(S)-α-(2-Chlorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridine-5(4*H*)-acetate Hydrogen Sulfate

$C_{16}H_{16}ClNO_2S \cdot H_2SO_4$ Base: 321.83 Salt: 419.9

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable): None

CONSULTS: Division of Biopharmaceutics

REMARKS/COMMENTS:

A Request for Trademark Review, dated 11 Feb 97, was sent to the Labeling and Nomenclature Committee from HFD-530. A response was received from the Committee, dated 27 Mar 97, finding the proposed name unacceptable because of similarities to Flarex, Flavin and Lasix. The Division has decided to accept the proposed trademark.

A request was sent to HFD-324 *via* the EES system on 3 Jun 97 requesting inspection of Sanofi's plant at Sisteron and plant at for manufacture of the drug substance; inspection of Sanofi's plant at Ambares for manufacture of the drug product; and inspection of 6 other facilities for packaging of the drug product. All facilities have been found acceptable as of 8 Oct 97.

The Division of Biopharmaceutics has recommended a dissolution specification of Q= 20 min at . The applicant has agreed to accept the proposed specification, but is opposed to the paddle speed. They have agreed to carry out feasibility studies (teleconference, 6 Oct 97) to determine if a speed of is practical.

Methods Validation will be requested now that the dissolution specification has been set.

Still unresolved is whether the tablet imprint satisfies 21 CFR 206.10. The applicant has agreed to work with the Agency to resolve this problem, which is not an approvability issue.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable as far as the CMC section is concerned.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/JShort/10/1/97
HFD-110/CSO
District
HFD-810/CHoiberg
R/D Init by: Rwolters/10/9/97

James H. Short, Ph.D., Review Chemist
filename: **N20-839.CR3**

10/9/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20839

PHARMACOLOGY REVIEW(S)

Kcedic

SEP 15 1997

NDA 20-839

OVERVIEW OF PRECLINICAL PHARMACOLOGY AND TOXICOLOGY

Albert DeFelice, Ph.D
September 15, 1997

This consolidates previously reviewed core animal pharmacology and toxicology studies of the anti -thrombotic agent clopidogrel (SR 25990C; Plavix® : Sanofi Pharmaceuticals Inc.). Sponsor's study reports were originally submitted to HFD-180 under IND and reviewed there by Tanveer Ahmad, Ph.D. and team leader Jasti Choudary, Ph.D. For study details and original reviewer evaluations, see Dr. Ahmad's reviews referenced below as: (HFD-180: date of issue).

SYNOPSIS OF OVERVIEW:

Sponsor provided evidence that clopidogrel selectively inhibits binding of ADP to platelets ,and, consequently,ADP-mediated activation of a glycoprotein GPIIb-IIIa complex, binding of fibrinogen to that complex, platelet aggregation, and thrombosis. This cascade is initiated by irreversible high-affinity binding of a putative clopidogrel metabolite to platelets.

Results of animal assays, in toto, predicted clinical pharmacology and metabolism : therapeutic potency of clopidogrel (mg/ M^2 based) was comparable in all species and humans, as was pharmacokinetic estimates based on tracer and major metabolite levels. Full dose - response profiles of anti-platelet aggregating and anti-thrombotic activities were identified in several species and disease models. Both activities occurred over the same dose range. Clopidogrel was tested in a battery of acute, chronic, and system-specific safety assays. Mild reversible hepatic, clinical chemistry, and hemogram changes were the only remarkable findings in protracted (3 and 12 mo.) assays. Depending on whether hemogram or adaptive liver changes was provoked, the threshold toxic dosage in the rat was ca. 35 to 114 times the anti- aggregating ED_{50}% dosage. This therapeutic ratio, based on the same minimal toxicity, was 330 in the baboon. The safety ratio as multiples of anti-thrombotic ED_{50}% dosage in rats and rabbits was ca. 60. Based on the size of these conservative (i.e.,minimal toxicity-based) ratios, and the nature of the pathology , the animal data project no clinical safety concerns other than consequent to prolonged bleeding time.

PHARMACOLOGY : Clopidogrel pre-treatment clearly interfered with *ex vivo* ADP binding and ADP-dependent inhibition of adenylate cyclase activity in harvested rat, rabbit, and human platelets. In all species, clopidogrel - at dosages 0.6 to 5 mg/Kg - inhibited ADP-induced platelet aggregation *ex vivo*, as well as thrombus formation *in situ* in several models of arterial and venous thrombosis. Oral and intravenous activity was comparable, long lasting ($T_{1/2}$ = 2-3 days), and delayed in onset.

Clopidogrel also suppressed myointimal hyperplasia in vascularly injured rabbits.
Irreversible binding of a putative metabolite(s) to platelets accounts for activities of this pro-drug. Neither the *R* -enantiomer metabolite (< 10%) nor the main circulating metabolite (SR 26334) were active in platelet binding/function studies.
Acute Safety Pharmacology: At up to 125-250 mg/Kg. enteral dosage (> 50 X anti-platelet aggregation dose), clopidogrel did not acutely affect overt CNS (mice, rats), autonomic (dog), cardiovascular (dog), respiratory (dog, guinea pig), gastrointestinal (mice, rat), or renal (rat) function.
It had no anticoagulant or fibrinolytic activity, but did prolong bleeding time in rats and rabbits at therapeutic dosages - a basis for cautious clinical use when lesions predisposed to bleeding exist, e.g. gastric ulcers.
TOXICITY:
a. Acute:
Target organs of single high-dose exposures (LD 50% > 2g/Kg in 3 species) were GI tract (erosions; bleeding), lung (congestion), and kidney (tubulo-interstitial necrosis). These pathologies were not seen in repeat dose studies at up to approx. 400 mg/Kg (>100 X ED50% dosage).
b. Sub-chronic.
Mice tolerated up to 383 mg/Kg/day for 3 months - except for 10-20% change in weight of body and liver at lethal dosages (≥ 766 mg/Kg).
Rats tolerated up to 400 mg/Kg daily (52 x clinical mg/M^2 dose) for 3 months except for reversible increases in liver wt. , plasma cholesterol, and platelet count.
Baboons tolerated, in a 2-week study, up to 250 mg/Kg daily; 500 mg/Kg provoked lethal hemorrhagic GI irritation.
c. Chronic: In a 78 week tumorigenicity study, mice developed no excess tumors when exposed to 27 to 47 times the human AUC . Rats tolerated up to 123 mg/Kg for 1 year except for slightly elevated cholesterol and liver weight, and - in a 2-year tumorigenicity study - exposures of up to 47 times the human AUC with no tumorigenic response. Baboons given up to 200 mg/Kg (approx. 52 x clinical dose as mg/ M^2) of clopidogrel daily for 1 year revealed (only) slight reversible changes in RBCs, serum albumin , and liver weight.
d. Reproductive:
Clopidogrel was non-fetotoxic in a comprehensive (Segment 1-3) test battery in the rat, and also in a rabbit fetal organogenesis study : In rats given up to maternotoxic dosages (52 x clinical mg/ M^2 dose) clopidogrel had no remarkable effect on a.) fertility and reproductive function of treated dams and their offspring, b.) *in utero* morphology of the F1 and F2 generations, or c.) post-natal development of the F2 generation. It was neither embryotoxic in higher dose rat or rabbit teratology studies at up to maternotoxic dosages of 500 and 300 mg/Kg , respectively (65 and 78 x clinical mg/ M^2 dosages), nor deleterious to peri- and post-natal development of pups delivered of rats that received up to 400 mg/Kg in the 3rd trimester through weaning interval.
d. Genotoxic:
Results of five assays involving adequate drug challenge were uniformly negative. Mutagenicity was not observed, at up to cytotoxic concentrations, in three *in vitro* tests (Salmonella; rat ; hamster) with or without rat liver metabolizing enzymes present. No clastogenicity was seen either in vitro (human lymphocytes) at up to cytotoxic concentrations, or

in vivo (rat erythrocytes) at up to systemically toxic dosages. Positive controls behaved as expected. An Ames test of clopidogrel's main metabolite (SR26334A) was also negative.

PHARMACOKINETICS: In all species and humans, absorption of radiolabeled clopidogrel was at least 50 - 80% based on excretion balance data. Oral bioavailability of intact clopidogrel was low due to rapid and extensive hydrolysis to SR26334 in the liver (primates) and, also, plasma (rats). The ^{14}-C label dispersed primarily to organs of metabolism and excretion in all species. Plasma radioactivity elimination T1/2 was approx. 7 days, reflecting plasma protein binding. Excretion was mainly biliary and fecal.

Toxicokinetics: Using relative AUC (rodent vs. human) or relative plasma Cmax (baboon vs. human) values of the major metabolite as the (only feasible) marker of clopidogrel exposure , the dosages tested in the 3 - month baboon, the 1- year rat, and the lifetime rodent tumorigenicity safety assays afforded, respectively, up to 20, 75, and 47 times human steady state clopidogrel burden.

OVERVIEW OF PHARMACOLOGY, TOXICOLOGY, and PHARMACOKINETIC STUDIES:

A. Primary pharmacology:

1. Mechanism of action (HFD-180: 7/16/90;6/28/95).

A hepatic metabolite of clopidogrel specifically inhibits a sequence of thrombotic platelet events initiated by ADP , i.e., platelet ADP binding , glycoprotein activation, binding of fibrinogen to glycoprotein , and aggregation. Oral pre-treatment of rats with at least 1 mg/Kg of the agent dose-dependently antagonized *ex vivo* binding of ADP to specific platelet receptors. Oral dosing at 25 to 50 mg/Kg. also interferes with ADP- dependent inhibition of adenylate cyclase activity in rat and rabbit platelets *ex vivo* . Ability to inhibit ADP receptor-mediated activation of GTP-binding protein in rat platelet membrane is also documented (Thromb. Haemat., 1992,68: 79 -83).

There is evidence that clopidogrel requires hepatic conversion to an unidentified active metabolite to express it's effect : rat and human platelets exposed for one hour *in vitro* to up to 10^{-4} M clopidogrel respond normally to ADP; the agent had no anti-aggregating effect in rats with a porto-jugular shunt (Sanofi report no. RS 260890324); and it's anti-aggregating effect was potentiated or reduced by pre-treatment with, respectively, inducers or inhibitors of *CYP* 1A (HFD-180:6/9/94).

2. Anti-platelet aggregating activity:

Oral clopidogrel dose-dependently and uniformly inhibited *ex vivo* platelet aggregation provoked by multiple agents in mice, rats, rabbits and

baboons (HFD-180: 7/16/90 ; 8/2/94). After 3 to 5 days oral dosing to rats and baboons, and harvesting of platelets 2 hrs. after the last dose, the ED 50% for blocking ADP, collagen, or thrombin -induced aggregation ranged from 0.6 (baboon) to 4 (rat) mg/Kg daily - values several fold less than seen after a single administration. Maximum activity occurred 2-6 hours after oral dosing in rats and baboons, with multiple daily dosing needed to reach steady state. Duration of anti-aggregating effect was similar to that of platelet life span, which indicated irreversible binding to platelet receptors. As expected of its restricted mechanism of action, clopidogrel did not affect prothrombin time or euglobulin fibrinolytic activity in the rat, or plasma fibrinogen levels in rabbits, but it prolonged bleeding time of rat and rabbits (HFD-180: 7/16/90).

3. Anti-thrombotic activity:

After a single oral administration, clopidogrel demonstrated dose-related prophylactic anti-thrombotic activity in five different rat and rabbit models of thrombosis (foreign body; venous stasis; and electrical.) , with an $ED_{50\%}$ range of approx.1.5 to 5 mg/Kg (HFD-180: 7/16/90; Sanofi report RS260890324). After i.v. dosing in female rats, the onset and potency of both the anti-thrombotic and the *ex vivo* anti-aggregating effects were comparable. This suggests that both are closely correlated (HFD-110:6/9/94; Sanofi no. RS260890324/MA1). This agent also reduces frequency and appearance of cyclic flow variations (which are thought to be platelet -aggregate related) in stenosed canine coronary arteries by 50 and 100% at 2.5 and 5 mg/Kg i.v., respectively (Sanofi study no. RS200891213/ML1).

4. Anti-atherogenic activity:

In a rabbit model of atherogenesis provoked by carotid artery de-endothelialization, daily oral administration of clopidogrel at 25 mg/Kg/day for 16 days - beginning 2 hrs. prior to injury - inhibited both sub-endothelial platelet adhesion (after one dose) and myointimal proliferation (examined on day 16) by approximately 40-45% (HFD-180: 7/16/90). Since the agent does not directly inhibit smooth muscle proliferation (HFD-110: 9/4/91; Sanofi report no. RS260901015/MA1), prevention of platelet adhesion may underlie the anti-proliferative effect of clopidogrel on the intima.

5. Potentiation of streptokinase thrombolysis (Sanofi report no. RS260901127/MA).

Neither standard heparin (100 IU / Kg) nor clopidogrel (10 mg/Kg i.v.) had any thrombolytic activity in rabbits with established ^{125}Iodine-labeled jugular vein clots, whereas streptokinase increased rate of spontaneous lysis by

ca. 5.5 -fold. However, when given concurrently with streptokinase, these drugs appreciably enhanced lytic activity of the latter by approx. 33% when co-administered individually, and by approx. 60% when heparin and clopidogrel were both administered with the kinase. The dose-response for this heparin-streptokinase and clopidogrel-streptokinase co-operativity was not reported. We can conclude that neither clopidogrel nor heparin revealed any thrombolytic activity but that each agent significantly enhanced that of streptokinase. Sponsor believed, based on analysis of blood vs. clot radioactivity , that the synergistic effect of clopidogrel was due to inhibition of thrombus accretion rather than to any direct dissolution of the clot. Apparently, rate of thrombolysis effected by streptokinase is the net of it's lytic activity vs. an opposing thrombotic process of local platelet aggregation.

B. Safety and secondary pharmacology (HFD-180: 7/16/90)

I. Acute Neural Activity

Oral neurobehavioral (CNS), anticonvulsant (vs. pentetrazol), or analgesic (vs. heat; acetic acid) activities were assessed in conscious mice dosed at up to 250 mg/Kg . Activity was uniformly absent except for weak peripheral analgesia and enhanced pentobarbital narcosis at the latter dosage. In the rat ,slight EKG, but no behavioral, alterations were observed at 125 and 250 mg/kg.

2. Cardiovascular and respiratory systems

The only acute CV activity reported in dogs that received clopidogrel at up to 250 mg/Kg. i.d. was a decrease in cardiac output (>125 mg/Kg) and a slight respiratory analeptic effect (>62.5 mg/Kg). Except for relief of serotonin - induced bronchospasm, neither basal nor spasmogen - enhanced bronchial tonus were altered in guinea pig dosed at up to 250 mg/Kg.

3. Gastrointestinal system

Neither intestinal motility (mice) nor gastric acid secretion (rat) were affected by oral administration of 250 mg/Kg of clopidogrel. Rat gastric emptying was retarded after oral treatment with 200 mg/Kg of clopidogrel.

4. Urinary

In the rat, a single oral dose of up to 500 mg/kg did not overtly affect renal function.

5. Hemostatic.

In the rat , clopidogrel was devoid of any *ex vivo* anticoagulant or fibrinolytic activities at 10 mg/Kg (Sanofi report no. RS 260890324/MA1) whereas a standard dose of heparin significantly prolonged partial time, prothrombin time, and thrombin time. However, after a single oral dose to female rats of 5 mg/Kg (the approx. ED 50% for anti-aggregating activity), clopidogrel prolonged bleeding time of transected tail by approx. 5-fold (Sanofi report no. RS260890324/MA1). In the rabbit , an effective anti-platelet aggregating dosage of clopidogrel does not appreciably prolong bleeding time, but does significantly potentiate the hemorrhagic effect of streptokinase and enhance the slight increase in bleeding time seen after heparin administration.

C. Toxicology. (HFD-180: 7/16/90)

Toxic affects of clopidogrel were assessed in a standard battery of *in vitro* and *in vivo* studies. Sponsor stated that batches used in the pivotal studies contained all main impurities:

1. Acute (oral; intravenous) . (HFD-180: 7/16/90)
Acute oral $LD_{50\%}$ in mice, rats, and baboons exceeded 2000 mg/ Kg.; acute intravenous $LD_{50\%}$ (mice, rats) was 110 to 160 mg/Kg. Target organs of single dose oral toxicity were digestive tract (erosions, hemorrhage),lung (congestion) and kidneys (necrotic tubulopathy); target of intravenous toxicity was cardio-respiratory (rapid death after cyanosis, dyspnea, and apnea). The gastric and renal toxicity was not observed in the repeat dose oral studies, described below, that were performed using up to approx. 400 mg/Kg./day of clopidogrel

2. Sub-chronic: (HFD-180: 7/16/90)
a. Two-week :
Dose-ranging studies were performed in two species:
Rat:
Administration at 125 to 4000 mg/Kg daily (5M/5F/group) provoked an elevated plasma cholesterol and triglycerides, and an increased liver weight; the latter reflected centrilobular hypertrophy and smooth endoplasmic reticulum increase. Drug was lethal at 1000 mg/Kg and above due to an esophagitis, gastritis and/or gastritis also seen with sub-lethal severity at lower dosages. Results were confirmed in a second study performed at up to 1000 mg/Kg daily.
Baboon:
Administration at 500 to 4000 mg/Kg daily (1M/1F/group) provoked prostration, emesis (often hemorrhagic), and death at 500 mg/Kg and above. Autopsy revealed gastric ulceration, renal congestion, and pale livers. Lower doses were tolerable except for slight laryngitis or tracheitis.

b. Three-month :
A total of five 3-month oral toxicity studies were performed in mice (2 dietary studies, one with a 6-week recovery period), rats (1 gavage with 5 -week recovery period; 1 dietary), and baboons (1 gavage with a 5-week recovery period) . Absorption of clopidogrel was confirmed by the presence of it's carboxylic acid derivative (SR26334) in plasma (mice; baboons) or urine (rat):

Mouse:
Two studies, involving 10M/10F/group, were performed using dietary admixtures which afforded up to 306 or 3065 mg/Kg /day, respectively. The first study (Sanofi study # RA860900710/cb1) - performed to allow selection of doses for a carcinogenicity study - revealed no histopathology. However, 10 to 20% increases in liver weight occurred in both sexes at the two high doses (153 and 306 mg/Kg, respectively.). Maximum plasma level of the main metabolite(SR26334) was 40 mg/L at the top dose in both sexes. In the second

study(RS 0006950601/03), excess deaths occurred in males only receiving 766mg/Kg ,or more, daily. At necropsy, dose-related increase in liver weight was observed but no other macroscopic changes. Histology was not performed.

Rat:

Rats gavaged with up to 400 mg/Kg dosage (25M/25F/group) revealed ca. 20% weight loss at the high dose, and - at 100 mg/Kg /day and above - increases in platelet count (up to 20%), liver weight (up to 45%) and plasma cholesterol (up to 20%), and enlarged centrolobular hepatocytes. All chānges were reversible within 5-weeks. (HFD-180:7/16/90)

In the 3-month dietary admixture study (RA860900717/JV1), where rats (10M/10F/group) were dosed at up to 306 mg/Kg/day, increases in liver weight and or plasma cholesterol, but no liver histopathology, were observed from the dose level of 153 mg/Kg/day. Drug absorption was confirmed by dose-related urinary presence of the major metabolite. As the mean anti-thrombotic ED 50% is 3.5 mg/Kg in several rat models, the therapeutic ratio based on the reversible hemogram and liver changes at the high dose is 114 in this 3-mo. study (i.e., 400 /3.5).

Baboon:

Young primates gavaged with up to 400 mg/Kg daily (5M/5F/group) presented with vomiting (or gastric erosion at necropsy), a slight leukocytosis , and depressed body weight gain (35-50%) at the high dose. There was no in-life interference with BSP dye clearance at end of treatment phase, although at necropsy enlarged livers (+ 15% vs. control) were present. EKG changes were seen in high-dose group at 1, but not 3, month treatment interval. *Ex vivo* platelet aggregation induced by ADP was inhibited 100% in the 25 mg/Kg group at 2 hrs. post-dosing. After a 5-week recovery period (3M/3F/group), treated and control animals were essentially indistinguishable, indicating reversibility of gastric and body weight effects.

Based on absence of toxicity at 100 mg/Kg and the reversible pathology at high dose, and an anti-platelet aggregating ED 50% of 0.6 mg/Kg, the therapeutic ratio in this 3-mo. study lies between 166 (100/0.6) and 660 (400/0.6). [The 1-year study(see below) identifies 200 mg/Kg as the chronically tolerated dose with minimal toxicity].

3. Chronic

a. One year (HFD-180: 1/12/93):

Two studies were performed: a rat dietary study (20M/20F/group), affording up to 123 mg/Kg of clopidogrel base, and executed concomitantly with the carcinogenicity study; and a dose- by- gavage study in baboons (9M/9F/group performed at dosages up to 200 mg/Kg daily. Baboon study included a 5-week recovery period, and assessment of immunotoxicity(see below under special tests).

Rat:
There was no excess treatment-related mortality within the 1-year interval. At the end of treatment , plasma cholesterol was elevated up to 19 and 42 % in high-dose males and females, respectively. Liver weight in high-dose groups was also increased by approx. 20%, reflecting the hypertrophy of centrilobular hepatocytes seen at microscopy. Since the mean anti-thrombotic ED 50% in the rat models is 3.5 mg/Kg, a conservative therapeutic ratio based on these minor liver and clin. chem. changes in the high-dose group is 35 (i.e.,123/3.5).

Baboon:
There was no excess treatment-related mortality through a dose-range adequate to depress body wt. gain of the young primates by ca. 50-75% at high dose, and to achieve peak and trough SR26334 levels of ca. 100 and 8 mg/L, respectively, over a majority of the treatment interval.. The only remarkable effects - other than reduced body weight gain - in a study that involved periodic opthalmoscopy, electrocardiography, urinalysis, and blood sampling were high- dose reduction in RBC count and hemoglobin (ca. 10%) and urine pH, and ca. 30% increase in liver weight but no gross or histopathology. Bromsulphothalein liver function test was negative. All changes had reversed at the end of a 5-week recovery period.
Since the antiplatelet- aggregating ED 50% is 0.6 mg/Kg in the baboon, the therapeutic ratio based on the liver and hemogram changes at 200 mg/Kg is 330 (i.e.,200/ 0.6)

b. Tumorigenicity assays (HFD-180: 8/2/94):

Standard 18 and 24-month carcinogenicity assays were performed in mice and rats, respectively, at up to 77 mg/Kg base /day i.e., approx. 60 times recommended clinical dose of 75 mg. (1.25 mg/Kg). Tumor incidences were analyzed by sponsor using Peto trend and Fisher's Exact tests. Results of both assays were brought before the Executive CAC primarily to judge adequacy of high-dose exposure in both studies since there were no remarkable differences in mean tumor incidences across cohorts.
A letter from HFD-180 (dated Sept. 8, 1994) indicated that the full package of available toxicology data, including the negative mutagenicity findings, provided adequate information on the carcinogenic potential for clopidogrel hydrogen sulfate, and that both rodent studies were adequate and acceptable.
Mice:
Although the high dose (100 mg/Kg) provoked no excess mortality, chronic histopathology, or body weight change , the CAC Executive Committee agreed with the primary review pharmacologist (Dr. Ahmad) that 100 mg/Kg still provided an adequate high-dose challenge. The basis was a follow-up 1-month study (RS 0005940322/01), showing that that dose afforded 47 (male) and 27 (female) times the SR 26334 AUC level seen in humans taking the maximum

recommended daily dose. [recall that SR26334 is an inactive metabolite of clopidogrel formed in rodents and humans, and necessarily used as a surrogate of clopidogrel exposure in all animal and clinical studies]. . These AUC ratios exceed the value(25) established by International Conference on Harmonization (ICH step4.Carcinogenicity : Testing for carcinogenicity of chemicals, recommended for adoption 16 July1997, Brussels).
Regarding autopsy findings, the exec. CAC judged that there was no evidence of excess benign or malignant tumor burden (Exec. CAC final report of 8/23/94) in treated mice of either sex. There was also no decrease in latency of spontaneous tumor appearance based on tumors observed at each 150 day interval in animals which died or were sacrificed prematurely.
Tables of neoplastic lesions provided by the sponsor (IND 34663, amend. 160, 1/24/97, vol. 11), revealed that there was, across all groups: a comparable incidence of animals with tumors (Control vs. treated Males: 28 vs. 32, 30, and 30%, ; C vs. treated Females: 30 vs. 36, 30, and 18 %); a comparable incidence of animals with more than one primary neoplasm (C vs. Treated M: 5 Vs. 2,5, and 4%; C vs. Treated F: 5 vs. 4, 2, and 2%); a comparable number of benign and malignant tumors (C vs. treated M: 15 Vs. 15,15, and 17; C vs. treated F: 13 Vs. 21,16, and 10); and a comparable number of animals with metastases (C vs. treated M: 0 Vs 0, 0, and 0%; C vs. treated F: 3 vs 0, 0, and 0%) .

Rats:

As with the mouse study, the high dose (100 mg/Kg) provoked no excess histopathology or mortality, and no change in body weight. The Exec. CAC Committee again agreed with the primary review pharmacologist that the 100 mg/Kg high dose was acceptable on a pharmacokinetic basis according to current ICH guidelines. In a separate 4-week study(RS 0005931202/01), that dosage afforded large multiples of clinical maximum exposures, i.e., 42 (male) and 28 (female) times steady-state SR 26334 AUC levels in patients receiving clopidogrel daily at the recommended dose.
There were no findings of non-neoplastic histopathology or gross pathology except for a 12% increase in liver weight in high dose males. The Exec CAC concurred with Dr. Ahmad's finding of no evidence of excess benign or malignant tumor burden (Exec. CAC final report of 8/23/94) in treated rats of either sex. Peto analysis (combined prevalence and death rate method) , using standard confidence levels, confirmed absence of any dose-related tumorigenicity, or any decrease in latency of spontaneous tumor appearance (IND , amend. 52, vol. 26).
Dr. Ahmad mentions a 4-6% incidence of adrenocortical adenoma in treated males, but notes that this is within the historical control incidence for this strain (1.4-16.4%; Charles River; February 1992). The Exec. CAC did not acknowledge this as a real finding. In any case, the only adrenocortical *carcinomas* observed resided in 1 control male, 2 control females, and 1 low-dose female.

Tables of neoplastic lesions provided by the sponsor (IND amend. 52, vol. 26), revealed that there was, across all groups: a comparable incidence of animals with neoplasms (Control vs. treated Males: 78 vs. 60, 70, and 68%; C vs. treated Females: 92 vs. 86, 96, and 94 %); a comparable incidence of animals with more than one primary neoplasm (C vs. Treated M: 28 Vs. 22, 26, and 24%; C vs. Treated F: 52 vs. 38, 52, and 54%); and comparable number of benign and malignant tumors (C vs. treated M: 59 Vs. 43, 51, and 49; C vs. treated F: 87 Vs 67, 88, and 87). Clopidogrel had no effect on incidence, latency, or histomorphologic type of spontaneous tumors.

4. Genotoxicity assays: (HFD-180:7/16/90; HFD-180:6/9/94)

Mutagenicity

a. Ames (S. Typhimurium) test.

Genotoxicity tests proper were preceded by toxicity tests to identify cytotoxic and /or insoluble concentrations. Ames tests, each involving 5 strains of S. Typhimurium, were then performed on clopidogrel (2 different batches), it's major metabolite (SR26334A), the R-enantiomeric impurity/metabolite (SR 25989C), and the SR24726 impurity of synthesis at up to 2500,5000, 2500, and 2500 micrograms / plate, respectively. Strains used detect frame shift as well as base pair substitution mutations.. Results for clopidogrel were uniformly negative both in the presence and absence of rat hepatic metabolic enzymes (S-9). Dose-related increase in number of revertant colonies (2 or 3-fold depending on bacterial strain) was the criterion for a positive finding. Results for the 2 previously unreviewed impurities were also negative (Sanofi reports: RS0006961015/01; RS0006911219/02). Positive, including metabolically dependent, controls behaved as expected, confirming integrity of rat S-9 metabolic enzyme system.

b. Chinese hamster cells: HPRT locus, *in vitro*

One assay was conducted with , and 2 independent assays were conducted without , a metabolic activation system (rat S9) present. These tested whether clopidogrel could provoke point mutation in lung fibroblasts exposed for 24 hrs. to up to 40 (S9 absent) or 150 (with S9) µg / ml levels of clopidogrel. Positive controls (S9-dependent and independent) were included. At up through cytotoxic concentrations (40µg /ml without S9; 80 µg /ml with S9) and beyond, clopidogrel provoked no increase in mutant frequency. Both positive controls tested positive.

Clastogenicity

a. Metaphase chromosome analysis: lymphocytes

Cultured human cells, stimulated to divide with a mitogen, were exposed to up to cytotoxic levels of clopidogrel with and without S9 metabolic system present.

There was a maximum 1.4% incidence of chromosomal aberrations observed in metaphase-arrested cells that had been exposed to up to 80 µg/ml of clopidogrel vs. 0 or 0.25% incidence in negative control cultures, and 11.5 and 12% incidence in positive controls. Accordingly, clopidogrel clearly was not clastogenic at up to concentrations which markedly suppressed cell division (mitotic index was reduced to 18.4 % of control at the highest clopidogrel concentration).

b. *In vivo* Mouse micronucleus test.

Based on preliminary toxicity testing ,where marked clinical signs and mortality occurred at and beyond 2300 mg/Kg, mice were gavaged with up to 2000 mg/ Kg. of clopidogrel daily for 3 days . At that dosage (which prostrated the males) there was no evidence of genotoxicity, i.e., incidence of micronucleated polychromatic RBCs was not elevated. Ratio of polychromatic to normochromatic RBCs was also normal which indicates that there was no bone marrow cytotoxicity. Conversely, cyclophosphamide markedly elevated the incidence of micronucleated polychromatic RBCs. Accordingly, there was no evidence of any clastogenic activity for clopidogrel at up to a systemically toxic dose administered for 3 consecutive days.

Other genotoxicity assays

In vitro DNA repair test (Fisher rat hepatocytes in primary culture):

Two assays for unscheduled DNA synthesis were performed. No net increase in nuclear incorporation of tritiated thymidine was seen over a 5-25 µg /ml concentration range in one assay, and 15-40 µg / ml with another batch number, indicating absence of any unscheduled DNA repair. Genotoxicity could not be evaluated at higher concentrations where clopidogrel was cytotoxic (highest tested was 1000 µg /L). Accordingly, clopidogrel was negative in initial and confirmatory assays. Positive controls were genotoxic (mean nuclear grain count > 5), whereas no excess repair was induced by pyrene (negative control). Mixed function oxidative (Cyt p-450)) enzymes were functional in these primary culture cells since the metabolically dependent control (2-AAF) was positive.

5. Reproductive toxicity. (HFD-180: 7/16/90 ; 9/4/91)

Effects of clopidogrel on reproductive function and on peri - and post-natal development were comprehensively assessed in four studies in rats and rabbits covering all three reproduction segments - including both male and female fertility, teratogenicity, and any next-generation carry-over effect. The dose range examined in each assay, i.e., up through slight parental toxicity, was

chosen on the basis of maternal or paternal toxicity in preliminary dose-range finding studies and/or results of the 3-month toxicity study. Excretion into milk was also examined.

a. Segment 1. Study: Rat (HFD-180:9/4/91)
Clopidogrel was studied at up to 400 mg/Kg (34M / 34F per group). Males were treated for 71 days prior to pairing and through successful littering of females. Females were dosed for 15 days prior to pairing through to the end of weaning. Uteri and fetuses of 2/3 of the dams were examined at day 20 caesarian section for parameters which included no. of dead and resorbed fetuses, and external or internal malformation; rest of dams were allowed to deliver spontaneously. Growth, reproductive performance, and fertility of the F1 generation, and growth of the F2 generation until weaning , were evaluated. (See HFD-180: 9/4/91 for full details).
Results: *Parental* : Dose-related hypersalivation and, at high dose, depressed parental body weight gain and 2 possibly drug -related male deaths were observed. There were no effects on fertility and mating performance of males or females. *F1 generation* : At 100 mg/Kg and higher, there was a slight retardation of post-natal body weight gain and development , significant at the high dose where 25-day old pup weight was about 90% of control, and times to eye and vaginal opening were slightly delayed. However, this was reversible, since after weaning body weights were similar to control. Moreover, no abnormal effects on fertility or mating performance of F1 generation, or on survival and development of F2 pups up to weaning were seen.
Accordingly, the only remarkable effect observed was a reversible retardation of F1 neonatal growth.

b. Segment 2 (Teratogenicity) .

Rat: (HFD-180: 9/4/91)
This study also included an evaluation of effects of *in utero* exposure on development and reproductive performance of the F1 generation: Groups of 35 gravid rats were treated at up to 500 mg/Kg daily from day 6 to day 17 of gestation, and 23 from each group were sacrificed on gestation day 20 for evaluating embryotoxicity and teratogenicity. Remaining dams (12/gp) gave birth, and F1 pups evaluated for growth and reproductive performance.
Results: High-dose dams experienced rales, hypersalivation, and increased water consumption. F1 pups ,at caesarian , revealed no remarkable anomalies.Dams allowed to deliver spontaneously had normal litter size; their F1 progeny had normal post-natal development and reproductive performance at sexual maturity
Accordingly, clopidogrel was not teratogenic at up to 500 mg/Kg, and exposure *in utero* to this parental dosage did not affect F1 development or fertility.

Rabbit: (HFD-180: 7/16/90)
Gravid rabbits (14-15/gp) were dosed at up to 300 mg/Kg daily on days 6 through 18 of gestation. [The highest dose tested was based on a preliminary study in gravid females where clopidogrel was lethal at 400 mg/Kg , and, at 200 mg/Kg ,reduced their body wt..] At near term (i.e., day 29), all dams were sacrificed and the uteri and fetuses examined for fetal deaths, resorptions, and external and/or internal anomalies.
Results: Maternal food intake was depressed at the high dose but body weight gain was depressed only in the earlier gestation period. Number of corpora lutea , implants, live fetuses, or dead or resorbed fetuses was unchanged. Fetal and placental weight were also unaffected by clopidogrel. Neither skeletal nor visceral development was affected in these fetuses at up to slightly materno-toxic dosages administered during the stages of major organogenesis i.e., through the second trimester.

c. Segment III. Peri- and post-natal development: rat (HFD-180: 9/4/91)
Dose selection was based on a 3-month toxicity study. Gravid rats were dosed at up to 400 mg/Kg /day from day 15 of gestation through weaning (neonatal day 25). Number of live/dead pups were recorded. Twenty males and 20 females were culled at day 4, their development to sexual maturity was monitored (testis descent,eye opening, vaginal opening, learning ability etc.), and they were paired to yield an F2 generation . Remainder of F1 pups were sacrificed and autopsied for anatomic anomaly. Dams were killed at weaning and the uteri were examined.
Results: Slight reductions in mean numbers of corpora lutea, implantations, and live young at the highest dosage were the only findings. No external, visceral, or skeletal abnormalities were observed in F1 or F2 pups, and - except for ca. 10% lower body weight of weaned high-dose F1 pups . No developmental or reproductive capacity deviations were observed in pups of either generation which were allowed to develop to sexual maturity.

d. Excretion in milk:

Lactating SD rats given a single labeled clopidogrel dose of 5 mg/kg excreted ^{14}C in milk for more than 48 hours. Peak level occurred 2 hr. after dosing, and was comparable to peak (i.e., 1-hour) maternal plasma level.

6. Special toxicity tests

Immunotoxicity

a. Immunoglobulins and lymphocytes.

Rat: (HFD-180: 9/4/91)

Young SD rats (6M/6F per group) were given up to 100 mg/Kg/ day of clopidogrel for 4 weeks, and blood obtained on days - 7 and 27 for lymphocyte subpopulations, globulins, IgG, and IgM. Splenocytes were harvested for functional testing of lymphoblasts, lymphocytes, and natural killer (NK) cells. No treatment-related effects were seen on clinical signs, clinical chemistries, or at necropsy except for slightly increased liver weight of high-dose females. Hematology revealed, in males, slight dose-related increase in RBC count, HgB level, and PCV. Functional tests on splenocytes were negative for tritiated thymidine incorporation in lymphoblasts (i.e.,DNA turnover), proliferation index in mixed lymphocyte culture, and NK cytotoxicity index.

Baboon: (HFD-180: 6/9/94)

During the 1-year baboon toxicity study (see above: 2.C. Baboon.), blood was drawn at 1, 3, 6, 12, and 15 mo. intervals for monitoring immunoglobulin levels (IgG; IgM), and lymphocyte function at 2 or more time intervals:

There were no treatment-related effects on immunoglobulin levels, or on tritiated thymidine incorporation in lymphoblasts, proliferation index in mixed lymphocyte culture, and NK cytotoxicity index.

b. Antigenicity in guinea pig: (HFD-180: 9/4/91)

Clopidogrel was administered 3 times, at 14-day intervals, to young guinea pigs at up to 50 mg/Kg s.c. to test for anaphylaxis - either systemic (25 mg/Kg i.v. challenge) or passive cutaneous (intradermal injection of serum followed by 25 mg/Kg i.v clopidogrel challenge):

Neither anaphlaxis nor elevated IgG responses were evident. Conversely, 3 of 5 ovalbumin -treated controls died with systemic anaphylaxis, and 5/5 others had marked cutaneous anaphylaxis down to 7241-fold serum dilution.

c. Phototoxicity / Photoallergy in Guinea Pig: (HFD-180: 6/9/94).

Guinea pigs received clopidogrel at 200 mg/Kg. daily for 8 days .They were irradiated with both UVA and UVB one hour after dosing on days 1- 3, and 6-8, and graded for erythema. After a 3-week washout , the same animals and treatment schedule (with a single dose) were used to assess photoallergy to UVA and UVB inflicted separately:

Clopidogrel revealed no phototoxicity potential . However, sponsor did not include a positive control.

Myelotoxicity (HFD-180: 7/16/90)

Male mice were orally treated with up to 500 mg/Kg. of clopidogrel per day for 5 days. Busulfan, at 40 mg/Kg (single dose), was used as the positive control.

Their bone marrow was transplanted to irradiated mice, and 9 days later the number of splenic colonies and the relative number of nucleated and stem (blast) marrow cells was determined at sacrifice:
Clopidogrel did not affect incidence of nucleated bone marrow cells whereas the count was depressed 40% by busulfan. The number of splenic colonies in mice which received marrow implants from clopidogrel-treated was approx. 90 % of the count in negative controls vs. 25% for mice receiving busulfan-treated marrow. Accordingly, there was no evidence of myelotoxicity - at least with respect to *in vivo* colonizing potential of transplanted cells.
[It would have been of interest to perform this study with autologous grafts, i.e., using this sequence: treatment, harvesting of marrow, whole body irradiation, and re-implanting of cells .

D. Biopharmaceutics (HFD-180: 7/16/90; 9/4/01; 6/9/94; 8/2/94; 6/28/95; 6/28/ 95).

Absorption, distribution, and excretion of radioactive clopidogrel was tracked as migration of label (^{14}C in the pyridine ring). Due to rapid and extensive hepatic hydrolysis of clopidogrel to SR 26334 in the liver (primates) and /or serum(rodents),the latter compound was monitored as a marker of (evanescent) clopidogrel burden. Pharmacokinetics and excretion balance of clopidogrel have been studied in rats and baboons following single intravenous and single / repeated oral administration. Tissue distribution and placental transfer was investigated in rodents (mice; 2 strains of rat) and rabbits, respectively, using radiolabelled clopidogrel. Major metabolites were characterized in plasma (rodents, baboon), urine (rodents, rabbit, baboon), and bile (rat; baboon). Effect of pretreatment with cytochrome P450 modulators on *ex vivo* anti-aggregating activity of clopidogrel was also studied (rat).
Intravenous pharmacokinetics (single dose): (HFD-180: 7/16/90)
Pk parameters were determined after an intravenous dose in rats (25 mg/Kg) and baboon (50 mg/animal): Parent compound had a short elimination $T_{1/2}$ in both species, and large plasma clearances and volumes of distribution. Metabolite SR26334 peaked at approx. 15 min. in both species, and accounted for most of the biotransformation of clopidogrel : SR26334 AUC was approx. 500 (rat) and 50 (baboon) times that of parent compound, and about 80% of clopidogrel was converted in the rat. Conversion after oral dosing is even more extensive (see immediately below).

Absorption:

a. Single oral dose:
Absorption of single oral doses of. of clopidogrel was studied in rats (both sexes) and male baboons at dosages used in the 3-month toxicity studies, i.e. 25, 100, and 400 mg/Kg. Plasma was assayed for unchanged drug as well as it's major metabolite - the carboxylic acid derivative SR26334 , an *S* -

enantiomer like it's parent. Limits of detectability were 0.002 and 0.050 mg/L for clopidogrel and SR 26334, respectively.
Results: In both species, Tmax for clopidogrel was 1-2 hrs., and it's C max and/or AUC 0-infinity, were much smaller than corresponding values for the major metabolite SR26334. That is, peak plasma levels and AUCs of SR 26334, in both rats and baboons, quickly reached values several thousand -fold those of the parent compound. In the rat, body burden of parent and metabolite was 3 to 10 times greater in females than males (only male baboons were tested), reflecting lower volume of distribution and clearance in females (HFD-180:7/16/90). The AUC for the metabolite was dose-linear in the rat but not the baboon. This metabolite represents about 85% of circulating drug-related compounds in plasma and did not accumulate in repeated dose rat toxicity study.

The very low clopidogrel / major metabolite ratio in venous blood reflects an extensive hepatic first pass effect: Following a single 5 mg/Kg oral dose to a portal vein- catheterized male baboon, the concentration of clopidogrel in portal blood was much higher than in peripheral blood(HFD-180: 6/28/95). Due to the hepatic clearance, bioavailability of clopidogrel in the rat is only several percent, although at least 50 to 70% is absorbed from the rat gut based on regional absorption from ligated GI tracts (HFD-180:6/9/94).

The AUC values for SR26334 obtaining at the 400 mg/Kg clopidogrel dosage (namely, ca. 5000 and 1400 mg. h/L for rat and male baboon, respectively) were approx. 175 to 600 times that measured in humans receiving 75 mg/day. The clinical dose affords patients close to peak inhibition (approx. 50%) of platelet response to ADP *ex vivo*. (HFD-180:6/28/95). Accordingly, dosages (up to 400 mg/Kg) tested in such animal toxicity studies afforded body burdens of clopidogrel several orders of magnitude greater than necessary for clinical target pharmacology.
Animal body burdens noted above reflect at least 50% absorption based on urinary excretion of clopidogrel-related metabolites (see Metabolism below).

b. Repeated dose:
Pharmacokinetics of clopidogrel and SR 26334 were studied after repeated administration in rodents and baboon to support interpretation of safety study data. Clopidogrel *per se* was not assayed in rodent plasma samples due to their high esterase activity:

Baboon: (HFD-180: 9/4/91)

1. Sub-acute 14-day study:
Male primates received 5 mg/Kg p.o. of radio-labeled clopidogrel for 14 consecutive days, and blood was sampled on days 1 through 14, and during washout, for parent drug, SR 26334 metabolite, and total plasma plasma radioactivity. Urine and feces were not monitored. Results: Parent drug was not detectable in plasma, and SR26334 represented approx. 50 % of plasma.

radioactivity. Half-life of plasma radioactivity decay following drug withdrawal was approx. 7 days.

2. Sub-chronic (3 mo.) and chronic (12- mo.) studies:
Plasma levels of clopidogrel and/or SR26344 were measured at peak and trough i.e., at 2 and 24 hours after gavage, on days 9, 40, and 98 of the 3 month toxicity study (High dose: 400 mg/ Kg/day), and on days 100, 191, 282, and 370 of the 1 year study (High dose: 200 mg/Kg/day): Results: In the 3-mo. study, low plasma levels (<0.015 mg/L) of intact clopidogrel were found, but approx. dose-proportional levels of metabolite SR26334 were seen at peak and trough (125 and 7 mg/L, respectively, at high dose). There was no gender effect. In the 1- year study, peak and trough SR26334 levels at 100 days / 200 mg/Kg were comparable to values in the shorter trial at 3 months / 400 mg/Kg. Peak plasma SR 26334 level during the one year duration of this trial (approx. 175 mg /L) is several orders of magnitude greater than that which obtains at the 75 mg clinical dose.

Rodents:
4-week studies (HFD-180: 8/2/94)
The diet afforded mice and rats dosages up to 100 mg/Kg (and beyond in the rat), matching those tested in the carcinogenicity studies. Blood was sampled on days 27-29, and steady- state drug exposure was determined using 0-22 hr. AUC of the SR26334 *S* -metabolite as a surrogate. Levels of the R-isomer of SR26334 were also measured to assess for any *in vivo* chiral transformation. Results: In both species, dose-related increases in SR26334 AUCs were observed. AUC values up to 47 times those seen clinically, thereby establishing the acceptability of the exposures achieved in the tumorigenicity bioassays. . There was minimal chiral conversion to the R-enantiomer of SR26334 (approx. 2% in mice; 7% in rat).

Distribution: (HFD-180: 7/16/90; 9/4/91)

Single oral dose:
Tissue distribution, and placental transfer, of ^{14}C- clopidogrel has been identified in the mouse and rat (2 strains), and pregnant rats and rabbits, by measuring tissue radioactivity and by whole body autoradiography following an oral dose of 5 to 77 mg/Kg. The latter was the mid-dose tested in the teratology study. A total of 6 distribution studies in Sprague-Dawley rats and in mice uniformly indicate rapid (peak concentrations within 15 to 30 min.) and extensive tissue distribution of radioactivity. Gut , liver, and kidney had higher - and brain, heart, muscle, and fat lower - levels than in plasma. In a separate study, whole body autoradiography confirmed this distribution pattern except radioactivity was also associated with melanin in eye, inner ear, pigmented skin, and hair follicles. Three days after dosing of rats, radioactivity was still detectable in liver, kidneys, lung, fat, and skin. Radioactivity in other tissues was less than 0.01% of administered dose.

Repeated oral dose:
In 21-day rat studies, highest levels of radioactivity again occur in the liver, kidney, and lungs from which it departs with half-lives of approx. 1 week (Sanofi report no. RS0005911218/01).
Single intravenous dose:
After i.v. administration to SD rats, uptake of radioactivity by the tissue is rapid, and highest in liver, kidneys, fat, and gut (indicating biliary excretion), and lowest in eyes, brain, and muscle.
Studies in pregnant rats: (HFD-180: 6/9/94)
Clopidogrel and/or it's metabolites cross the placenta of rats, is detectable in fetal liver and gut, and is also excreted in the milk of lactating animals: After a single oral dose of labeled clopidogrel at gestation day 11 or 19, maternal ^{14}C distribution was similar to that in non-gravid animals, and ovary ,uterus, and mammary tissue levels were approx. 50% of plasma concentrations. Within 30 min. of dosing, the major fetal organs had 3% (liver) to 50%(brain) of the corresponding maternal ^{14}C radioactivity. However, approx. 90% of both fetal and maternal tissue radioactivity had cleared within 24 hours based on sacrifice of gravid rats at 0.5, 4, and 24 hr. post administration.

Plasma protein binding: (HFD-180: 6/9/94) At an *in vitro* concentration of 100 mg/ml, approx. 98% of clopidogrel is bound to baboon plasma protein; such binding could not be reliably studied in rats or rabbits where plasma esterases rapidly hydrolyze clopidogrel. The major circulating metabolite binds to human serum protein up to 95%, reaching saturation at *in vitro* incubation concentration of 100 mg/ml.
After single oral dosing with labeled clopidogrel, radioactivity covalently bound to plasma protein has been detected in rodents and baboons. Such binding decays with a $T_{1/2}$ of approx. 8 days. (Sanofi report RS0005951201/06)

Metabolism (HFD-180:7/16/90; 9/4/91; 6/9/94; 6/28/95 :2 reports)

Biotransformation has been identified *in vivo* and *in vitro* , and main metabolites in plasma, urine, and bile characterized by LC-MS. Chiral inversion of clopidogrel - an *S* -enantiomer - has also been assessed. Because metabolism is primarily hepatic in primates, interaction with the Cyt. P_{450} enzymes was also assessed.
Plasma profiles:
Metabolic profiles in plasma have been studied following single (i.v., p.o.) and repeated oral dosing in baboons and rodents. After either route of administration, a stable *S* -carboxylic acid derivative (SR26334) predominates, comprising 45 to 95% of extractable plasma radioactivity across all species and time points. Studies in portal vein-cannulated baboons reveal that this conversion is primarily hepatic in that species; however, *in vitro* studies show that rat and rabbit (but not baboon or human) also have plasma esterases

capable of performing this hydrolysis. . Two other minor metabolites also occur in the plasma of baboons.

Stereo-specific assay of blood collected from baboons for up to 8 hr. after single oral dosing revealed chiral stability of clopidogrel i.e., only the *S*- and not the *R* - metabolite was detected. However, after repeated clopidogrel administration, up to 10% of this carboxylic acid derivative metabolite is the *R* - enantiomer, both in rodents and baboons.

Hepatic metabolism:

Ability of liver to metabolize clopidogrel has been studied in vitro and in vivo, and in the presence of Cyt P450 enzyme inducers and inhibitors. Ability of clopidogrel to modulate those hepatic mixed function oxidases was also assessed.

In vitro: Rat, dog, rabbit, baboon, and human liver microsomal fractions, in the presence of NADPH, are capable of hydrolyzing clopidogrel to SR26334 and oxidizing the thiophenic ring without major species differences.

Interactions with Cyt P450: Studies of livers excised from rats and baboons which had been dosed with up to 100 and 400 mg/Kg of Clopidogrel, respectively, for 3 months show that the drug is able to induce certain Cyt P_{450} oxidases while inhibiting others. In the primate, clopidogrel's effects at 100 mg/Kg dosage were similar to, or less than, those of the structurally related ticlopidine at the same dosage except that clopidogrel did not induce aniline hydroxylation (*CYP* 2E) activity. Both agents doubled *CYP* 3A activity, inhibited *CYP* 1A activity at least 50%, and increased weight of liver and it's Cyt P450 content by 25-50%.

To put these cytochrome P450 results into perspective, it should be noted that enzyme modulation was not observed in the rat or baboon at the end of 3 months dosing at 25 mg/Kg. That regimen afforded rats 10 to 15 times the human clopidogrel body burden (using AUC of main metabolite as a surrogate), and the baboon 7 times the human mg / M^2 dosage.

Pretreatment of female rats with a variety of selective modulators of Cyt P450 isozymes indicated that clopidogrel was mainly a substrate for Cyt P450 1A (HFD-180: 6/9/94). That is, beta-naphtoflavone and SKF 525A markedly enhanced or completely suppressed, respectively, the anti-aggregating activity of clopidogrel.

Excretion (HFD-180: 9/4/91)

Elimination of [14 -C]-clopidogrel, given orally or intravenously, was tracked in rats, rabbits , and baboons.

Biliary: A dose-dependent biliary metabolite profile was identified in bile duct-cannulated rats and baboons which received labeled clopidogrel enterally.Metabolites included a glutathionyl sulfoxide of clopidogrel (rats), free SR26334 (baboon), and glucuronides of SR26334 (both species). No free clopidogrel was detected.

In rats, approx. 80% of the administered dose (i.e., radioactivity) was excreted in the bile within 48 hours in the context of significant entero-hepatic recirculation of radioactivity.

Excretion Balance:

Within 6 days of i.v. or oral dosing to rats, approx.70- 80 % of radioactivity was fecally excreted, 10-20% was in the urine, and 1 - 4 % remained in the carcass. In the pregnant rabbit, 85% of the dose was recovered in urine, and 20% in feces after a single oral (100mg/Kg) dose given on gestation day 28. In male baboons repeatedly dosed at 5 mg/Kg /day, approx. 60 and 30 % of the radioactivity was recoverable in the feces and urine, respectively.

Summary:

Safety Evaluations:

Therapeutic Ratios:

Sponsor identified full dose-response profiles for both the anti-thrombotic and the anti platelet- aggregating activities of clopidogrel in multiple species. Anti-atherogenic as well as streptokinase-enhancing effects, at a specific clopidogrel dosage, were also identified in rabbits and rats, respectively. Safety tests conforming to GLP standards were performed up through acutely or chronically toxic dosages. In some cases, efficacy and repeated dose safety assays were performed in the same species , namely rat and baboon. In the latter species, ratios of median effective to threshold toxic dosages were large enough to project no clinical safety concerns in my judgment. Based on reversible gastric irritation and/or slight increase in liver weight, the therapeutic ratios were 35 (rat) and 660 (baboon). Using slight reversible changes in RBCs and/or platelets as toxicity markers, the ratios were 114 (rat) and 330 (baboon). This impression of low risk of serious or irreversible toxicity is reinforced by the consistency of these safety ratios and of other animal observations, namely: a.) the uniform maximum efficacy and potency of this agent across species (ED_{50}'s of 1- 5 mg/Kg) and models of thrombosis; b.) the close correlation of anti-aggregating, anti -thrombotic , and bleeding time-prolonging activities; and c.) the uniform absence across species of any remarkable functional or histologic aberration below 200 mg/Kg/day delivered by gavage (baboon: 1 year) or 400 mg/Kg /day via the diet (rat: 3-month). Furthermore, the slightly aberrant hemograms, clinical chemistries, and liver wt. increases - which were the only remarkable findings in the 12 mo. studies - were uniformly reversible. Lesions of the digestive tract primarily seen at high dose levels ($\geq$ 500 mg/Kg in baboons or $\geq$ 1000 mg/Kg in rats) during the sub-acute studies were not observed in either species in the one-year studies performed at lower doses.

Hematotoxicity:

Potential hematotoxicity was of concern in view of the structural and pharmacological similarity of clopidogrel to ticlopidine. Ticlopidine can cause neutropenia and thrombocytopenia (Moloney, B., : Ticlopidine , Platelets, and Vascular Disease., New York, Spr. Ver. , 1993:117-139.). Only slight, and reversible hemogram changes (platelet/ RBC count) were seen in rats (≥ 400 mg/Kg for 3 months) and baboons (200 mg/Kg for 1 year) and, then, at dosages producing GI irritation and health deterioration. No oral myelotoxicity was seen in mice at up to 500 mg/Kg/day/5 days. However, sponsor, to their credit , reminds us that ticlopidine, a known human myelotoxin, was similarly nontoxic in animal models.

Safety Pharmacology:

Beyond standard assaying for histopathologic or clinical chemistry changes, sponsor also tested for any central or peripheral functional aberrations - including those of the immune system. Based on results of such safety pharmacology studies, where doses at least 30-50 times higher than the anti-aggregating or anti-thrombotic dose produced no remarkable side effects, it could be concluded that the risk of interrupting any vital function at recommended dosages is low. Immunotoxicity was tested in 3 species. Absent were any histologic, immunoglobulin, or lymphocyte function changes in either the 1-year baboon study , executed at 330- fold the therapeutic dosage in that primate, or in 4-week rat studies. Lack of antigenicity or photoallergy in the guinea pig would further reduce the likelihood of eliciting any immunotoxicity or "hypersensitivity" reactions e.g., an autoimmune-based blood dyscrasia.

Noteworthy is the absence of any specific central nervous system toxicity. Potential for CNS toxicity was of concern because the *R* - enantiomer of clopidogrel , which is present in current formulation at up to 1%, provokes CNS toxicity in animals at dose levels greater than 250 mg/Kg.

Effects on Hemostasis:

In rats and rabbits the agent will , as expected , prolong bleeding time of fresh wounds dose-dependently, and in parallel with interference of ADP - induced platelet activation. Accordingly, at therapeutic doses it could promote bleeding of certain lesions e.g., ulcers - as occurred at sites of GI tract lesions in acute high-dose rodent and baboon studies.

Clopidogrel lacks any anticoagulant or profibrinolytic activity both of which are, as I understand, independent of platelet activation. It affects neither prothrombin or thrombin times nor levels of prothrombin or fibrinogen. The experience in the CAPRIE trial - where, according to sponsor, clopidogrel provoked less bleeding than aspirin - would be consistent with the virtual absence of hemorrhages in intact mice, rats, and baboons..

Reproductive function:

Assays of clopidogrel effects on reproductive function and on peri- and post-natal disturbances examined all standard parameters in rats and rabbits. As

reprotox. tests were performed over the same dose ranges as in the subacute toxicity studies, similar parental toxicity was observed at the highest dosages - confirming appropriateness of high dose selection. Although sponsor showed that radiolabelled compound enters rat and rabbit fetuses and rat milk, there was no fetotoxicity, teratogenicity, or irreversible neonatal aberration. The only remarkable finding was a slight delay in physical development of neonates nursing from dams receiving 100 or 400 mg/Kg daily. This effect, which was not observed unless the lactating dams were receiving clopidogrel, was confined to the lactation period and reversed rapidly after weaning.

Genotoxicity /Tumorigenicity:

A comprehensive battery of *in vitro* mutagenicity tests were performed at up to cytotoxic concentrations and with rat S-9 present to compensate for the limited oxidative metabolism capacity of bacteria or cells in culture. Such assays were uniformly negative for genotoxicity vs. unequivocally positive results for the active controls. Ancillary to these findings was the absence of clastogenicity in a mouse micronucleus test performed at up to 26 times the high dose used in the tumorigenicity study.

In lifetime carcinogenicity assays, dosages of clopidogrel which afforded up to 50 times the human clopidogrel body burden (based on relative levels of the major metabolite), were neither lethal nor - according to standard Peto analysis - carcinogenic in rodents. A slight increase in incidence of palpable masses in treated rats was recorded for both the male [3% in control (3/100) Vs 7% in treated (12/ 150)] and female [64% in control (64/100) vs. 74% in female (111/150)]. The raw data show 3 "excess" malignant tumors in mid/high-dose males, and 4 in mid/high-dose females. However, statistical analysis according to Peto et al (1980) revealed no positive trend for any specific tumor type in either sex. Dr. Ahmad and the Exec. CAC agreed that clopidogrel - over an appropriate dose range - provoked no excess tumors in either sex of either species.

Biopharmaceutics:

Pharmacokinetic studies necessary to support pharmacodynamic and toxicity studies characterized ADME of clopidogrel, and confirmed drug exposures in the critical rat and primate studies. Results of the pharmacokinetic studies of [^{14}C]- clopidogrel are considered to be reliable since radiochemical purity (>99%) was confirmed prior to each investigation, and the low exhalation of radioactive carbon dioxide (0.2%) after single oral administration to rats showed that the ^{14}C labeling on the pyridine ring was appropriate for the PK studies. The low percentage of SR 26335 (the *R* - enantiomer of major metabolite SR 26334) formed *in vivo* by chiral conversion supported the general use of non-stereospecific methods for assaying SR 26334.Assay of the latter was the only feasible way of tracking clopidogrel's

fleeting exposure. All plasma drug/metabolite assay methods were said to be validated for each animal species used.

Oral absorption was extensive in all species. In the baboon, sponsor clearly established that the low oral bioavailability of intact clopidogrel reflected rapid hepatic bio-transformation rather than poor absorption. Clopidogrel was primarily hydrolyzed to SR26334 (one of twenty metabolites) which was observed in plasma 0.2 to 0.5 hr. after dosing. This metabolite was approximately 95% protein bound in rats and primates (primarily to albumin in humans), and did not accumulate in the 2 to 4 week safety studies in rodents and baboons. Acute distribution studies in mice, rats (2 strains), and pregnant rats and rabbits at a pharmacologic dose (rats) or dose within range tested in toxicology (mice; rabbits) revealed similarly wide distribution patterns (preponderance of label in gut, liver, and kidney; minimal uptake in eyes, muscle, and CNS), and rapid tissue clearance. In repeat dose rat studies, some accumulation of label did occur, reached steady state in 14 days, and was eliminated from all tissues with half-lives of 4 to 8 days. Label will cross the placenta, and can be detected in fetal liver and gut at low levels, and is excreted in milk . Extensive fecal elimination of intravenously administered label in both rats and baboon showed that biliary excretion was a major route of elimination which, along with the kidney, accounted for the extensive clearing of systemic radioactivity within 48 hr. of dosing.

Because this pro-drug is rapidly and extensively metabolized, it's effect on liver mixed function oxidase and interaction with modulators of this system was characterized. Microsomes prepared from animal and human liver homogenates hydrolyzed clopidogrel. Microsomes also oxidized it's thiophene ring if NADPH needed for a functional P450 system was present. Livers excised from baboons exposed for 3 months to supra-therapeutic clopidogrel AUC values i.e., a minimum of 10 times that of treated patients - have up to 150% of the weight and total CYT P450 activity of control, and double it's Cyp 3A activity. There was no appreciable modulation of liver enzymes at lower clopidogrel exposures in these baboons. This would be consistent with the Sponsor's observation that humans treated for 10 days with clopidogrel metabolized/cleared the P450 substrates antipyrine and 6 -β hydroxy cortisol normally. Pretreatment of rats with agents known to modulate CYT 1A, however, markedly enhanced or even abolished anti-aggregating activity of clopidogrel. Since baboons were not tested to see if this interaction extended to primates, the possibility of a drug-clopidogrel interaction in humans cannot be dismissed *a priori*.

LABELING:

Under Carcinogenesis, Mutagenesis, Impairment of Fertility: Add to the third sentence: (52 times the recommended human dose on a mg/ M^2 basis).

Under Pregnancy: Replace the first sentence with: Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/Kg per 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.

Albert De Felice, Ph.D.

9/13/97

cc: NDA 20-839
HFD-110
HFD-110/DRoeder

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20839

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OCT 15 1997

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20,839

Submission Date: April 28, 1997
July 14, 1997
July 23, 1997
August 14, 1997
Fax dt: July 28, 1997

IND January 20, 1997,
faxed to us on May 21, 1997

Drug Name and Formulation: Plavix® (Clopidogrel) tablets, 75 mg strength

Sponsor: Sanofi Pharmaceuticals, Inc., Malvern, PA 19355

Reviewers: Venkata Ramana S. Uppoor, Patrick J. Marroum & Ameeta Parekh

Type of Submission: New Drug Application, NME, 1P

SYNOPSIS: Plavix tablets contain clopidogrel bisulfate, a platelet aggregation inhibitor, in a dosage strength of 75 mg. This is indicated for the prevention of vascular ischemic events (myocardial infarction, stroke, vascular death) in patients with a history of symptomatic atherosclerotic disease. Clopidogrel is an inhibitor of ADP-induced platelet aggregation acting by direct inhibition of ADP binding to its receptor and by subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. The recommended oral dose is 75 mg once daily. This contains a single enantiomer (S-enantiomer) of clopidogrel (the R-enantiomer causes CNS toxicity). Neither the parent moiety, clopidogrel nor its major carboxy metabolite, SR26334 (S-enantiomer) showed any activity in vitro. The active species has not been isolated yet, but it is known that clopidogrel has to be biotransformed for it to be active (CYP1A2 involved in this biotransformation). It is felt that the active moiety is a reactive species (may be a sulfoxide of clopidogrel). The major metabolite (SR26334) is the moiety that was measured in pharmacokinetic trials since this is the only moiety that could be quantitated. Only peak levels of the parent clopidogrel could be obtained. Since the active moiety is not known, most studies included both pharmacokinetic and pharmacodynamic information.

The Human Pharmacokinetics and Bioavailability (Item 6) section of this NDA contains several pharmacokinetic (33 in vivo and 10 in vitro) studies. The pharmacokinetics are generally based on SR26334. The absolute bioavailability of clopidogrel is unknown. The relative bioavailability of clopidogrel tablet compared to capsules was almost 100% based on the inactive clopidogrel carboxy metabolite.

The to-be marketed formulation is similar to the one used in the Phase III clinical trial. The safety and efficacy of Plavix in preventing vascular ischemic events has been evaluated in a comparison with aspirin (clopidogrel versus aspirin in patients at risk of ischemic events, CAPRIE

trial) in 19,185 patients (in one clinical trial) with documented atherosclerotic disease as manifested by myocardial infarction, ischemic stroke or peripheral arterial disease.

The sponsor has adequately validated the assay methodology for clopidogrel (SR25990) and its major carboxylic acid metabolite (SR26334). The sponsor also adequately characterized the pharmacokinetics (single and multiple dose) of SR26334 in healthy volunteers, hepatically impaired patients and renally impaired patients. Pharmacokinetics were also studied in peripheral arterial disease and coronary artery disease patients. Effect of age and gender were also investigated. Metabolic enzymes (cytochrome P450 isozymes) responsible for clopidogrel metabolism have been identified. About 50% of the clopidogrel dose administered is excreted in urine (mostly as metabolites) and about 46% in feces. No unchanged drug is found in urine. Clopidogrel is metabolized by hepatic esterases to SR26334 (major metabolite). Other minor metabolites were also found. The carboxy metabolite (major) of clopidogrel found in human plasma and urine was found to be inactive. The active metabolite appears to be a labile species (S-oxide) which binds irreversibly to plasma proteins or the proteins of platelet membrane. The half-life of radioactivity is about 7 days. Absolute bioavailability information on the tablets is not available. Clopidogrel is absorbed rapidly with a t_{max} of about 0.5 - 1 hour. The tmax for SR26334 is also about 1 hour. SR26334 has a half-life of about 8 hours. It is highly protein bound (90%). The pharmacokinetics of SR26334 appear to be linear over a dose range of 50 to 150 mg. At steady state, accumulation index for SR26334 was 1.2 compared to single dose indicating no accumulation. Food decreased the C_{max} of SR26334 by 14% (formulation 1A1) and by 21% (formulation 2Q2). In hepatic impairment (child-pugh class A and B), parent clopidogrel C_{max} increased 60 fold following administration of 75 mg single and multiple dose. There were no significant changes in the pharmacokinetics of SR26334 and in the pharmacodynamic endpoints. In renal impairment, although higher levels of clopidogrel were observed in patients with severe renal impairment, no control subjects were included in the study and thus the study design is inadequate. Pharmacokinetics of SR26334 were similar in peripheral arterial disease patients and normal volunteers. The PK-PD relationship of clopidogrel has not been studied by the sponsor. No PK-PD relationship could be established with the available data.

Several doses were tested during clopidogrel drug development. However, 75 mg is the dose that has been selected for use. The to-be marketed formulation is very similar to the one utilized in the pivotal Phase III clinical trial.

When administered concomitantly with clopidogrel, no notable changes in clearance of antipyrine were observed. Coadministration of clopidogrel and digoxin did not result in any changes in pharmacokinetics of digoxin. Concomitant administration of clopidogrel and theophylline did not affect the pharmacokinetics of theophylline. Administration of clopidogrel with antacid (maalox) did not affect the pharmacokinetics of SR26334. Cimetidine did not affect the pharmacokinetics and pharmacodynamics when concomitantly administered with clopidogrel. Neither estrogen replacement therapy nor gender had any effects on the pharmacokinetics of SR26334. However, the study indicates that clopidogrel may be less effective in women taking estrogen replacement therapy. Coadministration of phenobarbital with clopidogrel decreased the Cmax of clopidogrel by 60% accompanied by a slight increase in Cmax and AUC of SR26334. An increase in % inhibition of platelet aggregation was also seen. Coadministration of clopidogrel

with atenolol or nifedipine did not have any effect on the pharmacological activity of clopidogrel in patients. In vitro inhibition studies carried out using human liver microsomes indicate that SR26334 inhibits metabolic reactions catalyzed by cytochrome P450 2C9 with Ki value of 28 μM.

RECOMMENDATION: The present submission (NDA 20-839) has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics. The submission is acceptable provided that a) labeling comments # 1 - 8, b) comments to the sponsor # 1 - 5 and c) a phase IV commitment to are adequately addressed by the sponsor. A biowaiver can be granted for the to-be marketed tablet based on comparable dissolution data between the to-be marketed tablet and the clinical tablet formulation. The dissolution method and specifications set by the agency as provided in comment # 4 (Q = in 20 minutes) should be adopted.

TABLE OF CONTENTS:

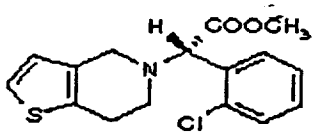
I. BACKGROUND

Plavix® Tablet contains clopidogrel bisulfate (75 mg clopidogrel base) with potent antiplatelet activity. This drug is a thienopyridine derivative, an S-enantiomer and exists as a single polymorph. Clopidogrel, like ticlopidine, selectively inhibits the binding of ADP to its platelet receptor and the subsequent ADP-mediated activation of the GPIIb/IIIa complex, thereby inhibiting platelet aggregation.

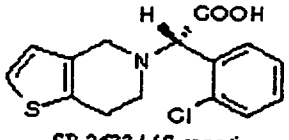
Due to the antiplatelet activity, this drug has potential for prevention of ischemic stroke, myocardial infarction and vascular death in patients with increased risk of such outcomes, including those with established atherosclerosis or history of atherosclerosis. The sponsor has proposed to market the Plavix tablets at a dose strength of 75 mg. The proposed indication for Plavix is for the prevention of vascular ischemic events (myocardial infarction, stroke, vascular death) in patients with a history of symptomatic atherosclerotic disease. The proposed dose is 75 mg tablet to be taken once a day with or without food. Plavix tablet is a pink, round, film-coated tablet.

STRUCTURE OF DRUG ENTITY: Clopidogrel is chemically methyl (S)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate sulfate (1:1) with a molecular weight of 419.9. Clopidogrel is an S-enantiomer with the structure shown in figure below.

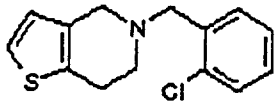
Figure:



SR 25990 (S-enantiomer)
clopidogrel



SR 26334 (S-enantiomer)
Carboxylic acid derivative



Ticlopidine

SOLUBILITY CHARACTERISTICS: Clopidogrel is moderately insoluble in water at neutral pH but freely soluble at pH 1.

II. FORMULATION: During the course of drug development, the sponsor changed formulations several times. The 1A1 tablet and capsule were used in phase I and II studies. The pivotal phase III clinical trial utilized the 2Q2 tablet formulation which is very similar to the to-be marketed tablet formulation. The details of the final tablet formulation and the clinical tablet formulation are given below.

CLOPIDOGREL FINAL AND CLINICAL TABLET FORMULATION

INGREDIENT	Clinical 2Q2 tablet mg/tablet	To-be marketed tablet, 2AB7 mg/tablet
CORE Clopidogrel Bisulfate (equivalent to 75 mg base) Anhydrous Lactose, NF Pregelatinized Starch, NF Polyethylene Glycol 6000, NF Microcrystalline Cellulose, NF (average size 90 µm) Hydrogenated Castor Oil, NF	97.875 mg	97.875 mg
COATING Hydroxypropylmethylcellulose 2910, USP Polyethylene Glycol 6000, NF Titanium Dioxide, USP Ferric Oxide, NF (red) Purified Water, USP (eliminated during manufacture)		
POLISHING Carnauba Wax, NF *Total coated tablet weight*		

III. STUDIES THAT WERE NOT REVIEWED:

Several studies have been submitted as part of the NDA, however, studies that are not pivotal will not be included in this review. List of studies not reviewed with reasons are provided below.

1. P1305 (volume 47): Evaluation of the pharmacological activity of SR25990C administered as a single dose of 400 mg to patients suffering from arteriopathy. This study included a very high dose which is not relevant to this NDA (proposed dose is 75 mg), hence it has not been reviewed.

2. PDY1981 (volume 37): Effect of clopidogrel (SR25990C) on the ADP receptor in healthy volunteers. This study did not have any pharmacokinetic data, hence it has not been reviewed.

3. P1345 (volumes 29, 30 and 31): Pharmacological activity of 3 repeated doses of SR25990C (10, 25 and 50 mg) administered for 14 days to healthy volunteers, in comparison with 500 mg ticlopidine. This study included much lower doses than recommended. Since such data on

relevant doses is available from other studies, this study has not been reviewed.

4. P1365 (volumes 31 and 32): Pilot study of SR25990C administered to healthy volunteers at the daily dose level of 10 mg for 14 days. This study included much lower dose than recommended. Hence this study has not been reviewed.

IV. PHARMACOKINETICS AND BIOAVAILABILITY:

The summary of pharmacokinetics of the drug obtained from clopidogrel tablets is provided here.

a. ABSOLUTE BIOAVAILABILITY (and RELATIVE BIOAVAILABILITY):
Pharmacokinetics of the drug have not been determined following intravenous route of administration. Hence, information on absolute bioavailability is not available. However, information from mass balance study, where radiolabeled drug was administered, indicates that at least 50% of administered drug crossed the gastrointestinal barrier (based on radiolabel in urine). No data is available from solution to compute relative bioavailability of clopidogrel. Information on relative bioavailability can be obtained from a relative bioavailability study where a capsule arm was included. It was found that bioavailability of the tablets relative to capsule was 100% based on AUC and C_{max} of the inactive carboxy metabolite (study # P1064).

b. ABSORPTION: Following oral doses up to 400 mg (either via single or multiple administration) in healthy volunteers, clopidogrel was absorbed rapidly. The mean T_{max} across all formulations ranged from 0.5 - 1 hour for clopidogrel and 1 hour for SR26334. Mean C_{max} of SR26334 following 75 mg single dose in healthy male volunteers ranged from 2.62 to 3.21 mg/l. AUC_{0-} at 75 mg single dose ranged from 7 - 9 mg.hr/l. No accumulation was seen upon multiple dosing. Intersubject variability in SR26334 pharmacokinetics was found to be about 30%.

c. DISTRIBUTION: The true volume of distribution was not estimated due to non-availability of an intravenous formulation.
Plasma protein binding: In vitro protein binding studies indicate that binding is saturable for both clopidogrel and SR26334 at concentrations above 100 mg/l. Clopidogrel is 98% bound to plasma proteins and SR26334 is 94% bound as shown by determination of protein binding in vitro using equilibrium dialysis technique. SR26334 binds primarily to albumin. In vitro data indicates that there was no significant distribution (<10%) of clopidogrel and SR26334 to red blood cells.

d. ELIMINATION (METABOLISM AND EXCRETION):

Terminal phase half-life: Half-life of SR26334 is approximately 8 hours in healthy male volunteers. The half-life of radioactivity (covalent binding to platelets) was about 7 days. Mean Cl/F was found to be 9.66 l/hr.
Metabolism: Clopidogrel is highly metabolized as indicated by no unchanged drug found in urine upon oral administration. It is metabolized by hepatic esterases to SR26334 (no metabolism by plasma esterases). In vitro studies indicated that in absence of NADPH, clopidogrel underwent hydrolysis to SR26334, and in presence of NADPH, it underwent hydrolysis and S-oxidation

(sulfoxide) followed by dimerization or intra-molecular rearrangement to give 2-oxo clopidogrel which is further hydrolyzed and oxidized (see figure below). None of these metabolites, except sulfoxide, are active. The SR26334 undergoes further glucuronidation (data obtained from in vivo metabolism). No SR26335 (R-enantiomer) could be identified in plasma indicating lack of interconversion of the enantiomers.

IN VITRO BIOTRANSFORMATION OF CLOPIDOGREL

Excretion: Upon administration of 75 mg of radiolabeled clopidogrel, mean cumulative urinary and fecal recoveries of total radioactivity were 51% and 46% respectively after administration of ^{14}C-clopidogrel as single dose, and were 41 and 50% after administration as multiple dose. Expired carbon dioxide represented 0.15% of the administered dose. No unchanged drug was detected in urine. The urinary excretion of SR26334 represented about 2% of the administered dose. This indicates that most of clopidogrel and SR26334 is excreted as metabolites. The terminal half-life of radioactivity was about 7 days and half-life of SR26334 was about 8 hours. Renal clearance of SR26334 was about 4 ml/min in healthy male volunteers after dosing with 75 mg clopidogrel.

e. DOSE PROPORTIONALITY: When studied at four dose levels of 50, 75, 100 and 150 mg clopidogrel administered as multiple units of 25 mg tablets (study LIN 2264), the pharmacokinetics of clopidogrel carboxy metabolite are linear. AUCs and C_{max}s were dose-proportional (AUC = 4.51, 7.05, 9.45 and 15.76 mg-hr/l and C_{max} = 1.59, 2.78, 3.08 and 4.85

mg/l at 50, 75 100 and 150 mg dose levels respectively). When dose-normalized parameters were analyzed, there were no significant treatment effects. This data indicates that total plasma clearance, half-life and bioavailability (or at least Cl/F) are dose-independent. Renal clearance and fraction excreted in urine are also dose-independent. While this study did not monitor the pharmacodynamic effects of clopidogrel, a clinical study P1264 measured the PD effects. The % inhibition of ADP-induced platelet aggregation increased with dose in the dose range of 10 to 150 mg qd, however these were not exactly dose proportional. The % inhibition was almost constant in the dose range of 50 to 100 mg qd (clinical study P1404).

f. FOOD EFFECT: Food decreased SR26334 (clopidogrel carboxy metabolite) C_{max} by 21% (90% confidence interval 0.57 - 0.97) and had no effect on AUC (90% confidence interval 1.05 to 1.12) when clopidogrel 2Q2 75 mg clinical trial tablet formulation was administered within 0.5 hours after high fat breakfast (study P1717). However, the reviewer of this study Dr.Colangelo felt that the Cmax values measured were not very convincing and concluded that food has a minimal effect on the pharmacokinetics of the primary metabolite of clopidogrel. No pharmacodynamic effects were reported. Another food effect study P1298 conducted on the 1A1 tablet indicated that the coadministration of clopidogrel with food decreased Cmax by 14% and increased Tmax by 0.5 hours (from 1 to 1.5 hours). AUC remained unchanged. The observed lowering of Cmax is likely to be due to delay in gastric emptying of the drug when taken with meals. This study showed no difference in the pharmacodynamics (% inhibition of platelet aggregation) whether clopidogrel 1A1 tablet was administered with or without food.

g. SPECIAL POPULATIONS:

Age: Study P1331 was conducted to study the effect of age on pharmacokinetics of clopidogrel carboxy metabolite. Age-related effects were analyzed by comparing elderly subjects (75 years of age) versus healthy adults (24 years of age). Cmax and AUC values of clopidogrel carboxy metabolite were higher in the elderly (30% higher for Cmax and 75 - 100% higher for AUC). Accumulation of this metabolite occurs upon multiple dosing in elderly and not in young subjects. The decrease in maximal platelet aggregation upon treatment with clopidogrel is higher in elderly than in young subjects. Based on pretreatment data, the elderly subjects also appear to be more susceptible to ADP-induced platelet aggregation. This leads one to conclude that elderly are more susceptible to platelet aggregation and also more sensitive to clopidogrel treatment. Hence, dosage adjustment may be considered in elderly subjects. However, this decision should be based on the results from the pivotal clinical trial which includes a large number of subjects.

Gender: Study P1423 conducted in postmenopausal women and men of the same age indicates that there is no gender effect on the pharmacokinetics of clopidogrel carboxy metabolite.

Hepatic impairment: Pharmacokinetics of clopidogrel and its major metabolite SR26334 were studied after administration of 75 mg single and multiple doses of clopidogrel to cirrhotic patients belonging to Child-Pugh class A and B and corresponding matched normal subjects. Mean C_{max} for clopidogrel was approximately 60 fold higher in patients with hepatic cirrhosis than in the control group. Mean Cmax and AUC were slightly higher for SR26334 in patients with hepatic impairment. The Cmax was not significantly different. The % inhibition of platelet aggregation

and bleeding time prolongation factor were comparable for both cirrhotics and normal subjects. Hence, dose-adjustment may not be necessary as these levels seemed to be well tolerated and found to be safe in the population studied. However, patients with severe hepatic impairment (that have not been studied here) should be carefully monitored when clopidogrel is administered to these patients, unless suitable clinical data is available in this patients.

Renal impairment: This is a multiple dose study carried out in subjects with moderate (Cl_{Cr} 30 - 60 ml/min) and severe renal impairment (Cl_{Cr} 5 - 15 ml/min). No control (healthy) subjects were included in this study. The parent clopidogrel Cmax was higher in severe renal failure patients compared to the moderate renal failure patients (4.13 vs. 2.70 mg/l), however these differences were not statistically significant. The Mean C_{max}, AUC and Cmin values for SR26334 were higher in patients with moderate renal impairment compared to severe impairment. There was no difference in pharmacodynamics between the two patient populations. Across study comparisons to normal subjects was not possible since there was large variability in the pharmacodynamic parameters. Based on this lack of control subjects in this study, decisions on dosage adjustments in renal impairment cannot be made. Therefore, caution should be exercised unless there is clinical data that indicates otherwise.

PK in patients: Pharmacokinetics of clopidogrel and its metabolite in healthy volunteers were found to be similar in patients with peripheral arterial disease (PAD).

h. BIOEQUIVALENCE BETWEEN FORMULATIONS:

Several changes were made to the clopidogrel formulations during the drug development. The 1A1 tablet and capsule were used in phase I and II a studies while the 2Q2 tablet was used in pivotal phase III trial and in hepatic impairment study. The sponsor conducted several pilot and one pivotal bioequivalence study to link the 1A1 capsule to 1A1 tablet and 2Q2 tablet formulation. While data from these studies is useful, they are not essential since the 2Q2 formulation has been studied in pivotal clinical trial for safety and efficacy. The 2Q2 formulation is very similar to the to-be marketed tablet formulation (2AB7).

A waiver of a bioequivalence study between the clinical and to-be marketed tablet is granted based on in vitro dissolution data since the changes are minor (iactose, color addition and change of film-coating solvents from mixture to water alone). When the dissolution profile (testing at 75 rpm, 6 tablets per batch) of the to-be marketed tablet was compared to dissolution profiles from 2 different batches of clinical tablet formulation, the resultant f_2 values were 78.896 and 76.326. Similar comparison of dissolution profiles (testing at 50 rpm, 12 tablets per batch) for one batch of clinical and to-be marketed tablets resulted in an f_2 value of 93.108.

Since the active moiety of clopidogrel is not known and no PK-PD relationship has been established with any known moiety, bioequivalence studies for post-approval changes should be based on the pharmacodynamic effects of clopidogrel (and not on pharmacokinetics). Bioequivalence criteria for this product should be discussed with the agency prior to making any post-approval changes.

V. DISSOLUTION: The proposed dissolution method for the clopidogrel tablet formulation is

VI. PHARMACODYNAMICS:

PK-PD: Since the active moiety is not yet known, specific attempts were not made by the sponsor to develop a relationship between pharmacokinetics of clopidogrel and/or its metabolite and % inhibition of ADP-induced platelet aggregation. At the proposed dose of 75 mg, % inhibition of ADP-induced platelet aggregation was about 50% and bleeding time prolongation factor was about 1.5 (study P1065). With the existing data, when attempts were made (by the reviewer), no PK-PD relationship was found (see appendix II). However, this could be due to lack of knowledge about the active moiety, i.e. wrong moiety being monitored for PK-PD relationship.

VII. DRUG INTERACTIONS:

a. In-vitro inhibition studies in human liver microsomes: These studies indicate that the parent clopidogrel did not inhibit reactions catalyzed by human cytochrome P450. SR26334 (carboxy metabolite) did not significantly inhibit CYP1A2, CYP3A4, CYP2C19, CYP2D6, CYP2E1 or CYP2A6. SR26334, however, inhibited cytochrome P450 2C9 (tolbutamide hydroxylation) with a Ki value of 28 μM. Considering the expected Cmax of SR26334 of 10 μM, the inhibition of CYP2C9 was calculated as 26.3% . Results of these studies indicate that coadministration of clopidogrel with 2C9 substrates (e.g. S-warfarin, tolbutamide, torsemide, phenytoin, tamoxifen) could result in drug interactions. However, since SR26334 is extensively protein bound, the unbound concentrations will be much lower than the concentrations that cause inhibition of CYP2C9 mediated metabolism. Hence there is no concern of potential drug interactions involving this pathway.

Another in vitro interaction study with glibenclamide (glyburide) indicated that the parent clopidogrel does not inhibit glyburide metabolism. However, the SR26334 moiety inhibits the formation of one of glyburide's metabolite (I). The formation of the second metabolite is not inhibited. Since all metabolic pathways of glyburide are not inhibited by SR26334, this interaction may not be potentially clinically significant.

b. In-vitro protein binding interaction studies: Nifedipine, atenolol, digoxin, ranitidine, bilirubin and palmitic acid did not compete with clopidogrel and SR26334 for the binding sites of plasma proteins. In addition, SR26334 had no effect on the binding of parent drug (clopidogrel), digoxin and ranitidine to plasma proteins. Effects on warfarin binding were not studied.

c. In-vivo drug interaction studies:

Antipyrine: When antipyrine (10 mg/kg i.v. single dose) was co-administered with clopidogrel (75 mg qd for 10 days), no significant change in antipyrine clearance was observed. No evidence for either inhibitory or inductive effect of clopidogrel on formation or clearance of antipyrine metabolites and clearance of antipyrine was seen.

Digoxin: A fixed sequence, multiple dose design study in 12 healthy male volunteers indicated that coadministration of 75 mg clopidogrel qd for 10 days with 0.25 mg digoxin at steady state did not have any effect on the pharmacokinetics of digoxin.

Theophylline: A fixed sequence, multiple dose design study in 12 healthy male volunteers indicated that coadministration of 75 mg clopidogrel either as single or multiple dose did not have any effect on the steady state pharmacokinetics of theophylline at a dose of 300 mg twice daily.

Antacid (maalox): A crossover single dose study in 12 healthy male volunteers indicated that coadministration of 75 mg clopidogrel with 800 mg maalox did not have any effect on the plasma profile of SR26334.

Cimetidine: A fixed sequence multiple dose design study in 18 healthy male volunteers indicated that coadministration of 400 mg cimetidine bid for 14 days with 75 mg clopidogrel did not affect the pharmacokinetics of SR26334. The changes in ADP induced maximum % platelet aggregation were not considered clinically significant since they were less than 10%. No dosage adjustments for clopidogrel are necessary when it is coadministered with cimetidine.

Estrogen: A parallel group multiple dose design study in postmenopausal women (with and without estrogen replacement therapy) and healthy male volunteers indicated that neither estrogen replacement therapy nor gender had any effects on the pharmacokinetics of SR26334. However, clopidogrel seems to be less effective in women taking estrogen replacement therapy.

Phenobarbital: A fixed sequence multiple dose design study in 12 healthy male volunteers indicated that coadministration of 100 mg phenobarbital for 21 days with 75 mg clopidogrel decreased the Cmax of clopidogrel by 60% with a corresponding increase of 27% in Cmax and 8.6% in AUC of SR26334. The pharmacokinetic interaction was accompanied by an increased inhibition of ADP induced platelet aggregation of clopidogrel from 41.6 to 49.1% with no effect on bleeding time.

Atenolol/Nifedipine: A placebo-controlled crossover multiple dose study in 24 patients with peripheral arterial disease or coronary artery disease who were previously stabilized on atenolol or nifedipine indicated that coadministration did not have any effect on the pharmacological activity

of clopidogrel.

VIII. ANALYTICAL METHODS VALIDATION: Several analytical methods have been used during development of this drug/drug product for determining concentrations of clopidogrel and its carboxylic acid metabolite in plasma and urine. Clopidogrel was

COMMENTS TO THE MEDICAL OFFICER:

1. The moiety responsible for the anti-platelet aggregation activity of clopidogrel has not been identified. The pharmacokinetics section of this NDA is based on the major carboxylic acid metabolite of clopidogrel (SR26334). The plasma concentrations of parent moiety were well below the quantifiable limits during the entire dosing interval except for the first 2 hours. Hence, only Cmax for parent clopidogrel were determined. While it is generally important to look at the pharmacokinetics of the drug, since the active moiety is not known in this case, it is important to place more emphasis on the pharmacodynamic activity of clopidogrel.

2. Results of study P1331, conducted to study the effect of age on pharmacokinetics of clopidogrel carboxy metabolite, indicate that the Cmax and AUC of this metabolite were 30 and 75 - 100% higher in elderly (75 years old) compared to young adults (24 years old). Also, the % inhibition of platelet aggregation was higher in elderly than younger subjects. Based on pretreatment data, elderly appear to be more susceptible to platelet aggregation and also more sensitive to clopidogrel treatment. This data indicates that caution/dosage adjustment may be considered in elderly subjects. This caution may be necessary if such results were also observed in pivotal clinical trials. The sponsor has stated in the label, under Dosage and Administration section, that no dosage adjustment is necessary for elderly patients or patients with renal disease. This statement needs to be appropriately modified based on the analysis of clinical trial data.

3. The pharmacokinetics/pharmacodynamics of clopidogrel and its carboxy metabolite have been studied in subjects with hepatic impairment (Child-Pugh class A and B). While the peak plasma concentrations of parent clopidogrel were 50 to 65 fold higher than normal subjects, there was very little effect on the pharmacokinetics of the carboxy metabolite and on the pharmacodynamics of clopidogrel. Hence, no dosage adjustment is necessary in this population. Such study was not, however, conducted in patients with severe liver impairment. Hence caution is needed for clopidogrel dosing in this population unless adequate data is available from clinical trials which

indicates that caution is not necessary.

4. The pharmacokinetics/pharmacodynamics of clopidogrel and its carboxy metabolite have been studied in patients with moderate and severe renal impairment. However, this study did not include matched control (healthy) subjects. Hence, recommendations regarding dosage adjustment in this population cannot be made. Caution may be necessary in administration of clopidogrel to this patient population unless adequate data is available from clinical trials, that indicates otherwise.

5. Since warfarin is likely to be coadministered with clopidogrel in clinical setting, a caution in the label during concomitant administration of these two drugs is warranted. A drug interaction study between clopidogrel and warfarin, as a phase IV study, may be considered.

6. The drug interaction study with estrogen indicated that clopidogrel seems to be less effective (with respect to % inhibition of platelet aggregation) in women taking estrogen replacement therapy. The medical officer is requested to please confirm this finding in clinical trial data.

7. The to-be marketed formulation is very similar to the formulation (2Q2 tablet) tested in the pivotal clinical trial. Since the changes are minor, no bioequivalence study is necessary. The in vitro dissolution profiles for the two formulations are comparable. Hence, there are no bioequivalence issues in this application.

8. Food resulted in a small decrease in Cmax of the carboxy metabolite of clopidogrel (21% decrease on 2Q2 tablet and 14% decrease on 1A1 tablet). No changes in AUC were observed. Further, there was no difference in % inhibition of platelet aggregation whether the 1A1 tablet was taken with or without food. The small change in Cmax was attributed to delay in gastric emptying and no specific labeling changes are recommended. Plavix tablets can be taken with or without food.

COMMENTS TO THE SPONSOR:

1. The active moiety responsible for the activity of this drug has not been identified.

3. Some pharmacokinetic studies in this NDA have not included data on quality control samples in the assay validation reports. In future, the sponsor should provide a complete validation report when the study report is submitted. Please refer to the journal article in *Pharmaceutical Research 9: 588 - 592, 1992* for general information on assay validation.

4. The dissolution method is not acceptable.

5. Pharmacokinetic studies in patients with either renal impairment or hepatic impairment should include a control group. This will help in comparison and interpretation of results from the study. A design without a control group is inadequate.

LABELING COMMENTS:

1. Under the Pharmacokinetics section, it should be mentioned that the active moiety of clopidogrel is not identified. Neither the parent clopidogrel nor its major carboxylic acid metabolite are active.

2. Under the distribution subsection of Pharmacokinetics, the sentence "The binding is nonsaturable in vitro over a wide concentration range." should be changed to "The binding is nonsaturable in vitro up to a concentration of 100 μg/ml."

3. Under the excretion/elimination subsection, please include "Covalent binding to platelets accounted for 2% of radiolabel with a half-life of radioactivity of 11 days."

4. Under Special populations subsection, please include the results from hepatic impairment study.

5. Under Precautions section, please change the section on "Use in hepatically impaired patients" to reflect the new data available in this population. Also, include information that patients with severe hepatic impairment have not been studied and caution needs to be exercised in this population.

6. Under Precautions - drug interactions - other concomitant therapy section, please remove the paragraph "Data from studies with human liver microsomes indicated that clopidogrel could inhibit.....which are metabolized by CYP2C9." Since the in vitro study that showed these results was conducted at concentrations many fold greater than therapeutic concentrations achievable (based on unbound concentrations), this statement is not valid.

7. Under Pharmacokinetics and metabolism - metabolism subsection, please remove the following: "In vitro, the isoenzymes responsible for metabolism of

clopidogrel.....hydroxylation of tolbutamide (CYP2C9 isoenzyme involved), which was not inhibited by clopidogrel." This reference to oxidative metabolism of and inhibition by clopidogrel and its metabolite is not necessary in the label for this drug since oxidative metabolism is a minor metabolic pathway for clopidogrel and inhibition does not occur at expected therapeutic concentrations (based on unbound concentrations).

8. Under Precautions - drug interactions, please modify the sentence "Antacids did not modify the extent of Plavix absorption" to "Antacid did not modify the pharmacokinetics of the metabolite of Plavix."

10/15/97

Venkata Ramana S. Uppoor, Ph.D.
Division of Pharmaceutical Evaluation - I

Clinical Pharmacology & Biopharmaceutics' Briefing 10/07/97 (Al-Habet, Balian, ChenM, Collins, Fenichel, Fredd, Huang, Hunt, Lazor, Lesko, Malinowski, Marroum, Uppoor, Yuan).

FT initialed by Patrick J. Marroum, Ph.D. 10/15/1997

cc: HFD-110: NDA 20-839; Division file; Roeder; HFD-860: Venkata Ramana S. Uppoor; HFD-340: Viswanathan; CDR: Attn: Barbara Murphy.

APPENDIX I

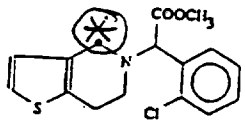
STUDY P1644: MASS BALANCE STUDY

BLOOD KINETICS AND EXCRETION BALANCE OF RADIOCARBON AFTER INTAKE OF 75 MG [^{14}C]-LABELED SR 25990C (S-ENANTIOMER OF CLOPIDOGREL) IN HEALTHY VOLUNTEERS

Reference: Volume 8
Investigator:
Study Location:
Study period: December 1990 - March 1991

Objectives: To evaluate blood distribution, plasma kinetics and excretion balance of radiocarbon, after administration of [^{14}C]-labeled SR 25990C to healthy volunteers.

Radiolabeled Form:



Study Design:

This was a single-center, open-label, non-randomized, single dose study of the metabolism of clopidogrel radiolabeled with ^{14}C. Six healthy adult male volunteers of age 21 - 35 years participated in the study. After an overnight fast, subjects received one 75 mg capsule of the radiolabeled drug (containing 1.4 MBq) along with 200 mL of water. Subjects continued to fast for 2 hours after dosing. Blood was drawn at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 216, 264, 312 and 360 hours after dosing for determination of plasma concentration of the drug and radioactivity in plasma. Expiratory carbon dioxide samples were to be obtained simultaneously. Urine was collected at intervals of -2 - 0, 0 - 4, 4 - 8, 8 - 12, 12 - 24 and thereafter at 24 hour intervals until the end of day 15 after dosing. Feces were collected at each voiding for up to 15 days after dosing. Total radioactivity was determined in blood, plasma, expired air, urine and feces. Metabolic profile was determined in urine (study MET0109, volume 9).

Criteria for evaluation:

Blood distribution and plasma kinetics: measurement of radioactivity level in blood and plasma.
Excretion balance: measurement of radioactivity in stool, urine and expired CO_2.

DETERMINATION OF TOTAL RADIOACTIVITY:

METABOLITE PROFILING, ISOLATION AND IDENTIFICATION: Concentrations of radioactivity in plasma and urine samples were determined by

Concentrations of radioactivity in whole blood and fecal homogenates were determined by

of trapped $^{14}CO_2$ after sample combustion.

Pharmacokinetic statistical methods:

Descriptive statistics of either radioactivity data (as Bq/mL) or SR 25990C equivalent (as mg base/L) were calculated. Linear, log-linear and polynomial regression equations were computed from plasma radioactivity values to evaluate apparent terminal half-life.

Results:

Recovery of radioactivity in urine and feces following administration of the radiolabeled dose is shown in the table below. Approximately 51% of dose was eliminated in urine and about 46% in feces.

Results	Range	Mean ± s.d.	Units
Plasma			
C_{max}		86.7 ± 19.6	Bq/ml
		4.82 ± 1.05	mg SR 25990C base equiv/l
t_{max}			hours
t_{λ}		263	hours
Whole blood			
C_{max}		47.9 ± 10.3	Bq/ml
		2.55 ± 0.55	mg SR 25990C base equiv/l
t_{max}			hours
ratio $\frac{\text{plasma}}{\text{whole blood}}$		1.98	
Expired carbon dioxide			
C_{max}		0.80 ± 0.16	Bq/mmol
AUC_0^6		0.15	% of dose
Urinary excretion			
U_{∞}		51.3 ± 4.8	% of dose
time for 0.5 U_{∞}			hours
time for 0.95 U_{∞}			hours
Fecal excretion			
F_{∞} 4 subjects		46.4 ± 6.4	% of dose
F_{∞} 2 subjects*			% of dose
Excretion balance			
4 subjects		97.5 ± 0.4	% of dose
2 subjects*			% of dose

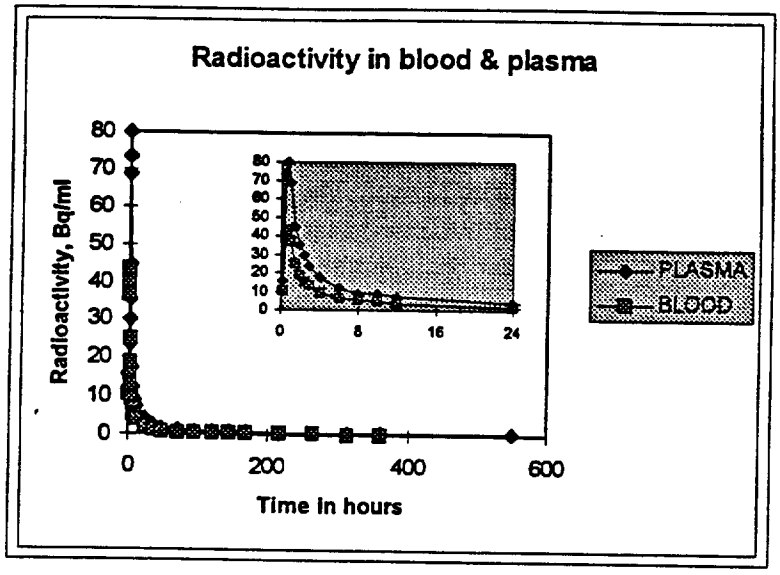
* incomplete stool collection

Most of the radioactivity in urine was recovered by day 5 as shown in the following table:

Period (hours) from	to	Mean urinary radiocarbon Bq/mℓ ± s.d. (n=6)	Mean urinary radiocarbon kBq/fraction ± s.d.
0	4	1109 ± 875	338 ± 81
4	8	548 ± 141	156 ± 31
8	12	249 ± 101	61.3 ± 19.6
12	24	171 ± 93	87.3 ± 8.5
24	48	46.7 ± 17.9	53.6 ± 11.6
48	72	8.82 ± 3.61	12.8 ± 2.7
72	96	2.51 ± 0.87	4.02 ± 0.86
96	120	2.23 ± 1.04	2.02 ± 0.53
120	144	1.01 ± 0.46	1.62 ± 0.45
144	168	0.83 ± 0.25	1.13 ± 0.32
168	192	0.58 ± 0.21	0.89 ± 0.35
192	216	0.59 ± 0.23	0.70 ± 0.15
216	240	0.49 ± 0.22	0.48 ± 0.13
240	264	0.49 ± 0.27	0.68 ± 0.24
264	288	0.32 ± 0.15	0.45 ± 0.15
288	312	0.36 ± 0.22	0.45 ± 0.10
312	336	0.33 ± 0.14	0.34 ± 0.18
336	360	0.31 ± 0.07	0.38 ± 0.13
approx.	550	0.21 ± 0.06 *	

(* n = 5)

Total radioactivity in blood and plasma: These are presented in the following figure:



The concentrations of radioactivity in whole blood declined in parallel to those in plasma. Mean plasma-to-whole blood radioactivity concentration ratios remained constant and ranged from which is quite comparable to the ratio of 1/(1-hematocrit) which ranges from tc .. .. Therefore, the proportion of radiocarbon bound to blood cells may be negligible.

METABOLIC PROFILE IN URINE:

The urine samples collected in the 0 - 4 hour and 4 - 8 hour intervals were analyzed for metabolites of clopidogrel by method with

No parent drug was detected in urine. Several minor peaks were found in the urine samples. The metabolite associated with the major peak was isolated and characterized as the *carboxy metabolite of clopidogrel (SR26334)*. 2 other peaks found in the chromatogram was tentatively assigned as the two glucuronides of SR26334 after comparison with the data previously obtained in baboon and rat biliary and urinary metabolites.

CONCLUSIONS:

Radiocarbon was detected early in plasma about 0.25 hours after drug intake. Radioactivity was detectable until the last sampling time (day 15). Apparent terminal elimination half-life was 11 days. Ratio of radiocarbon levels in plasma to whole blood was about 1.9. A small amount of radiocarbon was found in the expired carbon dioxide (measured for 6 hours after dosing) which was estimated to total about 0.15% of the dose given. Renal excretion was about 50%, half of which was excreted in 4 to 8 hours and 95% in 48 hours. Fecal excretion of the label totaled about 46% of the dose. The excretion balance of radiocarbon was 97.5% of the dose.

STUDY PKS2449: MULTIPLE DOSE MASS BALANCE STUDY

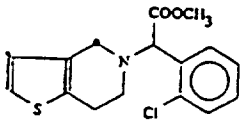
COMPARISON OF THE PHARMACOKINETIC PROPERTIES OF RADIOCARBON WHEN [^{14}C]-LABELED SR25990C (S-ENANTIOMER OF CLOPIDOGREL) IS GIVEN DURING STEADY-STATE AND IN CLOPIDOGREL-FREE HEALTHY VOLUNTEERS

Reference: Volumes 8 and 9
Investigator:
Study Location:
Study period: May 1994 - September 1994

Objectives:

1. To compare the plasma kinetics of radiocarbon after ^{14}C-labeled clopidogrel given (i) as a single dose and (ii) at steady-state
2. To check excretion balance
3. To collect biological samples for further analytical investigations (metabolic profiling).

Radiolabeled Form: Same as the previous study P1644 but with 2.8 MBq/capsule



Study Design:

This was a single-center, open-label, non-randomized, single and multiple dose study of the metabolism of clopidogrel radiolabeled with ^{14}C. Six healthy adult male volunteers of age 18 - 35 years participated in the study. In period I, after an overnight fast, subjects received one 75 mg capsule of the radiolabeled drug (containing 2.8 MBq) along with 200 mL of water. Subjects continued to fast for 2 hours after dosing. In period II, subjects received 75 mg of unlabeled drug once a day for 7 days (days 29 to 35), 75 mg labeled drug the next day (day 36) and 75 unlabeled drug once a day from day 37 to 64. Period I and II are separated by a 4-week washout.

Blood was drawn in period I at 0, 1, 2, 4, 8, 12, 24, 36, 48, 96, 144, 216, 264, 356 and 672 hours after dosing for determination of plasma concentration of the drug and radioactivity in plasma and blood. In period II, blood was drawn at 0, 1, 2, 4, 8, 12, 24, 36, 48, 96, 144, 216, 356 and 672 hours after the intake of second radiolabeled dose. Expiratory carbon dioxide samples were to be obtained at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours after dosing in periods I and II. Urine was collected in periods I and II at 0 hours and at intervals of 0 - 12, 12 - 24, 24 - 48, 48 - 72, 72 - 96 and 96 - 120 hours after dosing. Feces were collected at each voiding for days 1 - 6 in period I and days 36 - 41 in period II. Total radioactivity was determined in blood, plasma, expired air, urine and feces.

Criteria for evaluation:
Blood distribution and plasma kinetics: measurement of radioactivity level in blood and plasma.
Excretion balance: measurement of radioactivity in stool, urine and expired CO_2.

DETERMINATION OF TOTAL RADIOACTIVITY:
METABOLITE PROFILING, ISOLATION AND IDENTIFICATION: Concentrations of radioactivity in plasma and urine samples were determined by
Concentrations of radioactivity in whole blood and fecal homogenates were determined by
of trapped $^{14}CO_2$ after sample combustion.

Pharmacokinetic statistical methods:
Descriptive statistics of either radioactivity data (as Bq/mL) or SR25990C equivalent (as mg base/L) were calculated. Linear, log-linear and polynomial regression equations were computed from plasma radioactivity values to evaluate apparent terminal half-life. ANOVA was used for analysis of log transformed PK parameters and standard 95% confidence intervals computed for the ratio of repeated/single dosing. Wilcoxon paired rank test was used to compare T_{max}.

Results:
Recovery of radioactivity in urine and feces following administration of the radiolabeled dose is shown in the table below. Approximately 46% of dose was eliminated in urine and about 48% in feces after multiple dosing with clopidogrel.

	Subject no.						
	1	2	3	4	5	6	mean ± SD
Period I							
Recovery in urine (% dose)							41.3 ± 8.2
Recovery in faeces (% dose)							50.5±9.7
Total recovery (% dose)							91.7±13.5
Period II							
Recovery in urine (% dose)							45.6 ± 4.9
Recovery in faeces (% dose)							47.7±8.6
Total recovery (% dose)							93.3 ±7.0

Total radioactivity in blood and plasma: The mean radiocarbon plasma concentration profiles in each period were very similar as shown in the following figure:

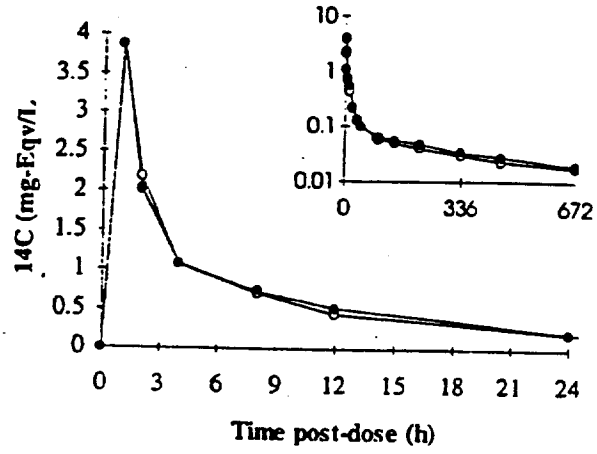


Fig. : Average radiocarbon plasma concentration after administration of 75 mg ^{14}C clopidogrel given as single dose (period I) or during steady-state (period II) in healthy subjects.
Values are means (N=6)
Inset: semi-logarithmic coordinates.
Period I (-O-); period II (-●-).

Mean pharmacokinetic parameters for radioactivity along with 95% confidence intervals are provided in the table below:

Parameters	Single	Administration at steady-state	p *	95%CI for repeated/single ratio **
Cmax (mg-Eqv/L)	3.89	3.86	0.8	89.5-115.1
Tmax (h)	1.00	1.00	>0.99	0.0-0.02
AUC24h (mg-Eqv.h/L)	18.0	18.5	0.39	92.9-118.7
AUCt (mg-Eqv.h/L)	40.0	44.9	0.12	96.3-136.3
AUCe (mg-Eqv.h/L)	49.0	55.5	0.08	99.0-131.8
T1/2el	338	367	0.18	96.0-121.1

Tmax values are median.. Other values are arithmetic mean (N=6). see tables I.2.a and b (Appendix I):
** : Statistical significance of the difference between formulation means (paired t-test, except for Tmax: Wilcoxon paired rank test):*
*** : Standard 95% confidence interval for the expected mean repeated/single ratio, derived from ANOVA for continuous parameters; for Tmax: 95% confidence interval of the expected difference test - reference (h) calculated with the non-parametric method for paired values.*

The mean radiocarbon whole blood concentration profiles in each period were very similar as shown in the following figure:

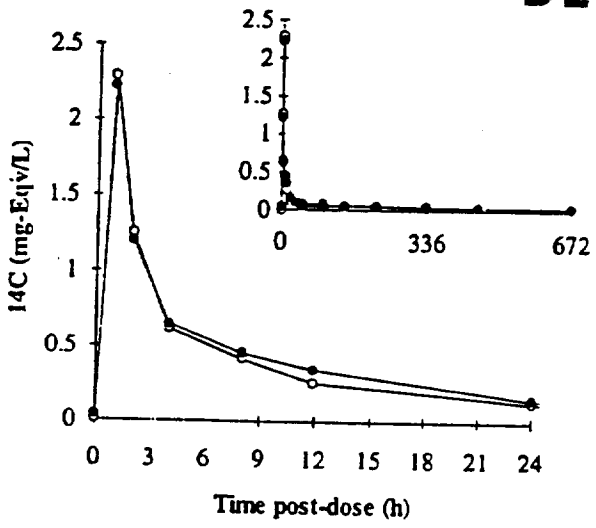


Fig. .: Average radiocarbon whole blood concentration after administration of 75 mg ^{14}C clopidogrel given as single dose (period I) or during steady-state (period II) in healthy subjects. Values are means (N=6) Inset: semi-logarithmic coordinates. Period I (-O-); period II (-●-).

The concentrations of radioactivity in whole blood declined in parallel to those in plasma. Mean plasma-to-whole blood radioactivity concentration ratios (after correction for hematocrit) remained constant and ranged from after single and multiple dosing. Therefore, the proportion of radiocarbon bound to blood cells may be negligible.

Radiocarbon excretion over 10 hours post-dose, in expired carbon dioxide accounted for about 0.35 and 0.31% of the administered dose after single dose and multiple dosing of clopidogrel.

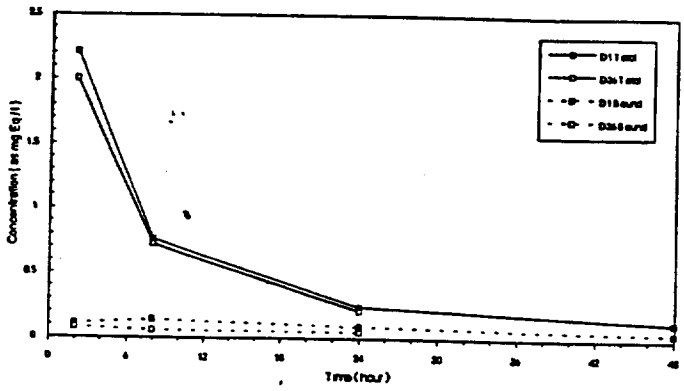
Bleeding time was prolonged by about 2.4 times after repeated administration of clopidogrel. ADP-induced maximum platelet aggregation decreased by about 74% after repeated administration of clopidogrel.

PROFILE AND IDENTIFICATION OF URINARY AND PLASMA METABOLITES FOLLOWING SINGLE OR REPEATED ORAL ADMINISTRATION OF 75 MG (^{14}C)-SR25990 TO MALE HUMAN VOLUNTEERS (study MET0264, volume 9)

was used to determine plasma covalent binding.

were used for the determination of metabolic profiles and their structures.

The mean covalently bound and total plasma radioactivity concentrations are shown in following figure and tables:



Period 1

Time (h)	Total	Bound
2	2.21 ± 0.40	0.10 ± 0.02
8	0.75 ± 0.19	0.13 ± 0.09
24	0.23 ± 0.07	0.14 ± 0.12
48	0.13 ± 0.03	0.05 ± 0.02

Period 2

Time (h)	Total	Bound
2	2.00 ± 0.33	0.08 ± 0.01
8	0.70 ± 0.21	0.06 ± 0.01
24	0.22 ± 0.10	0.05 ± 0.01

METABOLITE PROFILES IN URINE: Unchanged drug was not detected in urine at any sampling time. The main identified compounds were the carboxy metabolite (SR26334) and its glucuronides (3 isomers) (see structures below). The relative percentage of the carboxy metabolite in urine (based on peak area ratios) ranged from

METABOLITE PROFILES IN PLASMA: Unchanged clopidogrel was not detected in plasma. The main identified circulating compound was the carboxylic acid derivative of clopidogrel (SR26334) (see structure below). SR26334 accounted for 85.3 ± 3.4% and 84.1 ± 3.4% of the detected radioactive peaks one hour after drug administration in periods I and II.

Two other minor compounds were also identified (structures shown below).

CONCLUSIONS:

The plasma radioactivity was very similar when radiolabeled clopidogrel was administered as a single dose or at steady state. The two treatments were equivalent with respect to both rate and extent of absorption as well as elimination phase of radioactivity. The whole blood/plasma ratio, assuming average hematocrit, is around 1. The mean excretion balance was about 93% for each treatment period. The sponsor also concluded that the behavior of the radiolabel was not influenced by the daily intake of 75 mg clopidogrel over one month. No unchanged drug was found in either plasma or urine. SR26334 was the main metabolite in plasma. In urine, SR26334 and its glucuronides were detected. Plasma covalent binding was 0.10 mg Eq/L during the first 24 hour period after dosing.

COMMENTS: The sponsor concluded that there was no accumulation upon multiple dosing. Since labeled drug was not administered everyday (administered only as last dose of the multiple dosing period) accumulation of clopidogrel and its metabolites, if any, cannot be detected from this study design.

STUDY P1064: (RELATIVE BIOAVAILABILITY STUDY)

COMPARISON OF ORAL BIOAVAILABILITY OF SR 25990 (CLOPIDOGREL) ADMINISTERED AS A SINGLE DOSE (400 MG), EITHER IN THE FORM OF CAPSULES (4 x 100 MG), OR IN THE FORM OF TABLETS (8 x 50 MG)

Reference: Volume 38
Investigator:
Study Location:
Objective:

1. To compare the oral bioavailability of two formulations (1A1 capsules and 1A1 tablets).
2. To compare the pharmacological activity and safety observed with two formulations.

Study design:

This is a randomized open-label two-way crossover design study in 12 healthy male volunteers (of Indo-European race) of age 18-35 years. The first arm of the study included a single 400 mg dose of clopidogrel tablet administered as eight 50 mg tablets, while the second arm consisted of a capsule (dose 400 mg) given as four 100 mg capsules. Both the treatments were administered under fasting conditions with 150 mL water. Each dosing was separated by a 1 week washout period.

Batch #s: Clopidogrel 50 mg tablet: RFF17
Clopidogrel 100 mg capsule: REN04

Blood samples were drawn for determination of plasma concentration of SR26334 (carboxy metabolite of clopidogrel) at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48 and 72 hours after dosing. Urine samples were collected at 0 - 2, 2 - 4, 4 - 8, 8 - 12, 12 - 24, 24 - 36, 36 - 48 and 48 - 72 hours after dosing. ADP-induced platelet aggregation was measured at 0, 2, 5, 24, 48 and 72 hours after dosing. Bleeding time was determined at 0 and 5 hours after dosing. Pharmacokinetic parameters were determined by non-compartmental methods. These parameters for capsule and tablet were compared by the sponsor using ANOVA model consisting of subject, treatment and sequence as factors. Westlake's 95% confidence intervals were computed. Wilcoxon's non-parametric test was used to compare T_{max} values. Comparison of aggregation and bleeding times were also done using ANOVA.

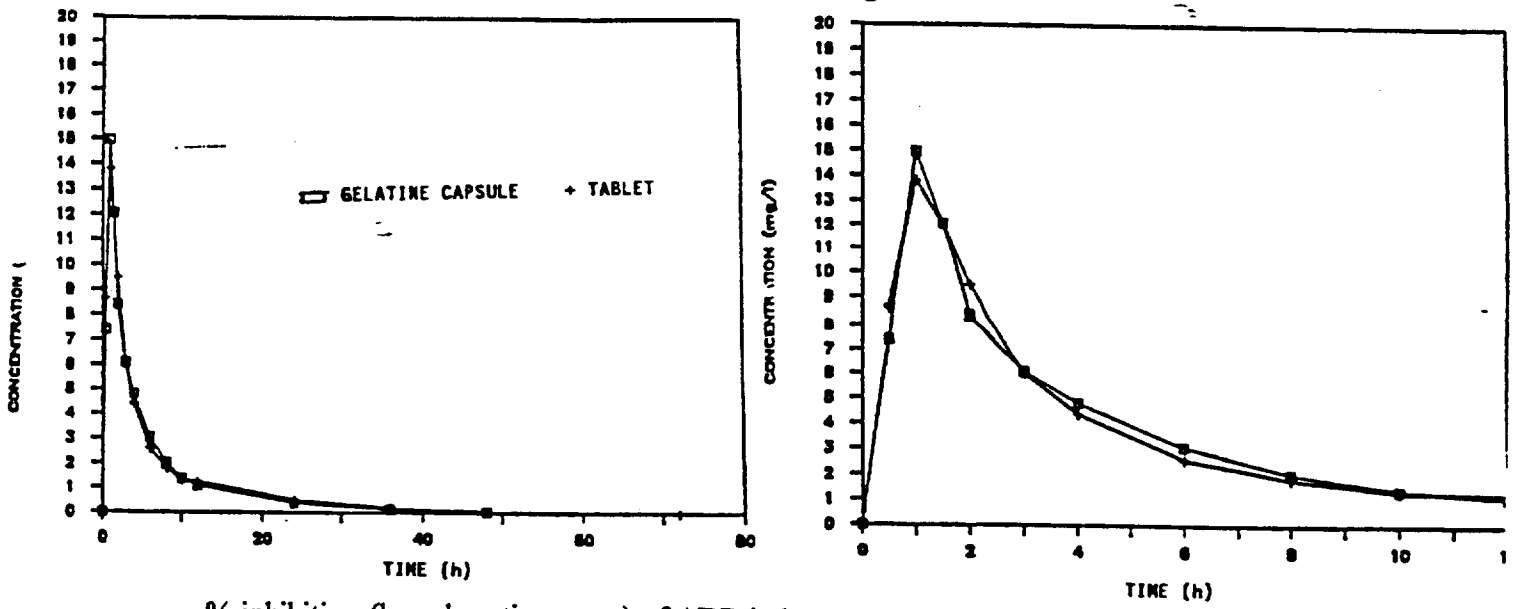
Results:

ASSAY PERFORMANCE: Assay performance details were only provided for analysis of plasma samples and not for urine samples.

Mean (SD) PK parameters are provided in the following table:

Parameter	Capsule	Tablet	Ratio
$AUC_{0-\infty}$ (mg.hr/l)	65.2 (15.0)	68.2 (16.5)	1.046
C_{max} (mg/l)	15.6 (3.8)	15.2 (4.0)	0.974
T_{max}, hours	1.2 (0.6)	1.1 (0.4)	----
A_e (0-72 hours), mg	17.2 (5.9)	16.9 (6.5)	0.983

Mean plasma concentration profiles are shown in figures below:



% inhibition (based on time zero) of ADP-induced platelet aggregation following administration of clopidogrel as tablet and capsule is shown in the following 2 tables:

At ADP levels of 5 µmol/l

Formulation	2 hours	5 hours	24 hours	48 hours	72 hours
Capsule	47	48	47	46	48
Tablet	47	42	40	39	33
Difference (tab - caps)	0	-6	-7	-7	-15

At ADP levels of 10 µmol/l

Formulation	2 hours	5 hours	24 hours	48 hours	72 hours
Capsule	39	39	42	38	41
Tablet	32	35	36	38	24
Difference (tab - caps)	-7	-4	-6	0	-17

There was no significant difference in aggregation inhibition after administration of clopidogrel either as a capsule or tablet.

Bleeding time following clopidogrel administration as either tablet or capsule is shown below:

	Bleeding time (seconds)	Multiplication factor
Before treatment	252.50 ± 10.74	
5 hours after taking capsule	425.00 ± 40.09	1.71
5 hours after taking tablet	409.17 ± 30.73	1.67

No significant difference was noted in bleeding time after administration of clopidogrel either as tablet or capsule.

Conclusions:

The relative bioavailability of the tablet was 100% relative to the capsule based on PK data on the carboxy metabolite. % inhibition of ADP-induced platelet aggregation was about 40% and was not different between capsule and tablet. Bleeding time was prolonged after administration of clopidogrel. This prolongation was consistent both after capsule and tablet administration.

Comments:

1. The relative bioavailability is shown to be 100%. This is relative to capsule and is not absolute bioavailability.
2. Quality control sample data for assay of clopidogrel in plasma has not been provided.
3. Assay methodology of clopidogrel in urine has not been provided.
4. Statistical analysis reports have not been provided.
5. The PK parameters provided are body weight-adjusted parameters and not actual values calculated.
6. The sponsor concluded from the above results that the two formulations were bioequivalent since there were no differences in absorption rate data (C_{max}, T_{max}) and bioavailability data (AUC and A_e). This conclusion is not acceptable since 90% confidence intervals were not computed to reach the decision of bioequivalence.

STUDY LIN 2264: (DOSE PROPORTIONALITY STUDY)

DOSE PROPORTIONALITY OF THE PHARMACOKINETIC PARAMETERS OF SR26334A (CLOPIDOGREL METABOLITE), AFTER A SINGLE DOSE INTAKE OF 50, 75, 100 AND 150 MG OF CLOPIDOGREL (SR25990C) IN HEALTHY VOLUNTEERS

Reference: Volumes 9, 10, 11 and 12
Investigator:
Study Location:
Objective:

To evaluate the dose proportionality of SR26334 plasma and urine pharmacokinetics following single dose administration of 50, 75, 100 and 150 mg doses of clopidogrel.

Study design:

This is a randomized, open-label, 4 period trial, with a balanced incomplete block design. 12 healthy male volunteers of age 18 - 35 years participated in this study. Each subject took single doses of clopidogrel (50 (2 x 25 mg), 75 (3 x 25 mg), 100 (4 x 25 mg) and 150 mg (6 x 25 mg)) as per the sequence to which the subjects were randomly assigned. Thus, all subjects received all 4 doses. Dose was taken with 100 mL of water. Subjects fasted for 8 hours before and 4 hours after dosing in each period. There was a 2 week washout period between doses.

BATCH #S: Test product: SR 25990C (clopidogrel hydrogen sulfate): 25 mg tablets, administered at doses of 50, 75, 100 and 150 mg, batch # 2Q1 K0290.

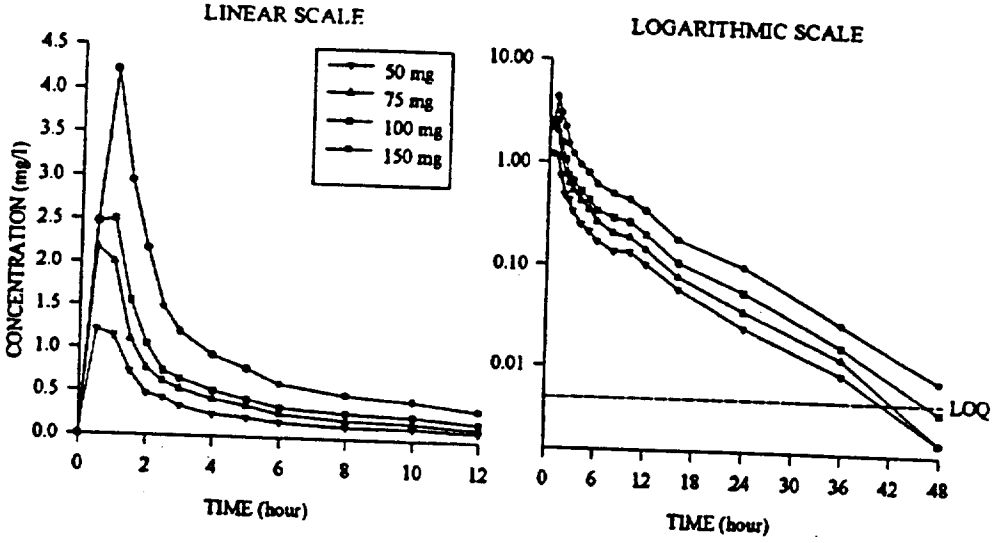
Blood was drawn from the subjects at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours after dosing for each period. Plasma samples were kept frozen until analyzed for SR26334 concentrations. Urine samples were collected at 0, 0-12 hours, 12 - 24 hours and 24 - 48 hours after dosing. Pharmacokinetic parameters were determined by non-compartmental methods. Statistical analyses were conducted on log transformed parameters, C_{max}, AUC and A_e by ANOVA using a model including subject, period, treatment and carry-over effects. When analyses confirmed that carry-over effect could be ruled out, secondary analyses were performed using a model including subject, period and treatment effects. For assessing dose proportionality, ANOVA analysis was performed on dose normalized parameters of C_{max}, AUC and A_e using a model including subject, period and treatment. When the treatment effect is not significant, then dose proportionality is demonstrated.

Results:

ASSAY PERFORMANCE:

Assay was found to be acceptable.

Mean plasma concentration-time profiles following 50, 75, 100 and 150 mg clopidogrel single doses are shown in the figures below:

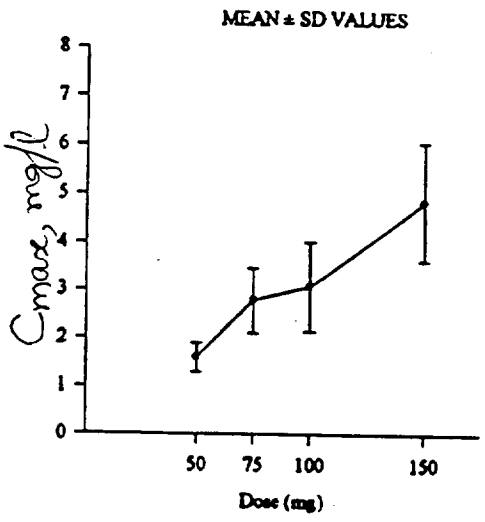


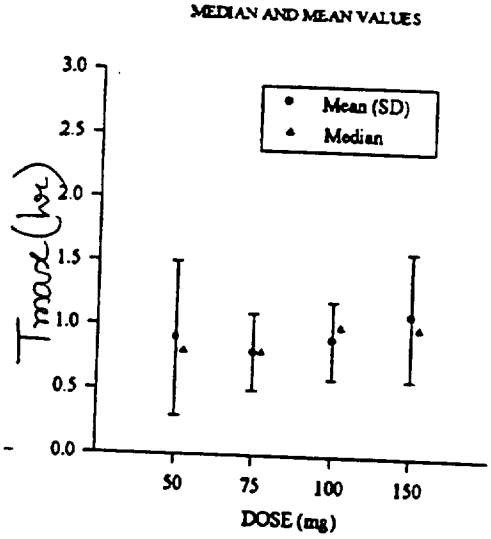
The table below shows the means (and standard deviations) for the SR26334 (clopidogrel acid metabolite) PK parameters.

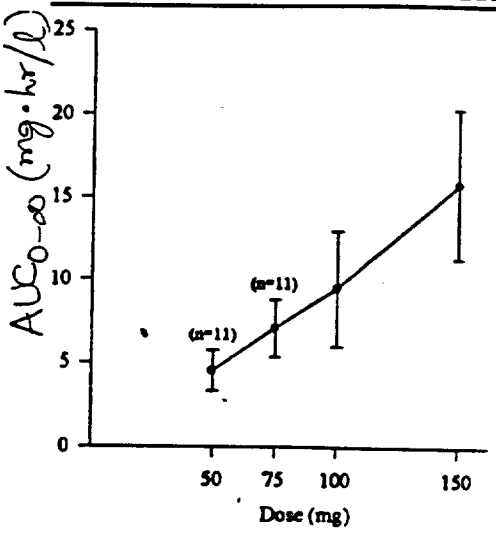
Parameter	50 mg	75 mg	100 mg	150 mg
C_{max}, mg/l	1.59 (0.30)	2.78 (0.68)	3.08 (0.94)	4.85 (1.22)
T_{max}, hr	0.9 (0.6)	0.8 (0.3)	0.8 (0.3)	1.1 (0.5)
AUC_{0-t}, mg.hr/l	4.56 (1.22)	7.12 (1.76)	9.33 (3.49)	15.60 (4.51)
$AUC_{0-\infty}$, mg.hr/l	4.51(1.20)*	7.05 (1.71)*	9.45 (3.47)	15.76 (4.52)
$t_{1/2}$, hr	7.5 (1.9)	7.3 (1.6)	7.6 (2.8)	7.2 (1.2)
Ae 0-24hr, mg	1.138 (0.485)	1.639 (0.425)	1.933 (0.601)	3.484 (1.273)
Ae 0-48 hr, mg	1.146 (0.482)	1.689 (0.427)	2.197 (1.061)	3.622 (1.316)
Fe 0-48hr	2.29 (0.97)	2.25 (0.57)	2.20 (1.06)	2.42 (0.88)
Cl_r 0-24hr, mL/min	4.69 (2.84)	4.14 (1.18)	4.03 (1.43)	4.05 (1.47)

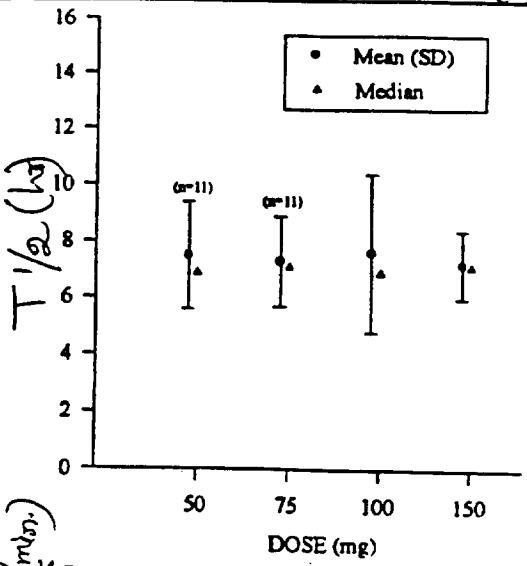
* n = 11

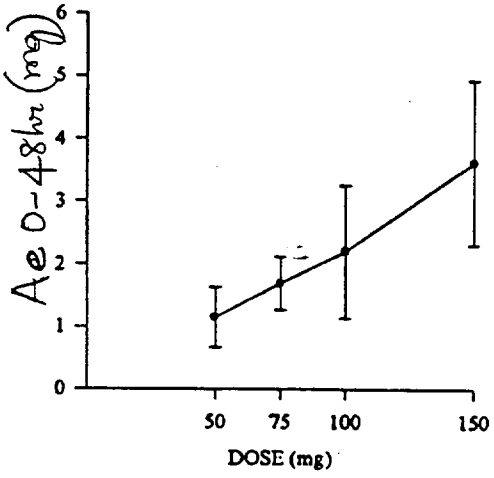
Plots to show dose proportionality in pharmacokinetics of SR 26334 are shown in 6 figures below:

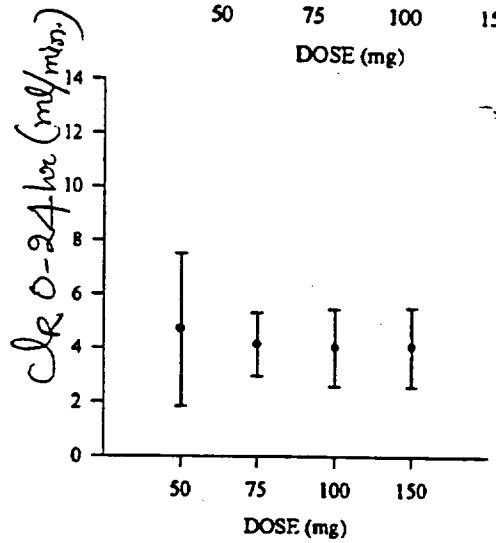












No dose-dependent changes in C_{max}, AUC, T_{max}, renal clearance and half-life were observed (non-significant treatment effects on dose-normalized parameters).

Conclusions:

Pharmacokinetics of clopidogrel acid metabolite (SR 26334) were dose-proportional in the clopidogrel dosing range of 50 to 150 mg.

Comments:

1. This dose-proportionality is based on the carboxy metabolite of clopidogrel and not the parent moiety.
2. Since the carboxy metabolite that has been monitored in this study is not the active moiety, it would have been beneficial to have data on the pharmacodynamic endpoints. In this study, no PD data is available.
3. The sponsor stated that the design of this study is a balanced incomplete block design. However, all subjects received all treatments. Hence it is not clear, how this study falls under incomplete block design category.

IN VIVO INTERCONVERSION OF SR 26334 (S-enantiomer) TO SR 26335 (R-enantiomer):

Plasma samples from the above dose proportionality study were further analyzed to determine the concentrations of R-enantiomer of carboxy metabolite of clopidogrel.

RESULTS: SR 26335 (R-enantiomer) was not detected in plasma samples. This suggests lack of interconversion of S-enantiomer of carboxy metabolite of clopidogrel.

Comments: 1. Although it is possible that the results are accurate, since the assay is not very sensitive to quantitate low concentrations of SR 26335, it cannot be concluded that there is no interconversion based on this data.
2. Not enough information about the assay has been provided in this submission. Hence, the specificity of this assay cannot be evaluated.

APPEARS THIS WAY
ON ORIGINAL

STUDY P1062: (SAFETY AND TOLERABILITY STUDY)

TOLERABILITY AND PHARMACOLOGICAL EFFECTS OF SINGLE ASCENDING DOSES OF SR25990C

Reference: Volumes 13 and 14
Investigator:
Study Location:
Objective:

1. To assess the tolerability and laboratory safety of clopidogrel
2. To assess the pharmacological effects: platelet aggregation and bleeding time, and
3. To obtain preliminary information on pharmacokinetics of clopidogrel and its carboxylic acid metabolite.

Drug Dosage Forms:
Clopidogrel 100 mg 1A1 capsules, batch 1A1 REN 04

Study Design:

This study is a randomized, double-blind, ascending-dose escalation study of single doses of 100, 200, 400 or 600 mg in comparison to placebo. This study included 10 healthy male volunteers (18-35 years old).

Each subject was randomized to receive throughout 5 study periods of treatment (separated by a 7-day washout interval) of placebo and all (four) doses of clopidogrel. Dosing administration for each period are shown below. Each dose was administered with 150 mL of water.

PERIOD 1:	Placebo: 6 capsules	2 subjects (P)
	Placebo: 5 capsules + clopidogrel 1 capsule	8 subjects (100 mg)
PERIOD 2:	Placebo: 6 capsules	2 subjects (P)
	Placebo: 5 capsules + clopidogrel 1 capsule	2 subjects (100 mg)
	Placebo: 4 capsules + clopidogrel 2 capsules	6 subjects (200 mg)
PERIOD 3:	Placebo: 6 capsules	2 subjects (P)
	Placebo: 4 capsules + clopidogrel 2 capsules	2 subjects (200 mg)
	Placebo: 2 capsules + clopidogrel 4 capsules	4 subjects (400 mg)
PERIOD 4:	Placebo: 6 capsules	2 subjects (P)
	Placebo: 2 capsules + clopidogrel 4 capsules	6 subjects (400 mg)
	Clopidogrel 6 capsules	2 subjects (600 mg)
PERIOD 5:	Placebo: 6 capsules	2 subjects (P)
	Clopidogrel 6 capsules	8 subjects (600 mg)

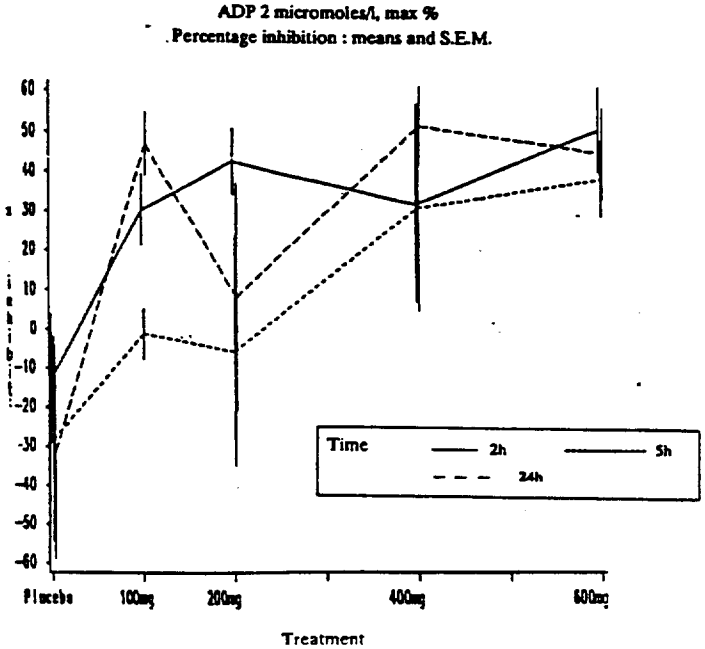
Blood samples were collected for determination of clopidogrel and its carboxy metabolite plasma concentrations at 0, 2, 5, 12 and 24 hours after drug administration. ADP-induced platelet aggregation was measured at 0, 2, 5 and 24 hours after drug administration in each period.

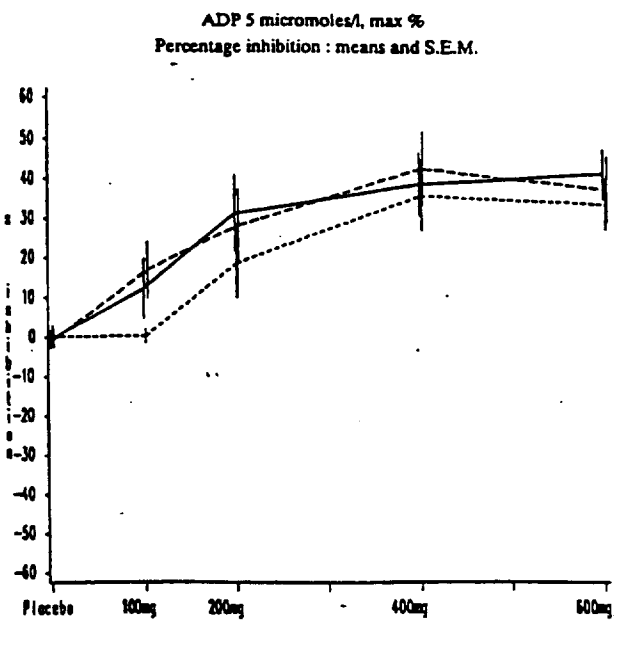
Bleeding time was measured at 0, and 5 hours after each treatment administration.

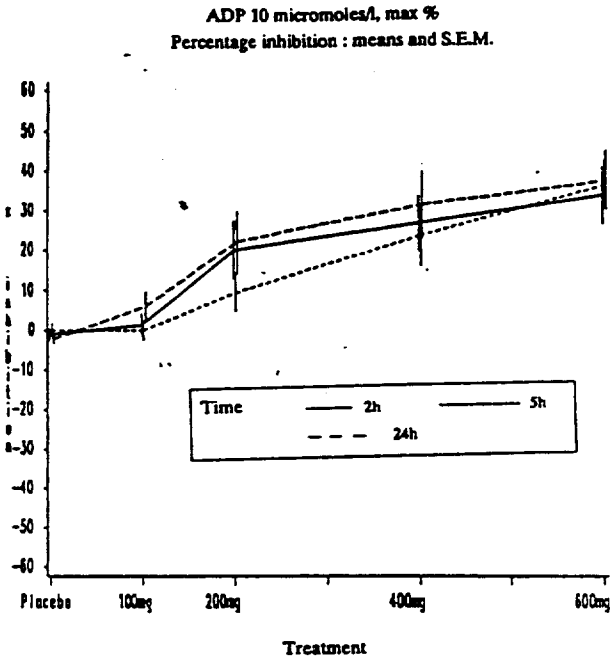
Data Analysis:
Plasma concentrations at each time were compared across doses using ANOVA. ANOVA was also used for analysis of results of aggregation and bleeding time.

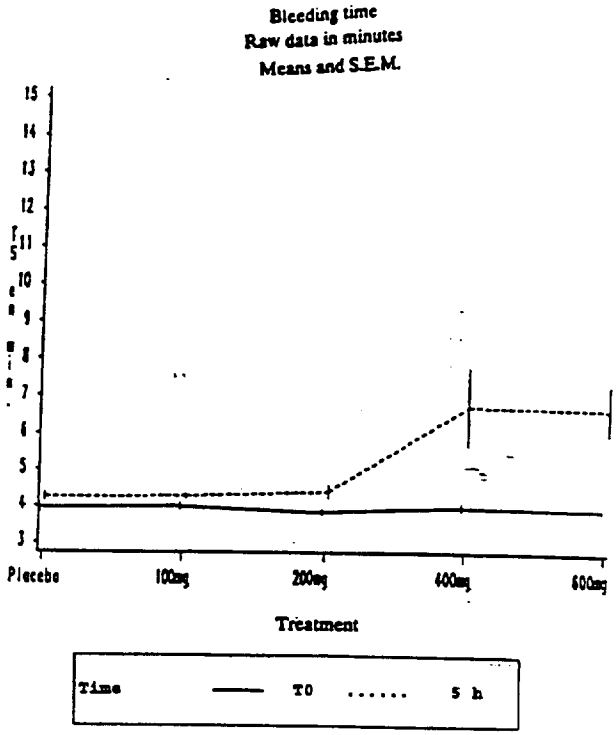
Assay was found to be acceptable with respect to calibration of assay. However, quality control data has not been provided.

% inhibition of ADP-induced platelet aggregation (with 2, 5 and 10 µmoles/l of ADP) and bleeding time following clopidogrel administration at different doses are shown in the four figures below:









The effects of increasing doses of clopidogrel on platelet aggregation induced by 5 μM ADP are summarized in the following table:

Dose (mg)	% inhibition (mean ± SEM)		
	Time after administration (hours)		
	2	5	24
0 (placebo)	-0.6 ± 2.1	0.2 ± 2.7	-0.6 ± 1.9
100	12.4 ± 7.5	0.4 ± 1.8	17.1 ± 7.1*
200	31.4 ± 9.7*	18.7 ± 8.7	28.4 ± 9.0*
400	39.0 ± 7.9*	36.2 ± 8.9*	43.1 ± 9.1*
600	42.0 ± 6.2*	34.3 ± 6.6*	38.0 ± 8.2*

* statistically significant

The effects of increasing doses of clopidogrel on bleeding time are summarized in the following table:

Dose (mg)	Minutes (mean ± SEM))		Prolongation factor
	Before treatment	After treatment	
0 (placebo)	3.95 ± 0.12	4.25 ± 0.11	1.08
100	4.00 ± 0.11	4.27 ± 0.08	1.07
200	3.85 ± 0.08	4.40 ± 0.18	1.14
400	4.00 ± 0.11	6.75 ± 1.06	1.69
600	3.95 ± 0.05	6.70 ± 0.67*	1.70

* statistically significant

Pharmacokinetics: Clopidogrel (SR 25990) was detected in plasma only in 2 subjects (0.039 and 0.054 mg/l), 2 hours after administration of 400 mg, and in 8 subjects (mean level: 0.048 mg/l), 2 hours after administration of 600 mg.

The following table summarizes the plasma concentrations of SR 26334:

Dose (mg)	Time after administration (hours)			
	2	5	12	24
100	1.36 ± 0.65	0.43 ± 0.25	0.17 ± 0.24	ND
200	2.92 ± 0.59	1.55 ± 0.56	0.57 ± 0.15	0.26 ± 0.19
400	10.55 ± 2.61	4.72 ± 1.62	1.93 ± 0.85	0.83 ± 0.48
600	14.59 ± 3.80	7.15 ± 2.35	2.84 ± 1.07	1.17 ± 0.46

In this study, the plasma samples were also analyzed to determine the in vivo interconversion of SR26334 to its R-enantiomer (SR26335) (study MET103, vol. 9). Plasma samples, obtained at 2, 5 and 12 hours after dosing with 200 and 400 mg clopidogrel, were analyzed by for measuring the concentrations of SR26335. SR26335 was not detected in any of these plasma samples. Therefore, SR26334 may not convert to SR26335 in vivo (no QC data has been provided for the assay).

Conclusions: Clopidogrel was well tolerated by healthy male volunteers. Plasma concentrations of clopidogrel were below the detection limit, except in subjects receiving 400 and 600 mg doses. Plasma levels of clopidogrel metabolite were detected up to 24 hours after dosing and increased as a function of dose. Bleeding time was prolonged by a factor of about 1.7 following clopidogrel doses of 400 and 600 mg. Significant dose-related inhibition of platelet aggregation was obtained from 100 to 400 mg of clopidogrel. No additional inhibition was found at 600 mg dose. Inhibition appeared to occur as early as 2 hours after dosing and persisted until 24 hours after.

STUDY P1264: (MULTIPLE DOSE SAFETY AND TOLERABILITY STUDY)

ASCENDING DOSE TOLERANCE AND ACTIVITY STUDY IN HEALTHY VOLUNTEERS

Reference: Volumes 25, 26, 27 and 28
Investigator:
Study Location:

Objective:

1. To assess the tolerance to rising doses of SR 25990C administered orally for 16 days in healthy volunteers.
2. To assess the pharmacodynamic activity of SR 25990C in terms of its inhibitory effect on platelet aggregation, as evidenced by ex vivo platelet aggregation tests and bleeding time.
3. To assess the pharmacokinetics of clopidogrel and its carboxylic acid metabolite, in plasma.

Drug Dosage Forms:
Clopidogrel 25 mg 1A1 tablets, batch 1A1 RFF 22; placebo batch 1A1/XRFF23
Clopidogrel 50 mg 1A1 tablets, batch RFF 16 and RFG 24 (Glasgow), RFN 25 (Edinburgh); placebo batch 1A1/XRFF24

Study Design:

This study is a randomized, double-blind, placebo-controlled, ascending-dose escalation study of single doses of 25, 50, 100 or 150 mg qd for 16 days in comparison to placebo. This study included 32 healthy male volunteers (18-40 years old) and was conducted at 2 study centers.

At each dose level (8 subjects per group/dose) six subjects received the active treatment and two received placebo. The lowest dose (25 mg) was given to the first group of volunteers, with the subsequent 3 groups receiving 50, 100 and 150 mg respectively, in ascending order, following establishment of satisfactory tolerance at the preceding lower dose levels. Dosing administration for each period are shown below. Each dose was administered with 150 mL of water.

PERIOD 1:	25 mg SR25990C (1 x 25 mg tablets)	6 subjects
	Matched placebo	2 subjects
PERIOD 2:	50 mg SR25990C (1 x 50 mg tablets)	6 subjects
	Matched placebo	2 subjects
PERIOD 3:	100 mg SR25990C (2 x 50 mg tablets)	6 subjects
	Matched placebo	2 subjects
PERIOD 4:	150 mg SR25990C (3 x 50 mg tablets)	6 subjects
	Matched placebo	2 subjects

The 25, 50 and 100 mg dose groups were studied at and the 150 mg dose group was studied a

Blood samples were collected for determination of clopidogrel and its carboxy metabolite plasma concentrations at 0, 2, 5, 7 and 12 hours after drug administration on days 1 and 16 and at 2 hours after dosing on days 2, 3, 5, 8 and 12. ADP-induced platelet aggregation and bleeding time were measured at 0, 2 and 5 hours after drug administration on day 1, 2 hours after administration on days 2, 3, 5, 8 and 12 and at 0, 2 and 5 hours after dosing on day 16.

Data Analysis:
Plasma concentrations at 2 hours after dosing were compared across doses using ANOVA. ANOVA was also used for analysis of results of aggregation and bleeding time.

Assay was found to be acceptable.

The effects of increasing doses of clopidogrel on platelet aggregation induced by 5 μM ADP (mean ± SEM) are summarized in the following table:

Dose (mg)	% aggregation, pre-drug (day 1, 0 hours)	% aggregation at plateau (days 8 - 16, 2 hours post-dose)	% inhibition
0 (placebo)	67.0 ± 3.5	66.8 ± 4.7	0.3
25	67.0 ± 7.0	45.9 ± 4.4	31.5
50	68.7 ± 3.1	35.9 ± 4.1	47.7
100	60.4 ± 2.5	27.8 ± 2.5	54.0
150	80.3 ± 3.2	21.6 ± 2.7	73.1

The effects of increasing doses of clopidogrel on bleeding time (arithmetic mean, min:sec) are summarized in the following table:

Dose (mg)	Bleeding time, pre-drug (day 1, 0 hours)	Bleeding time at plateau (days 8 - 16, 2 hours post-dose)	Prolongation factor
0 (placebo)	2:56	3:01	1.03
25	3:27	4:42	1.36
50	3:50	6:34	1.72
100	2:38	8:34	3.26
150	3:31	20:05	5.70

Dose-dependent prolongation of bleeding time and inhibition of platelet aggregation was observed. Plateau effects were reached by 5 days treatment with 8 days required for reversal. Values showed wide intersubject variability. Mean bleeding time was prolonged by about 5.7 times the baseline value at 150 mg dose.

Pharmacokinetics

Clopidogrel (SR25990C) was detected in plasma only in 3 subjects (traces: 0.001 to 0.002 mg/l), after administration of 150 mg.

The following table summarizes the plasma concentrations (mean ± SD, mg/l) of SR 26334 obtained 2 hours after dosing with clopidogrel. Plasma concentrations of the metabolite increased with increasing doses of SR25990C.

Day	Group 1 25 mg	Group 2 50 mg	Group 3 100 mg	Group 4 150 mg
1	0.291 ± 0.117	0.869 ± 0.613	1.585 ± 0.876	1.977 ± 0.357
2	0.275 ± 0.176	0.674 ± 0.272	1.898 ± 1.711	1.530 ± 0.264
3	0.221 ± 0.095	0.736 ± 0.486	1.842 ± 0.729	2.002 ± 0.418
5	0.233 ± 0.131	0.525 ± 0.074	1.683 ± 0.740	2.470 ± 1.811
8	0.242 ± 0.090	0.398 ± 0.251	2.456 ± 2.088	1.297 ± 0.677
12	0.271 ± 0.181	0.366 ± 0.156	1.237 ± 0.332	1.843 ± 0.344
16	0.324 ± 0.144	0.584 ± 0.225	2.164 ± 1.193	2.772 ± 0.784

Conclusions:

Clopidogrel was well tolerated by healthy male volunteers up to 100 mg once daily for 16 days. Plasma concentrations of clopidogrel were below the detection limit, except in subjects receiving 150 mg doses. Plasma levels of clopidogrel metabolite increased as a function of dose. Bleeding time prolongation and % inhibition of ADP-induced platelet aggregation increased in a dose-dependent manner.

STUDY P1065: (MULTIPLE DOSE SAFETY AND TOLERABILITY STUDY AND COMPARISON TO TICLOPIDINE)

TOLERABILITY AND PHARMACOLOGICAL ACTIVITY OF 3 DOSES OF SR25990C ADMINISTERED FOR TWO WEEKS TO HEALTHY VOLUNTEERS AND COMPARISON WITH 500 MG OF TICLOPIDINE

Reference: Volumes 23 and 24
Investigator:
Study Location:
Objective:

1. To assess the tolerance and pharmacological effects to rising doses of SR25990C administered orally for 2 weeks in comparison with ticlopidine, in healthy volunteers.
2. To assess the pharmacokinetics of clopidogrel and its carboxylic acid metabolite, in plasma.

Drug Dosage Forms:
Clopidogrel 50 mg 1A1 tablets, batch 1A1 RFF 16 and 1A1 RFG 24
Clopidogrel 75 mg 1A1 tablets, batch RFM 01
Ticlopidine (PCR 5332) 250 mg tablets, batch D01 76702
Placebo, matched tablets

Study Design:

This study is a randomized, double-blind, placebo-controlled study of multiple ascending doses of 50, 75 or 100 mg clopidogrel qd for 14 days in comparison to placebo and ticlopidine 500 mg (250 mg bid). This study included 45 healthy male volunteers, as 3 groups of 15 volunteers in each group (18-35 years old).

In each of the groups, the volunteers were randomized to receive either clopidogrel (as 50 mg/day (n=9), 75 mg/day (n=9), or 100 mg/day (n=9) in dose-escalating manner) or 250 mg bid ticlopidine (n=3) or placebo (n=3). The lowest dose of clopidogrel (50 mg) was given to the first group of volunteers, with the subsequent 2 groups receiving 75 and 100 mg respectively, in ascending order, following establishment of satisfactory tolerance at the preceding lower dose levels. Dosing administration for each period are shown below.

Blood samples were collected for determination of clopidogrel and its carboxy metabolite plasma concentrations at 0 hours before drug administration on days 1, 2, 3, 4, 7, 9, 11 and 14, at 2, 5, 7 and 12 hours after dosing on days 1 and 14 and on days 15, 17 and 21 while fasting. ADP-induced platelet aggregation was measured at 0, 2 and 5 hours after drug administration on day 1 and 14, and at 0 hours before dosing on days 2, 3, 4, 7, 9 and 11 and at 0 hours on day 15, 17, 18 and 21. Bleeding time was measured on days 3, 4, 7, 9, 11 and 14 before administration and on days 17 and 21 in the morning while fasting.

Data Analysis:

Plasma concentrations on days 1 and 14 were compared across doses using ANOVA. The dose

effect was assessed on SR25990 plasma levels adjusted to 50 mg dose. ANOVA was also used for analysis of results of aggregation and bleeding time.

Although the performance of this assay for ticlopidine is acceptable, it is generally recommended that QC samples at low, mid and high end of the linearity range be included in the assay method.

The effects of increasing doses of clopidogrel (% inhibition, mean ± SEM) on platelet aggregation induced by 5 μM ADP (mean ± SEM) are summarized in the following table:

Day	Placebo	50 mg qd clopidogrel	75 mg qd clopidogrel	100 mg qd clopidogrel	500 mg/day ticlopidine
PERIOD OF TREATMENT					
D2	-2.1 ± 10.9	29.8 ± 10.3*	24.6 ± 6.7*	26.7 ± 8.9*	-5.9 ± 26.3
D3	-0.1 ± 10.6	36.3 ± 10.7*	40.0 ± 7.0*	37.7 ± 9.7*	35.0 ± 8.9*
D4	-3.6 ± 10.8	30.5 ± 9.2*	43.4 ± 7.9*	45.6 ± 8.4*	23.6 ± 13.5
D7	-9.1 ± 8.4	48.2 ± 10.2*	66.5 ± 4.6*	48.3 ± 5.7*	53.6 ± 9.0*
D9	-0.9 ± 11.1	57.5 ± 8.2*	53.2 ± 5.9*	42.4 ± 8.1*	40.2 ± 13.5*
D11	-3.4 ± 11.0	61.0 ± 7.4*	48.3 ± 4.9*	37.8 ± 7.3*	40.2 ± 8.2*
D14	-5.4 ± 9.4	46.5 ± 8.9*	47.5 ± 6.9*	56.7 ± 5.2*	36.3 ± 25.1
D15	-7.8 ± 8.9	55.4 ± 6.6*	46.0 ± 7.9*	48.6 ± 4.7*	42.2 ± 15.9
AFTER TREATMENT					
D17	4.6 ± 11.8	33.5 ± 7.4*	21.4 ± 7.2*	18.4 ± 5.2*	18.3 ± 26.5
D18	-4.3 ± 11.8	29.3 ± 9.2*	8.5 ± 5.0	18.5 ± 7.9*	7.6 ± 30.0
D21	2.2 ± 11.0	25.8 ± 11.0*	-6.7 ± 7.9	-4.1 ± 16.6	-0.1 ± 25.7
D28	-12.1 ± 8.5	-	-7.6 ± 8.4	-17.4 ± 19.1	-38.5 ± 35.3

*** P < 0.05**

The effects of increasing doses of clopidogrel on bleeding time (prolongation factor, mean ± SEM) are summarized in the following table:

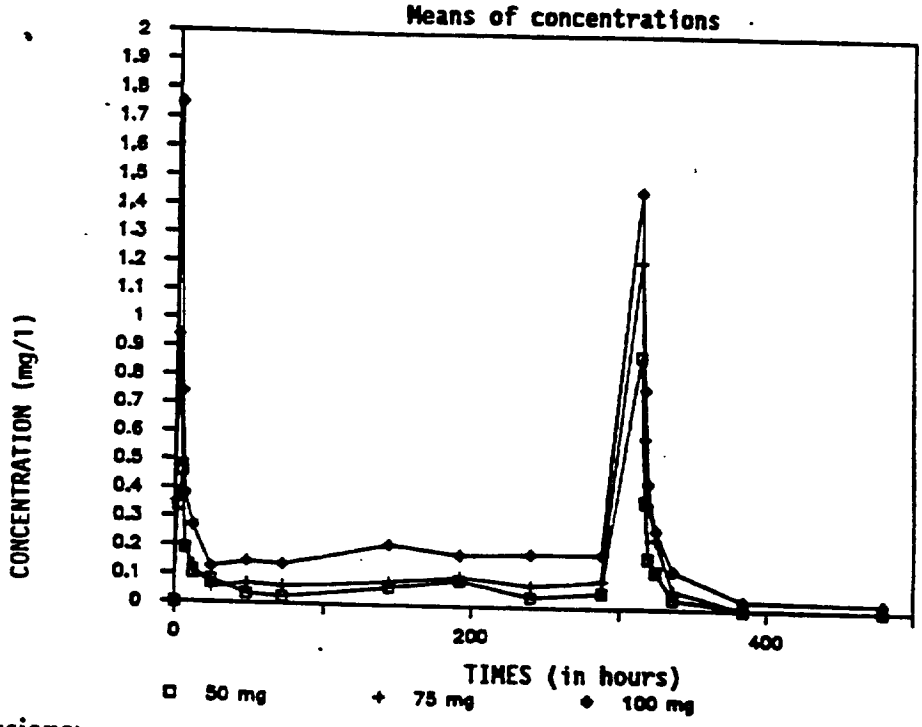
Day	Placebo	50 mg qd clopidogrel	75 mg qd clopidogrel	100 mg qd clopidogrel	500 mg/day ticlopidine
PERIOD OF TREATMENT					
D3	0.90 ± 0.05	1.13 ± 0.09	1.42 ± 0.06*	1.44 ± 0.14*	1.19 ± 0.07*
D4	0.98 ± 0.05	1.34 ± 0.12*	1.58 ± 0.14*	1.41 ± 0.12*	1.32 ± 0.08*
D7	0.92 ± 0.05	1.24 ± 0.10*	1.81 ± 0.22*	1.93 ± 0.24*	1.56 ± 0.17*
D9	0.97 ± 0.07	1.38 ± 0.15*	2.17 ± 0.31*	1.85 ± 0.20*	1.57 ± 0.16*
D11	0.98 ± 0.09	1.35 ± 0.18	2.07 ± 0.24*	1.55 ± 0.20*	1.61 ± 0.17*
D14	0.95 ± 0.05	1.67 ± 0.23*	1.92 ± 0.21*	1.86 ± 0.27*	1.52 ± 0.14*
AFTER TREATMENT					
D17	1.01 ± 0.07	1.19 ± 0.10	1.43 ± 0.16*	1.55 ± 0.15*	1.10 ± 0.11
D21	0.93 ± 0.04	0.91 ± 0.06	1.17 ± 0.07*	1.04 ± 0.06	1.07 ± 0.10
D28	0.89 ± 0.06	-	1.10 ± 0.09	1.09 ± 0.06	0.89 ± 0.07

Dose-dependent prolongation of bleeding time was observed.

Pharmacokinetics

Clopidogrel (SR25990) was below LOQ in plasma for all subjects studied.

The following figure shows the plasma concentration-time profiles of SR 26334 obtained after the 3 dosing levels, 50, 75 and 100 mg of clopidogrel. Plasma concentrations of the metabolite increased with increasing doses of SR25990C.



Conclusions:

Clopidogrel was well tolerated by healthy male volunteers up to 100 mg once daily for 14 days. Plasma concentrations of clopidogrel were below the detection limit. Plasma levels of clopidogrel metabolite increased as a function of dose. Bleeding time prolongation increased in a dose-dependent manner. A statistically significant inhibition of ADP-induced platelet aggregation was observed on second day of treatment. At pharmacological steady-state (D7 to D15), the mean percentage inhibition 24 hours after dosing was 40 to 60%. There was no statistically significant difference between the clopidogrel dosing groups of 50, 75 and 100 mg and the group treated with ticlopidine.

Comments: Although the performance of the assay is acceptable, it is generally recommended that QC samples at low, mid and high end of the linearity range be included in the assay method.

STUDY LSC2304: (MULTIPLE DOSE LONG TERM STUDY)

ASSESSMENT OF LONG TERM PHARMACOLOGICAL ACTIVITY OF CLOPIDOGREL IN YOUNG HEALTHY VOLUNTEERS

Reference: Volumes 34, 35 and 36
Investigator:
Study Location:
Objective:

To assess the effect of clopidogrel on primary hemostasis (bleeding time and platelet aggregation) after three months of administration to young, healthy, caucasian volunteers.

Drug Dosage Forms:
Clopidogrel 75 mg 2Q2 tablets, batch # 102D9

Study Design:

This study is a phase I, open-label, single center study to measure the pharmacokinetics, pharmacodynamics and safety of multiple daily dose administration of 75 mg clopidogrel once a day for 12 weeks. This study included 35 healthy male volunteers (18-35 years old), of which 29 completed the study. On day 1, subjects took the test drug after an overnight fast and before breakfast, with 150 mL of water. On all subsequent days, subjects took the drug at around 8 a.m. each day.

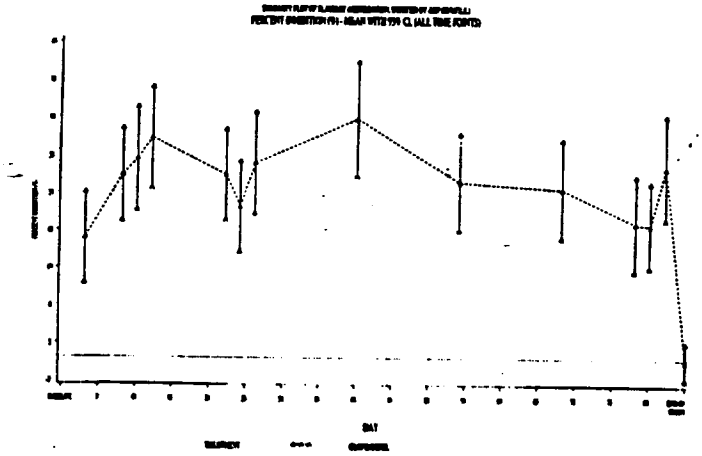
Blood samples were collected for determination of clopidogrel carboxy metabolite plasma concentrations at 0 hour on day 1 and at 0 hour (trough, pre-dose) and 1 hour after drug administration on days 3, 10, 24, 54 and 80. ADP-induced platelet aggregation was measured at 0 hour (pre-dose) on days 3, 8, 10, 12, 22, 24, 26, 40, 54, 68, 78, 80, 82 and at follow-up. Bleeding time was measured at 0 hour (pre-dose) at baseline and on days 10, 16, 80 and at follow-up.

Data Analysis:
Plasma concentrations at each time were compared using ANOVA to assess day effect. A paired, one-tailed, Student's t-test was used to test for any differences in % inhibition of platelet aggregation induced by ADP, from steady state (average of days 8, 10 and 12) to 3 months (days 78, 80 and 82). For bleeding time, a 95% confidence interval for the ratio of mean prolongation factor between steady state and three months was calculated based on log-transformed data.

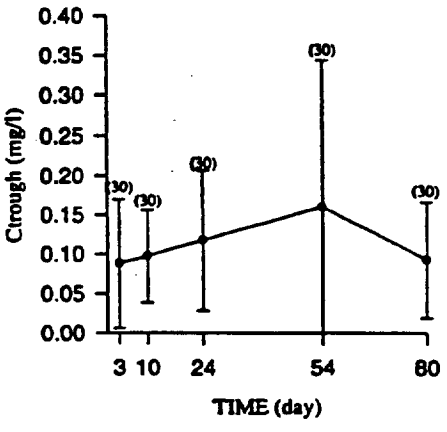
Assay was found to be acceptable.

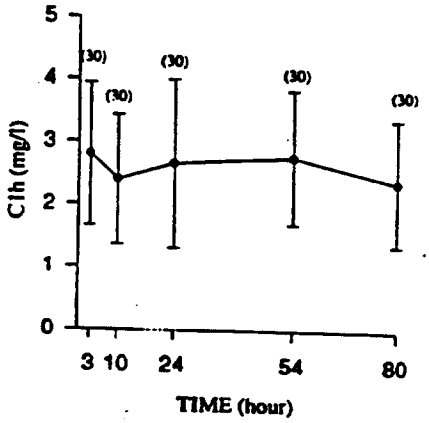
Of the 35 enrolled subjects, six were withdrawn from the study (one due to non-compliance, one due to lack of pharmacological response and four due to adverse events of rash, urticaria, bleeding time increase and mild hepatic enzyme elevations).

% inhibition of ADP-induced platelet aggregation (with 5 μM of ADP) following clopidogrel administration 75 qd for 12 weeks is shown in the following figure:



Plasma concentrations of SR26334 at 0 hour (pre-dose) and 1 hour following clopidogrel administration 75 qd for 12 weeks is shown in the following two figures:





The mean ± SD % inhibition of ADP-induced platelet aggregation and bleeding time are summarized in the following table:

PD measure	Steady state	1 month (day 24 for bleeding time)	3 months (80 days for bleeding time)
% inhibition of ADP-induced aggregation	42.9 ± 11.6	42.3 ± 14.3	39.0 ± 17.0
Bleeding time (prolongation factor)	2.15 ± 1.07	2.11 ± 0.96	2.12 ± 0.88

The results of ADP-induced platelet aggregation revealed that the increase from steady state to 3 months was significantly less than 10%. For bleeding time, there was no significant change from steady state to three months as shown by the 95% confidence intervals for the ratio of mean prolongation factor between steady state and 3 months (-32%, 37%).

Pharmacokinetics

The following table summarizes the plasma concentrations (mean ± SD) of SR26334:

Parameter	Time after administration (days)				
	3	10	24	54	80
C_{trough} (mg/l)	0.088 ± 0.082	0.097 ± 0.059	0.117 ± 0.089	0.160 ± 0.184	0.096 ± 0.073
$C_{1\ hour}$ (mg/l)	2.799 ± 1.144	2.397 ± 1.035	2.650 ± 1.344	2.760 ± 1.066	2.398 ± 0.962

The pharmacokinetic data indicated that there was no significant difference in plasma SR26334 levels between day 3 and day 80.

Conclusions:

Plasma concentrations of SR26334 indicated that steady state was achieved by day 3. Bleeding time was prolonged by a factor of 2 following clopidogrel administration. % platelet aggregation inhibition induced by 5 μM of ADP was 43%. These pharmacological effects were observed even after 3 months of drug administration. This study, therefore, demonstrates long term (3 months) activity of clopidogrel.

STUDY P1398: (STUDY IN PATIENTS)

PHARMACOLOGICAL ACTIVITY OF 3 DOSES OF SR25990C (50, 75 AND 100 MG) ADMINISTERED AFTER AORTO-CORONARY BYPASS IN COMPARISON WITH TICLOPIDINE

Reference: Volumes 57, 58 and 59
Investigator:
Study Location:
Objective: 1. To assess the pharmacological activity of 3 doses of clopidogrel in comparison with ticlopidine in patients with aorto-coronary bypass surgery and extracorporeal circulation.
2. To assess clinical and laboratory safety of the administration of SR25990C in patients after aorto-coronary bypass surgery.

Drug Dosage Forms:
Clopidogrel 25 mg tablets, batch # RFO 18 and RGE 18
Clopidogrel 50 mg tablets, batch # RFO 12 and RGE 17
Ticlopidine (PCR 5332) 250 mg tablets, batch # D04/767/04

Study Design: This phase II study is a randomized, single-blind, parallel design study of multiple doses of 50, 75 and 100 mg (qd) of clopidogrel in comparison to ticlopidine (500 mg as 250 mg bid). This included 62 (57 male and 5 female) patients of age 40 to 75 years, who had aorto-coronary lesion documented by coronary angiography and for whom an aorto-coronary bypass surgery was performed. 16 patients were assigned to group 1 (50 mg clopidogrel qd for 28 days), 15 patients to group 2 (75 mg clopidogrel qd for 28 days), 15 patients to group 3 (100 mg clopidogrel qd for 28 days) and 16 patients to group 4 (500 mg ticlopidine as 250 mg bid for 28 days). The treatment started 24 hours after surgery and continued for 28 days. Each dose was administered to fasting subjects (before breakfast and before evening meals). Patients were allowed to continue taking the medications that they were taking prior to enrollment in this study.

Blood samples were collected for determination of clopidogrel carboxy metabolite plasma concentrations on days 1, 3, 9 and 28 prior to drug administration. ADP-induced platelet aggregation and bleeding time were measured at the same time.

Data Analysis: ADP-induced platelet aggregation and bleeding time data were analyzed by paired student's t-test or Wilcoxon's test to assess change from day 1. ANOVA (repeated measures) or Kruskall-Wallis test were used to assess the treatment effect (inter-group comparison). Plasma concentrations of SR26334 and ticlopidine were summarized and no further statistical analysis was conducted.

Assay was found to be acceptable.

The effects of ticlopidine and increasing doses of clopidogrel on platelet aggregation induced by 5 μM ADP are summarized in the following table:

Dose (mg)	% inhibition (mean ± SEM)	
	Time after administration (days)	
	Day 9	Day 28
50 mg clopidogrel	-2.0 ± 12.7	29.4 ± 8.9*
75 mg clopidogrel	1.1 ± 12.8	40.8 ± 6.7*
100 mg clopidogrel	4.6 ± 9.2	43.7 ± 7.3*
500 mg ticlopidine	29.1 ± 7.4*	36.9 ± 7.0*

* statistically significant (calculated versus day 1)

On day 9, the mean values of platelet aggregation indicated no inhibition of platelet aggregation in clopidogrel treated group while 30% inhibition was found in ticlopidine group. The individual results, however, indicate that 20 to 40% inhibition of ADP-induced platelet aggregation occurred in 27 of 46 patients treated with clopidogrel on day 9.

The % inhibition obtained on day 28 were comparable for all doses of clopidogrel studied and ticlopidine.

The effects of ticlopidine and increasing doses of clopidogrel on bleeding time are summarized in the following table:

Dose (mg)	Bleeding time prolongation factor (mean ± SEM)	
	Time after administration (days)	
	Day 9	Day 28
50 mg clopidogrel	1.4 ± 0.2	2.1 ± 0.5*
75 mg clopidogrel	1.6 ± 0.4	3.4 ± 0.5*
100 mg clopidogrel	1.5 ± 0.1*	3.3 ± 0.6*
500 mg ticlopidine	2.2 ± 0.3*	3.3 ± 0.4*

* statistically significant (calculated versus value at selection)

Pharmacokinetics: The following table summarizes the plasma concentrations of SR 26334 and ticlopidine:

Dose (mg)	Plasma concentration (mean ± SD) mg/L	
	Time after administration (days)	
	Day 9	Day 28
50 mg clopidogrel	0.157 ± 0.258	0.062 ± 0.062
75 mg clopidogrel	0.851 ± 1.115	0.329 ± 0.777
100 mg clopidogrel	0.163 ± 0.121	0.170 ± 0.094
500 mg ticlopidine	0.198 ± 0.082	0.296 ± 0130

The plasma concentrations obtained in this study were not useful since the assay method for clopidogrel metabolite was not validated under the specific conditions of the study i.e. with co-administrations of other drugs. The trough levels obtained were highly variable.

Conclusions: Clopidogrel was well tolerated by patients following aorto-coronary bypass surgery. Significant inhibition of platelet aggregation was noted on day 28 with both clopidogrel and ticlopidine. However, no effect was seen on day 9 with clopidogrel (although some individuals showed aggregation inhibition). Bleeding time was significantly prolonged on day 9 and day 28 in clopidogrel and ticlopidine treated groups. On day 28, the mean prolongation factor was similar for both 75 and 100 mg clopidogrel groups and ticlopidine treated group.

Comments: Data indicates that achievement of steady state with respect to efficacy was delayed in these patients compared to normal volunteers. Even on day 9, efficacy of clopidogrel was not seen.

STUDY P1490: (PILOT BIOEQUIVALENCE STUDY BETWEEN 50 MG TABLET 2J1 AND 100 MG CAPSULE 1A1)

COMPARATIVE PILOT STUDY OF THE PHARMACOKINETICS OF TWO PHARMACEUTICAL FORMULATIONS OF SR25990C ADMINISTERED AS A SINGLE DOSE (TABLET 2J1 AND CAPSULE 1A1)

Reference: Volume 39
Investigator:
Study Location:
Objective:

To compare the pharmacokinetic profiles of two formulations of clopidogrel (1A1 capsules and 2J1 tablets).

Study design:

This is a randomized open-label two-way crossover design study in 6 healthy male volunteers of age 18-35 years. The first arm of the study included a single 100 mg dose of clopidogrel tablet administered as two 50 mg tablets, while the second arm consisted of a capsule (dose 100 mg) given as one 100 mg capsule. Both the treatments were administered under fasting conditions with 150 mL water. Each dosing was separated by a 1 week washout period.

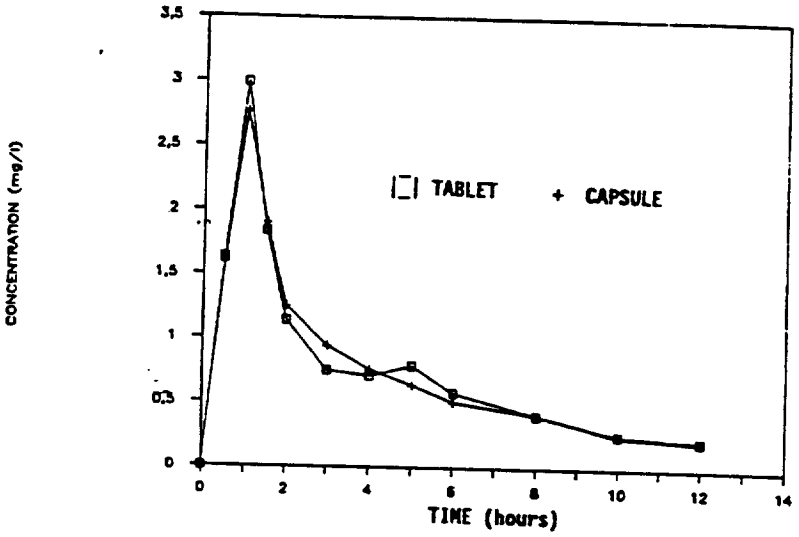
Batch #s: Clopidogrel 50 mg tablet: 2J1/RGG13
Clopidogrel 100 mg capsule: 1A1/RGE29

Blood samples were drawn for determination of plasma concentration of SR26334 (carboxy metabolite of clopidogrel) at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36 and 48 hours after dosing. Pharmacokinetic parameters were determined by non-compartmental methods. These parameters for capsule and tablet were compared by the sponsor using ANOVA model consisting of subject, treatment and sequence as factors. Wilcoxon's non-parametric test was used to compare T_{max} values.

Mean (SD) PK parameters are provided in the following table:

Parameter	Capsule 1A1	Tablet 2J1	Ratio
AUC_{0-12} (mg.hr/l)	8.70 (0.89)	8.76 (0.86)	1.02
C_{max} (mg/l)	3.08 (0.98)	3.11 (0.48)	1.07
T_{max}, hours	1.5 (1.3)	0.9 (0.2)	----

Mean plasma concentration profiles are shown in figure below:



No significant difference was noted in C_{max}, T_{max} and AUC after administration of clopidogrel either as 2J1 tablet or 1A1 capsule.

Conclusions:

The relative bioavailability of the tablet was 100% relative to the capsule based on PK data on the carboxy metabolite. The sponsor concluded from this data that both 2J1 tablet and 1A1 capsule are bioequivalent.

Comments:

1. The bioavailability of clopidogrel from 2J1 tablet and 1A1 capsule is comparable.
2. The sponsor concluded from the above results that the two formulations were bioequivalent since there were no differences in absorption rate data (C_{max}, T_{max}) and bioavailability data (AUC). This conclusion is not acceptable since 90% confidence intervals were not computed to reach the decision of bioequivalence. Also, this study is a pilot study with only 6 subjects and does not have enough power to demonstrate bioequivalence.
3. Statistical analysis reports have not been provided.
4. The sponsor stated that the standard curve for assay of SR 26334 was linear. However, no standard curve was provided.

STUDY P1558: (PILOT BIOEQUIVALENCE STUDY BETWEEN 75 MG TABLET 2Q2 AND 75 MG TABLET 1A1)

PILOT STUDY OF THE PHARMACOKINETICS OF TABLET 2Q2 OF SR25990C AFTER A SINGLE DOSE COMPARED WITH THAT OF TABLET 1A1

Reference: Volumes 40 and 41
Investigator:
Study Location:
Objective:

To compare the pharmacokinetic profiles of two formulations of clopidogrel (1A1 tablets and 2Q2 tablets).

Study design:

This is a randomized open-label two-way crossover design study in 6 healthy male volunteers of age 18-35 years. The first arm of the study included a single 150 mg dose of clopidogrel 2Q2 tablet administered as two 75 mg tablets, while the second arm consisted of a 1A1 tablet (dose 150 mg) given as two 75 mg tablets. Both the treatments were administered under fasting conditions with 150 mL water. Each dosing was separated by a 1 week washout period.

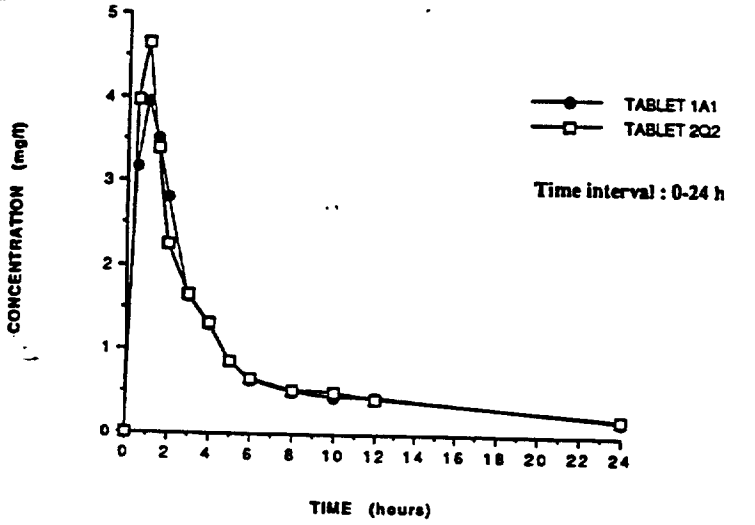
Batch #s: Clopidogrel 75 mg tablet: 2Q2/RHL19
Clopidogrel 75 mg tablet: 1A1/RHG08

Blood samples were drawn for determination of plasma concentration of SR26334 (carboxy metabolite of clopidogrel) at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36 and 48 hours after dosing. Pharmacokinetic parameters were determined by non-compartmental methods. These parameters for both tablets were compared by the sponsor using ANOVA model consisting of subject, treatment and sequence as factors. Wilcoxon's non-parametric test was used to compare T_{max} values. 90% confidence intervals were computed on log-transformed C_{max} and AUC using a two one-sided test.

Mean (SD) PK parameters are provided in the following table:

Parameter	Tablet 1A1	Tablet 2Q2	90% confidence intervals
AUC_{0-24} (mg.hr/l)	17.91 (4.58)	18.48 (6.10)	0.86 - 1.24
C_{max} (mg/l)	5.38 (2.07)	5.65 (2.34)	0.89 - 1.15
T_{max}, hours	1.09 (0.59)	1.00 (0.45)	----

Mean plasma concentration profiles are shown in the following figure:



No significant difference was noted in C_{max}, T_{max} and AUC after administration of clopidogrel either as 2Q2 tablet or 1A1 tablet. There were no period, treatment or sequence effects. All the 90% confidence intervals lie within 80 - 125% interval.

Conclusions:

The sponsor concluded from this data that the 2Q2 tablet is bioequivalent to the 1A1 tablet.

Comments:

1. The bioavailability of clopidogrel from 2Q2 tablet and 1A1 tablet is comparable.
2. The sponsor concluded from the above results that the two formulations were bioequivalent since 90% confidence intervals fall within the bioequivalence criteria of 80 - 125%. This conclusion is not acceptable since this study is a pilot study with only 6 subjects and does not have enough power to demonstrate bioequivalence.

STUDY P1648: (PIVOTAL BIOEQUIVALENCE STUDY BETWEEN 75 MG TABLET 2Q2 AND 75 MG TABLET 1A1)

A COMPARISON OF THE BIOEQUIVALENCE AND BIOEQUIPOTENCY OF TWO 75 MG SR 25990C TABLETS (TABLET 1A1 AND TABLET 2Q2) GIVEN AS REPEATED DOSES

Reference: Volumes 41, 42, 43 and 44
Investigator:
Study Location:
Objective:

To compare the pharmacological activity and pharmacokinetic profiles of two formulations of clopidogrel (1A1 tablets and 2Q2 tablets) following repeated administrations.

Study design:

This is a randomized double-blind, two-way crossover design, single center, multiple dose study in 24 healthy male volunteers of age 18-35 years (18 completed the study). Each subject was to receive one of the formulations containing 75 mg of SR 25990C once daily for 14 days, then, in the next treatment period the other formulation according to the random order. Both the treatments were to be administered under fasting conditions before breakfast. Each dosing period was separated by a 14 day washout.

Batch #s: Clopidogrel 75 mg tablet: 2Q2/RHL19
Clopidogrel 75 mg tablet: 1A1/RHG08

Blood samples were drawn for determination of plasma concentration of SR26334 (carboxy metabolite of clopidogrel) at 0 hours on days 1, 2, 3, 4, 7, 9, 11 and 13 and at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours after dosing on day 14. Pharmacokinetic parameters (C_{max}, AUC_{0-24h}, C_{min}) were determined by non-compartmental methods. These parameters for both tablets were compared by the sponsor using ANOVA model consisting of subject, treatment and sequence as factors. Wilcoxon's non-parametric test was used to compare T_{max} values. 90% confidence intervals were computed on log-transformed C_{max} and AUC using a two one-sided test.

For pharmacodynamic analysis, inhibition of aggregation induced by ADP (5 and 10 µmol/l) and bleeding time were the principal criteria. Measurement of inhibition of aggregation was performed at 0 hours on days 1, 2, 3, 4, 7, 9, 11 and 15 and at 0 hours and 2 hours after dosing on day 15 and on days 17, 18, 21 and 28 while fasting. Bleeding time was measured at 0 hours on days 1, 3, 7, 9, 11 and 14 and on days 17, 21 and 28 while fasting in the morning. The bioequipotency was analyzed on % aggregation inhibition (with respect to baseline) and bleeding time using ANOVA and Deheuvels method.

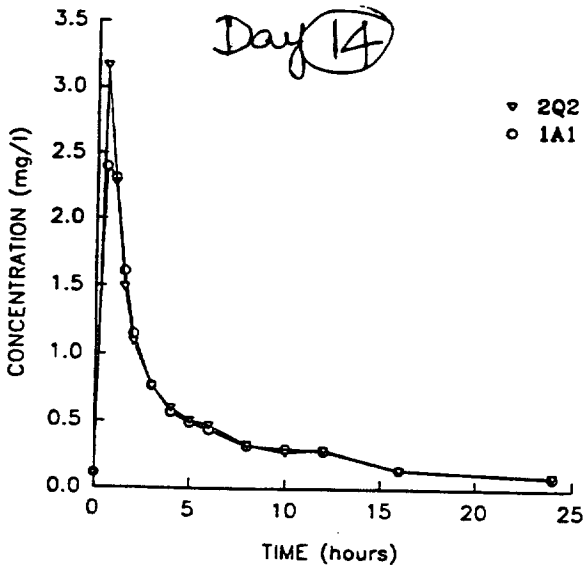
Mean (SD) PK parameters on day 14 are provided in the following table:

Parameter	Tablet 1A1	Tablet 2Q2	90% confidence intervals
AUC_{0-24} (mg.hr/l)	9.83 (2.81)	10.17 (2.33)	0.97 - 1.13
C_{max} (mg/l)	2.92 (0.95)	3.27 (0.67)	0.99 - 1.32
C_{min} (mg/l)	0.09 (0.05)	0.09 (0.05)	
C_{max} - C_{min} (mg/l)	2.84 (0.93)	3.18 (0.67)	
FR (Rel. Bio, 2Q2/1A1)	1.06 ± 0.19		
T_{max}, hours	0.81 (0.35)	0.58 (0.19)	----

Mean $\pm$ SD values of C_{min} (C_{bt}) obtained with both tablet formulations are shown in the following table. The results indicate that steady state is achieved in 3 days for clopidogrel carboxy metabolite. No significant difference between days were noted in C_{min} values.

Time (day)	Cbt (mg/l)	
	Tablet 1A1	*Tablet 2Q2*
D2	0.06 ± 0.04	0.06 ± 0.04
D3	0.08 ± 0.04	0.08 ± 0.06
D4	0.09 ± 0.05	0.09 ± 0.05
D7	0.10 ± 0.06	0.10 ± 0.04
D9	0.08 ± 0.06	0.09 ± 0.05
D11	0.10 ± 0.06	0.08 ± 0.04
D13	0.09 ± 0.07	0.09 ± 0.06
D14	0.11 ± 0.07	0.10 ± 0.05
D15	0.09 ± 0.05	0.10 ± 0.05

Mean plasma concentration profiles are shown in the following figure:



No significant difference was noted in C_{max}, T_{max} and AUC after administration of clopidogrel either as 2Q2 tablet or 1A1 tablet. There were no period, treatment or sequence effects. The 90% confidence intervals on AUC lie within 80 - 125% interval.

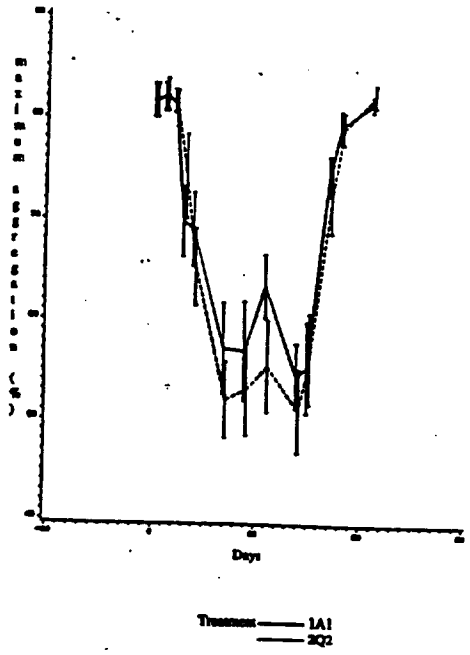
PHARMACODYNAMICS:

Maximum aggregation (%) induced by ADP is summarized in the following table and graph:

Maximum aggregation (%) induced by ADP 5 and 10 µmol/l (subjects who completed the study, n=18)

		Form.	mean	min-max	
D1	ADP 5 µmol/l	1A1	82.1±1.4		
		2Q2	82.3±1.6		
	ADP 10 µmol/l	1A1	83.2±1.0		
		2Q2	82.6±1.0		Treatment-effect
Steady state	ADP 5 µmol/l	1A1	57.9±3.2		p = 0.01*
		2Q2	53.0±3.3		
	ADP 10 µmol/l	1A1	64.4±2.7		NS
		2Q2	63.1±2.9		
Relative difference	ADP 5 µmol/l	1A1	-29.0±4.2		p = 0.09 (1)
		2Q2	-34.8±4.8		
	ADP 10 µmol/l	1A1	-22.1±3.5		NS (1)
		2Q2	-22.5±3.5		

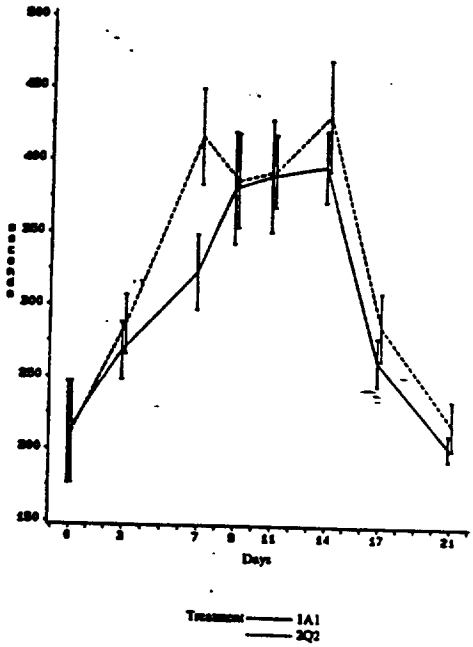
(1) significance based on the difference



Bleeding time recorded after both the formulations are summarized in the following table and figure:

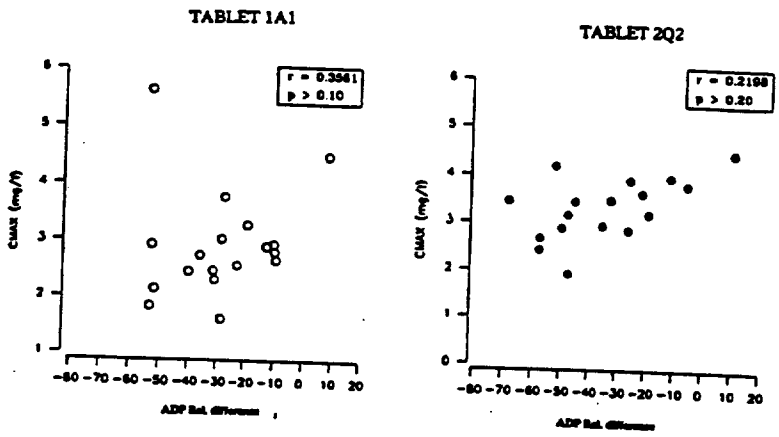
Bleeding time (s) and logarithm (subjects who completed the study n =18)

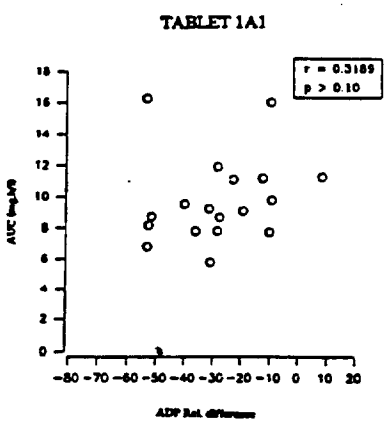
		Form.	m±sem	min-max	
Inclusion	BT (sec)	1A1-2Q2	178±11		
	log(BT)	1A1-2Q2	5.23±0.10		Treatment effect
Steady state	BT (sec)	1A1	373±24		NS
		2Q2	407±21		
	log(BT)	1A1	5.86±0.07		NS
		2Q2	5.96±0.05		

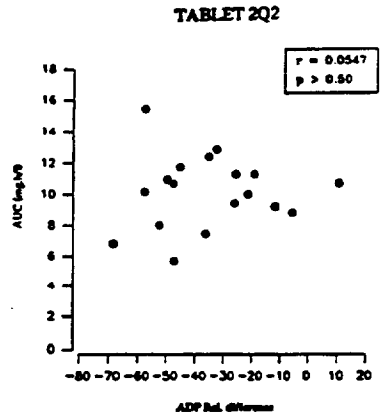


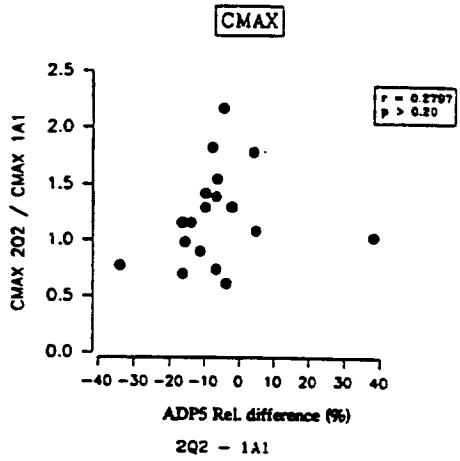
The study of bioequipotency using the Deheuvels method demonstrated equipotency for the 1A1 and 2Q2 formulations for ADP-related aggregation parameters and for bleeding time. Equipotency ± 15% can be confirmed for maximum aggregation induced by ADP 5 µmol/l.

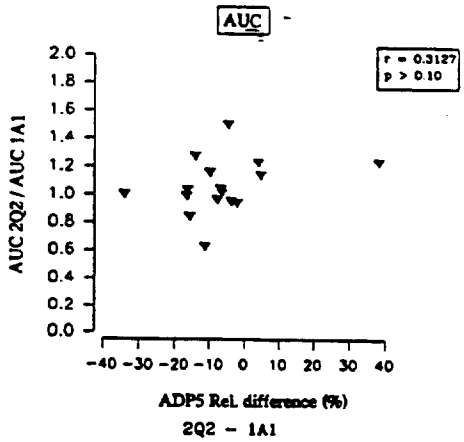
It was also shown that the C_{max} and AUC have no relationship to the ADP induced aggregation as shown in the following figures.











Conclusions: The sponsor concluded from this data that the 2Q2 tablet is bioequivalent to the 1A1 tablet based on 90% confidence intervals being within 70 - 143% and 80 - 125% for C_{max} and AUC respectively. It was also concluded that the 2 formulations are bioequipotent (based on pharmacodynamic parameters analyzed by Deheuvel's method).

Comments: 1. The bioavailability of clopidogrel from 2Q2 tablet and 1A1 tablet is comparable with respect to AUC of SR26334. C_{max} was higher for 2Q2 tablet. The 2Q2 tablet was used in the pivotal clinical trials that evaluated the clinical safety and efficacy.

2. The sponsor concluded from the above results that the two formulations were bioequivalent since 90% confidence intervals on AUC falls within the bioequivalence criteria of 80 - 125% and C_{max} falls between 70 - 143%. This conclusion is not acceptable since the confidence intervals on C_{max} do not fall within the bioequivalence criteria of 80 - 125%.

3. Since the active moiety of clopidogrel is not known, bioequivalence should not be based on pharmacokinetic data. Pharmacodynamic measurements of % inhibition of ADP-induced platelet aggregation should be used as a measure for determining bioequivalence. Appropriate bioequivalence criteria should be discussed, with the agency, in future for this drug.

STUDY BEQ2266: (PILOT BIOEQUIVALENCE STUDY BETWEEN 3 CLOPIDOGREL TABLETS 2Q2, 2Y3 AND 2Z4)

BIOEQUIVALENCE PILOT STUDY OF 75 MG SINGLE DOSE OF THREE FORMULATIONS OF CLOPIDOGREL

Reference: Volumes 44, 45 and 46
Investigator:
Study Location:
Objective:

To compare the pharmacokinetic profiles of SR 26334 obtained from 3 formulations of clopidogrel in a preliminary pilot study after a single oral administration.

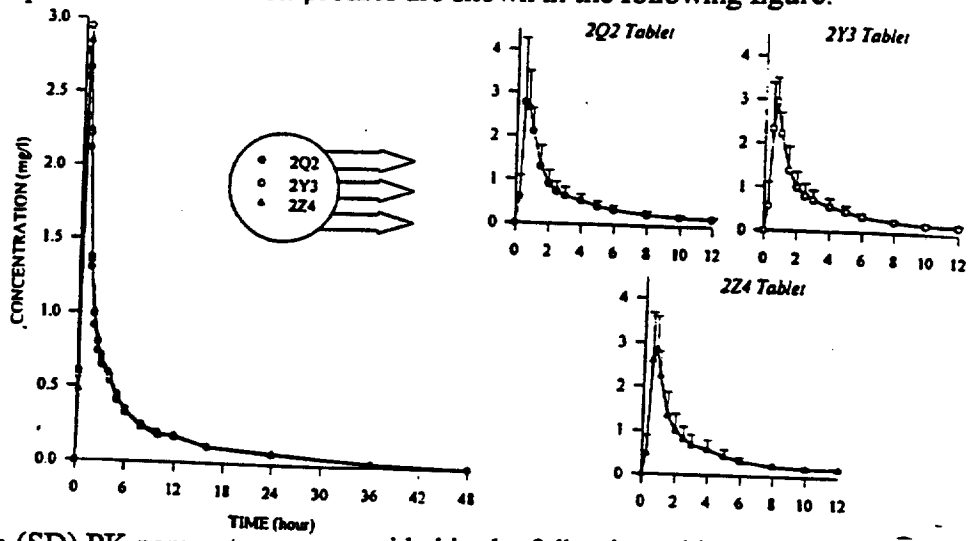
Study design:

This is a randomized open-label three-way crossover design study in 12 healthy male volunteers of age 18-35 years. Subjects received 3 treatments as single oral dose of 75 mg in separate periods. All the treatments were administered under fasting conditions with 150 mL water. Each dosing was separated by a 1 week washout period.

Batch #s: Clopidogrel 75 mg tablet: 2Q2/K053D; formulation used in clinical phase III
Clopidogrel 75 mg tablet: 2Y3/L125E; formulation from a new manufacturing process (white color tablet)
Clopidogrel 75 mg tablet: 2Z4/L129G; formulation same as 2Y3 but with pink color

Blood samples were drawn for determination of plasma concentration of SR26334 (carboxy metabolite of clopidogrel) at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours after dosing. Pharmacokinetic parameters were determined by non-compartmental methods. These parameters for the 3 tablets were compared by the sponsor using ANOVA model consisting of subject, treatment and sequence as factors. Friedman's non-parametric test was used to compare T_{max} values. 90% confidence intervals were computed on log-transformed C_{max} and AUC using a two one-sided test.

Mean plasma concentration profiles are shown in the following figure:



Mean (SD) PK parameters are provided in the following table:

Formulation	C_{max} (mg/L)	T_{max} (hr)	AUC_{0-obs} (mg.hr/L)	$AUC_{0-\infty}$ (mg.hr/L)	$T_{1/2}$ (hr)
2Q2	3.206 (0.974)	0.67 (0.22)	8.723 (2.234)	8.841 (2.227)	7.95 (1.43)
2Y3	3.209 (0.397)	0.76 (0.27)	9.050 (1.815)	9.159 (1.835)	7.89 (1.65)
2Z4	3.096 (0.769)	0.67 (0.19)	9.002 (2.243)	9.110 (2.256)	7.97 (1.16)

90% confidence intervals on the ratio of log-transformed parameters are shown in the following table:

Parameter	90% confidence intervals		
	2Y3 vs 2Q2	2Z4 vs 2Q2	2Y3 vs 2Z4
C_{max}	0.90 - 1.17	0.84 - 1.10	0.94 - 1.22
AUC_{0-obs}	1.00 - 1.11	0.98 - 1.10	0.96 - 1.07
$AUC_{0-\infty}$	0.99 - 1.11	0.98 - 1.10	0.96 - 1.07

No significant difference was noted in C_{max}, T_{max} and AUC after administration of clopidogrel either as 2Q2, 2Y3 or 2Z4 tablets. There were no period, treatment or sequence effects. All the 90% confidence intervals lie within 80 - 125% interval.

Conclusions: The two new clopidogrel tablet formulations (2Y3 and 2Z4) are bioequivalent to the 2Q2 tablet based on the pharmacokinetics of SR26334. However, the decision of bioequivalence should not be based on PK. Since the active moiety is not known, the bioequivalence decision should be based on pharmacodynamic measurements.

STUDY PDY3079 (Protocol # CV149-001): (HEPATIC IMPAIRMENT STUDY)

SINGLE AND MULTIPLE DOSE PHARMACOKINETICS AND PHARMACODYNAMICS OF CLOPIDOGREL IN SUBJECTS WITH CIRRHOSIS COMPARED WITH HEALTHY SUBJECTS

Reference: Volumes 1 and 2 of NDA amendment dated July 14, 1997
Investigator:
Study Location:
Objective:

1. To assess and compare the single dose and steady-state pharmacokinetics of clopidogrel in subjects with hepatic impairment and subjects with normal hepatic function.
2. To assess the safety and pharmacodynamics of clopidogrel in subjects with hepatic impairment and subjects with normal hepatic function.

Drug Dosage Forms:
Clopidogrel 2Q2 tablets 75 mg, lot # 1638, finished lot # 1655

Study Design:

Twelve cirrhotic subjects, male and female, aged 21 - 60 years with biopsy or scintigraphy proven Child-Pugh class A or B hepatic cirrhosis (mild to moderate impairment) and 12 healthy subjects matched pairwise for age and gender to cirrhotic subjects, participated in this open-label, multiple dose, parallel group study.

The stabilized cirrhotic subjects were graded by severity of liver disease by 5 criteria in accordance with the following Child-Pugh classification.

Grading of severity of liver disease in accordance with **Child-Pugh classification**

Measurement	Numerical score for increasing abnormality		
	1	2	3
Ascites	None	Slight	Moderate
Encephalopathy stage	0	1 - 2	3 - 4
Bilirubin (mg/dl)	<2	2 - 3	>3
Albumin (g/dl)	>3.5	2.8 - 3.5	<2.8
Prothrombin time (sec prolonged)	1 - 4	4 - 6	>6

Addition of above scores for five criteria gives the risk grade by which a subject was classified. Classes A (mild), B (moderate) and C (severe) were defined by the ranges 5-6, 7-9, and 10-15, respectively for the sum of scores.

In this study, subjects with moderate to severe ascites or edema were excluded from participation. Liver cirrhosis was determined by liver biopsies previously obtained in these

patients or by other appropriate tests.

On day -1, following an 8 hour fast, ICG (indocyanine green) clearance was determined in plasma to estimate hepatic blood flow prior to treatment with clopidogrel. Hematocrit was measured prior to the clearance study to permit conversion of plasma clearance to blood clearance. ICG was administered at a dose of 0.5 mg/kg i.v. and blood samples were obtained at 0, 2, 4, 8, 15, 25, 40, 50, 60 and 80 minutes following ICG injection.

Clopidogrel was administered as 75 mg once daily for 10 days. Blood samples were collected for determination of concentrations of clopidogrel and its carboxy metabolite on days 1 and 10 at 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 hours postdosing and at 0 hours predosing on days 4, 6 and 8. Bleeding time measurements were made at baseline and 2 hours post-dosing on days 2, 3, 4, 7 and 10. ADP-induced platelet aggregation was measured at baseline and 2 hours post-dosing on days 7 and 10.

Pharmacokinetic parameters of clopidogrel and its metabolite were estimated by non-compartmental methods. % inhibition of platelet aggregation was determined as follows:

$$\% \text{ inhibition} = [(A0-A\#)/A0]*100$$

where A0 is the maximum platelet aggregation on day 1 before treatment and A# is the maximum platelet aggregation on day #.

The bleeding time (BT) prolongation factor was determined as follows:

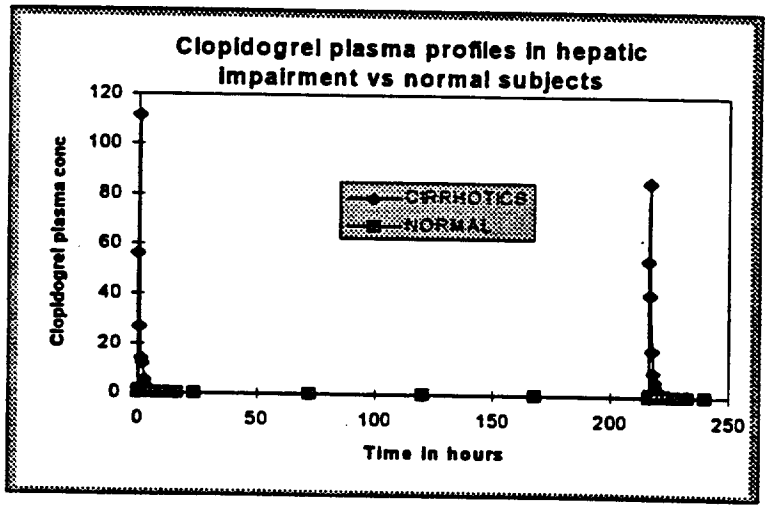
$$\text{BT prolongation factor} = \text{BT at a given point} / \text{BT at baseline}$$

Effect of hepatic impairment on PK profile of clopidogrel and its carboxy metabolite was examined using one-way analysis of variance.

LOQ selected is not acceptable.

The plasma concentrations of clopidogrel were below the LOQ for most time points and therefore only C_{max} and T_{max} could be determined. The mean C_{max} ($\pm$ SD) for clopidogrel for cirrhotics on day 1 was 111.6 $\pm$ 157.5 ng/mL and on day 10 was 99.7 $\pm$ 147.7 ng/mL. In normal healthy volunteers, the corresponding values were 1.72 $\pm$ 2.0 ng/mL on day 1 and 1.9 $\pm$ 1.5 ng/mL on day 10. The T_{max} values were comparable. Large variability in clopidogrel plasma concentrations was seen between subjects.

Following figure show the mean plasma concentration-time profiles of clopidogrel in cirrhotic and healthy subjects:



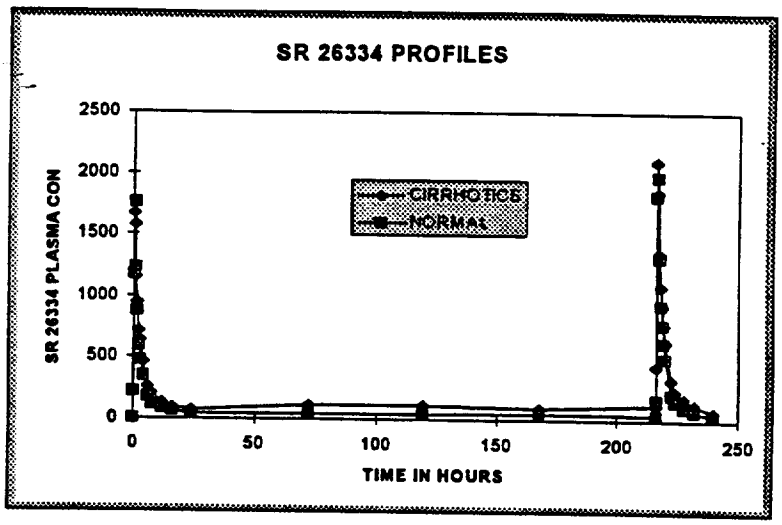
The pharmacokinetic parameters of clopidogrel carboxy metabolite (SR26334) for each group of subjects are shown in table below:

Mean Pharmacokinetic Parameters (± SD) for SR 26334 Day 1 and Day 10

Dose 75 mg		Cmax (ng/mL)	Tmax* (hr)	AUC(tau) (ng x hr/mL)	AI AUC(Day 10) / AUC(Day 1)
Cirrhotic	Day 1	1982.2 (936.4)	1.0 (0.5,2.5)	6584.8 (1996.8)	N/A
	Day 10	2453.8 (844.9)	0.75 (0.5,1.5)	8278.5 (2658.7)	1.3 (0.2)
Healthy	Day 1	2192.1 (675.9)	1.0 (0.5,2.0)	5128.6 (732.1)	N/A
	Day 10	2671.4 (1018.8)	1.0 (0.5,1.5)	6385.8 (1916.5)	1.2 (0.2)

* = median, (range)

Following figure show the mean plasma concentration-time profiles of clopidogrel carboxy metabolite (SR26334) in cirrhotic and healthy subjects:



There was no difference in C_{max} on both days 1 and 10 for SR 26334 between cirrhotics and normal subjects. Steady state was achieved with 3 days. Half-life was about 8 hours. Mean AUC for cirrhotics was comparable to healthy volunteers. Confidence intervals on the PK parameters for SR26334 are shown in the following 2 tables for days 1 and 10.

Day 1

Pharmacokinetic Parameter	Status	Geometric Mean	p-value	Ratios of Geo. Means Pt. Estimate (90% C.I).
AUC(tau) (ng•h/ml)	Cirrhotic Normal	6321.173 5078.700	0.03	1.245 (1.055, 1.468)
CMAX (ng/ml)	Cirrhotic Normal	1789.048 2095.435	0.35	0.854 (0.643, 1.134)

Day 10

Pharmacokinetic Parameter	Status	Geometric Mean	p-value	Ratios of Geo. Means Pt. Estimate (90% C.I).
AUC(tau) (ng•h/ml)	Cirrhotic Normal	7900.529 6123.101	0.06	1.290 (1.036, 1.606)
CMAX (ng/ml)	Cirrhotic Normal	2297.451 2509.110	0.58	0.916 (0.700, 1.198)
Accumulation Index	Cirrhotic Normal	1.250 1.206	0.63	1.037 (0.915, 1.174)

Mean (SD) % inhibition of platelet aggregation and bleeding time prolongation factor are shown in the table below:

	Day 1	Day 7	Day 10	Day 18
Mean % Inhibition, Cirrhotics	0	58.6 (28.8)	49.2 (38.6)	-0.2 (34.3)
Mean % Inhibition, Normals	0	68.1 (17.1)	66.7 (7.5)	- 21.1 (29.0)
Mean Prolongation Factor, Cirrhotics	1.0	1.43 (0.63)	1.64 (0.49)	1.20 (0.40)
Mean Prolongation Factor, Normals	1.0	1.32 (0.58)	1.54 (0.87)	0.99 (0.31)

Clopidogrel had a comparable effect on inhibition of maximal platelet aggregation in both healthy (matched subjects) and cirrhotic subjects. The mean BT prolongation factor was also comparable.

Conclusion: Clopidogrel dosing to healthy subjects and subjects with mild to moderate hepatic impairment for 10 days was well tolerated. Clopidogrel C_{max} after both single dose and at steady state was many fold higher in cirrhotic patients when compared to normal subjects (65 fold after single dose and 50 fold at steady state). The carboxy metabolite concentrations were higher in cirrhotic patients, however, this increase was not statistically significant. The pharmacodynamic events of % inhibition of ADP-induced platelet aggregation and bleeding time prolongation factor were comparable in both hepatically impaired patients and matched normal volunteers. These results indicate that no dosage adjustment is needed for subjects with cirrhosis of Child-Pugh class A or B.

Comments: 1. In the summary portion of this study report, it was mentioned that capsules were used, while in another section it was stated that tablets were used. It was clarified by the sponsor during a telephone conversation that this was an error and 2Q2 tablets were used in this study.
2. This was an interesting study in that the high levels of clopidogrel (parent) seem to have no effect on the pharmacodynamic endpoints of platelet aggregation and bleeding time.
3. This study did not include severely impaired patients. Hence, this drug should be used with caution in subjects with severe hepatic impairment. However, if such patients were included in pivotal clinical trials, then data from those trials should be used to decide whether caution is necessary for use of clopidogrel in these patients.

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DISSOLUTION:

A. DISSOLUTION TESTING METHOD DEVELOPMENT:

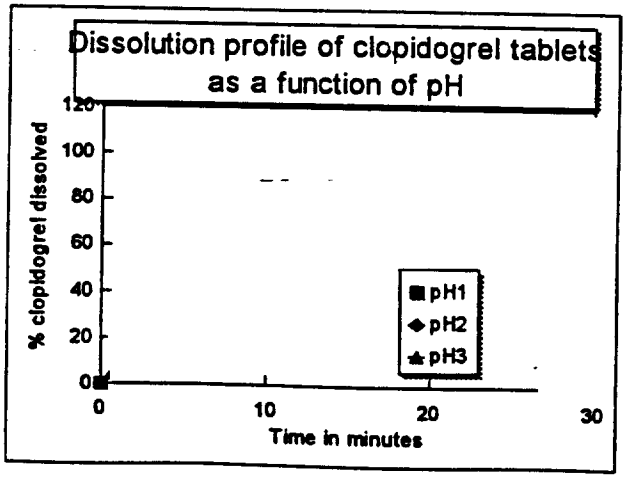
The sponsor provided solubility data for the drug substance at various pH values (details shown in the following table). The solubility of clopidogrel bisulfate significantly decreases above pH

pH	Medium	Solubility (expressed as mg base per mL)
1		
2		
3		
2.6		
3		
4		
6		
8		

* determined at 37°C, while at other pH values, solubility was determined at 25±1°C.

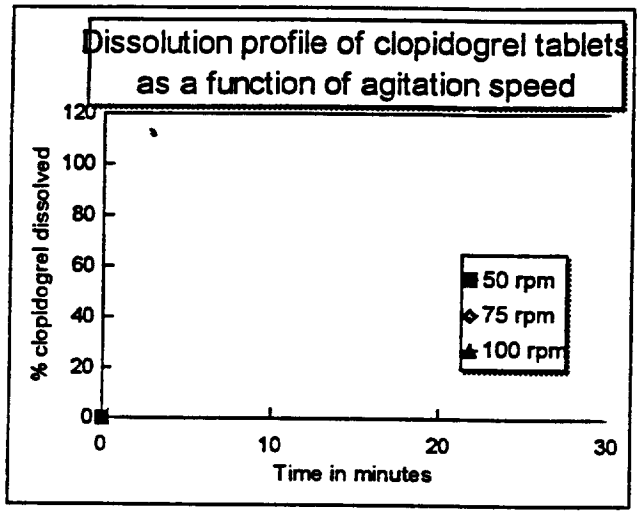
During the development of dissolution method for clopidogrel tablets, the sponsor investigated the effect of dissolution medium and agitation speed on dissolution rate of clopidogrel. USP apparatus II (paddle) was used at agitation speeds of 50, 75 and 100 rpm. Dissolution media with pH values of 1, 2 and 3 were also tested. Using the above conditions, dissolution samples were collected at different times up to 1 hour and analyzed. The dissolution samples were assayed for clopidogrel by

The graph provided below shows the dissolution profiles (tested using apparatus II at rpm) for clopidogrel tablets as a function of pH (1 to 3).

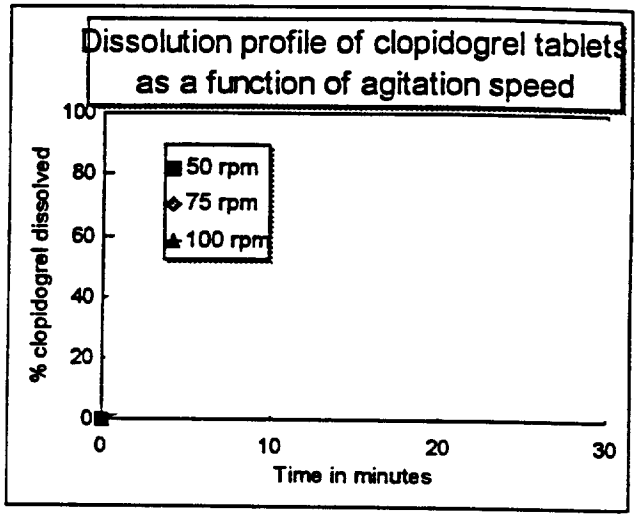


Figures below show the dissolution profiles of clopidogrel tablets using USP apparatus II (paddle) at different agitation speeds.

At Release



After 9 months of storage at 40°C/75% RH



CONCLUSION: Results indicate that the solubility of clopidogrel sharply declines above pH resulting in non-sink conditions for dissolution if a dissolution medium of pH greater thar was selected. Dissolution of clopidogrel tablets increases with agitation speed. **The final testing conditions selected by the sponsor are: USP paddle apparatus, 75 rpm, pH 2 dissolution medium at 37°C.** This method appears to be satisfactory. However, the agitation speed should be reduced to 50 rpm, since this condition will be more discriminatory and can potentially detect batches that may not have optimal performance.

FDA therefore recommends the following dissolution testing conditions for clopidogrel 75 mg tablets: **USP paddle apparatus, 50 rpm, pH 2 dissolution medium (containing KCl and 0.1N HCL) at 37°C.**

B. WAIVER FOR A BIOEQUIVALENCE STUDY BETWEEN THE 2Q2 TABLET (CLINICAL FORMULATION) AND THE 2B7 (TO-BE MARKETED FORMULATION):

2Q2 tablet formulation was used in the pivotal CAPRIE clinical trial. The to-be marketed formulation is 2AB7 tablet which only differs slightly from the 2Q2 formulation. The 2AB7 tablet has not been tested in humans. The differences in formulation between the 2Q2 and 2AB7 tablet are as follows: 1. 2AB7 contains lactose (for 2Q2) and includes a new colorant, Ferric oxide, NF (red) which gives pink color to the tablet. The formulation otherwise remains the same as 2Q2 tablet. Film coating of 2Q2 tablet utilized and purified water as solvent for coating, which gets removed in the final processing. The only

difference in film coating is that the to-be marketed formulation eliminates the use of as solvent for coating. Since these are minor changes, the sponsor provided dissolution data as justification for biowaiver. Dissolution data was provided on 6 tablets each for 2AB7 tablet and for two batches of 2Q2 clinical formulation. This data was generated with dissolution testing using USP apparatus 2, KCl/HCl medium pH 2.0 buffer, 1000 mL at 75 rpm.

The mean (% CV) for the 3 batches are shown in the following table:

Time in minutes	Mean % (% CV) clopidogrel dissolved		
	2AB7	2Q2 (batch 1)	2Q2 (batch 2)
5	30.4 (27.8)	35.1 (22.26)	25.6 (18.1)
10	74.1 (8.4)	75.9 (7.2)	78.5 (8.8)
15	95.1 (3.6)	93.9 (1.6)	96.2 (3.3)
20	98.9 (2.2)	96.9 (1.4)	99.2 (1.1)
25	98.9 (2.1)	97.2 (1.4)	100.3 (0.8)
30	98.9 (2.2)	97.4 (1.4)	100.1 (0.8)

The f_2 values for comparison of the dissolution profiles of 2AB7 tablet to 2Q2 (batch 1) tablet and 2Q2 (batch 2) tablet are 78.896 and 76.326 respectively.

Although this appears to be acceptable, the reviewer requested the sponsor to provide comparative dissolution data generated at similar dissolution testing conditions except the agitation speed which is changed to 50 rpm since this is more discriminatory. Data was obtained for 12 units each of 2AB7 tablet and 2Q2 tablet formulation. This data is provided in the following tables and figure. The corresponding f_2 value for comparison of the 2 dissolution profiles is 93.108.

Batch 0001 Commercial Formula 2AB7
Manufacturing date: 02/97

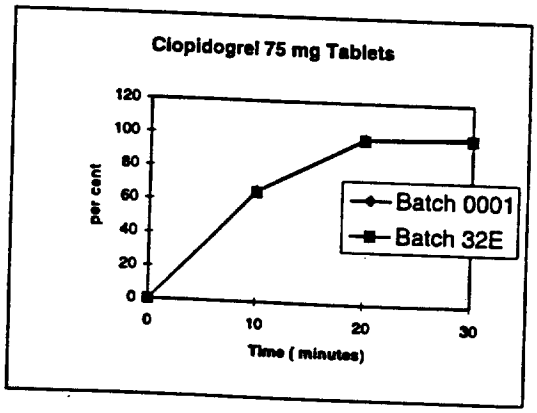
Dissolution at 50 rpm
% dissolved

Comp.	10min	20min	30min
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Avg.	65.9	98.6	100.3

Batch 32E = Batch L146 G CAPRIE Formula 2Q2
Manufacturing date: 07/94

Dissolution at 50 rpm
% dissolved

Comp.	10min	20min	30min
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Avg.	65.0	97.8	99.2



CONCLUSION: The dissolution profiles for the to-be marketed formulation are comparable to the clinical trial formulation. Hence, a biowaiver can be granted.

C. DISSOLUTION SPECIFICATIONS:

SPONSOR SELECTED DISSOLUTION SPECIFICATIONS:
The sponsor selected dissolution conditions and specification for clopidogrel 75 mg tablets are as follows:

USP APPARATUS 2 (PADDLE), 75 RPM, 1000 ML, 37°C, pH 2.0 BUFFER (KCl/HCl)
SPECIFICATION: Q = 'N 30 MINUTES

Using these conditions, dissolution data on 6 units from two pivotal clinical trial batches (2Q2), 6 units from one to-be marketed tablet batch and 3 to-be marketed production batches (2AB7) were generated and have been summarized in the following tables:

Time in minutes	Mean % (% CV) clopidogrel dissolved		
	2AB7	2Q2 (batch 1)	2Q2 (batch 2)
5	30.4 (27.8)	35.1 (22.26)	25.6 (18.1)
10	74.1 (8.4)	75.9 (7.2)	78.5 (8.8)
15	95.1 (3.6)	93.9 (1.6)	96.2 (3.3)
20	98.9 (2.2)	96.9 (1.4)	99.2 (1.1)
25	98.9 (2.1)	97.2 (1.4)	100.3 (0.8)
30	98.9 (2.2)	97.4 (1.4)	100.1 (0.8)

Mean of cumulative % clopidogrel dissolved (n=12, production/validation batches)

TIME (minutes)	2AB7 (batch 1)	2AB7 (batch 2)	2AB7 (batch 3)
10	78.6	78.7	79.1
20	98.6	100.3	101.1
30	98.9	100.3	101.3

As mentioned previously, 75 rpm for paddle apparatus is faster than the normally accepted agitation speed of 50 rpm. Since the lower agitation speeds are more discriminatory, it is recommended that 50 rpm be used as the dissolution testing condition. The only data available at 50 rpm is from one batch of clinical 2Q2 formulation and one production batch of to-be marketed

(2AB7) formulation, hence only an interim dissolution specification can be set at this time. The corresponding dissolution data is provided in the following 2 tables.

Batch 0001 Commercial Formula 2AB7
Manufacturing date: 02/97

Dissolution at 50 rpm
% dissolved

Comp.	10min	20min	30min
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Avg.	65.9	98.6	100.3

Batch 32E = Batch L146 G CAPRIE Formula 2Q2
Manufacturing date: 07/94

Dissolution at 50 rpm
% dissolved

Comp.	10min	20min	30min
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Avg.	65.0	97.8	99.2

CONCLUSION:
FDA SELECTED DISSOLUTION CONDITIONS AND INTERIM DISSOLUTION SPECIFICATIONS:

USP APPARATUS 2 (PADDLE), 50 RPM, 1000 ML, 37°C, pH 2.0 BUFFER (KCl/HCl) INTERIM SPECIFICATION: Q = IN 20 MINUTES. The sponsor should provide dissolution data using these conditions on 3 production batches.

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PROTEIN BINDING:

LPR301 - INTERACTIONS TO PLASMA PROTEIN BINDING SITES OF SR25990C - "IN-VITRO" STUDY

Study ID: LPR301
Volume: 1.60
Objective:
1. To determine possible protein binding interactions between SR25990C (parent clopidogrel) and its main metabolite (SR26334) and other drugs, nifedipine, atenolol, digoxin and ranitidine (effect of these drugs on protein binding of clopidogrel).
2. To study the effect of bilirubin and palmitic acid as endogenous compounds on the binding of SR25990C.

Concentrations of clopidogrel selected for this study were 0.15 and 25 μg/mL. The C_{max} for clopidogrel obtained in normal volunteers (2 ng/mL) is much lower than the concentrations studied here.

Study Design:

Human plasma was obtained. An aliquot of radiolabeled drug (^{14}C) stock solutions was added to normal saline to obtain final concentration as shown in the table below.

Protein binding was determined by equilibrium dialysis conducted at 37°C. SR25990C in normal saline at concentrations of 0.15 and 25 μg/mL with appropriate amounts of radioactivity were dialyzed against plasma samples spiked with xenobiotics at their usual therapeutic concentrations or endogenous compounds at 3-fold their usual physiological concentrations. At the end of dialysis, the radioactivity and protein concentrations were measured in each compartment of the dialysis cells by . Percent binding was then determined from these results. The dpm in the buffer compartment represents free drug concentration. Dpm in protein compartment represents free + bound drug concentrations. The difference in dpm between the protein cell and buffer cell represent the bound drug concentrations. The percent bound is determined by dividing the dpm bound by the dpm in the protein cell multiplied by 100.

Results:

Addition of SR26334, nifedipine, atenolol, digoxin, ranitidine, bilirubin and palmitic acid to SR25990C did not have any effect on protein binding of SR25990C (see table below).

Drug	Competitor concentrations (µg/mL)	% binding of clopidogrel at	
		0.15 µg/mL	25 µg/mL
SR25990C alone		94 ± 0.6	96 ± 0
+ SR26334	1	95 ± 1	96 ± 0
+ Nifedipine	0.2	94 ± 0	96 ± 0
+ Atenolol	0.5	94 ± 0.6	96 ± 0
+ Digoxin	0.002	94 ± 0.6	96 ± 0
+ Ranitidine	0.1	95 ± 0	96 ± 0
+ Bilirubin	20	94 ± 0.6	95 ± 1
+ Palmitic acid	100	94 ± 0	95 ± 0

Conclusion: Results of this study show that these potentially coadministered drugs do not alter SR25990C binding when present in plasma at therapeutic concentrations or at 3 fold their physiologic concentrations.

Comment: It is not clear why the sponsor has not studied the effect of warfarin on the protein binding of clopidogrel and vice versa. This could be especially important since these 2 drugs are very likely to be co-administered.

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LPR303 - SR26334A (METABOLITE OF SR25990C) AND INTERACTIONS ON SERUM BINDING SITES - "IN VITRO" STUDY

Study ID: LPR303
Volume: 1.60
Objective:

1. To determine possible protein binding interactions between SR26334A (metabolite of clopidogrel) and its parent drug (SR25990C); other drugs, nifedipine, atenolol, digoxin and ranitidine and endogenous compounds, bilirubin and palmitic acid (effect of these drugs on protein binding of SR26334A).
2. To study the effect of SR26334A on protein binding of SR25990C, digoxin and ranitidine.

Concentrations of clopidogrel carboxy metabolite selected for this study were 0.1, 25 and 100 µg/mL. These concentrations encompass the therapeutic concentrations of SR26334 achieved.

Study Design:

Human serum sample was obtained. An aliquot of radiolabeled drug (^{14}C) stock solutions was added to Sorensen buffer to obtain final concentrations as shown in the table below.

Protein binding was determined by equilibrium dialysis conducted at 37°C. SR26334A in Sorensen buffer at concentrations of 0.1, 25 and 100 µg/mL with appropriate amounts of radioactivity were dialyzed against serum samples spiked with xenobiotics at their usual therapeutic concentrations or endogenous compounds at 10 times higher than their usual physiological concentrations. At the end of dialysis, the radioactivity and protein concentrations were measured in each compartment of the dialysis cells by
Percent binding was then determined from these results. The dpm in the buffer compartment represents free drug concentration. Dpm in protein compartment represents free + bound drug concentrations. The difference in dpm between the protein cell and buffer cell represent the bound drug concentrations. The percent bound is determined by dividing the dpm bound by the dpm in the protein cell multiplied by 100.

When radiolabeled competitors were available, the reverse effect (effect of SR26334A on their protein binding) was also studied.

Results:

The % binding of SR26334A in the absence or presence of competitors are shown in the following table. Results indicate that clopidogrel and other competitors studied have no effect on binding of SR26334A.

Model	Competitor concentrations (mg/l)	% binding at 0.1 mg/l	% binding at 25 mg/l	% binding at 100 mg/l
SR 26334A alone		93 ± 0.8(21)	93 ± 0.7(21)	93 ± 1.1(19)
+ SR 25990C	25 0.1	93 ± 0.6 (3) 91 ± 0.7 (2)	92 ± 0.6 (3)	92 ± 0.7 (2)
+ NIFEDIPINE	2 0.2[1])	93 ± 0 (3) 93 ± 0 (2)	94 ± 0.6 (3)	93 ± 0 (3)
+ ATENOLOL	5 0.5[2])	92 ± 0.6 (3) 94 ± 0.7 (2)	94 ± 0 (3)	93 ± 0.6 (3)
+ DIGOXINE	0.02 0.002[3])	94 ± 0.6 (3) 95 ± 0 (2)	94 ± 0.6 (3)	93 ± 0 (3)
+ RANITIDINE	1.1 0.1[4])	94 ± 0 (3) 94 ± 0 (2)	94 ± 0 (3)	94 ± 0 (3)
+ BILIRUBINE	20[5]) 7	92 ± 0.6 (3) 94 ± 1.4 (2)	92 ± 0.6 (3)	92 ± 1.0 (3)
+ PALMITIC ACID	100[5]) 30	93 ± 0.7 (3) 93 ± 0.7 (2)	93 ± 0 (3)	92 ± 0.6 (3)

(n)

The effect of SR26334A on the % binding of SR25990C, digoxin and ranitidine are shown in the following table. Results indicate that SR26334A has no effect on clopidogrel binding. A small effect is seen on binding of digoxin and ranitidine (2 - 5%).

DRUGS	MODEL	% binding at drug concentrations	
SR 25990C		0.06 mg/l	25 mg/l
% binding	alone	89 ± 0.6 (3)	92 ± 0 (3)
% binding	+ SR 26334A (0.1 mg/l)	89 ± 0.6 (3)	92 ± 0 (3)
% binding	+ SR 26334A (100 mg/l)	89 ± 0 (3)	92 ± 0 (3)
DIGOXINE		0.002 mg/l	0.02 mg/l
% binding	alone	51 ± 1.5 (3)	46 ± 4.6 (3)
% binding	+ SR 26334A (0.1 mg/l)	48 ± 1.4 (2)	47 ± 1.5 (3)
% binding	+ SR 26334A (100 mg/l)	49 ± 1.5 (3)	44 ± 3.5 (2)
RANITIDINE		0.1 mg/l	1 mg/l
% binding	alone	16 ± 1.5 (3)	15 ± 1.5 (3)
% binding	+ SR 26334A (0.1 mg/l)	15 ± 2 (3)	19 ± 1 (3)
% binding	+ SR 26334A (100 mg/l)	18 ± 2 (3)	10 ± 2.5 (3)

(n)

Conclusion: Results of this study show that these potentially coadministered drugs do not alter SR26334A binding when present in plasma at therapeutic concentrations or at 10 fold their physiologic concentrations. SR26334A has no effect of SR25990C binding and has minimal effect on digoxin and ranitidine binding.

Comment: It is not clear why the sponsor has not studied the effect of warfarin on the protein binding of clopidogrel carboxy metabolite and vice versa. This could be especially important since warfarin and clopidogrel are very likely to be co-administered.

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LPR201 - HUMAN SERUM PROTEIN BINDING OF CARBOXYLIC ACID DERIVATIVE OF CLOPIDOGREL (SR26334) - IN VITRO STUDY

Study ID: LPR201
Volume: 1.60
Objective:

To determine the in vitro protein binding of SR26334 (99% pure S-enantiomer) in human serum.

Concentration range of drug selected for this study was 0.04-2500 µg/mL, so as to accommodate the anticipated therapeutic plasma levels.

Study Design:

Human serum sample was obtained. An aliquot of radiolabeled drug (^{14}C) stock solutions was added to Sorensen buffer to obtain final concentrations as shown in the table below.

Protein binding was determined by equilibrium dialysis conducted at 37°C. SR26334A in Sorensen buffer at concentrations of 0.04 to 2500 µg/mL with appropriate amounts of radioactivity was dialyzed against serum. At the end of dialysis (after 2 hours of incubation), the radioactivity and protein concentrations were measured in each compartment of the dialysis cells b) Percent binding was then determined from these results. The dpm in the buffer compartment represents free drug concentration. Dpm in protein compartment represents free + bound drug concentrations. The difference in dpm between the protein cell and buffer cell represent the bound drug concentrations. The percent bound is determined by dividing the dpm bound by the dpm in the protein cell multiplied by 100.

Results: At concentrations ranging from 0.04-100 µg/mL, the protein binding of SR26334-^{14}C averaged 94-95% in human serum. Protein binding appears to be saturable at higher concentrations of drug.

% protein binding of SR26334A in human serum

Concentrations, µg/mL	0.04	0.08	1.0	5.1	10	25	50	100
% binding	94±1.5	95±2.8	94±1.5	95±2.1	95±1.7	94±1.7	94±1.5	94±1.7
Concentrations, µg/mL	250	500	750	1000	1500	2000	2500	
% binding	91±1.1	90±2.1	86±1.5	83±3.2	76±2.3	72±3.2	67±3.7	

Conclusion: The binding of SR26334A to human serum protein appears to be saturable at concentrations greater than 100 µg/mL. At concentrations that are equal to or higher than (up to 30 fold) the therapeutically achievable concentrations of SR26334A, the binding was found to be linear and high (94 - 95%).

IN VITRO BINDING OF SR25990C AND SR26334A TO PLASMA PROTEINS AND TO ERYTHROCYTES IN MALE CAUCASIAN HUMANS

Study ID: RA850890906/ML1
Volume: 1.60
Objective:
1. To determine the in vitro red blood cell binding of clopidogrel-^{14}C and its carboxy metabolite in human whole blood.
2. To determine the protein binding of clopidogrel-^{14}C and its carboxy metabolite in human plasma.

Study Design:

Blood obtained from healthy male caucasian humans (n = 6), of age range 31 to 39 years, was used for this study. For protein binding experiments, blood samples were centrifuged to separate erythrocytes from plasma. For erythrocyte binding experiments, hematocrit was measured in these blood samples. Appropriate aliquots of stock solutions were added to whole blood aliquots to give various concentrations of ^{14}C-clopidogrel or ^{14}C-SR26334. Experiments were performed at 0.025, 0.05, 0.10, 0.25, 0.50, 1, 5, 10, 25, 50 and 100 µg/mL for SR25990C and at 0.10, 0.50, 1, 5, 10, 25, 50, 100, 250, 500 and 1000 µg/mL for SR26334A. These concentrations were selected to encompass the levels that may occur in human clinical studies.

PLASMA PROTEIN BINDING: Protein binding was determined by . Plasma containing increasing drug concentration with appropriate amounts of radioactivity was dialyzed against normal saline solution. At the end of dialysis (after 2 hours of incubation), the radioactivity was measured in each compartment of the dialysis cells by and drug concentrations calculated. Percent binding was then determined from these results. The dpm in the buffer compartment represents free drug concentration. Dpm in protein compartment represents free + bound drug concentrations. The difference in dpm between the protein cell and buffer cell represent the bound drug concentrations. The percent bound is determined by dividing the dpm bound by the dpm in the protein cell multiplied by 100.

COVALENT BINDING OF SR25990C AND SR26334A: Plasma covalent binding was determined at various concentrations of clopidogrel and its metabolite after incubation with plasma and precipitation with trichloroacetic acid/methanol mixture. The precipitated proteins are washed to remove unbound drug. Then concentrations of drug covalently bound to proteins is determined by liquid scintillation counting of the sample containing precipitated proteins. Plasma covalent binding is obtained by dividing the radiolabel recovered in protein pellet after extensive washing by the total initial radiolabel.

BINDING TO ERYTHROCYTES: An appropriate volume of drug was dried and suitable volume of blood was added. After incubation, an aliquot was weighed, dried and mineralized and then analyzed by . Another aliquot was centrifuged to separate the

erythrocytes from plasma. Radioactivity was determined in plasma by
The % binding to erythrocytes is then determined as follows:

E% = 1 - [(1-H)*S/T] where E = radiolabel bound to erythrocytes; H = hematocrit; S = radioactivity in plasma and T = total drug.

Results: The results of % binding to plasma proteins are shown in the following tables:

SR 25990C concentration (mg/l)	(μM)	Plasma Protein Binding (%) (mean ± SD)
0.025	0.059	-
0.050	0.119	-
0.10	0.238	96.08 ± 3.41
0.25	0.595	98.50 ± 0.20
0.50	1.19	97.68 ± 0.39
1.0	2.38	98.58 ± 0.44
5.0	11.91	98.79 ± 0.0
10.0	23.81	98.73 ± 0.11
25.0	59.53	98.54 ± 0.14
50.0	119.07	98.32 ± 0.07

SR 26334A concentration (mg/l)	(μM)	Plasma Protein Binding (%) (mean ± SD)
0.10	0.29	92.46 ± 0.95
0.50	1.45	94.28 ± 0.94
1.0	2.90	94.48 ± 0.62
5.0	14.50	94.51 ± 0.79
10.0	29.00	94.58 ± 0.48
25.0	72.60	95.03 ± 0.13
50.0	145.20	93.28 ± 1.65
100.0	290.5	93.82 ± 1.09
250.0	726.3	90.86 ± 3.80
500.0	1452.6	88.34 ± 2.28
1000.0	2905.1	80.79 ± 5.05

The results of plasma covalent binding of both clopidogrel and its metabolite are presented below:

SR 25990C concentration (mg/l)	(μM)	Plasma covalent binding (%) (mean ± S.D.)
0.025	0.059	1.45 ± 1.03
0.25	0.595	1.41 ± 0.16
1.0	2.38	1.31 ± 0.10
10.0	23.81	1.23 ± 0.17
50.0	119.07	1.17 ± 0.27

SR 26334A concentration (mg/l)	(μM)	Plasma covalent binding (%) (mean ± S.D.)
0.1	0.29	1.73 ± 0.27
1.0	2.90	1.35 ± 0.26
10.0	29.05	1.30 ± 0.08
100.0	290.46	1.42 ± 0.32
500.0	1452.30	1.32 ± 0.22

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% binding of clopidogrel and SR26334 to erythrocytes are summarized in the following tables:

SR 25990C concentration (mg/l)	(μM)	Erythrocyte binding (%)
0.025	0.059	-a
0.050	0.119	-
0.10	0.238	5.38 ± 4.98
0.25	0.595	4.82 ± 2.29
0.50	1.19	6.86 ± 7.14
1.0	2.38	4.61 ± 4.00
5.0	11.91	5.31 ± 5.20
10.0	23.81	13.52 ± 21.80
25.0	59.53	20.73 ± 17.14
50.0	119.07	10.34 ± 10.32
Mean S.D.		8.94 ± 5.34

SR 26334A concentration (mg/l)	(μM)	Erythrocytes binding (%)
0.10	0.29	11.55 ± 2.51
0.50	1.45	13.22 ± 4.16
1.0	2.90	9.89 ± 6.16
5.0	14.50	9.28 ± 7.33
10.0	29.00	9.71 ± 8.83
25.0	72.60	8.38 ± 7.59
50.0	145.20	8.14 ± 5.80
100.0	290.5	8.76 ± 6.18
250.0	726.3	13.75 ± 8.85
500.0	1452.6	15.50 ± 3.93
Mean S.D.		10.81 ± 2.42

Conclusion:

1. % binding of SR25990C and SR26334 to plasma proteins is 98 and 94% respectively and is not saturable up to 100 μg/mL concentrations. Binding is saturable at higher concentrations.
2. About 2% of radiolabel for clopidogrel and its carboxy metabolite is covalently bound to plasma proteins.
3. % binding to erythrocytes was about 10% for both clopidogrel and its metabolite.

STUDY LPR0602: BINDING OF SR25990C TO ISOLATED HUMAN SERUM PROTEINS: This study has already been reviewed by Dr. Phil Colangelo (see review dated August 31, 1995). It was concluded that binding of clopidogrel was extensive (80 - 90%) to physiological concentrations of human serum albumin and low density lipoproteins, and moderate (30 - 60%) to α_1-acid glycoprotein and high density lipoproteins. This binding to HSA, LDL and HDL was not saturable in the concentrations studied, but binding to AAG was saturable. The extensive binding to albumin suggests potential binding displacement interactions may occur with other drugs. However, since therapeutic concentrations of clopidogrel are extremely low, this protein binding may be of limited clinical importance.

STUDY LPR0603: BINDING OF SR26334A TO ISOLATED HUMAN SERUM PROTEINS: This study has already been reviewed by Dr. Phil Colangelo (see review dated August 31, 1995). It was concluded that binding of SR26334A was primarily to human serum albumin and was extensive (80 - 90%). This binding was saturable at high concentrations of SR26334A (893 - 2580 mg/l). Binding to other proteins, including AAG was low (<10%) to moderate (20 - 50%). The extensive binding to albumin may potentially result in protein binding displacement interactions with other highly bound drugs.

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IN VITRO METABOLISM:

MIH0012 - DETERMINATION OF THE CYTOCHROME P450 (CYP) ISOFORMS INVOLVED IN THE OXIDATIVE METABOLISM OF SR25990C AND SR26334A IN HUMAN LIVER MICROSOMES IN VITRO

Study ID: MIH0012
Volume: 1.60
Objective:

To identify the hepatic Cytochrome P-450 (CYP) isoforms involved in the oxidative metabolism of clopidogrel and its carboxylic acid metabolite by human liver microsomes.

IN VITRO METABOLISM OF CLOPIDOGREL : Clopidogrel concentrations in the range of 0.5 and 10 µM were incubated with human liver microsomes (0.1 mg/mL microsomal protein), pooled microsomes from 3 human livers (9 livers for CYP isozyme determination), at 37°C (optimal reaction conditions were used to produce linear rates of loss). This mixture also contained potassium phosphate buffer, magnesium chloride, ß-$NADP^+$, glucose 6-phosphate, and glucose 6-phosphate dehydrogenase. The reactions were allowed to proceed for about 15 minutes. The samples were centrifuged and analyzed by to monitor the disappearance of clopidogrel. K_m and V_{max} parameters for metabolism of clopidogrel were then determined from this data.

Specific cytochrome P450 enzymes responsible for metabolism of clopidogrel and its metabolite were identified by chemical inhibition studies, CYP-selective inhibitory antibodies and by incubation with purified CYP forms [individual CYP isoforms in microsomes from transfected β-lymphoblastoid cells (cDNA-expressed CYP systems)]. The isoforms investigated were CYP1A2, CYP2B6, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4.

Human liver microsomes and clopidogrel were incubated with an NADPH generating system, with and without competitive substrates, chemical inhibitors or antibodies, in potassium phosphate buffer (pH 7.4) at 37°C for 15 minutes. Rates of clopidogrel disappearance were compared to determine inhibition.

CYTOCHROME P-450 SELECTIVE INHIBITORS: A series of inhibitors were incubated with 0.5 and 5 µM clopidogrel to determine which compounds could inhibit the metabolism of this drug. The inhibitors (and competitive substrates) selected were 7,8-benzoflavone (0.1 - 1 µM) and furafylline (0.1 - 1 µM) for CYP1A2; pilocarpine (1 - 10 µM) for CYP2A6; orphenadrine (2 - 20 µM) and cyclophosphamide (2 - 20 µM) for CYP2B6; sulfaphenazole (1 - 10 µM) for CYP2C9; S-mephenytoin (10 - 100 µM) and tranylcypromine (2 - 20 µM) for CYP2C19; quinidine (0.1 - 5 µM) for CYP2D6; diethyldithiocarbamate (2 - 20 µM) and chlorzoxazone (10 - 100 µM) for CYP2E1; ketoconazole (0.05 - 0.5 µM) and troleandomycin (10 - 100 µM) for CYP3A4.

PURIFIED CYP FORMS AND cDNA-EXPRESSED CYP ACTIVITIES: Clopidogrel (at 0.5 and 5 µM concentration) in presence of an NADPH-generating system at 37°C was incubated with human ß-lymphoblastoid cells containing cDNA-expressed specific CYP-isoforms, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 for 15 minutes to investigate clopidogrel disappearance.

ISOFORM-SELECTIVE INHIBITORY ANTIBODIES: Clopidogrel (at 0.5 and 5 µM concentration) in presence of an NADPH-generating system at 37°C was incubated with isoform-selective inhibitory antibodies for 15 minutes to investigate clopidogrel disappearance.

Results:

All samples were analyzed by to monitor the oxidative metabolism of clopidogrel. LOQ of the assay was 0.1 µM. Within run and between run CV was less than 10.4%. Within run and between run accuracy ranged from -4 to 7%.

Mean apparent Km value for clopidogrel metabolism was found to be 6.6 ± 2.1 µM and Vmax = 2637 pmol/min/mg.

Results from chemical inhibition studies are shown in the following table. Inhibition was not extensive at clopidogrel concentrations of 0.5 µM.

Competitive Substrate/Inhibitor	Percent of Control Activity		
	0.5 µM	5 µM	Isoform-Selective Substrate
Furafylline (CYP1A2):			
0.1 µM	98	105	88
1 µM	91	86	38
7,8-benzoflavone (CYP1A2):			
0.1 µM	103	55	ND
1 µM	98	43	ND
Pilocarpine (CYP2A6):			
1 µM	104	88	77
10 µM	96	79	25
Orphenadrine (CYP2B6):			
2 µM	95	95	ND
20 µM	86	62	ND
Cyclophosphamide (CYP2B6):			
2 µM	102	46	ND
20 µM	102	41	ND
Sulfaphenazole (CYP2C9):			
1 µM	94	68	69
10 µM	83	47	24
S-Mephenytoin (CYP2C19):			
10 µM	103	85	ND
100 µM	91	55	ND
Tranylcypromine (CYP2C19):			
2 µM	94	93	86
20 µM	81	89	49
Quinidine (CYP2D6):	99 (0.1 µM) 101 (1 µM)	87 (0.5 µM)* 100 (5 µM)*	79 (0.1 µM) 35 (1 µM)
Diethyldithiocarbamate (CYP2E1):			
2 µM	93	103	92
20 µM	92	73	81
Chlorzoxazone (CYP2E1):			
10 µM	97	118	ND
100 µM	87	93	ND
Ketoconazole (CYP3A4):			
0.05 µM	88	71	60
0.5 µM	84	35	13
Troleandomycin (CYP3A4):			
10 µM	84	58	ND
100 µM	82	55	ND

Results from cDNA-expressed purified isozymes are shown in the following table:

Clopidogrel metabolism in microsomes containing heterologously expressed human CYP isoforms

Microsome preparation	Clopidogrel Metabolism (Percent of control activity)		Isoform-Selective Substrates
	0.5 μM*	5 μM*	Oxidation Rate
Vector alone	ND	103	–
CYP1A2 (17 pmol CYP)	44	78	263
CYP2A6 (14 pmol CYP)	106	102	8625
CYP2B6 (18 pmol CYP)	0	4	ND
CYP2C9 (5 pmol CYP)	99	94	13
CYP2C19 (3 pmol CYP)	14	80	81
CYP2D6 (5 pmol CYP)	106	113	355
CYP2E1 (25 pmol CYP)	107	98	175
CYP3A4 (9 pmol CYP)	30	36	1402

* Clopidogrel concentration

Results from antibody inhibition studies are shown in the following table:

Antibody preparation	Percent of Control Activity		
	0.5 μM*	5 μM*	Isoform-Selective Substrates
CYP1A2			
low	102	126	
high	101	100	64
CYP2A6			
low	110	103	
high	110	80	52
CYP2B6			
low	89	43	
high	89	29	ND
CYP2C9			
low	92	119	
high	94	57	86
CYP2C19			
low	92	119	
high	94	57	ND
CYP2D6			
low	104	74	
high	99	68	29
CYP2E1			
low	101	97	
high	89	67	80
CYP3A4			
low	92	72	
high	77	47	21

*Clopidogrel concentration

The following summary table shows the CYP isoenzymes involved in the metabolism of clopidogrel:

	Type of Experiment			Conclusion*
CYP Isoform	Substrates/ Inhibitors	Inhibitory Antibodies	Expressed Isoforms	Involved in clopidogrel metabolism
CYP1A2	++	–	++	Possible
CYP2A6	–	–	–	No
CYP2B6	+	++	++	Yes
CYP2C9	++	+	–	Possible
CYP2C19	++	+	++	Yes
CYP2D6	–	+	–	No
CYP2E1	+	+	–	Possible
CYP3A4	++	++	++	Yes

++ Active
+ Possibly active
– Not active
* 0 - 1 +. Isoform not involved in clopidogrel metabolism
2 - 4 +. Isoform possibly involved in clopidogrel metabolism
5 - 6 +. Isoform involved in clopidogrel metabolism

Conclusion: Results from this study indicate that CYP2B6, CYP2C19 and CYP3A4 are involved clopidogrel metabolism. CYP1A2, CYP2C9 and CYP2E1 may also possibly be involved. The bulk of metabolic clearance, however, is not due to cytochrome P450 mediated metabolism. This involves de-esterification, to form the carboxy metabolite (SR26334). The primary clearance pathway for the carboxy metabolite is glucuronidation. Attempts to identify the cytochrome P450 isozymes involved in its metabolism were inconclusive due to undetectable rates of metabolism in human liver microsomes.

Comments: Since this drug is metabolized by CYP1A2, 2C9, 2B6, 2C19 and 3A4, it may potentially interact with drugs like theophylline, warfarin, orphenadrine, phenytoin and ketoconazole.

STUDY MIH0011 (IN VITRO ENZYME INHIBITION STUDY):

INVESTIGATING THE POTENTIAL FOR SR25990C AND SR26334A TO INHIBIT CYTOCHROME P450 (CYP) ENZYMES USING HUMAN LIVER MICROSOMES IN VITRO

Reference: Volume 60
Investigator: Jennifer Brandl
Study Location: Sanofi Research Division, Malvern, PA
Objective:

To investigate the effects of clopidogrel and its carboxy metabolite on human cytochrome P450 activities (CYP1A2, CYP3A4, CYP2A6, CYP2C9, CYP2C19, CYP2D6 and CYP2E1) in vitro and to determine its potential to inhibit the metabolism of other drugs in man.

Study design:

Human liver microsomes obtained from 3 donor livers were incubated with various substrates (nifedipine: 40 μM; tolbutamide: 500 μM; phenacetin: 10 μM; coumarin 1 μM (for CYP2A6), bufuralol 25 μM, chlorzoxazone 100 μM and mephenytoin 100 μM), reaction cofactors and clopidogrel 0.4 μM and carboxy metabolite 200 μM (concentrations approximately 20 fold higher than expected plasma concentrations after a daily dose of 75 mg). Sodium fluoride was added to the reaction mixtures containing clopidogrel to inhibit de-esterification of the compound during incubation. Quantitation of the specific metabolites formed by various isozymes (1A2, 2C9, 2D6, 2C19, 2E1 and 3A4) of cytochrome P450 were performed using methods. .

Where inhibition was found, K_is (inhibition constants) for clopidogrel and its metabolite were determined for different isozymes using non-linear regression. % inhibition expected clinically was estimated using the following equation for competitive enzyme inhibitors:

$i = \{I/[I+Ki(1+S/Km)]\}*100$ where i = % inhibition; I = expected plasma concentration of inhibitor (10 μM for SR26334A based on C_{max} value after 75 mg dose); S = expected plasma concentration of substrate; Ki = apparent Ki value for inhibitor against drug metabolism; and Km = apparent Km value determined for substrate metabolite production.

Results:

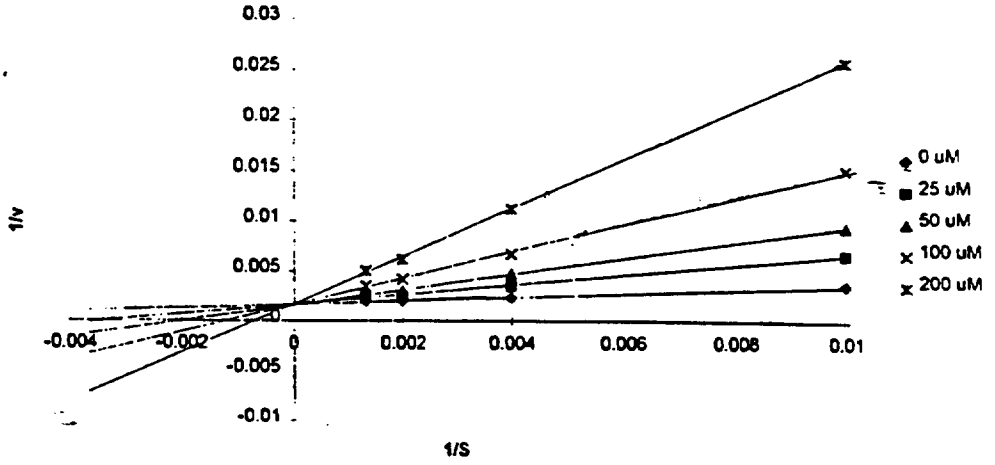
Clopidogrel did not significantly inhibit (defined as >30% inhibition relative to control values) any of the CYP isoform activities. Addition of isoform-selective inhibitors (CYP1A2, furafylline; CYP2D6, quinidine; CYP2E1, diethyldithiocarbamate; CYP2C9, sulfaphenazole; CYP2A6, pilocarpine; CYP2C19, tranylcypromine; and CYP3A4, ketoconazole), to reaction mixtures, however, resulted in significant inhibition relative to control reaction mixtures confirming the ability of these assays to show CYP inhibition.

SR26334A did not significantly inhibit phenacetin O-deethylation (CYP1A2), bufuralol 1'-hydroxylation (CYP2D6), coumarin 7-hydroxylation (CYP2A6), mephenytoin 4-hydroxylation (CYP2C19), nifedipine oxidation (CYP3A4), or chlorzoxazone 6-hydroxylation (CYP2E1).

SR26334A, however, decreased tolbutamide hydroxylation (CYP2C9) to approximately 45% of control values in all three microsomal preparations. In comparison to this, 50 μM sulfaphenazole, a selective 2C9 inhibitor, decreased tolbutamide hydroxylation by 90%.

Apparent Ki values for SR26334A inhibition (competitive inhibitor) of CYP2C9, were 25, 27 and 32 μM in the tested microsomes (see figure). Based on an expected SR26334A C_{max} of 10 μM and a mean apparent Ki value of 28 μM, the calculated % inhibition for CYP2C9 was 26.3%.

Lineweaver Burk representation of the effect of SR 26334A on tolbutamide hydroxylation in microsomes from human liver



Conclusions:

Clopidogrel did not inhibit cytochrome P450 mediated metabolism. SR26334A inhibited CYP2C9 (tolbutamide hydroxylation) in vitro. This suggests that inhibition of CYP2C9-mediated metabolism of drugs is possible upon concomitant administration with clopidogrel.

Comment:

Based on the above results, one can expect drug interactions with phenytoin, S-warfarin, tolbutamide and may be even torsemide. S-warfarin interaction is especially important since warfarin has a high potential to be used in patients taking clopidogrel due to the nature of the disease states in which both these drugs are used.

STUDY MIH0009 (IN VITRO ENZYME INHIBITION STUDY):

INVESTIGATING THE POTENTIAL OF SR25990C AND SR26334A TO INHIBIT THE OXIDATIVE METABOLISM OF GLYBENCLAMIDE (GLYBURIDE) IN HUMAN LIVER MICROSOMES

Reference: Volume 60
Investigator: Robert Van Horn
Study Location: Sanofi Research Division, Malvern, PA
Objective:

To investigate the potential of clopidogrel and its carboxy metabolite to inhibit the metabolism of glyburide in human liver microsomes.

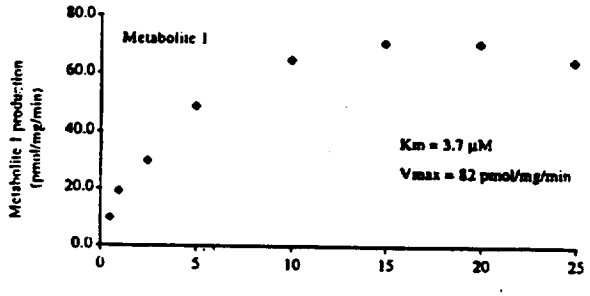
Study design:

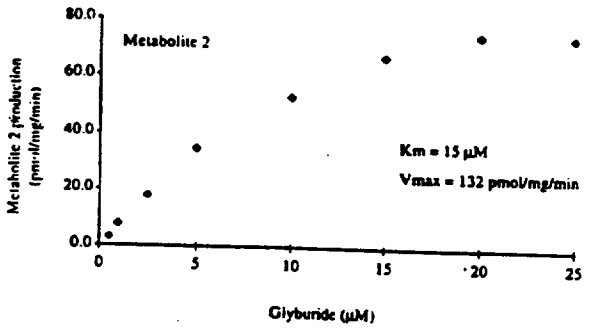
Human liver microsomes obtained from 3 donor livers were incubated (for 30 minutes using 0.5 mg/mL microsomal protein to be in the linear range) with various substrates (glyburide 1, 2.5, 5 and 10 µM), reaction cofactors and a range of clopidogrel (400 nM) and carboxy metabolite concentrations (0, 50, 100, 200, 400 and 600 µM). Quantitation of the metabolites 1 and 2 of glyburide were performed by Apparent Km and Vmax values for metabolites 1 and 2 and apparent Ki value for SR26334A with metabolite 1 were determined by non-linear regression. % inhibition expected clinically was estimated using the following equation for competitive enzyme inhibitors:

$i = \{I/[I+Ki(1+S/Km)]\}*100$ where i = % inhibition; I = expected plasma concentration of inhibitor (10 µM for SR26334A based on C_{max} value after 75 mg dose); S = expected plasma concentration of glyburide (1 µM based on a daily dose of 5 mg); Ki = apparent Ki value for inhibitor against glyburide oxidation; and Km = apparent Km value determined for glyburide metabolite production (metabolite 1 or 2).

Results:

Km and Vmax values for formation of glyburide metabolites are shown in the following figures:





Clopidogrel did not affect the oxidative metabolism of glyburide when incubated with human liver microsomes. SR26334A appeared to be a competitive inhibitor of metabolite 1 production (see tables below), with a mean apparent Ki of 111 μM, with a range of 68 to 140 μM (see figure below). However, SR26334A had no effect on metabolite 2 formation. Based on expected plasma concentrations and apparent Km and Ki values, the predicted inhibition of the metabolite 1 pathway is approximately 6.5%.

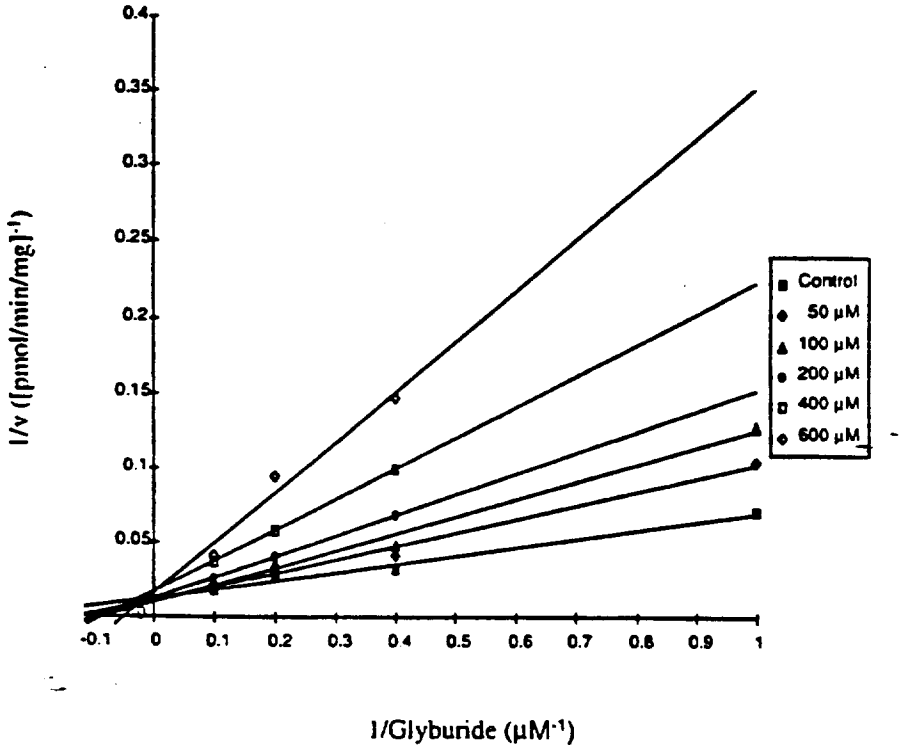
	Metabolite 1*	Inhibition (% of Control)	Metabolite 2*	Inhibition (% of Control)
HL 23-May-94				
Control†	0.25	100	0.24	100
Clopidogrel	0.25	100	0.24	100
HL 4-Sep-92				
Control†	0.29	100	0.23	100
Clopidogrel	0.28	96	0.23	100
HL 21-Jan-94				
Control†	0.19	100	0.06	100
Clopidogrel	0.19	100	0.06	100

* Values are expressed as μM amounts of metabolite produced
† Control reaction mixtures with clopidogrel contained 1 mM NaF

	Metabolite 1*	Inhibition (% of Control)	Metabolite 2*	Inhibition (% of Control)
HL 23-May-94				
Control	0.27	100	0.24	100
SR 26334A	0.18	67	0.23	96
HL 4-Sep-92				
Control	0.29	100	0.22	100
SR 26334A	0.19	66	0.21	95
HL 21-Jan-94				
Control	0.20	100	0.06	100
SR 26334A	0.12	60	0.06	100

* Values are expressed as μM amounts of metabolite produced

Lineweaver-Burk representation of the effect of SR 26334A on the production of metabolite 1 in microsome preparation HL



Conclusions:

Clopidogrel did not inhibit glyburide metabolism. However, the carboxy metabolite of clopidogrel inhibited the formation of glyburide metabolite 1. Therefore an interaction between SR26334A and glyburide is possible. However, this may not be clinically significant since all the metabolic pathways are not inhibited and glyburide when concomitantly administered with clopidogrel could possibly be cleared via the other pathways.

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STUDY P1549: (HEPATIC ENZYME INDUCTION/INHIBITION: EFFECT OF CLOPIDOGREL ON ANTIPYRINE METABOLISM)

A STUDY OF THE INDUCTION OF HEPATIC ENZYME SYSTEMS BY CLOPIDOGREL (SR25990C) IN HEALTHY MALE VOLUNTEERS

Reference: Volumes 15, 16, 17, 18 and 19
Investigator:
Study Location:
Objective:

To determine whether clopidogrel and/or its metabolites are capable of causing induction or inhibition of hepatic enzymes using antipyrine kinetics as a marker of both the inhibition and induction of hepatic oxidative activity.

Study design:

This is a randomized double-blind, parallel-group, placebo-controlled trial in 20 healthy young male volunteers (age 18 - 35 years) involving multiple oral doses of clopidogrel (75 mg qd for 10 days) or placebo and single oral doses of antipyrine (10 mg/kg pre-clopidogrel dose and on day 10).

Clopidogrel was administered as 75 mg dose (3 x 25 mg tablets) once a day for 10 days. Antipyrine was administered at a dose of 10 mg/kg before and after the 10 day treatment with clopidogrel. Antipyrine powder was reconstituted with 100 ml of bottled water prior to dosing. No food was permitted 12 hours prior to and 4 hours following antipyrine administration.

Blood samples were drawn for analysis of antipyrine at 0, 0.5, 1, 2, 3, 4, 5, 8, 12, 16, 24 and 36 hours on after antipyrine administration on days 2 (pre-clopidogrel dosing) and 10. Urine samples were collected at 12 hour intervals over a 48 hour period for determination of antipyrine and its metabolite levels (norantipyrine and 3-OH methylantipyrine) on days 2 and 10. Urine was also assayed for 6 β OH-cortisol. Plasma samples were collected on day -4, -3 and 9 for cortisol plasma concentration.

The primary analysis parameters were plasma antipyrine clearance and cumulative urinary recoveries of antipyrine and its metabolites. ANOVA was performed on log-transformed plasma antipyrine clearance and on the cumulative urinary recoveries of antipyrine and its metabolites to compare clopidogrel and placebo. To evaluate combined inductive and inhibitory effect, parameters obtained after coadministration of antipyrine with clopidogrel (day D10) were compared with antipyrine alone (D2).

Comparisons between clopidogrel and placebo groups were made for safety in terms of laboratory tests, bleeding time and vital signs (changes from baseline were compared between 2 groups).

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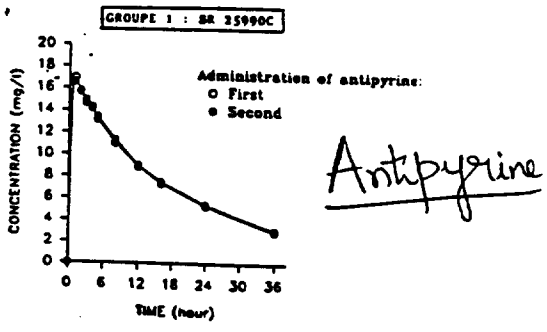
Assays were found to be acceptable.

PHARMACOKINETIC RESULTS:

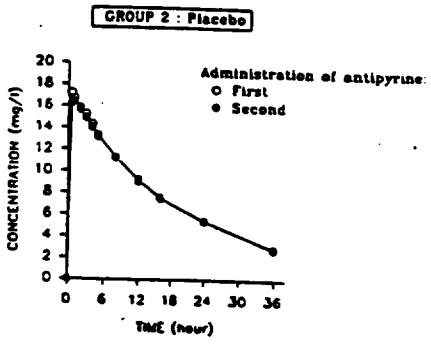
Mean PK parameters of antipyrine (before and after clopidogrel and placebo groups) is shown in the table and figure below:

	C max (mg/l)		T max (h)		AUC0-36h (mg-h/l)		T ½ (h)		Cl/F (l/h)	
	D-2*	D10*	D-2	D10	D-2	D10	D-2	D10	D-2	D10
SR										
Mean	17.5	17.7	0.7	1.0	280.9	285.3	14.7	14.9	2.3	2.2
SEM	0.5	0.8	0.1	0.2	20.2	18.7	1.9	1.8	0.3	0.2
Min										
Max										
Placebo										
Mean	17.9	17.1	0.8	0.9	285.3	284.6	14.0	14.4	2.3	2.2
SEM	0.4	0.3	0.2	0.1	10.8	11.2	0.6	0.7	0.1	0.1
Min										
Max										

* Day-2 administration of antipyrine before treatment
Day10 administration of antipyrine after 10 days of treatment



Antipyrine



Statistical analysis of $t_{1/2}$ and Cl/F is shown in the following table:

		Parameters			
		T ½		Cl/F	
Factors	**d.f.**	**F**	**p**	**F**	**p**
Treatment on Day-2	1,18	0.14	0.715	0.01	0.927
Treatment on D10	1,18	0.07	0.801	0.02	0.895
Visit	1,18	1.61	0.221	3.92	0.063
Treatment x visit	1,18	0.47	0.500	0.64	0.433

No significant differences in antipyrine plasma PK parameters were found.

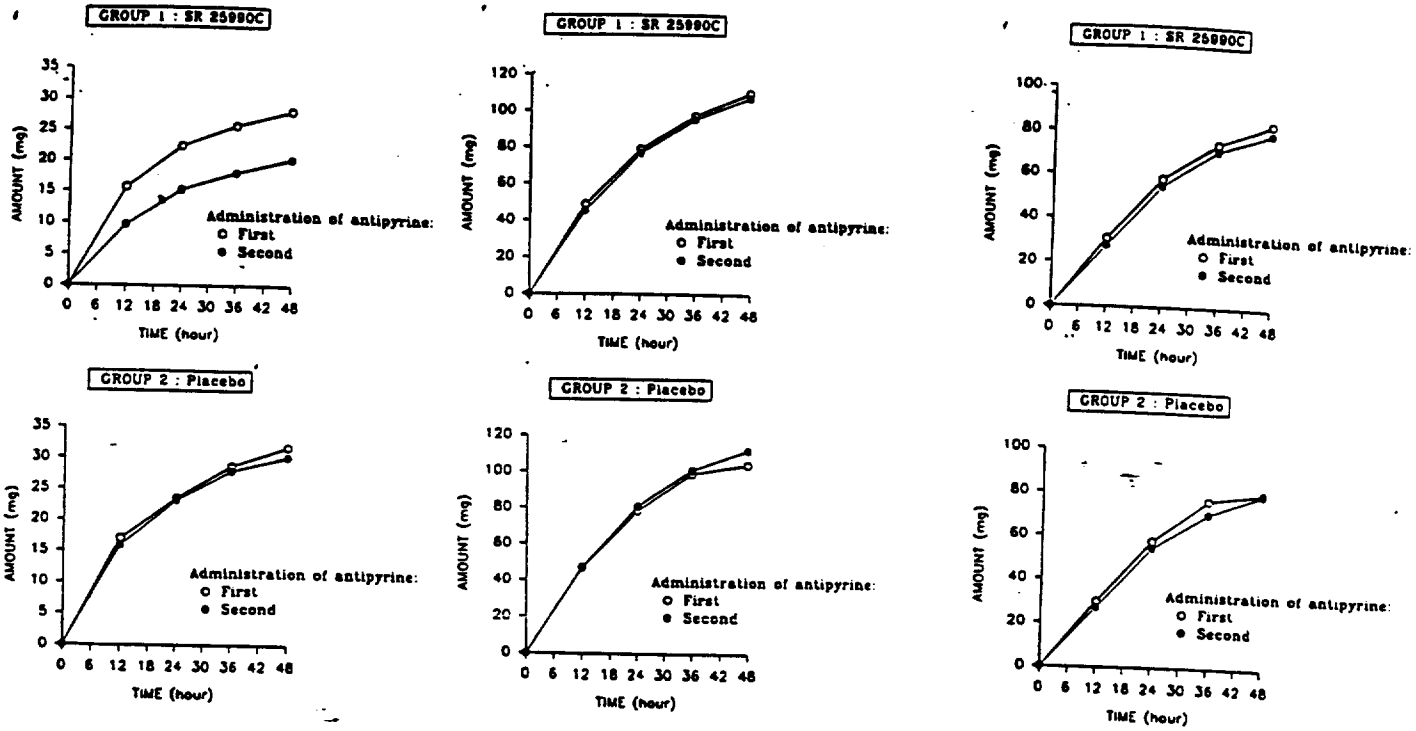
Mean urinary recovery of antipyrine, norantipyrine and 3-OH methylantipyrine (before and after clopidogrel and placebo groups) is shown in the table and the 3 figures below:

	Ae-Antipyrine (mg)		Ae Norant (mg)		Ae 3 HMA (mg)	
	D-2	D10	D-2	D10	D-2	D10
SR						
Mean	28.0	20.0	110.0	107.3	84.2	79.9
SEM	2.2	1.5	12.0	11.4	7.2	6.4
Min						
Max						
Placebo						
Mean	30.6	30.2	108.2	112.3	84.0	79.8
SEM	3.4	4.3	7.0	8.6	5.6	4.6
Min						
Max						

* Ae 0-36h

URINARY PHARMACOKINETICS

ANTIPYRINE NORANTIPYRINE 3-HMA



Statistical analysis of A_e for antipyrine and its metabolites is shown in the following table:

		Ae parameters					
		Antipyrine		Norant.		3 - HMA	
Factors	d.f.	F	p	F	p	F	p
Treatment Day-2	1,18	0.03	0.856	0.17	0.689	0.20	0.659
Treatment D10	1,18	5.09	0.037	0.28	0.603	0.02	0.902
Visit	1,18	3.53	0.076	0.78	0.388	0.30	0.594
Treatment x visit	1,18	4.60	0.046	1.12	0.305	0.14	0.708

Conclusions:

There was no significant difference in PK parameters of antipyrine (clearance and half-life) and in the urine excretion of antipyrine and the 2 metabolites obtained before and after clopidogrel treatment. There was no effect on γGT or on cortisol blood levels or urinary excretion of 6 β OH-cortisol. This indicates that clopidogrel does not significantly induce or inhibit hepatic enzyme activity.

CONCLUSION: This method is precise and accurate.

Comments: 1. The data for stability of clopidogrel and its metabolite in plasma samples upon storage and during freeze-thaw cycles has not been provided.
2. The calibration curve plot provided contains concentration (a truly independent variable) on Y-axis instead of X-axis. The sponsor, in future should plot concentration which is an independent variable on X-axis for calibration curves.

CONCLUSION: This method is precise and accurate.

Comments: 1. The data for stability of clopidogrel and its metabolite in plasma samples has not been provided.

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CONCLUSION: This method is precise and accurate and validation results are found to be acceptable.

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ASSAY PERFORMANCE: Conducted at Sanofi Research, Montpellier, France

CONCLUSION: This method is precise and accurate to determine the R and S enantiomers of clopidogrel carboxy metabolite and validation results are found to be acceptable. However, the method is not very sensitive.

STUDY P1717 (volumes 51, 52 and 53): RELATIVE BIOAVAILABILITY OF CLOPIDOGREL IN ELDERLY HEALTHY VOLUNTEERS IN THE FED AND FASTING STATES: This study has already been reviewed by Dr. Phil Colangelo (see review dated August 31, 1995). It was concluded that food did not alter the extent of SR26334 absorption/formation, as measured by AUC of SR26334 following single dose administration of clopidogrel (75 mg 2Q2 - clinical tablet). Although the rate of metabolite formation was, on average, rapid under both conditions, it may be slightly slower in the presence of food resulting in lower C_{max} (ratio of mean C_{max} fed/fasting = 0.79 and 90% C.I. 0.57 - 0.97). However, the C_{max} and T_{max} values were not overwhelmingly convincing to the reviewer, due to the truncation of the data. It was concluded that in general, food had a minimal effect on the pharmacokinetics of the primary metabolite of clopidogrel.

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STUDY P1298: (FOOD EFFECT BIOAVAILABILITY STUDY)

INFLUENCE OF FOOD INTAKE ON PHARMACOKINETIC PROFILE AND ANTIAGGREGATING ACTIVITY OF SR 25990C (CLOPIDOGREL)ADMINISTERED AS A SINGLE DOSE (400 MG) IN THE FORM OF TABLETS (8 x 50 MG) IN HEALTHY VOLUNTEERS

Reference: Volume 61
Investigators:
Study Location:
Objective:
1.To compare the pharmacokinetic parameters after administration under fasting or non-fasting conditions.
2.To compare efficacy of the compound in fasting to non-fasting conditions.
Study design:
This is a randomized open-label two-way crossover study in 12 healthy male volunteers (caucasians) of age 18-32 years. In the first arm of the study, a single 400 mg dose of clopidogrel was administered as eight 50 mg tablets taken with a glass of water under fasting conditions (and remaining so for another 4 hours), while the second arm consisted of the same administration at the end of a meal containing 50g bread, 100g potatoes, 1 egg, 50g York ham, 1 yoghurt, 1 fruit (approx. 700 calories with 30g protein, 47g fats, 60g carbohydrate). The interval between two treatment periods was 14 days.

Batch #s: Clopidogrel 50 mg tablet: 1A1 RFF16

Blood samples were drawn for the determination of plasma concentration of SR25990 and SR26334 (carboxy metabolite of clopidogrel) at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48 and 72 hours after dosing. ADP-induced platelet aggregation was measured at 0, 2, 4, 24, 48, 72 and 192 (upto 72 hours for second administration) hours after dosing. Bleeding time was determined at 5 and 24 hours after dosing. Pharmacokinetic parameters that were compared using ANOVA were AUC, Cmax, Tmax, t1/2 and MRT. Student's paired t-test was used to detect differences between plasma concentrations for the two treatments at each time point. Wilcoxon's non-parametric test was used to compare Tmax values. Comparison of aggregation and bleeding times were also undertaken using ANOVA.

Results:
ASSAY PERFORMANCE:

Mean (stdev) PK parameters for SR26334 are provided in the following table:

Parameter	Fasting	Non-Fasting	Statistical Significance
AUC_{0-} (mg.hr/l)	47.88 (11.52)	50.82 (13.63)	ns
C_{max} (mg/l)	12.34 (2.94)	10.56 (2.18)	ns
Tmax (hr)	1.04 (0.35)	1.50 (0.71)	ns
MRT (hr)	7.23 (1.39)	7.75 (2.04)	ns
T1/2 (hr)	7.71 (1.96)	7.38 (2.19)	ns

Mean plasma concentration profiles are shown in the figures below:

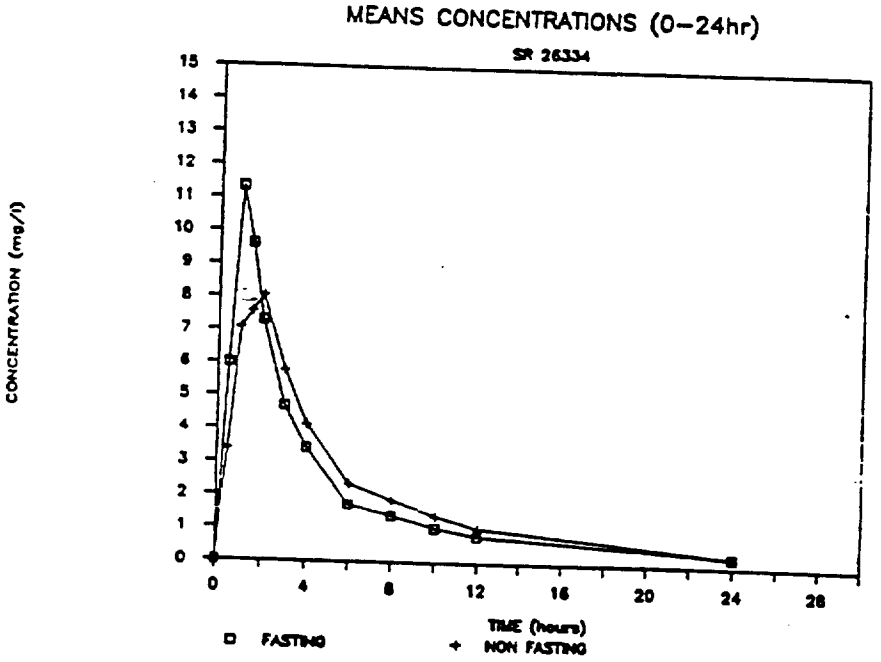


Figure (14.5)1

Mean plasma levels of SR 26334 after SR 25990C administration in fasting and non fasting conditions.

Percentage inhibition (based on time zero) of 5 µmol/l ADP-induced platelet aggregation following administration of clopidogrel under fed and fasted conditions are shown in the following table:

Treatment	2 hours	4 hours	24 hours	48 hours	72 hours	192 hours
Fasting	43	69	63	53	53	3
Non-Fasting	40	68	54	56	40	9

There was no significant difference in aggregation inhibition after administration of clopidogrel either under fasted or non-fasted conditions.

Bleeding time (seconds) following clopidogrel administration under fasted or non-fasted conditions is shown below:

Time of Measurement	Fasted	Multiplication factor	Non-Fasted	Multiplication factor
Before treatment	478		414	
5 hours after administration	1380	3	1200	3
24hours after administration	1080	2.4	900	2.2

No significant difference was noted in bleeding time after administration of clopidogrel either under fasted or non-fasted conditions.

Conclusions:
Co-administration with meals reduced the Cmax for SR26334 marginally, by about 14% and increased the Tmax by about 0.5 hours (from 1 to 1.5 hours). This is likely to be due to delayed gastric emptying time for the drug when it is administered with meals. AUC remained unchanged. Based on % inhibition of ADP induced platelet aggregation and bleeding times, administration under fasted or fed conditions showed similar results. In agreement with other study results, significant inhibition of platelet aggregation persisted upto about 72 hours (3 days) after dosing. Baseline values were regained by 8th day after drug administration.

Comments:
1. Although the meal used by the sponsor is not the typical meal generally recommended by the FDA for such studies, it appears to be a high calorie breakfast with adequate proportions of carbohydrate, fat and protein.

2. The sponsor should provide data on QC samples that are generally run with the plasma samples.

STUDY P1331: (PHARMACOKINETIC STUDY IN YOUNG, ELDERLY (WITHOUT ARTERIOPATHY), AND ELDERLY (WITH ARTERIOPATHY) SUBJECTS

COMPARISON OF PHARMACOKINETICS AND ANTIPLATELET ACTIVITY OF SR 25990 (CLOPIDOGREL) ADMINISTERED AS 75 MG ONCE DAILY FOR 10 DAYS (50MG + 25MG TABLETS), IN THREE POPULATION GROUPS

Reference: Volume 20
Investigator:
Study Location:

Objective: To assess in three different populations,
1. Platelet aggregation and bleeding time
2. Clinical and biological tolerability
3. Pharmacokinetic profile at steady state

Study design:
This is a non-randomized open-label parallel group study in healthy young (N=10, age 18-35y), elderly without arteriopathy (N=10, age >65y) and elderly with arteriopathy (N=10, age >65y), male subjects. A daily dose of 75mg (50mg + 25mg tablet) was administered for 10 days , once daily before breakfast. A follow-up continued for a further 14 days after cessation of study treatment.
Batch #s: Clopidogrel-50 mg tablet: RFN25, RGE17, RGN23; REF 1A1
Clopidogrel 25 mg tablet: RFN15, RGE18, RGN10; REF 1A1

Assessments for platelet aggregation (ADP conc. 1,2, and 5 μM, collagen 10, 20 μg/ml) were made pre-dose and then daily during the treatment period (days 1-9: 2 hours after the dose, day 10: 2, 5, 24 hours after dose) and on alternate days during follow-up, except weekends. Bleeding time assessments were made pre-dose and on days 10 (5 hours after dosing) and 18 (at 10 am). Plasma concentration of clopidogrel (not detectable in majority of the subjects) and SR26334 (carboxy metabolite of clopidogrel) were determined daily before dosing (except weekends) and on day 10 at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48 and 72 hours post-dose. Pharmacokinetic parameters determined were Cssmin, Cssmax, Tmax, AUC(0-24) and t1/2. Maximum % aggregation and velocity for each agonist was studied. Pharmacokinetic parameters were compared using Duncan's test (conc. and AUCs), Kruskal Wallis test (Tmax) and Spearman correlation coefficient (AUC vs. Clcr, Cmax and AUC vs maximum aggregation).

Demographic characteristics for subjects are as follows:

Characteristic	Healthy volunteers	Elderly subjects	Arteriosclerotics
n*	12	10	10
Age (years)	24.21 ± 0.86**	75.57 ± 1.92	75.69 ± 1.01
Weight (kg)	68.42 ± 1.47	61.50 ± 1.56	66.70 ± 2.19
Height (cm)	176.42 ± 2.15	164.60 ± 1.42	168 ± 1.79

mean ± SEM

At inclusion, ADP aggregation was significantly lower for young subjects than in the elderly population (Duncan's Test); the velocity of aggregation in response to increasing agonist concentrations was higher in the elderly, as well:

Result	Healthy volunteers	Elderly subjects	Arteriosclerotics	p[b]
ADP 1µM				
n	10	10	10	
% Max	10.00±1.83[a]	26.80±7.12	20.70±5.64	0.0984
velocity	9.50±2.20	19.60±3.92	13.70±3.18	0.0970
ADP 2µM				
n	10	10	10	
% Max	20.80±3.76	52.90±8.03	34.10±4.49	0.0020**
velocity	18.80±2.99	31.30±3.86	22.50±2.98	0.0358*
ADP 5µM				
n	10	10	10	
% Max	43.00±4.12	70.60±4.88	67.10±7.13	0.0027**
velocity	28.30±3.30	38.30±3.35	35.70±2.91	0.0894
Collagen 10µg/ml				
n	10	10	10	
% Max	44.10±10.94	55.50±8.37	24.40±6.86	0.0596
velocity	20.10±5.37	21.80±3.93	9.10±2.48	0.0767
Collagen 20µg/ml				
n	10	10	10	
% Max	44.80±9.12	69.20±5.65	60.20±7.11	0.0813
velocity	17.40±4.05	28.20±3.59	19.80±3.39	0.1129 NS

At steady state on drug, the data revealed a significant reduction (from baseline) of the maximum % aggregation (t-test for paired data). The decrease appears less marked in the young subjects as compared to the elderly:

Percentage inhibition of aggregation (%)	Healthy volunteers	Elderly subjects	Arteriosclerotics	p*
n	10	10	10	
Mean	- 25.8	- 41.3	- 39.5	0.1087 NS
SEM	3.9	5.2	6.9	
Minimum	- 44.0	- 58.3	- 69.3	
Maximum	- 7.7	- 16.3	- 6.0	

* ANOVA
NS : not significant

Although not statistically significant, a similar trend is observed for velocity of aggregation:

CHANGE IN VELOCITY AT STEADY STATE (ADP 5 µM)

Differences/ inclusion	Healthy volunteers	Elderly subjects	Arteriosclerotics	p* (ANOVA)
n	10	10	10	0.3563 NS
Mean	-11.0	-17.1	-15.8	
SEM	3.03	3.30	2.95	
Minimum	-29.3	-41.5	-36.7	
Maximum	-1.0	-6.3	-7.0	

The mean bleeding time between groups was not significantly different at pre-treatment. At steady state on drug, there was a significant lengthening of bleeding time in all groups and was similar across groups.

GROUP	INCLUSION	DAY 10	PROLONGATION FACTOR
Healthy volunteers	7:54±0:18* (n=10)	11:54±0:22 (n=10)	1:52
Elderly subjects	8:09±0:17 (n=10)	12:51±0:21 (n=10)	1:59
Arteriosclerotics	8:42±0:15 (n=10)	12:42±0:20 (n=10)	1:47

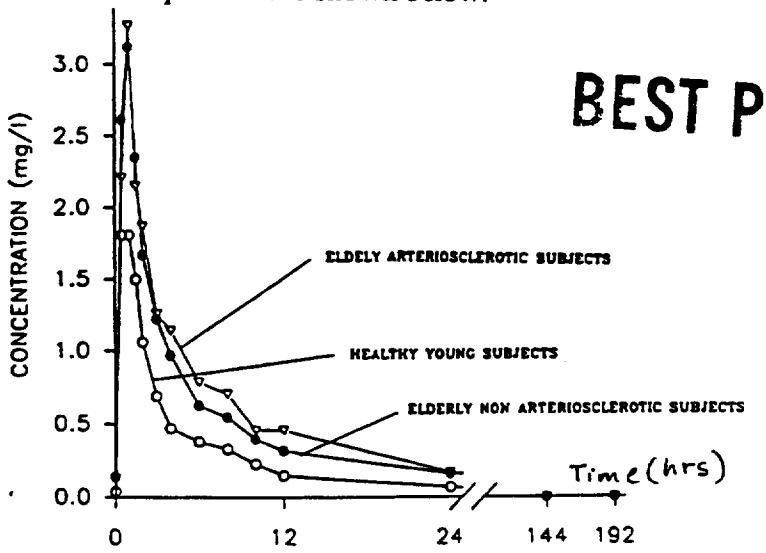
* mean ± SEM

Mean (stdev) PK parameters[a] of SR 26334 for day 10 are provided in the following table:

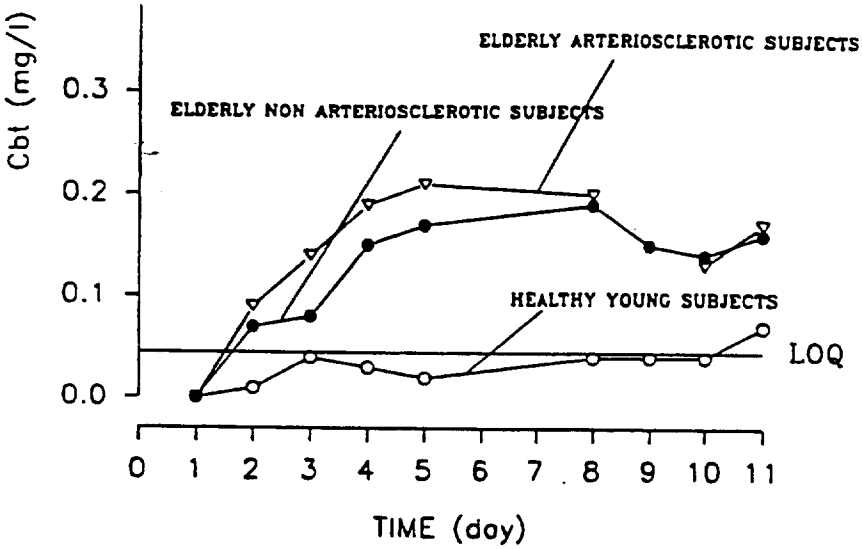
Parameter	Young	Elderly	Elderly arteriosclerotic
AUC_{0-24} (mg.hr/l)	8.33 (1.94)	14.45 (4.86)	16.97 (3.16)
C_{max} (mg/l)	2.65 (1.02)	3.39 (0.71)	3.47 (0.55)
Cmin (mg/l)	0.04 (0.05)	0.13 (0.09)	0.12 (0.08)
Tmax, hours	1 (0.5-1)	1 (0.5-1.5)	1 (0.5-1.5)

[a] Tmax is presented as mean (range)

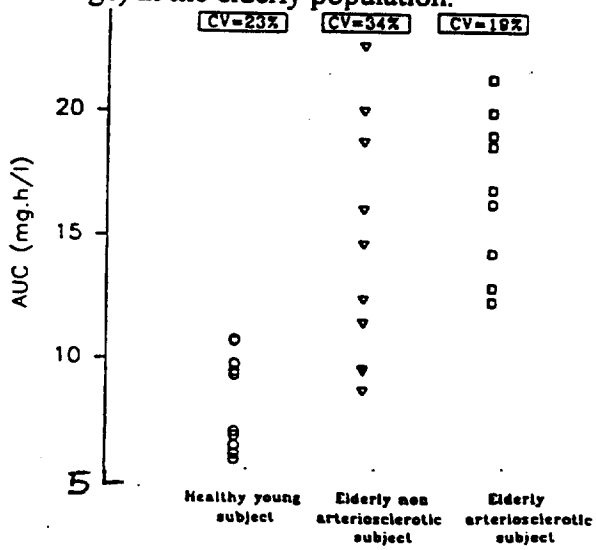
Mean plasma concentration profiles are shown below:

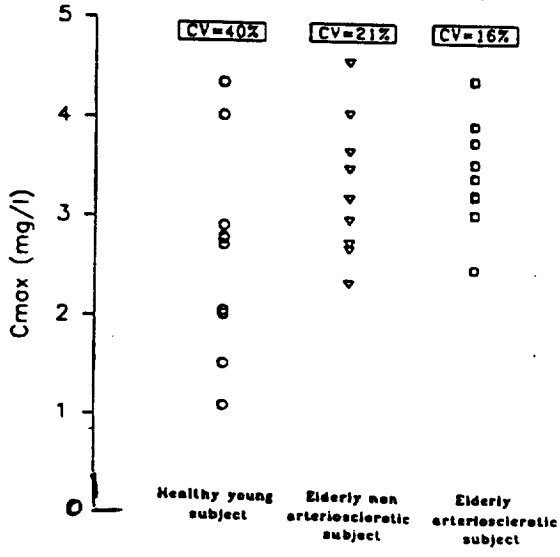


Based on concentration measurements before drug administration (Cmin), illustrated in the following figure, there appears to be a significant accumulation of drug in the elderly population, as compared to the young. This is an expected outcome of longer t1/2 in the elderly population.

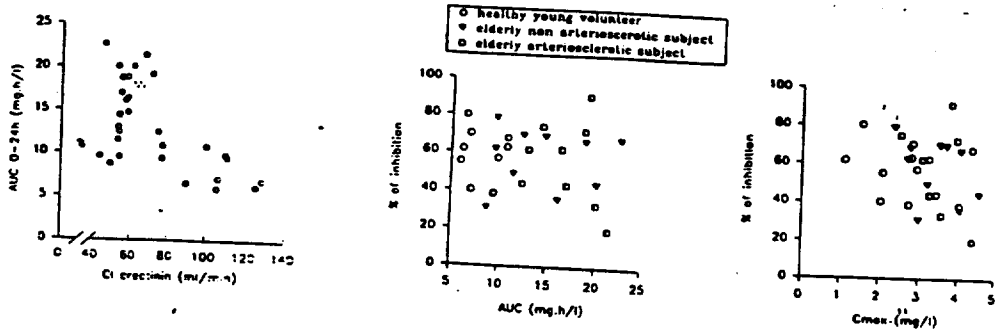


Cmax and AUC values were also higher (30% higher for Cmax and 75-100% higher for AUC, on average) in the elderly population.





Creatinine clearance, calculated as {(140-age) * wt/(72 * blood creatinine)}, correlated with age, however, no correlation was detected between the pharmacokinetic parameters and % inhibition of maximum amplitude of aggregation with ADP:



Conclusions:

Based on pre-treatment data, the elderly subjects appear to be more susceptible to ADP and collagen induced platelet aggregation. At steady state on clopidogrel, the decrease in maximal aggregation compared to pre-treatment was also higher in the elderly population. A similar trend (higher response in elderly) was also perceived for velocity of aggregation . This may lead one to conclude that the elderly population is more susceptible to the platelet aggregation and also more sensitive to the treatment. Dosage adjustment or caution should be considered. There appeared to be accumulation of SR 26334 in the elderly population but not in young subjects. An inverse correlation existed between creatinine clearance and AUCs however, in the concentration ranges available, AUCs and Cmax values did not correlate with the inhibition of aggregation.

Comments:

1. While the study ended in 6/1990, some lots used in the study had expiration dates of 5/1990.
2. Note that the alcohol consumption was more prevalent in the elderly groups (4/10 eldery, 9/10 elderly with arteriopathy) as compared to young (1/12) subjects. Five subjects (3 elderly and 2 with arteriopathy) were on co-medications (lorazepam, nitrazepam, flunitrazepam).
3. "velocity of aggregation" is not defined.
4. The sponsor determined terminal t1/2 for all subjects however this parameter was not reported. Examination of these numbers indicate a higher average terminal t1/2 in the elderly as compared to young subjects (15 and 9.7 hours resp.). Although variability was high (cv 50%), this seems to be the likely cause of higher accumulation in the elderly population. Elderly patients had an overall average t1/2 of 22 hours however, 106 hours t1/2 was calculated in one of the subjects. Excluding this value, average t1/2 was 11 hours in this group.

STUDY IRN2194: (PHARMACOKINETIC STUDY IN PATIENTS WITH CHRONIC RENAL FAILURE)

COMPARISON OF PHARMACOKINETICS, TOLERABILITY AND ANTIPLATELET ACTIVITY OF SR 25990 (CLOPIDOGREL) ADMINISTERED AS 75 MG TABLET ONCE DAILY FOR 8 DAYS IN CHRONIC RENALLY IMPAIRED PATIENTS

Reference: Volume 54
Investigator:
Study Location:

Objective: To assess in chronic renal failure patients,
1. Tolerability and anti-aggregation effect
2. Pharmacokinetic profile of metabolite at steady state

Study design:
This is a non-randomized study. Two groups, with 8 patients in each group (total 16), were included in the study. Group 1 was patients with Clcr of 5-15 ml/min (severe) and Group 2 was patients with Clcr of 30-60 ml/min (moderate), (Cockroft Gault). Patients went through 15 days of run-in phase, 8 days of treatment period, where a dose of 75mg of clopidogrel was administered for 8 days, once daily before breakfast. A follow-up continued for a further 14 days after cessation of study treatment.

Batch #s: Clopidogrel 75 mg bi-convex film coated tablet: 2Q2, batch J789F

Pharmacokinetics were evaluated for SR26334 from blood and urine. Blood samples were collected pre-dose on days 1, 3, 5 and 8 and at 0.5, 1, 1.5, 2, 4, 8, 12, 24, 48 and 96 hours after the last administration on day 8. Urine was collected before treatment and on day 8 (0-8 hours and 8-24 hours post-dose). Pharmacokinetic parameters determined were Cbt (pre-dose levels on dosing days), Cmin (day 8), Cmax (day 8), Tmax, AUC(0-24), t1/2, Ae(0-24) and Clr (renal clearance). Assessments for inhibition of platelet aggregation (5 μM ADP induced) and bleeding time were made at pre-dose and at 2 hours following blood sampling on days 1, 3, 5, 8, 9, 12, 15, 20. Clinical tolerability was assessed by occurrences of adverse events, vital signs, physical exam, ECG, bleeding time, hemogram and urinalysis. Only Cmax and Tmax were reported for SR25990C.

Changes in aggregation were reported as % inhibition, bleeding time and pharmacokinetic parameters were compared using t-test, Kruskal Wallis test (Tmax) and Spearman correlation coefficient (AUC, Cmax and Clr vs. Clcr).

Demographic characteristics for subjects are as follows:

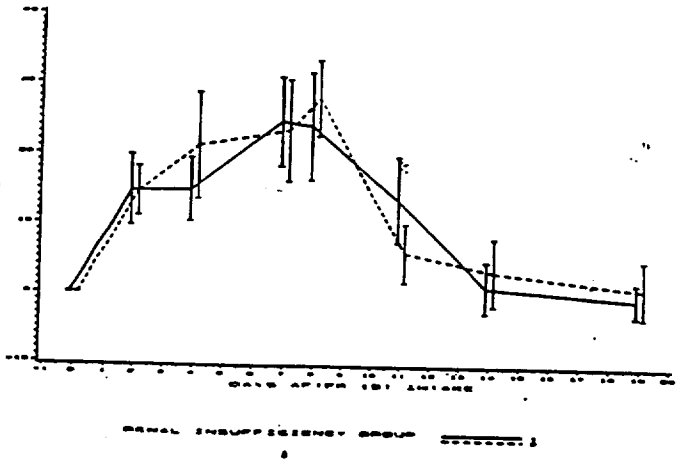
GROUP	CENTRE PATIENT	DATE OF BIRTH (dd/mm/yy)	SEX	AGE (years)	RACE	HEIGHT (cm)	WEIGHT (kg)	Clcr
1	10001	25/11/39	Female	53	Black	166.00	67.40	
	10002	04/06/23	Male	70	Caucasian	165.00	74.00	
	10005	11/03/21	Male	72	Caucasian	168.00	73.00	
	10011	13/05/35	Female	58	Caucasian	156.00	84.00	
	10012	06/06/54	Male	39	Black	179.00	87.00	5-15 ml/min
	10014	02/02/62	Female	32	Black	168.00	76.00	
	10015	28/08/35	Male	58	Caucasian	170.00	56.00	
	10016	16/12/37	Female	56	Caucasian	146.00	70.00	
2	10003	25/07/20	Male	73	Caucasian	163.00	73.00	
	10004	14/05/27	Female	66	Caucasian	163.00	52.00	
	10006	03/06/58	Male	35	Black	168.00	70.00	
	10007	12/12/47	Male	45	Caucasian	177.00	59.00	
	10008	18/07/47	Male	46	Caucasian	168.00	72.00	
	10009	03/06/31	Male	62	Caucasian	167.00	70.00	30-60 ml/min
	10010	01/01/32	Male	62	Caucasian	161.00	63.00	
	10013	14/09/45	Female	48	Caucasian	168.00	58.00	

Following are the ADP induced aggregation (pre-treatment) and its inhibition for the 2 chronic renally insufficient groups, mean (SEM) :

Group	baseline	Day 3	Day 5	Day 8	Day 9	Day 12	Day 15	Day 20
1[a]	77.3(2.7)	66.1(5.2)	66.4(5.2)	58.9(6.2)	59.4(7.1)	67.5(6.3)	76.1(2.7)	77.4(1.5)
2[a]	77.1(2.7)	65.6(3.1)	59.6(4.6)	58(5.7)	55.3(4.2)	72.1(2.6)	74(2.2)	76(2.2)
1[b]	-	14.8(5.1)	15(4.6)	24.7(6.3)	24(7.6)	13.5(6.2)	1(3.6)	-0.7(2.3)
2[b]	-	14.7(3.6)	21.3(7.6)	23.5(7.2)	28(5.4)	5.8(4.2)	3.1(4.8)	0.8(4.1)

a: maximum % induction of aggregation, b: inhibition of maximum % of induced aggregation

Although there were some differences between groups on specific days, the variability is high. Overall, the inhibition of platelet aggregation between the 2 groups is similar. Baseline values are approached by day 15 as illustrated below:

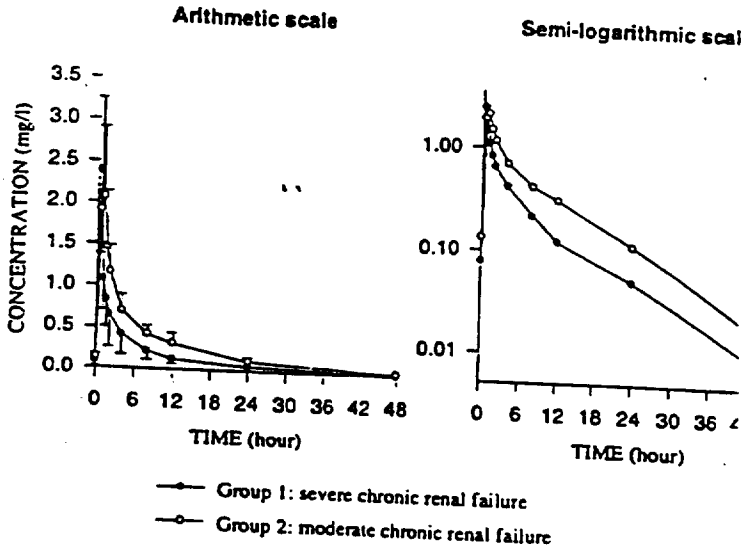


Mean plasma concentrations for the 2 groups before drug administration over the study period are reported in the table and figure below. Although the average values appear higher for the moderate patients, this was not statistically significant.

Mean and standard deviations (SD) of Cbt are presented below (n=8 per group):

	Cbt (mg/l)			
	Day 3	*Day 5*	*Day 8*	*Day 9*
Group 1	0.080 (0.110)	0.074 (0.058)	0.077 (0.056)	0.051 (0.032)
Group 2	0.111 (0.055)	0.119[a] (0.043)	0.131 (0.044)	0.115 (0.048)

a: n=7 (technical problem during the assay for Patient 10008)



Mean (SD) PK parameters of SR 26334 and mean Cmax and Tmax for SR25990 for day 8 are provided in the following tables:

SR 26334

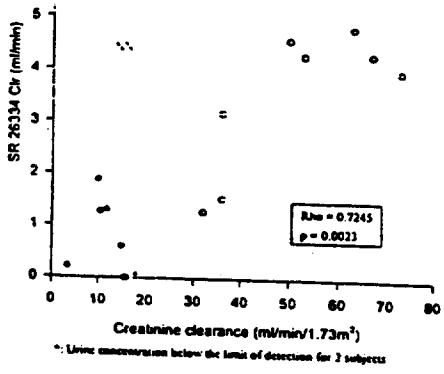
Patient (no.)	Cmax (mg/l)	Tmax (h)	Cmin (mg/l)	AUC 0-24h (mg.h/l)	T1/2 (h)	Ae 0-24h (mg)	CLR 0-24h (ml/min)
Group 1							
1							
2							
5							
11							
12							
14							
15							
16							
Mean	2.207	0.56	0.049	6.192	9.41	0.364	0.75
SD	1.038	0.18	0.033	2.368	5.65	0.419	0.74
Median	2.238	0.50	0.047	6.133	7.23	0.276	0.60
CV (%)	47	NR	67	38	60	115	99
Group 2							
3							
4							
6							
7							
8							
9							
10							
13							
Mean	2.591	0.94	0.108	11.027	8.25	2.288	3.49
SD	0.951	0.56	0.048	2.857	1.31	1.163	1.38
Median	2.677	0.75	0.106	11.180	7.82	2.237	4.13
CV (%)	37	NR	44	26	16	51	40

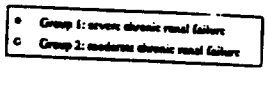
Group 1 : Severe chronic renal failure: 5 < creatinine clearance < 15 ml/min/1.73m²
Group 2 :Moderate chronic renal failure: 30 < creatinine clearance < 60 ml/min/1.73m²
: not determined (les than 3 points lined up on the regression curve)

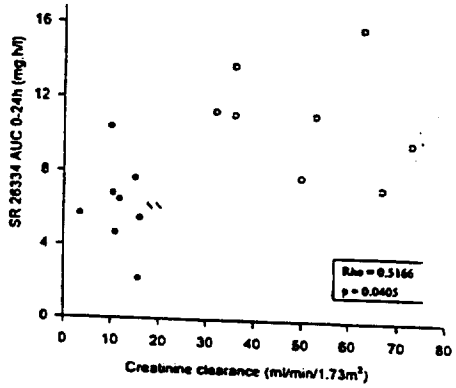
Patient (no.)	Age (yr)	Cmax (ng/ml)	Tmax (h)
Group 1			
1	54	9.640	0.52
2	70	2.670	0.50
5	73	4.150	0.50
11	38	3.840	0.50
12	34	1.010	0.50
14	32	3.790	0.50
15	58	7.910	0.50
16	57	0.000	-
Mean		4.126	0.50
SD		3.246	0.01
Median		3.815	0.50
CV (%)		79	NR
Group 2			
3	73	3.750	1.00
4	66	5.850	0.50
6	35	2.420	1.00
7	46	0.000	-
8	46	1.600	2.00
9	62	3.550	0.50
10	62	2.330	1.50
13	49	2.130	0.50
Mean		2.704	1.00
SD		1.723	0.58
Median		2.375	1.00
CV (%)		64	NR

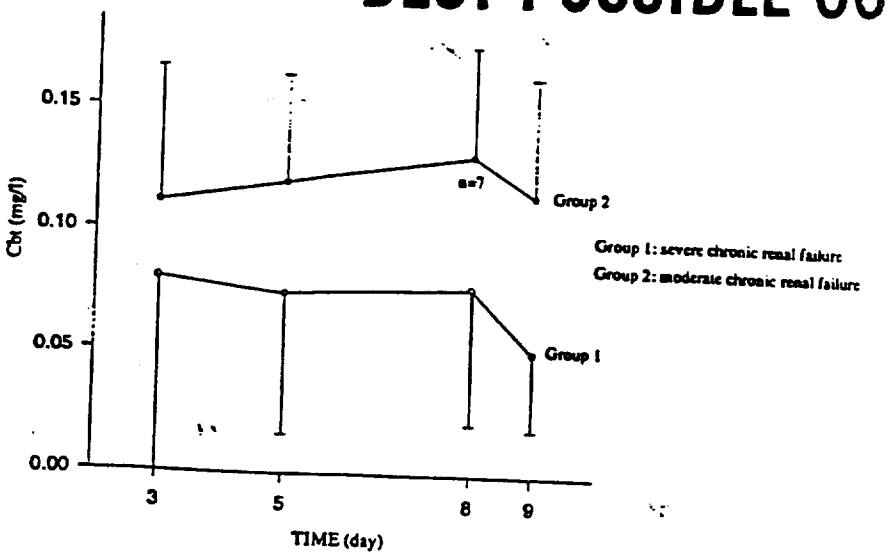
SR 25990

AUC values appear higher in moderate patients. Protein binding data is not available in the patients. Amount excreted in urine and renal clearance are lower for the severe patients. Renal clearance of the metabolite is proportional to creatinine clearance, and therefore renal function status of patients. Creatinine clearance did not correlate to Cmax values but, interestingly, unlike the relationship shown in the study with elderly subjects, there appears to be a positive correlation of AUC with creatinine clearance. This is contrary to what is expected.









Conclusions: As observed before, creatinine clearance correlated with the renal clearance of the drug. Contrary to the expectation however, an inverse relation was not observed for creatinine clearance and AUC. Cbt values were also higher in the milder group. A contributing factor may be high variability. There was no significant difference in the pharmacodynamic measurements for the 2 groups.

Comments:

1. It has been established that there is bleeding time prolongation in uremia. This is the purpose of the trial. Note however, that a control group is not included in the study.

2. Aspirin, anti-aggregating agents, NSAIDS, heparin, EPO and oral anticoagulants were prohibited during the 15 days preceding the screening and during the entire trial.

3. Patients in group 1: subject 10002 recorded a subconjunctival hemorrhage on day 2, subject 10005 had a vasovagal attack (sweating, stomach cramp, hypoglycemia) on day 3.

4. Cmax and Tmax values were reported for the parent drug. Although the overall average Cmax appeared higher for severe patients (4.13 vs 2.7 ng/ml), this seems to be due to subjects 1 and 15 who had Cmax of 9.64 and 8 ng/ml resp.

5. No control group. However, comparing the data on renal patients with the normals from other 2 studies I reviewed, here is what I see:

Bleeding time: vol 1.20/p249 and vol 1.54/p39: young normals and elderly normals at baseline: about 480 seconds; renal patients at baseline: about 180-280 seconds. Maximum change with drug for normal young and eldery +240 to 280 seconds; renal patients about +300 seconds.

Platelet aggregation: vol 1.20/p202, vol 1.54/p36 : 5 uM ADP induced platelet aggregation 77% for renal patiens at baseline and for young and elderly normals is about 50% and 75% resp. On drug, (vol 1.20/p214 and vol 1.54/p36) difference from inclusion at SS, about -30% and about -48% for young and elderly resp, and about -20% for both groups in renal impairment.

STUDY P1722: (DRUG INTERACTION STUDY WITH DIGOXIN)

EVALUATION OF THE INFLUENCE OF CLOPIDOGREL ON PLASMA CONCENTRATIONS OF DIGOXIN AFTER REPEATED ADMINISTRATION

Reference: Volume 65
Investigator:
Study Location:
Objective:
1. To assess the influence of clopidogrel on steady state digoxin plasma concentrations.
Study design:

This is an open label fixed sequence multiple dose design study in 12 healthy male volunteers of age 20-36 years. The participants received 0.25 mg digoxin once daily from day 1 up to and including day 20. From day 11 up to and including day 20, 75 mg clopidogrel once a day was coadministered. Both the treatments were administered under fasting conditions with 200 ml water after a 10 hour overnight fast. Plasma and urine samples for the assay of digoxin were collected on day 10 and day 20. ADP induced thrombocyte aggregation test was performed at screening and at days 18, 19 and 20 days two hours post dose administration.
Batch #s: Clopidogrel 75 mg tablet: batch # 1A1 RHG08
Lanoxin 0.25 mg tablet: batch# 90H17.

Blood samples were drawn for determination of plasma concentration of digoxin at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, after dosing. Urine samples were collected at 0 - 4, 4 - 8, 8 - 12, 12 - 24 hours after dosing. ADP-induced platelet aggregation was measured at 0, 2, 5, 24, 48 and 72 hours after dosing. Bleeding time was determined at 0 and 5 hours after dosing. Pharmacokinetic parameters were determined by non-compartmental methods. These parameters with and without clopidogrel were compared by the sponsor using two way ANOVA model determining the effect of day and subject as a source of variation. A 90 % CI for the ratio of the treatment mean of AUC_{0-24} on day 20 over the treatment mean of AUC_{0-24} on day 10.

Conclusions:

Coadministration of 75 mg clopidogrel with 0.25 mg digoxin at steady-state did not have any effect on the pharmacokinetics of digoxin.

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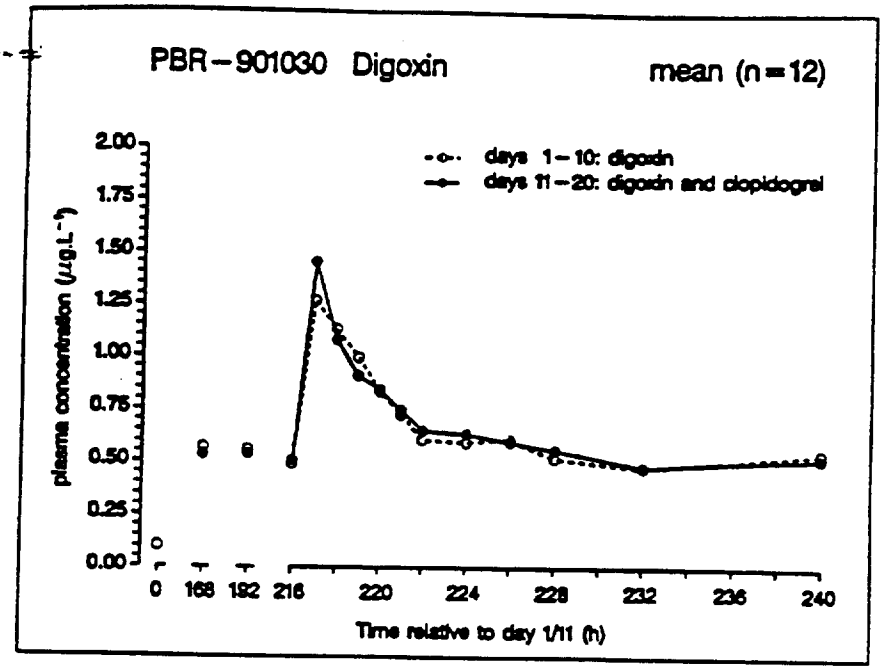

Figure 1. Mean digoxin plasma concentration-time curves during multiple oral administration of 0.25 mg digoxin daily from day 1 through day 20
Days 1-10 = without clopidogrel
Days 11-20 = during 75 mg clopidogrel daily from day 10 through day 20
Mean data, n = 12

Table 1. Mean pharmacokinetic parameters and summary statistics of digoxin as determined during multiple oral administration of 0.25 mg digoxin daily from day 1 through day 20
Days 1-10 = without clopidogrel
Days 11-20 = during 75 mg clopidogrel daily from day 10 through day 20
Mean data, n = 12

Parameter			geometric mean	Range	90%-confidence interval and point estimate of ratio (%)*	
c_{max}	($\mu g.L^{-1}$)	Day 10	1.42	1.14 - 1.92		
		Day 20	1.57	1.28 - 1.95	99.4 - 124.0	111.0
c_{min}	($\mu g.L^{-1}$)	Day 10	0.44	0.35 - 0.54		
		Day 20	0.44	0.32 - 0.58	91.9 - 107.8	99.6
AUC_{0-24}	($\mu g.L^{-1}.h$)	Day 10	15.17	12.61 - 18.54		
		Day 20	15.41	11.36 - 19.36	96.2 - 107.3	101.6
A^s_{24}	(mg)	Day 10	0.108	0.074 - 0.160		
		Day 20	0.107	0.077 - 0.174	94.0 - 103.5	98.7
t_{max}	(h)	Day 10	1.0**	0.5 - 2.0		
		Day 20	1.0**	0.5 - 2.0		

* 90%-confidence interval for ratio of means of test (day 20) and reference (day 10) (from ANOVA on log-transformed data of c_{max}, c_{min}, AUC_{0-24} and A^s_{24})

** median

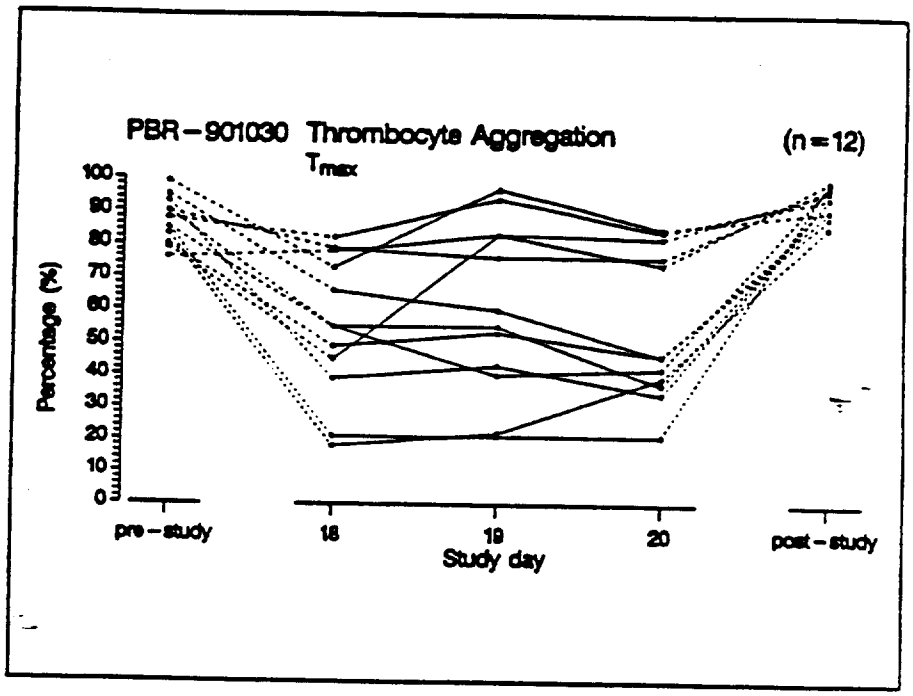

Figure 2. Individual ADP induced thrombocyte aggregation (T_{max}) versus time profiles during multiple oral administration of 0.25 mg of digoxin daily from day 1 through day 20

Days 1-10 = without clopidogrel

Days 11-20 = during 75 mg clopidogrel daily from day 10 through day 20

STUDY INT 1980: (DRUG INTERACTION STUDY WITH THEOPHYLLINE)

STUDY OF THE EFFECT OF SR 25990C AFTER A SINGLE INTAKE AND AT STEADY STATE ON THEOPHYLLINE AT THE STEADY STATE IN YOUNG HEALTHY VOLUNTEERS.

Reference: Volumes 66-67.
Investigators:

Study Location:

Objective:

1. To evaluate the effect of SR 25990C after a single intake and at steady state on theophylline blood levels in young healthy male volunteers.

Study design:

This is an open label fixed sequence multiple dose design study in 12 healthy male volunteers of age 18-35 years. The participants received 300 mg capsule of theophylline orally in the morning before breakfast and in the evening before dinner for thirteen days and on the morning of day 14. Moreover, each participants received a 75 mg clopidogrel tablet in the morning before breakfast for ten days (from day 5 to day 14). ADP induced thrombocyte aggregation test was performed at screening and at days 5, 7, 9, 11 and 14 two hours post dose administration.

Batch #s: Clopidogrel 75 mg tablet: batch # J789F
Armophylline 300 mg sustained release capsule batch # DJ 1341.

Blood samples were drawn for determination of plasma concentration of theophylline before the morning input of days 1, 6, 7, 8, 9 and 12 and on the following times on days 4, 5 and 14: 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 hours post dose administration. Pharmacokinetic parameters were determined by non-compartmental methods. Analysis of variance on repeated measurements was carried out on ADP induced aggregation data as was a Student's t test on the percentage of inhibition of aggregation in relation to time 0 at day 1. The influence of clopidogrel on the pharmacokinetics of theophylline was studied by comparing CMAX and AUC_{0-12} on day 4 (theophylline alone) and those on day 5 and 14 (theophylline +clopidogrel) using a Student's t test. Moreover, 90 % confidence intervals were calculated on the ratios of the geometric means of CMAX, CMIN and AUC_{0-12} .

Plot of mean concentration profiles for theophylline without and with clopidogrel (single and multiple dose) are given in Figure 1. Table 1 gives a summary of the main pharmacokinetic parameters for theophylline along with the corresponding 90 % confidence intervals.

TABLE 1

	CMAX µg/ml.	CMIN µg/ml.	AUC_{0-12} µg.hr/ml.
Theophylline	10.7	6.1	102.2
Theophylline +single dose clopidogrel	10.5 (.86-1.13)[a]	6.2 (0.9-1.15)	102 (0.89-1.11)
Theophylline + multiple dose clopidogrel	10.6 (0.86-1.14)	6 (0.87-1.12)	102.6 (0.9-1.12)

a=90 % confidence intervals of the ratios of the geometric mean of theophylline/clopidogrel.

It is to be noted that one of the subjects had to be withdrawn from the study due to bleeding times exceeding 20 minutes. This was linked to the pharmacodynamic activity of clopidogrel.

Conclusions:

Coadministration of 75 mg clopidogrel either in single or multiple dose did not have any effects on the steady state pharmacokinetics of theophylline at a dose of 300 mg twice daily.

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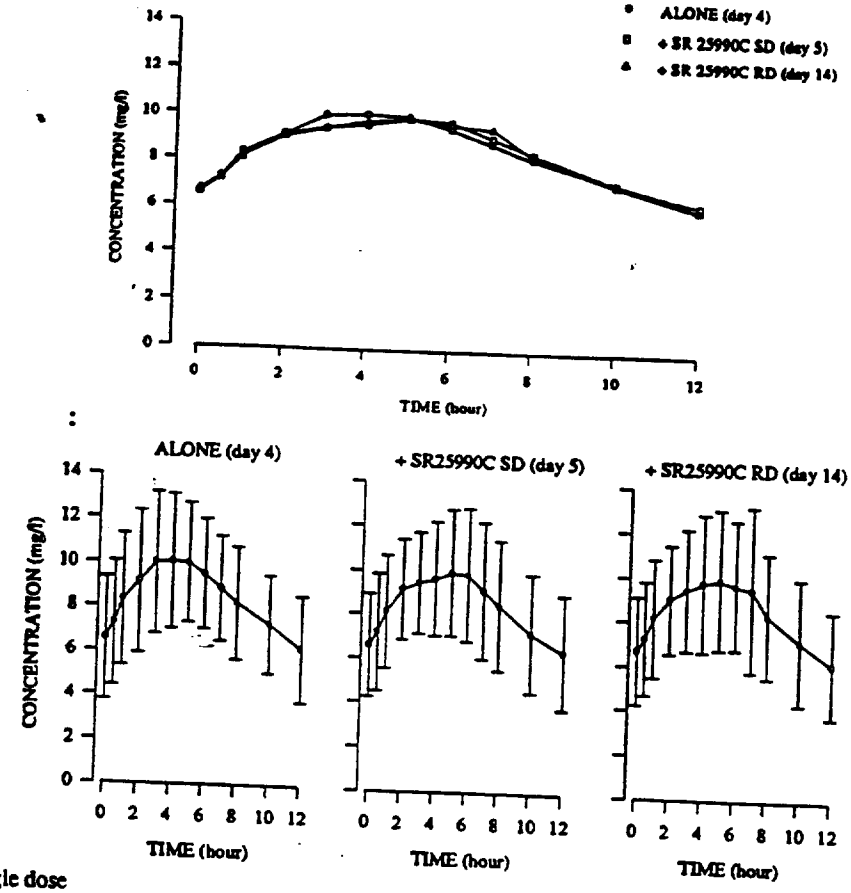


SD: single dose
RD: repeated dose

Figure 1: Superimposed means of plasma concentrations of theophylline (above) and with standard deviations (below) as a function of time after repeated administration of theophylline alone (D04), with a single 75-mg dose of SR 25990C (D05), and with 75 mg/day of SR 25990C for 10 days (D14)

STUDY P1978: (DRUG INTERACTION STUDY WITH ANTACID)

STUDY OF THE INFLUENCE OF ANTACID INTAKE ON THE BIOAVAILABILITY OF A SINGLE 75 MG DOSE OF SR 25990C (CLOPIDOGREL) IN HEALTHY VOLUNTEERS.

Reference: Volume 62-64.
Investigator:
Study Location:

Objective:

1. To assess whether antacid (Maalox) one hour before administration of SR 25990C, modifies the bioavailability of SR 25990C.

Study design:

This is an open label randomized crossover study in 12 healthy male volunteers of age 18-30 years. Each participant was randomized to the following two treatments:
Treatment 1: After an overnight fast each subject received 75 mg clopidogrel with 150 ml of water.
Treatment 2: After an overnight fast each subject received 2 400 mg tablets of Maalox to be chewed then 1 hour before a 75 mg tablet of clopidogrel with 150 ml of water.
Batch #s: Clopidogrel 75 mg tablet: batch # J789F.
Maalox 400 mg tablet: batch# 0663.

Blood samples were drawn for determination of plasma concentration of SR25990 and SR 26334 on days 1 at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours post dose administration, day 2 at 16, 24 and 36 hours and day 3 48 hours post clopidogrel administration. Pharmacokinetic parameters were determined using non-compartmental methods. The influence of Maalox on the pharmacokinetics of clopidogrel and its metabolite SR26334 was studied using the Wilcoxon non parametric test. Moreover, 90 % confidence intervals were calculated on the ratios of the geometric means of the pharmacokinetic parameters of interest.

Plot of mean concentration profiles for SR26334 after clopidogrel administration with and without the coadministration of Maalox is shown in Figure 1 while the corresponding pk parameters are summarized in Table 1.

Table 1

	Clopidogrel	Clopidogrel + Maalox
CMAX (mg/l)	2.62	2.47 (0.74-1.16)
TMAX (hours)	.71	.0.67
AUC_{0-12} (mg*hr/l)	5.65	5.18 (0.86-0.96)
AUC_{obs} (mg*hr/l)	6.25	5.84 (0.89-0.97)

Conclusions:

It can be seen from the above results that coadministration of Maalox 800 mg with 75 mg clopidogrel did not have any effects on the plasma profile of metabolite SR 26334. As for the parent compound, most of the plasma samples were below the detection limit and thus calculation of the pharmacokinetic parameters of interest was not possible.

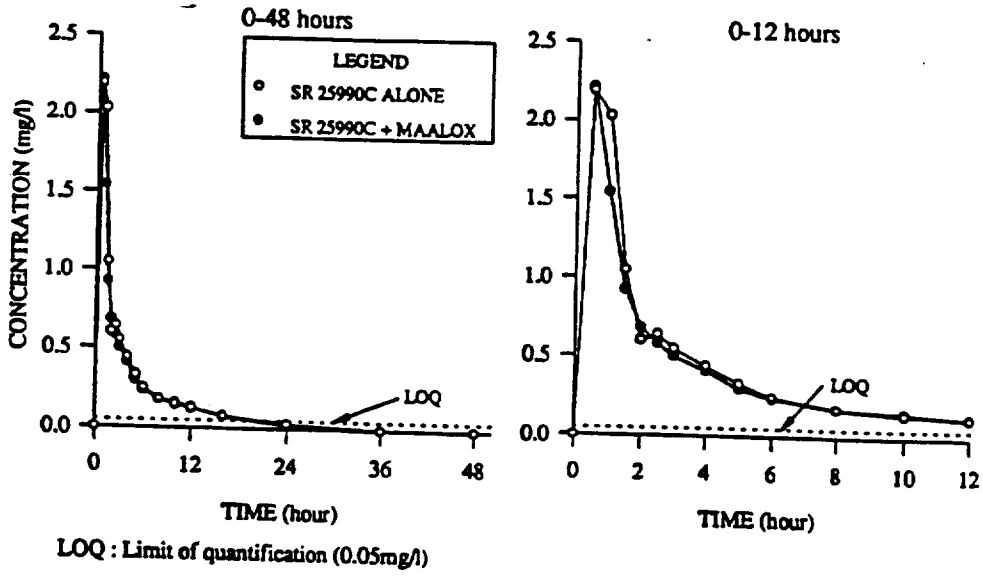


Figure 1 - Mean plasma concentrations of SR 26334 as a function of time after administration of 75 mg of SR 25990C alone and with 800 mg of Maalox® *(n=12)*
(left: 0-48h interval; right: 0-12h interval)

STUDY P1716: (DRUG INTERACTION STUDY WITH CIMETIDINE)

INTERACTION STUDY OF CIMETIDINE ON THE METABOLISM AND PHARMACODYNAMIC ACTIVITY OF SR25990C AFTER REPEATED ORAL ADMINISTRATION IN HEALTHY SUBJECTS.

Reference: Volume 68-70
Investigator:

Study Location:

Objective:

1. To determine whether cimetidine administration had an effect on platelet aggregation in subjects receiving therapeutic doses of SR 25990C.

2- To evaluate the effect of cimetidine on SR 26334 pharmacokinetic parameters in plasma. As cimetidine may inhibit SR 25990C metabolization, the influence of cimetidine on SR 25990 plasma levels was also investigated.

Study design:

This is an open label fixed sequence multiple dose design study in 18 healthy male volunteers of age 18-35 years. The participants received 75 mg clopidogrel once daily from day 1 up to and including day 28. From day 15 up to and including day 28, 400 mg cimetidine morning and evening was coadministered. Clopidogrel was administered under fasting conditions with 200 ml water after a 10 hour overnight fast. Cimetidine was administered at breakfast and during the evening meal. Plasma samples for the assay of SR 25990 were collected on day 14 and day 28. ADP induced thrombocyte aggregation test was performed before clopidogrel intake on days D1, D9, D10, D11, D14, D15, D17, D21, D23, D24, D25 and D28 and two hours after clopidogrel intake on D1, D14, D15 and D28 and also on Days 29 and 35. Aggregation test using collagen was performed on Day 1, D14 and D28 before drug intake then on days 29 and 35. Bleeding time using the modified Ivy-Nelson technique and APTT was performed two hours after clopidogrel intake on day 1, 14,28 and 35.

Batch #s: Clopidogrel 75 mg tablet: batch # 1720G expiration date June 24 1993.
Cimetidine 400 mg tablet: batch# BE 962 expiration date 30-11-1995.

Blood samples were drawn for determination of plasma concentration of SR25990 and SR 26334 on days 1, 9, 10, 11, 14, 15, 17, 21, 23, 24, 25, 28 and 29. Full plasma profiles on days 14 and 28 with samples drawn at the following times: 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 hours. On days 1 and 15 samples were collected 2 hours post clopidogrel administration. Pharmacokinetic parameters were determined using non-compartmental methods. The influence of cimetidine on the pharmacokinetics of clopidogrel and its metabolite SR26334 was studied using a Student's t test. Moreover, 90 % confidence intervals were calculated on the ratios of the geometric means of the pharmacokinetic parameters of interest.

Plasma samples:

Plot of mean concentration profiles for SR26334 after clopidogrel administration with and without the administration of cimetidine is shown in Figure 1 while the corresponding pk parameters are summarized in Table 1.

Table 1

	Clopidogrel	Clopidogrel +Cimetidine
CMAX (mg/l)	2.37	2.41 (0.81-1.25)
CMIN (mg/l)	1.06	.87
TMAX (hours)	.04	.06
AUC_{0-12} (mg*hr/l)	5.78	6.3 (1.01-1.19)
AUC_{obs} (mg*hr/l)	6.93	7.76 (1.01-1.26)

It can be seen from the above results that coadministration of cimetidine 400 mg bid with 75 mg clopidogrel did not have any effects on the plasma profile of metabolite SR 26334. As for the parent compound, most of the plasma samples were below the detection limit and thus calculation of the pharmacokinetic parameters of interest was not possible.
Table 2 shows the comparative analysis of the maximum thrombocyte aggregation % both for ADP and collagen induced while Table 3 shows the differences in mean maximum aggregation % between D35 and D1 as induced by ADP and collagen.
The above results show that there was a statistically significant increase in ADP induced maximum aggregation when cimetidine was added to clopidogrel. This increase ranged from 3.5 to 9.3 % in absolute value. However, the collagen induced values were not affected.
Table 4 shows that cimetidine did not have any effect on the prolongation of bleeding time observed with SR 25990C.

Conclusions:

Coadministration of 400 mg cimetidine bid for 14 days with 75 mg clopidogrel did not have any effects on the pharmacokinetics of SR 26334. Even though there was an increase ranging from 3.5 to 9.3 % in the ADP induced maximum % with the coadministration of cimetidine, this increase was not considered clinically significant because it was less than 10 %.

Moreover, there was no change in any of the other pharmacodynamic parameters with the coadministration of cimetidine. Therefore, no dosage adjustments are necessary for clopidogrel with the coadministration of twice a day 400 mg of cimetidine.

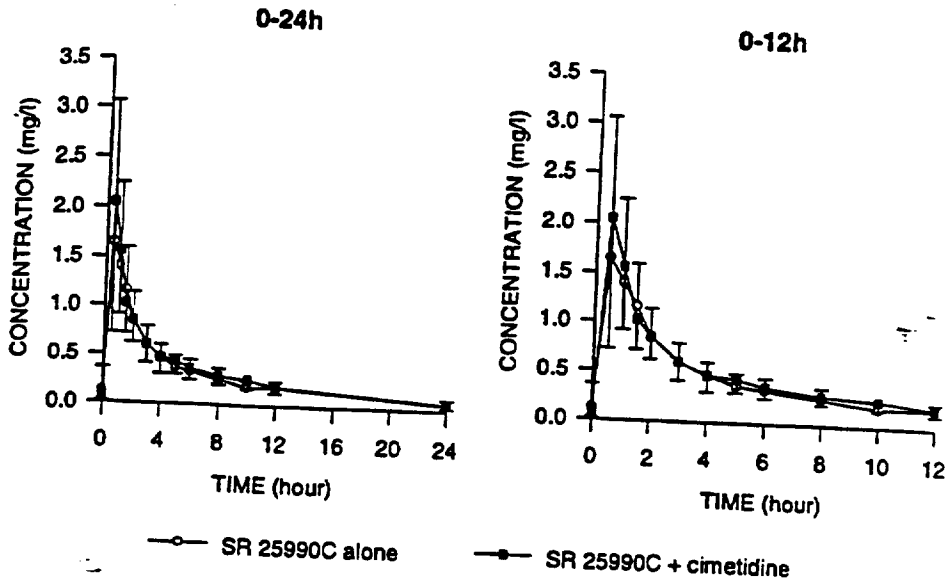


Figure 1: Mean values and standard deviations of plasma concentrations of SR 26334 obtained after administration for 14 days of 75 mg of SR 25990C o.d. alone (D14) and after co-administration for 14 days of 75 mg of SR 25990C o.d. and 400 mg of cimetidine b.i.d. (D28)
Left: 0-24h and right: 0-12h

TABLE (2) Comparative analysis of maximum aggregation percentage

ADP	n	Mean	SEM	Student t test	p	95% confidence interval
T0 value Mean with SR 25990C	18	49.7	2.79	-	-	-
T0 value Mean with SR 25990C + cimetidine	18	56.1	3.57	-	-	-
Difference at T0 D28/D14	18	6.4	1.46	4.40	<0.001 ***	[3.5 ; 9.3]
Difference on D28 (T + 2h) / D14 (T + 2h)	18	2.8	2.91	0.98	0.343	[-2.9 ; 8.5]
COLLAGEN						
T0 value Mean with SR 25990C	18	83.5	1.22	-	-	-
T0 value Mean with SR 25990C + cimetidine	18	81.8	1.72	-	-	-
Difference at T0 D28/D14	18	- 1.7	1.70	1.00	0.329	[- 5.0 ; 1.6]
Difference on D28 (T + 2h) / D14 (T + 2h)	18	- 5.1	3.71	1.38	0.187	[-12.4 ; 2.2]

Table 3 - Differences in mean maximum aggregation percentage between D35 and D01 T0 as induced by ADP and by collagen - Primary statistics

	n	Mean	SEM	Student t test	p	95% confidence interval
Percentage of aggregation induced by ADP D35 /D1 T0	18	-16.3	3.87	4.18	<0.001 ***	[-23.9 ; -8.7]
Percentage of aggregation induced by collagen D35/D1 T0	18	-13.5	4.79	2.82	0.012 *	[-22.8 ; -4.1]

TABLE (4) **Prolongation factor of bleeding time - Comparative analysis**

	Difference between means	n	SEM	95% confidence interval	Student t test	p	Ratio of geometrical means	95% confidence interval
D28 / D14	-0.087	18	0.107	[-0.313; 0.133]	0.817	0.425	0.917	[0.731 ; 1.143]
D35 / D-14	-0.086	18	0.111	[-0.320; 0.146]	0.775	0.449	0.918	[0.726 ; 1.157]

STUDY P1435: (GENDER AND DRUG INTERACTION STUDY WITH ESTROGEN)

COMPARATIVE STUDY OF THE ANTIPLATELET EFFECT OF REPEATED ADMINISTRATIONS OF SR25990C (75 MG/DAY) DURING 14 DAYS, IN POST-MENOPAUSAL WOMEN WITHOUT ESTROGEN REPLACEMENT THERAPY VERSUS MEN OF THE SAME AGE GROUP, AND IN POST MENOPAUSAL WOMEN RECEIVING ESTROGEN REPLACEMENT THERAPY.

Reference: Volume 48-50
Investigator:

Study Location:

Objective:
1. To compare postmenopausal women with no estrogen replacement therapy and men of the same age as regards to the:
-(a) effects of clopidogrel on platelet aggregation induced by ADP and collagen and on bleeding time;
-(b) SR26334 levels
-(c) the clinical and laboratory safety of SR25990C.
2-To assess the effects of clopidogrel therapy as regards to the same parameters in the same population of postmenopausal women while receiving estrogen replacement therapy.

Study design:
This is an open label non randomized parallel group trial with a washout period of one month between the two treatment periods. A screening period of 8 days was completed before enrollment into the study. Male subjects received the study drug (75 mg/day) for the first 14 day treatment period, female subjects received 75 mg/day clopidogrel for 2 14 day treatment periods separated by at least one month washout period. The treatment Period 1 population consisted of postmenopausal women who were not receiving estrogen replacement therapy and men of the same age group (between the ages of 55 and 75 years). The treatment Period 2 population consisted of the same group of postmenopausal women (from Period 1) who were given estrogen replacement therapy. An amendment to the protocol directed the conduct of an additional treatment period with three female subjects who had participated in the first two treatment periods. These women did not receive estrogen therapy in Period 3.
During treatment Period 1, all subjects received study drug (75 mg/day clopidogrel) every morning for 14 days. During treatment Period 2, the female subjects received estrogen replacement therapy (17-beta-estradiol valerate [Progynova] 2 mg/day) every morning for 29 days followed by 10 days of treatment with progesterone (Duphaston 10) in order to create an artificial menstrual cycle. They also took the study drug (75 mg/day clopidogrel) every morning for 14 days from day 16 until day 29. During treatment Period 3, the three female subjects received 75 mg/day of clopidogrel every morning for 14 days with a seven day follow up period.
The schedule of blood samples to determine platelet aggregation and plasma levels of SR26334 for the three treatment periods is summarized in Table 1. Bleeding time assessments were

measured at screening and on days 14 and 21 of treatment Periods 1 and 3 and at screening and on days 29 and 36 of treatment Period 2.

Batch #s: Clopidogrel 25 mg tablet: batch # RGT01 expiration date August 1 1990.
: batch# RF018 expiration date October 21 1989.
Clopidogrel 50 mg tablet: batch # RGN23 expiration date November 23, 1990.
Batch # RF012 expiration date October 21 1989.
17 beta-estradiol valerate (Progynova) 2 mg tablets
Progesterone (Duphaston 10) 10 mg tablets.

Pharmacokinetic parameters were determined using non-compartmental methods. The influence of estrogens on the pharmacokinetics of SR26334 as well as the effect of gender was studied using a Student's t test. Similar testing procedures were used on platelet aggregation and bleeding times.

Table 2 gives the summary of the steady state values for maximum intensity of platelet aggregation and % inhibition during treatment Period I. It can be seen from the above results that the % inhibition from baseline was greater in males than females (50 % vs 28 % at 5μM ADP). It was observed that in four females there was unusually lower levels of inhibition which might partially explain the differences between males and females. Table 3 gives a comparison of bleeding times during treatment Period I. The results show that unlike inhibition of platelet aggregation, the gender differences that were seen on day 1 disappeared on days 15 and 21. Table 4 gives the steady state values for the maximum intensity of platelet aggregation change from baseline and % inhibition in treatment Period 2 and shows that clopidogrel seems to be less active in women who were receiving estrogen replacement therapy compared to those not on therapy. Table 5 shows the comparison between treatment Period 1 and 3 for the three women that were retested. The results generally show a higher inhibition in Period 3 compared to Period 1. Plot of mean concentration profiles for SR26334 after clopidogrel in men and in women receiving and not receiving estrogen therapy are shown in Figures 1 to 3.

From the above results, it can be concluded that neither estrogen replacement therapy nor gender had any effects on the pharmacokinetics of SR26334.

Comments:

In view of the fact that this study seems to indicate that clopidogrel seems to be less

effective in women taking estrogen replacement therapy, the medical officer should confirm whether the same finding is seen in the clinical trial.

Table [illegible]1 - Schedule of Blood Samples

Period 1	Period 2	Period 3	Time
Day			
1	16	1	0 hours (before study drug intake, while fasting)
			+2 hours (before eating)
			+5 hours (before eating)
2	17	2	0 hours (before study drug intake)
4	19	4	0 hours (before study drug intake)
7	22	7	0 hours (before study drug intake)
11	24	11	0 hours (before study drug intake)
14	29	14	0 hours (before study drug intake, while fasting)
			+2 hours (before eating)
			+5 hours (before eating)
15	30	15	while fasting
21	36	21	while fasting

TABLE 2:- Summary of Steady-State Values for Maximum Intensity of Platelet Aggregation, Change From Baseline, and Percent Inhibition During Treatment Period 1 (5 µM ADP), Mean (SEM)

Parameter	Females	SEM	Males	SEM	p-Value[a]
Mean maximum intensity	51	3.8	39	3.6	not tested
Mean change from baseline	-21	4.5	-40	4.1	0.0050
Mean percent inhibition	28	5.9	50	4.6	not tested

a: Student's t-test

TABLE 3:- Comparison of Mean Bleeding Times During Treatment Period 1 (min:sec)

		Day 1 (Screening)	Day 15	Day 21
Women	Mean	6:00	11:21	6:09
	SEM	0:24	1:17	0:51
Men	Mean	4:48	11:51	5:38
	SEM	0:16	1:10	0:35

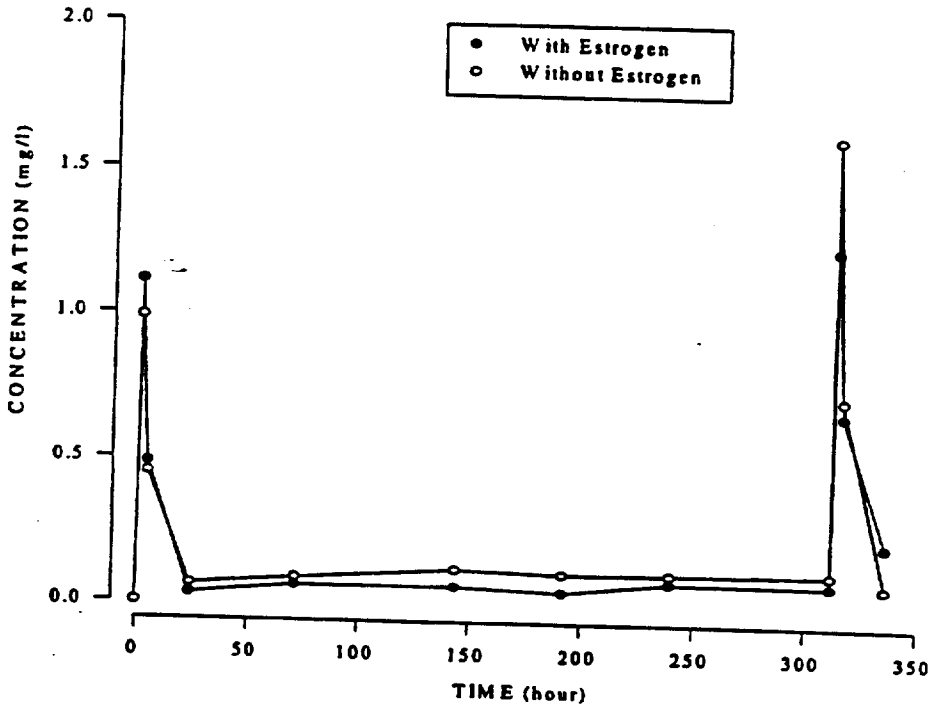
TABLE 4:- Steady-State Values for Maximum Intensity of Platelet Aggregation, Change From Baseline, and Percent Inhibition During Treatment Period 2 (5 µM ADP)

Parameter	Mean Value	SEM	p-Value[a]
Mean maximum intensity	55	3.8	
Mean change from baseline	-11	4.7	0.0626
Mean percent inhibition from baseline	16	7.3	
Change from P1 (Day 1, Time = 0 hours)	17	4	0.1719
% Inhibition from P1 (Day 1, Time = 0 hours)	23	6	

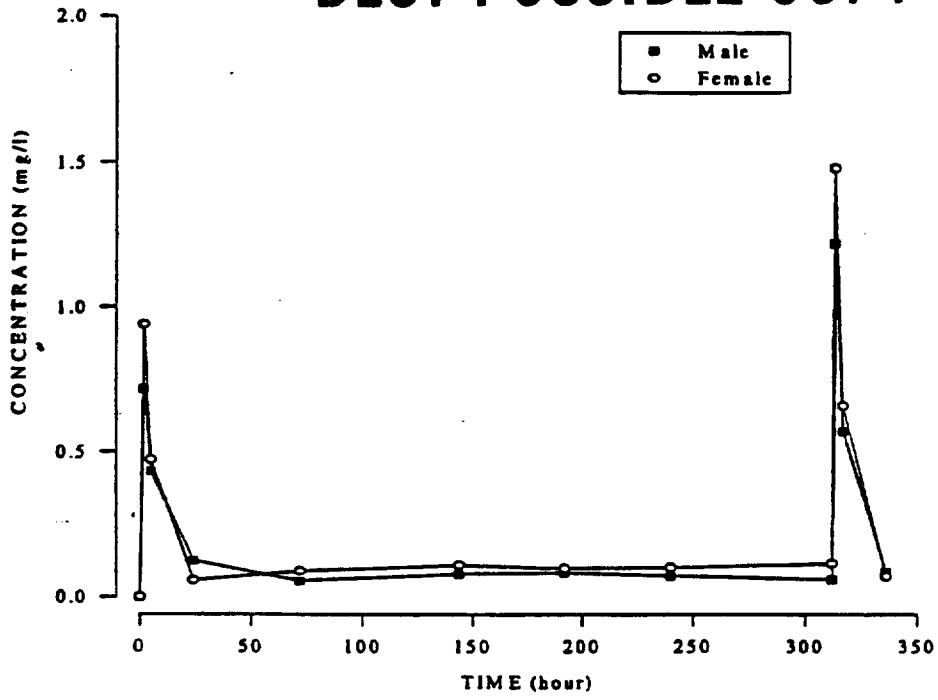
a: p-value from paired Student's t-test.

TABLE 5:- Maximum Intensity and Percent Inhibition of 5μM ADP-Induced Platelet Aggregation at Baseline and Steady State for Three Subjects for Treatment Periods 1 and 3

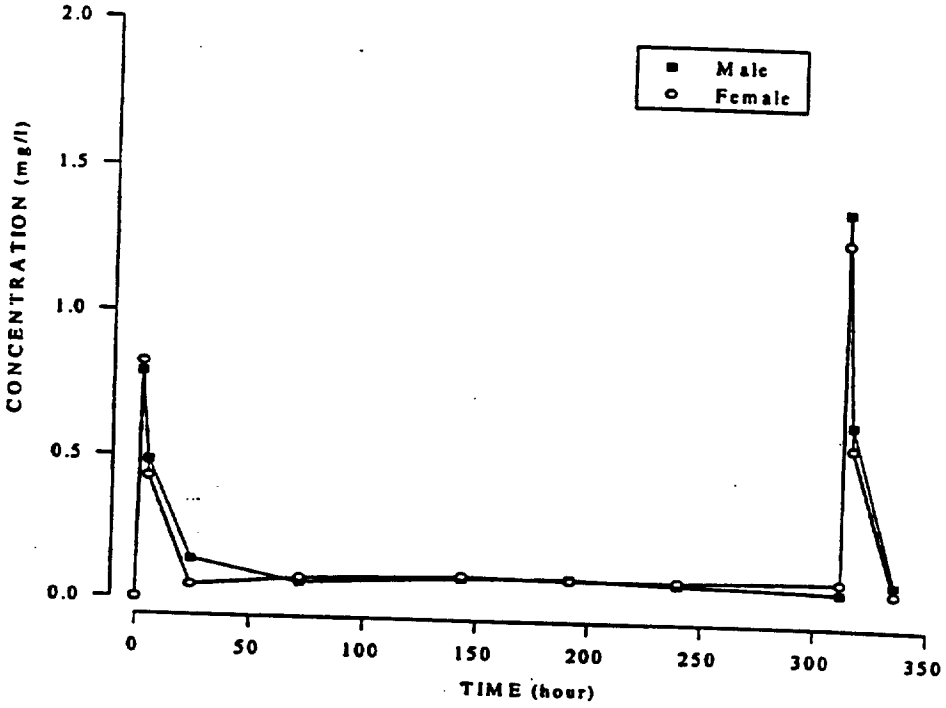
Subject No.	Period	Baseline Value	Mean Value (Steady State)	Difference	Percent Inhibition From Baseline
5	1				
	3				
9	1				
	3				
10	1				
	3				



Primary Figure 1 - Mean of SR26334 Plasma Levels Obtained After Oral Administration of 75 mg of SR25990C to Nine Postmenopausal Women Without and With Estrogen-Replacement Therapy



Primary Figure 2 - Mean of SR26334 Plasma Levels Obtained After Oral Administration of 75 mg of SR25990C to Men and Postmenopausal Women



Primary Figure 3 - Mean of SR26334 Plasma Levels Adjusted for 70 kg Body Weight, Obtained After Oral Administration of 75 mg of SR25990C to Men and Postmenopausal Women

STUDY ENZ2556: (DRUG INTERACTION STUDY WITH PHENOBARBITAL)

EFFECT OF PHENOBARBITAL (INDUCER OF METABOLISM) ON THE PHARMACOKINETIC AND THE PHARMACOLOGICAL ACTIVITY OF SR25990C AFTER REPEATED ORAL ADMINISTRATION IN HEALTHY VOLUNTEERS.

Reference: Volume 71-75
Investigator:

Study Location:

Objective:

1. To assess the influence of phenobarbital on SR26334 pharmacokinetic parameters and on platelet aggregation in subjects receiving repeated administration of 75 mg clopidogrel (SR25990).

Study design:

This is an open label randomized multiple dose design study in 12 healthy male volunteers of age 18-35 years. The participants received 75 mg clopidogrel once daily from day 1 up to and including day 7 during treatment Period A. During treatment Period 2 , subjects took one 100 mg phenobarbital tablet from days 1 to days 20. Additionally, after an overnight fast, subjects took 75 mg tablet of clopidogrel on days 15 to 21. A 21 day washout period was allowed between the two treatment. Plasma samples were collected on day 1 of clopidogrel administration and on the last day of clopidogrel administration for each treatment period according to the following time schedule: 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours after administration.. ADP induced thrombocyte aggregation was assessed by measuring the maximum intensity of platelet aggregation (expressed as a %) and the velocity (expressed as %/min). Values were recorded at baseline during the clopidogrel period only on days 1, day 7 at 8:00 , 9:30 and 11:00 am and on day 21 and during the clopidogrel + phenobarbital on days 1, 15 and 21 at 8:00, 9:30 and 11:00 am and at the end of the study.

Batch #s: Clopidogrel 75 mg tablet: batch # 102D5 expiration date May 31, 1996.

Phenobarbital 100mg tablet (Phenaemal^{R}): batch# 940023335 expiration date December 31, 1997.

Pharmacokinetic parameters were determined using non-compartmental methods. All statistical tests were performed at the 0.05 significance level using a two tailed test. 90 % confidence intervals of the ratios of the results on day 20 to day 14 were calculated. A non parametric Wilcoxon rank sum test was used to assess the treatment effect on CMAX for SR 25990.

Plot of mean concentration profiles for clopidogrel and its metabolite SR26334 after clopidogrel administration with and without the administration of phenobarbital is shown in Figure 1 while the corresponding pk parameters are summarized in Table 1.

Table 1

	SR26334		Clopidogrel	
	Clopidogrel	Clopidogrel +phenobarbital	Clopidogrel	Clopidogrel +phenobarbital
CMAX (mg/l)	1.93	2.44 (1.07-1.48)	2.07	.81
T1/2	7.19	7.55		
TMAX (hours)	0.75	.69	.82	.78
AUC_{0-24} (mg*hr/l)	6.11	6.64(0.84-1.26)		

( ) = 90% confidence intervals on the ratio of the geometric means.

Table 2 gives the summary of the % inhibition of platelet aggregation induced by ADP while Table 3 summarizes the analysis of maximum platelet aggregation induced by ADP. Table 4 gives the analysis of bleeding time prolongation factor.
It can be seen from the above results that coadministration of 100 mg phenobarbital with 75 mg clopidogrel decreased the CMAX of the parent drug clopidogrel by 60 % most probably due to the induction of Phase I metabolic enzymes. This decrease in the plasma levels of the parent drug was accompanied by a relatively moderate increase of CMAX (27 %) and AUC (8.6 %) of the metabolite SR26334. The sponsor speculates that since there was no change in the half-life of clopidogrel with the coadministration of phenobarbital, the observed increases in CMAX and AUC are not probably due to the inducing properties of phenobarbital.
Moreover, the results show that coadministration of phenobarbital increased the mean inhibition of ADP induced platelet aggregation by clopidogrel on day 7 from 41.6 % to 49.1 %. However this increase in pharmacological activity was not translated to an increase in bleeding time.

Conclusions:

Coadministration of 100 mg of phenobarbital for 21 days with 75 mg clopidogrel decreased the CMAX of clopidogrel by 60 % with a corresponding slight increase of 27 % in

CMAX and 8.6 % in AUC of SR 26334. This pharmacokinetic interaction was accompanied by an increased inhibition of ADP induced platelet aggregation of clopidogrel from 41.6 to 49.1 % with no effect on bleeding time.

TABLE (2) :-

Summary of Analysis of Bleeding Time Prolongation Factor by Day*

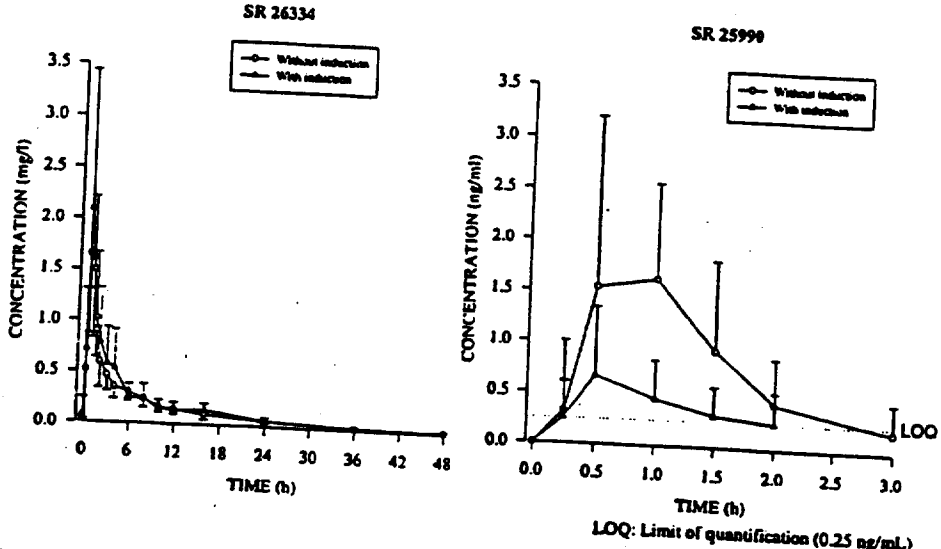
Time Day 7*	Geometric Mean (log transformed) of Treatments		p-Values		
	Clopidogrel	Phenobarbital + Clopidogrel	Treatment	Sequence	Period
8:00	1.96	1.81	0.545	0.823	0.966
9:30	1.89	1.83	0.802	0.840	0.561
11:00	2.00	1.83	0.489	0.693	0.911

* Day 7 is the seventh day post-clopidogrel administration (Day 21 of the clopidogrel + phenobarbital period).

TABLE (3) :- **Summary of Analysis of Maximum Platelet Aggregation Induced by ADP (5 µM): Treatment Group Differences By Time**

Parameter	Time Day 7*	Mean (90% CI) of Treatment Difference (Phenobarbital + Clopidogrel Minus Clopidogrel)	p-Values		
			Treatment	Sequence	Period
Intensity (%)	8:00	-6.6 (-11.8, -1.4)	0.045	0.925	0.802
	9:30	-5.0 (-10.3, 0.4)	0.122	0.880	0.694
	11:00	-7.9 (-11.8, -4.0)	0.004	0.466	0.039
Velocity (%/min)	8:00	-13.9 (-22.1, -5.8)	0.011	0.963	0.493
	9:30	-11.5 (-24.5, 1.5)	0.141	0.936	0.937
	11:00	-22.0 (-33.3, -10.7)	0.006	0.378	0.147

* Day 7 is the seventh day post-clopidogrel administration (Day 21 of the clopidogrel + phenobarbital period).



LOQ: Limit of quantification (0.25 ng/mL)

Figure (illegible) 1 - Time course of mean plasma concentrations of SR26334 (left) and of SR25990 (right) following repeated administration of 75 mg of clopidogrel alone and after phenobarbital induction *(n=12)*

STUDY P1512: (DRUG INTERACTION STUDY WITH ATENOLOL/NIFEDIPINE)

DOUBLE BLIND STUDY OF PHARMACODYNAMIC INTERACTIONS BETWEEN SR25990C AND ATENOLOL/NIFEDIPINE IN PATIENTS WITH PERIPHERAL ARTERIAL DISEASE OR CORONARY ARTERY DISEASE.

Reference: Volume 76
Investigator:

Objective:
1. To assess the pharmacodynamic activity of SR25990C on the basis of inhibition of ADP induced platelet aggregation in patients with peripheral arterial disease or coronary arterial disease including patients who were stable following a myocardial infarction.
2. To assess the possible effects on other pharmacodynamic variables and to assess the effects of coprescription of atenolol and/or nifedipine on the plasma levels of SR25990C and its main metabolite. Plasma levels of atenolol and nifedipine were also measured for comparison.

Study design:
This was a double blind placebo controlled crossover study . Treatment was either clopidogrel 75 mg every day or placebo for seven days followed by a washout period of two weeks followed by placebo or clopidogrel 75 mg every day for seven days. A total of 24 patients were recruited in this study (8 in each standard therapy group) males aged over 35 years or females who were post menopausal or who had undergone surgical sterilization.
All blood samples for platelet aggregation measurements were taken 120 minutes post dose for simple studies at screening and on days 1, 22 and 36. Extended studies were done on days 7 and 28. Blood samples for the measurement of clopidogrel and its main metabolite, atenolol were collected at 120 minutes post dose on days 1, 7, 22 and 28.
Batch #s: Clopidogrel 25 mg tablet: batch # RHE31, RGT01.
Placebo: batch # XRFN25

Analysis of variance was used to compare the effects of placebo and clopidogrel on platelet aggregation at day 1 and day 7. No formal pharmacokinetic or statistical analysis was performed on the plasma levels of SR26334, nifedipine or atenolol. The purpose of plasma level measurements was to determine compliance.

Results:

Table 1 gives the summary of the % inhibition of platelet aggregation induced by ADP for all the three different treatments. It can be seen from the results that coadministration of nifedipine and/or atenolol to patients with peripheral arterial disease or coronary artery disease did not have any effects on the pharmacological activity of clopidogrel.

TABLE (1)

Mean (sd) 5 μmol/l ADP induced Platelet Aggregation (%)

Standard Treatment Group	Mean (sd) Platelet Aggregation (%)					
	Pre-study	Clopidogrel Day 1	Clopidogrel Day 7	Placebo Day 1	Placebo Day 7	Post study
PAD, nifedipine [n]	73.2 (4.5) [6]	81.0 (4.1) [6]	50.7 (21.9) [6]	78.6 (5.5) [5]	76.2 (9.8) [6]	84.7 (9.8) [6]
CAD, atenolol [n]	80.3 (15.6) [10]	82.2 (7.6) [8]	48.6 (20.1) [8]	82.4 (7.0) [10]	74.8 (10.7) [9]	78.1 (4.7) [8]
CAD, atenolol + nifedipine [n]	78.0 (5.9) [8]	85.7 (6.0) [8]	56.5 (10.7) [8]	81.2 (10.1) [8]	86.1 (8.2) [8]	76.7 (5.6) [8]
All patients [n]	77.7 (10.9) [24]	83.2 (6.3) [22]	52.0 (17.3) [22]	81.2 (7.8) [23]	79.1 (10.6) [23]	79.4 (7.2) [22]

PAD = peripheral arterial disease, CAD = coronary artery disease

APPENDIX II

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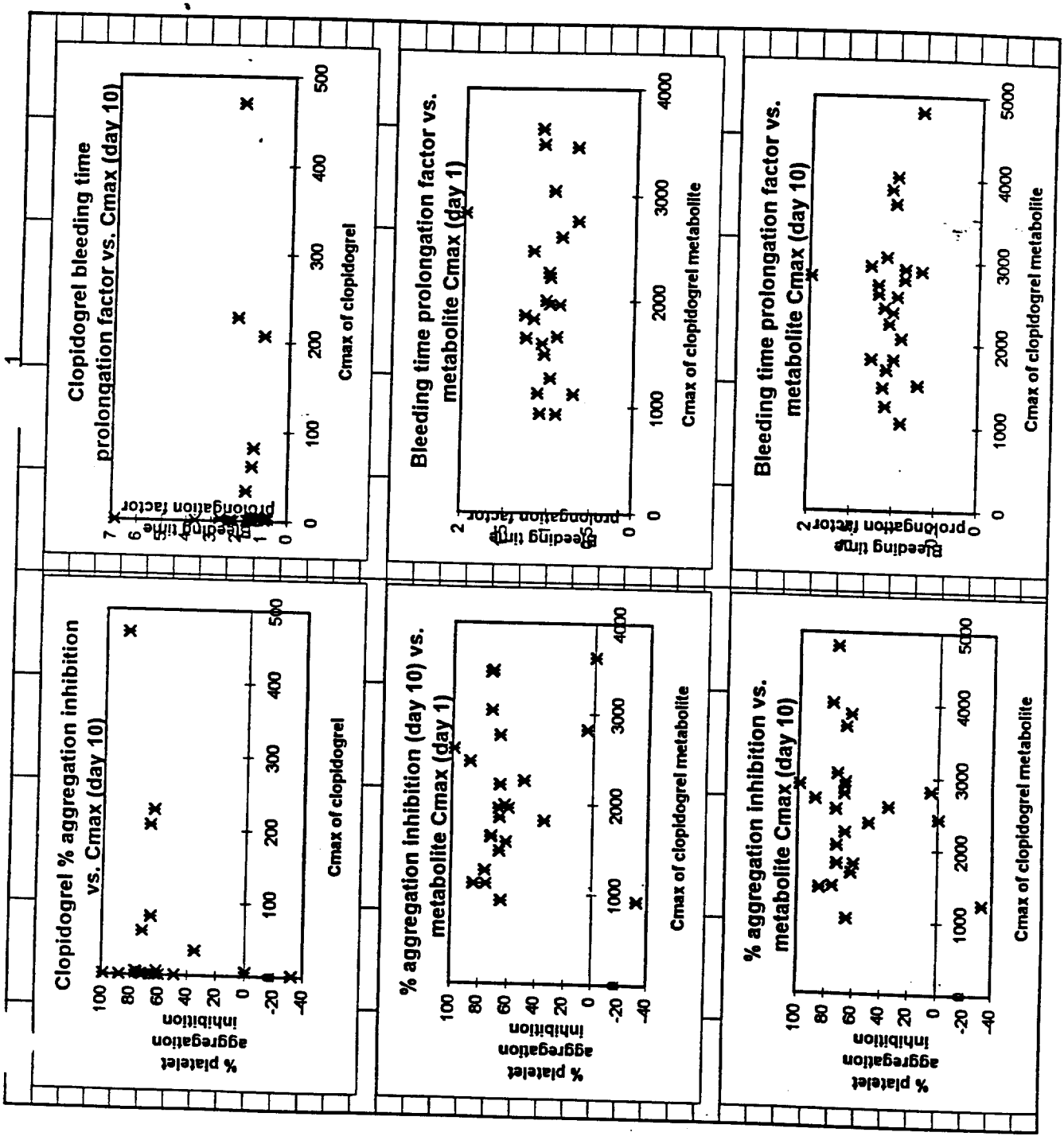

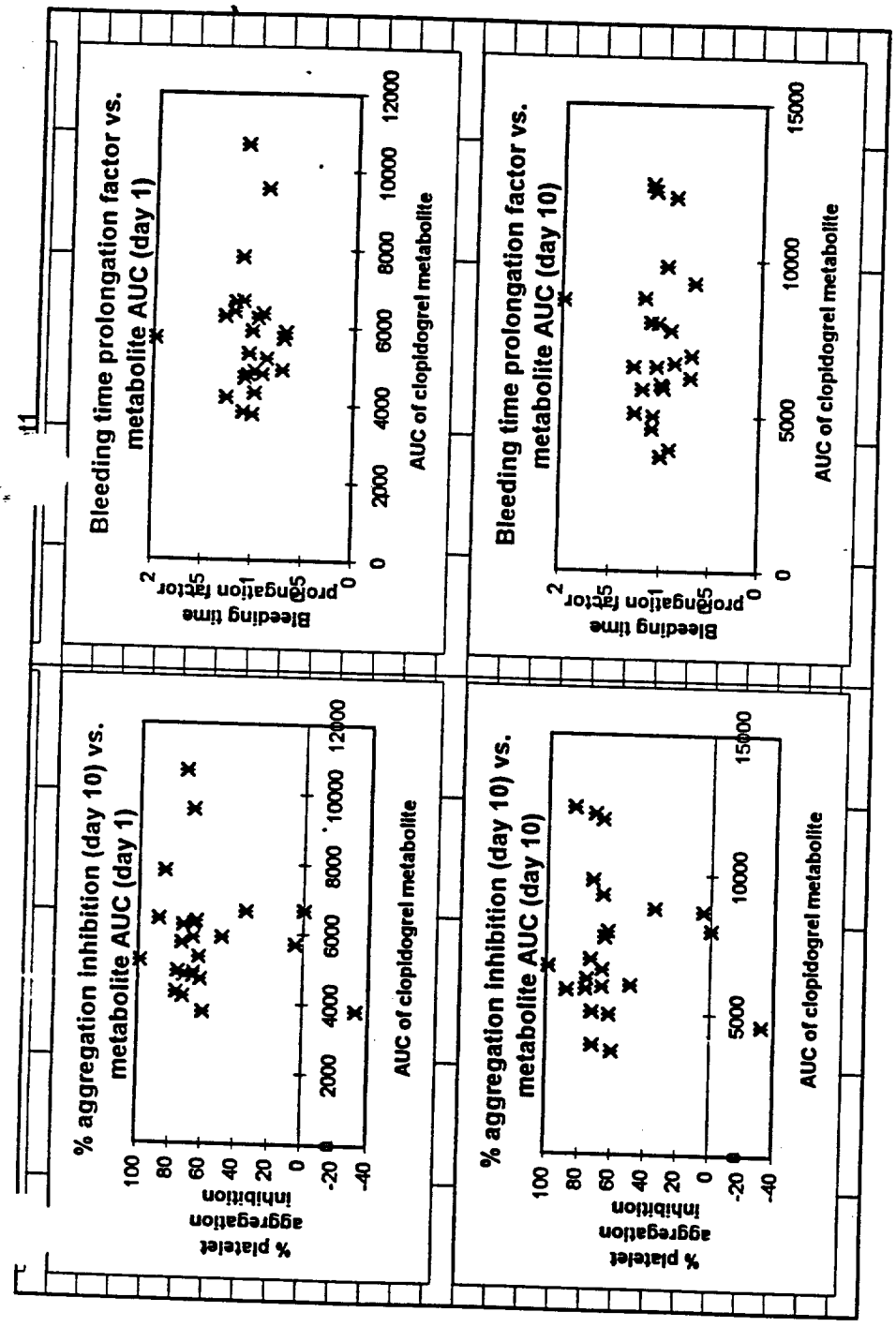

17 pages

PURGED

(DRAFT Labeling)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20839

ADMINISTRATIVE DOCUMENTS

ITEM 13. PATENT INFORMATION

BRANDNAME (clopidogrel bisulfate) drug, drug product, and method of use are covered by the following U.S. Patents. Sanofi Pharmaceuticals, Inc. believes that these patents would be infringed if a person, not licensed by the patent owner, engaged in the manufacture, use or sale of the drug product described in this application.

United States Patent Number	Expiration Date	Type of Patent	Patent Owner
4,529,596	July 5, 2003	Drug Drug Product Method of Use	Sanofi SA
4,847,265	February 12, 2008	Drug Drug Product	Sanofi
5,576,328	January 31, 2014	Method of Use	Elf Sanofi

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ON ORIGINAL

ITEM 14. PATENT DECLARATION

The undersigned declares that U.S. Patent No. 4,529,596, U.S. Patent No. 4,847,265, and U.S. Patent No. 5,576,328 cover the formulation, composition and/or method of use of clopidogrel bisulfate. This product is the subject of this application for which approval is being sought.

EXCLUSIVITY SUMMARY for NDA # 20-839 **SUPPL #** _____

Trade Name Plavix **Generic Name** clopidogrel bisulfate
Applicant Name Sanofi Pharmaceuticals Inc **HFD-** 110

Approval Date Nov 17, 1997

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA?

   YES /X/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /___/

   If yes, what type? (SE1, SE2, etc.) _____

   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 /X/ 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 /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /X/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

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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 /X/

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. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S 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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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 /___/
Investigation #3	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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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 /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

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 # _____ 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 /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____

_____

_____

NO /___/ 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: _____

_____

_____

_____

David L Roeder
Signature
Title: Regulatory Health Project Manager

8-22-97
Date

Ray Lipicky
Signature of Division Director

11/20/97
Date

cc: Original NDA Division File HFD-~~85~~ 93 Mary Ann Holovac

8/8/95

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-839 Trade (generic) names Plavix (clopidogrel bisulfate)

Check any of the following that apply and explain, as necessary, on the next page:

___ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

___ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

___ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

___ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

___ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

___ a. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing.
___ (2) Protocols have been submitted and approved.
___ (3) Protocols have been submitted and are under review.
___ (4) If no protocol has been submitted, on the next page explain the status of discussions.

___ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Signature of Preparer

10/3/97
Date

cc: Orig NDA
HFD-___/Div File
NDA Action Package

Item 15. OTHER: Debarment Certification

Sanofi Pharmaceuticals, Inc. certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug, and Cosmetic Act, in connection with this new drug application.

SEP 22 1997

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products

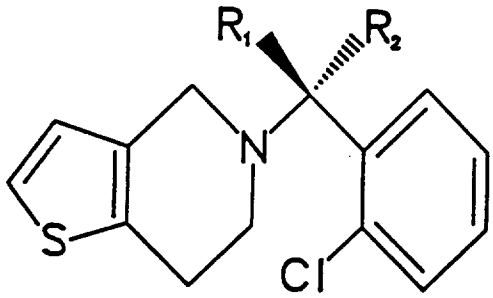
Date: 11 September 1997
From: Robert R. Fenichel (HFD-110) & James Hung (HFD-710)
Subject: clopidogrel (PLAVIX®, Sanofi), NDA 20-839
To: Raymond J. Lipicky, HFD-110

With this application, the sponsor proposes to market clopidogrel bisulfate, to be indicated for the prevention of vascular ischemic events in patients with histories of symptomatic atherosclerosis.

Some of the contents of the application are present only as references to portions of IND In this review, cited volumes of the NDA are all from volumes 1.XXX–6.XXX; those of the IND are generally from serial submissions 161 and above, cited as 161.1 (submission 161, Volume 1), 161.2, and so on.

Chemistry

Clopidogrel is a thienopyridine, chemically similar to ticlopidine (TICLID®, Roche). Ticlopidine and clopidogrel share the formula



For ticlopidine, R_1 and R_2 are both H. For clopidogrel, an *S*-enantiomer, R_1 and R_2 are H and $COOCH_3$, respectively. To produce the SR26334 metabolite of clopidogrel (important in the development process and mentioned below), R_2 is hydrolyzed to COOH.

Minor CMC deficiencies were described to the firm in a letter dated 6 August. Under the new environmental-assessment rules, the sponsor plans to withdraw its environmental-assessment submission and to submit a claim for categorical exclusion. The proposed tradename (PLAVIX) is said to be unacceptable to the Nomenclature Committee because of potential confusion with LASIX, but Dr. Lipicky has announced his intention to overrule them.

Pharmacology

For a more detailed review of clopidogrel pharmacology, see the review by Dr. DeFelice.

In multiple species (mouse, rat, rabbit, and baboon), clopidogrel inhibits ADP-induced platelet aggregation. The effective doses (1–5 mg/kg/day) are the same whether the drug is given enterally or intravenously, and clopidogrel's activity is potentiated by inducers of cytochrome P_{450} (1A), suggesting that metabolic activation is the rate-limiting step. Clopidogrel is inactive *in vitro*, and none of its isolated metabolites is active *in vitro* or *in vivo*, so the active molecular species is presumably an early, ephemeral intermediate.*

The *R*-enantiomer is inactive *in vitro* and *in vivo*.

After a single dose of clopidogrel, normal platelet aggregability returns slowly over a period of several days, and plasma from clopidogrel-treated animals (or humans) is inactive *in vitro*. These data suggest that the reaction between platelets and the (unidentified) active metabolite is irreversible.

In rats and rabbits, administration of clopidogrel caused dose-related prolongation of the bleeding time, without measurable effects on coagulation or fibrinolysis. In rats, the effect of clopidogrel could be antagonized by aprotinin,† but aprotinin was ineffective as an antagonist/antidote in human volunteers who received clopidogrel at the proposed therapeutic dose for 10–12 days.‡

Using doses in the same range as those used in the studies demonstrating inhibition of platelet aggregation, clopidogrel was protective in a variety of animal models of arterial and venous thrombosis. These models included one§ in which clopidogrel, apparently by suppressing accretion of new thrombus, effectively potentiated the thrombolytic activity of streptokinase. In another provocative study,‖ clopidogrel's platelet-calming activity appeared to reduce myointimal thickening in rabbits subjected to endovascular injury.

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* For a reasonable-sounding argument that the active compound is probably the sulfoxide, see Volume 1.2, pages 93–94.

† Aprotinin (TRASYLOL®, Bayer) is a protease inhibitor used in major surgery to mitigate the hemostatic defects that are associated with cardiopulmonary bypass and with any large-scale replacement of blood components.

‡ See Study INT1979 in Volume 1.170. Another human trial (Study P1629, described in Volume 1.165) examined the potential antidotal activity of **desmopressin** (DDAVP®, Rhône-Poulenc Rorer), with similarly disappointing results. Two others (P1875 in Volume 1.166 and PDY2239 in Volume 1.167) evaluated **methylprednisolone** for this purpose, but it didn't work either.

§ See Volume 4, page 68.

‖ See Volume 2, page 1, and Volume 4, page 203.

Toxicology

Because of its rapid and extensive metabolism, clopidogrel was barely detectable in plasma in any of the species studied, including humans, even though absorption (from mass-balance data) was always >80%. The evanescence of clopidogrel's putative active moiety has already been noted. Under the circumstances, all of the drug-exposure data had to be obtained by following serum concentrations of SR26334, the main circulating metabolite. The appearance of SR26334 seems to be qualitatively and quantitatively similar in humans and (at least) baboons.

In acute doses one or two orders of magnitude higher than those used to achieve full anti-platelet activity, clopidogrel caused a variety of toxicity (gastric erosions, renal tubular injuries, and pulmonary congestion) in dogs and rodents. Acute doses lower than these were nontoxic.

In subacute and chronic studies at similarly elevated doses, the same effects were seen. In addition, these doses in the test animals induced increases in platelet counts and in hepatic enzymes. As estimated by measurements of SR26334 levels, drug exposure in the treated baboons was 1–2 orders of magnitude greater than exposure to be expected in humans who receive the proposed therapeutic dose.

Worrisome toxicity was not seen in reproductive studies, but tracer studies suggest that clopidogrel (or a metabolite) crosses the placenta and also appears in milk. Carcinogenicity and mutagenicity tests were uniformly negative.

Clopidogrel was not myelotoxic in mice, rats, or baboons. The comfort derived from these results must be limited, inasmuch as ticlopidine (a known human myelotoxin) is similarly nontoxic in animal models.

Various other specialized studies (for immunotoxicity, phototoxicity, tumor promotion, and so forth) were also negative. Clopidogrel's *R*-enantiomer was neurotoxic in some models, but only at exposures about 4 orders of magnitude higher than those to be expected from use of clopidogrel at proposed doses. The SR26334 metabolite, administered as a pure compound, was not more toxic than clopidogrel.

Human Pharmacokinetics

Pharmacokinetic evaluation of clopidogrel has been necessarily indirect. As noted above, clopidogrel itself is so rapidly removed from the mammalian circulation that off-peak concentrations have been impossible to measure. As also noted above, the active moiety of clopidogrel is believed to be a labile, early metabolite, but this molecule has not actually been identified. Finally, the sponsor has been unable to develop an intravenous formulation, so direct human measures of absolute bioavailability could not be made. As in the animal studies, clopidogrel's human pharmacokinetics have been estimated by tracer studies and studies of the SR26334 metabolite.

The tested formulations are said to be bioequivalent to the formulation proposed for marketing.

Absorption of clopidogrel is at least 50%, and the t_{max} of SR26334 is less than 1 hour. In healthy volunteers, absorption of clopidogrel was not significantly affected by the co-ingestion of food or antacids. After a 75-mg dose of clopidogrel, the C_{max} of SR26334 is about 3 mg/L, and over 90% of circulating SR26334 is bound to serum proteins, mainly albumin.

Metabolism of clopidogrel and of SR26334 is complex and extensive, including hydrolysis, oxidation, dimerization, and glucuronidation. The clopidogrel→SR26334 hydrolysis is performed by plasma esterases in rodents, but in humans it is dependent on hepatic enzymes, probably of the P_{450} (1A) group. Neither racemization nor cleavage to ticlopidine were detected in human studies.

The **elimination** half-life of SR26334 was about 8 hours, but radioactivity from labeled clopidogrel had a half-life of about a week, presumably reflecting irreversible binding to platelets by the (hypothesized) active metabolite.

Antihemostatic Dose-Response

The application describes approximately twenty trials whose main purpose was the estimation of the antihemostatic response to various doses of clopidogrel. The trials ranged in size from 6 to 150 subjects, most of whom were healthy male volunteers. In almost all of the trials, the laboratory measures of hemostasis used were (a) percent inhibition of platelet aggregation induced by 5 μM ADP, and (b) proportional bleeding-time prolongation.

The proper interpretation of these trials is not clear, given the remoteness of their endpoints from clinical benefit and the vagueness of the links between the known pharmacokinetics and the presumed mechanism of that benefit. The trials were undertaken with the apparent intent of (a) identifying regimens of clopidogrel whose antihemostatic effects are similar to those of the approved regimen of ticlopidine, and (b) possibly identifying regimens of clopidogrel that are so toxic that they should be avoided. In addition, one trial explored the extent to which clopidogrel's PK and PD are affected by hepatic dysfunction.

Doses larger than 150 mg were not studied in multiple-dose trials. Single doses in the 200–600-mg range were studied in a total of about 75 healthy male volunteers.* Although peak levels of the SR26334 metabolite increased more than linearly with dose,† the highest tested doses were not associated with observed adverse responses. The antihemostatic effects of these single high doses were generally similar to those seen with 75-mg doses in multiple-dose regimens.‡

* See studies P1062 (Volume 1.89), P1560 (1.79), MET0103 (1.9), P1305 (1.47), P1590 (1.79), P1298 (1.61), and P1064 (1.91).

† In Study P1062 (Volume 1.89, page 7), for example, Hour-2 plasma concentration of SR26334 was 1.4±0.6 mg/L after a 100-mg dose and 14.6±3.8 mg/L after a 600-mg dose. In Study P1560 (Volume 1.79, page 248), the AUC of SR26334 was 1.96±0.44 μg•h/mL after a 25-mg dose and 70.41±18.17 μg•h/mL after a 400-mg dose.

‡ In Study P1062, the peak achieved inhibition of ADP-triggered platelet aggregation after

Almost all of the experience with **multiple-dose regimens of 150 mg** comes from Study P1264.§‖ This was a 16-day, escalating-dose trial in 32 normal male volunteers. The volunteers were divided into groups of 8; within each group, the subjects were randomized in double-blind fashion to receive either placebo or clopidogrel once daily, with the clopidogrel dose 25, 50, 100, or 150 mg, depending upon the group. The groups were not strictly comparable, since the 150-mg group was recruited and studied at one center, and the other groups at another center. The primary results (inhibition of platelet aggregation by ADP 5 μM and prolongation of Ivy-Nelson bleeding time) are shown in Table 1 below.

In the same table, we have included some of the results of Study P1404.¶ This was a 4-week, 139-patient, randomized, open-label trial in patients with atherosclerosis of the peripheral vessels, cerebrovascular circulation, or coronary arteries, objectively documented and sufficiently severe (as assessed by the investigator) to warrant antiplatelet therapy. Each patient received placebo; ticlopidine 250 mg bid; or clopidogrel 10, 25, 50, 75, or 100 mg qd. These results are tabulated with those of Study P1264 because they allow the antihemostatic effects of clopidogrel to be compared to those obtained with the conventional dose of ticlopidine.

Table 1
Antihemostatic effects of
Various Doses of Clopidogrel
As Percent of Baseline

	ADP-induced platelet aggregation		bleeding-time prolongation	
trial:	P1264	P1404	P1264*	P1404
placebo	100%	100%	110%	128%
clopidogrel 10 mg qd	---	86%	---	134%
clopidogrel 25 mg qd	68%	71%	148%	123%
clopidogrel 50 mg qd	52%	71%	164%	150%
clopidogrel 75 mg qd	---	61%	---	172%
clopidogrel 100 mg qd	46%	63%	278%	165%
clopidogrel 150 mg qd	27%	---	439%	---
ticlopidine 250 mg bid	---	54%	---	190%

* Geometric means.

from Volume 1.97, pp. 6-7, and Volume 1.12, pages 5-6

the 600-mg dose was 42±6%, and the peak prolongation factor of the the bleeding time was 1.7. In Study P1560, the analogous results with the 400-mg dose were 47±8% and 1.6. *Cf.* our Table 1 on the next page.

§ See Volume 1.97.

‖ The only other data come from Study LIN2264 (Volume 1.9). This was a 12-subject, 4-day, nonrandomized pharmacokinetic study that included doses of 50, 75, 100, and 150 mg.

¶ See Volume 1.112.

The results of these trials are consistent with the sponsor's expectation that the antihemostatic effects of clopidogrel 50–100 mg qd will be roughly similar to those of ticlopidine 250 mg bid, but more needs to be said. The results were characterized by wide inter- and intra-subject variation; for example, coefficients of variation of the aggregation data in Study P1264 were roughly 0.2–0.8.* In the same study, the bleeding-time results were so skewed that geometric means were thought to have been appropriate, and the confidence intervals around the tabulated figures are defined by factors about 1.4.†

In these trials, the observed increases in antihemostasis with increasing doses of clopidogrel were only weakly associated with increasing rates of bleeding and other hemostasis-related effects. In Study P1264, there was one withdrawal by a patient randomized to placebo, one (the only one related solely to hemostasis) by a patient randomized to 100 mg, and one by a patient randomized to 150 mg.‡ Another subject, receiving 50 mg of daily clopidogrel, did not withdraw despite bruising and prolonged bleeding from shaving nicks. These phenomena developed about midway through the trial, persisted for 7 days, and then remitted completely. On Day 16, his bleeding time was substantially prolonged (35 minutes).

In Study P1404, rate of withdrawal was not monotonically related to the dose of clopidogrel, and the only hemostasis-related withdrawal was in the ticlopidine group (for excessive inhibition of platelet aggregation). Hemostasis-related adverse effects that were reported but did not lead to withdrawal were seen in 1 of the 23 placebo patients (hemorrhoid problem); none of the 73 patients receiving 10–50 mg of clopidogrel; 2 of the 21 patients receiving 75 mg of clopidogrel (one hemorrhoid problem and one hemorrhage from a vessel torn during bleeding-time measurement); 2 of the 11 patients receiving 100 mg of clopidogrel (hematomas); and 1 of the 22 patients receiving ticlopidine (thrombocytopenia to 147 000/mm³).

Study PDY3079§ was a 24-subject, 18-day, nonrandomized, open-label study of the effect of **hepatic dysfunction** on the pharmacokinetics and pharmacodynamics of clopidogrel. Half of the subjects had biopsy- or scintigraphy-proven hepatic cirrhosis, and the other half were normal subjects matched pair-

* See Volume 1.97, pages 92–93. The sponsor did not present coefficients of variation *per se*. Platelet aggregation at baseline was typically 60–65%, and on-treatment platelet aggregation was as low as 15%, with standard deviations said to be about 13% throughout.

† See Volume 1.97, pages 105–106. When geometric means are used, the conventional interval $[\mu-2\sigma,\ \mu+2\sigma]$ is replaced by an interval $[G/F,\ G\times F]$, where G is the geometric mean and F is a factor chosen so that the $[G/F,\ G\times F]$ interval contains as much of the distribution as $[\mu-2\sigma,\ \mu+2\sigma]$ usually does.

‡ The subject randomized to placebo withdrew because of eczema.

The subject randomized to 100 mg was withdrawn on Day 4 when ADP-induced platelet aggregation had declined to only 8%.

The subject randomized to 150 mg was withdrawn on Day 14 because of glucosuria thought to have been "possibly" related to therapy; it later developed that this man had a fixed low renal threshhold for glucose excretion. He had been noted to have excessively prolonged bleeding time (76.5 minutes) and low ADP-induced platelet aggregation (11%) on Day 12, and he was thereafter subjected to more aggressive surveillance. The glucosuria was an incidental finding of urinalysis performed to screen for hematuria, which was not found.

§ See Volumes 6.1 and 6.2.

wise for age (±5 years), weight (±15%), and sex. The cirrhotic subjects were all in Childs-Pugh class A or B; their baseline serum bilirubin levels ranged from 0.4 to 2.5 mg/dL, with a mean of 1.2. In contrast, none of the normal subjects' bilirubin levels was more than 1, and the mean was 0.6. The mean baseline AUC of indocyanine green was 1.9±1.5 μg•h/mL in the cirrhotic subjects and 1.04±0.22 μg•h/mL in the normal subjects.

Each subject received daily clopidogrel 75 mg for 10 days; pharmacokinetic measurements were made at baseline and on Days 1 and 10. Pharmacodynamic measurements (ADP-induced platelet aggregation and bleeding time) were made at baseline and on Days 7, 10, and 18.

Hepatic dysfunction was associated with spectacular increases in the C_{max} of parent clopidogrel (on Day 10, from 1.9±1.5 ng/mL to 99.7±147.7 ng/mL). In contrast, the C_{max} and AUC of SR26334 were only 10–30% higher in the cirrhotic group, and these differences were consistently dwarfed by the intersubject variation.

The non-difference in SR26334 kinetics better predicted the pharmacodynamics than the huge difference in clopidogrel kinetics. On Day 10, ADP-induced platelet aggregation as a percentage of baseline was 51±39% in the cirrhotics and 33±8% in the normals, neither of these different from the other or from the analogous results in Studies P1264 and P1404. Similarly, the bleeding times on Day 10 were 164±49% and 154±87% of the baseline times.

Drug Interactions

In a series of *in vitro* studies, P_{450}(2C9)* was moderately inhibited by SR26334, but the other isozymes tested (1A2, 2A6, 2C19, 2D6, 2E1, 3A4) were inhibited by neither clopidogrel nor SR26334.

In healthy volunteers, coadministration of clopidogrel did not cause any significant change in the pharmacokinetics of **digoxin**† or **theophylline.**‡ Conversely, the pharmacokinetics of clopidogrel were not importantly affected by coadministration of **cimetidine.**§ In postmenopausal women, the effects of clopidogrel were not obviously changed by short-term **estrogen replacement therapy,** but the only data come from a weak trial.‖ When volunteers' hepatic

* Drugs metabolized by P_{450}(2C9) include **tamoxifen, tolbutamide,** the more potent enantiomer of **warfarin,** at least some **HMG CoA reductase inhibitors,** and many **non-steroidal anti-inflammatory agents.** P_{450}(2C9) is also contributory, but inessential, to the metabolism of **carbamazepine** and **phenytoin.**

† See Study P1722, Volume 1.65.

‡ See Study INT1980, Volume 1.158.

§ See Study P1716 in Volume 1.135. Cimetidine did cause a statistically-significant decrease in clopidogrel-related inhibition of ADP-induced platelet aggregation, but the magnitude of effect was small, and there were no significant changes in bleeding time or clopidogrel-related inhibition of collagen-induced platelet aggregation.

‖ See Study P1435 in Volume 1.123. In the pertinent portion of this open-label, nonrandomized study, the pharmacokinetics and antihemostatic effects of clopidogrel were measured in 10 postmenopausal women, once after 2 weeks of coadministered clopidogrel and hormone replacement, and once after 2 weeks of clopidogrel monotherapy.

enzymes had been induced by pretreatment with **phenobarbital,**¶ the clopidogrel/SR26334 C_{max} ratio was reduced, and the change in platelet-inhibitory activity (an increase from 42% to 49% inhibition) was statistically significant; bleeding time was unaffected.

Study P1512# was intended to assess the effects of **atenolol** and **nifedipine** on clopidogrel's pharmacokinetics, but the trial was not randomized; the recruited patients were heterogeneous and poorly compliant; and the difficulties of detecting clopidogrel in plasma were beginning to be recognized. In the end, the intended assessment was abandoned.

Similarly, Study PDY2189** was intended to address the (speculative) possibility that clopidogrel might potentiate the CNS dysfunction induced by moderate doses of **ethanol.** No such potentiation was observed, but the investigator believed that the tests as administered had not been adequately sensitive to form the basis of firm conclusions. Perhaps because of a mixup in the investigators' supply of ethanol,†† the actual blood-alcohol levels achieved were only 20–30 mg/dL, and these are below those at which the tests used have been validated.

Potential interactions with **heparin** were assessed in Study INT2193.‡‡ This was a 12-subject, randomized, double-blind, crossover study consisting of two 12-day test periods separated by a 3-week washout. During each test period, subjects received either placebo or clopidogrel 75 mg qd. For the last 4 days of each test period, intravenous heparin was administered, titrated so as to achieve an activated partial thromboplastin time (APTT) of 1.7–2.3 times control.

Clopidogrel's influence upon the effects of heparin was to be evaluated by comparing the total heparin consumption in the placebo and clopidogrel periods. With somewhat less confidence (because administration of heparin was neither blinded nor separable from a time-on-clopidogrel effect), heparin's influence upon the effects of clopidogrel was evaluated by the sponsor's usual measures of antihemostasis (bleeding time and ADP-induced platelet aggregation). Other tests of coagulation and hemostasis were also performed at various times during the study.

The target APTT ratios were achieved with equal success in the clopidogrel and placebo groups, and the amounts of heparin required were identical to

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¶ See Study ENZ2556 in Volume 1.138.

See Volume 1.56.

** See Volume 1.120.

†† See Volume 1.120, page 244:

> Ethanol was obtained from the University Hospital in a single bulk container. The Hospital normally supplies ethanol for use in volunteers participating in medical research in two concentrations: 99.8% *[sic]* and 70%. The former was ordered for this study but apparently the latter was delivered. The label "guaranteeing" the concentration was accepted at face value. As none of the ethanol supply remained for analysis when the apparent mistake was discovered, it is impossible to verify its concentration.

‡‡ See Volume 1.149.

within 2% ($P=0.51$). The bleeding-time tests were done only at baseline, during heparin administration, and during washout, so they were not useful for the detection of a clopidogrel-heparin interaction. Platelet aggregation studies were more usefully timed, and heparin did not appear to have any measurable effect on clopidogrel's inhibition of ADP-induced aggregation. Prothrombin times were unchanged throughout the trial, while thrombin times were greatly increased by heparin, significantly more in the absence of clopidogrel (3.3 times) than in its presence (2.4 times).*

A similar study was performed to look for interactions between clopidogrel and warfarin.† This was a 10-subject, randomized, double-blind, crossover study consisting of two 19-day test periods separated by a 3-week washout. During each test period, subjects were to receive either placebo or clopidogrel 75 mg qd. For the last 7 days of each test period, warfarin was to be administered, with doses adjusted so as to achieve a prothrombin time INR in the 1.8–2.2 range.

This study was a complete fiasco. As described on pages 29–31 of Volume 1.147, many of the protocol-specified laboratory studies were mistimed or omitted. Much more seriously, dosing of clopidogrel, placebo, and (especially) warfarin was almost whimsically irregular, and in the end "no subject received a complete, seven-day course of warfarin, and no subject received two complete 19-day periods of clopidogrel and placebo administration [emphasis added]." Some subjects received extraordinary doses of warfarin (up to 40 mg), with resulting INR values up to 4.01.

Minor Efficacy Studies

In Volume 1.79, the sponsor provides brief (2–5-page) descriptions of several small Phase II studies with clinical endpoints. These include

- Study P1742 (pages 266–269), an 8-week, open-label, forced-titration study of 10–75 mg of clopidogrel in 45 patients who had had thrombotic strokes. The investigator thought that during the course of the forced titration, patients got better.

- Study P1930 (pages 270–272), a 12-week, open-label, parallel-group study in 45 patients who had undergone successful thrombolysis after myocardial infarction. These patients were randomized to receive 10 mg or 50 mg of daily clopidogrel; the investigators could not distinguish the groups' outcomes.

- Study P2055 (pages 273–275), a 12-week, open-label, nonrandomized study of 25–75 mg of daily clopidogrel in 47 patients with atrial fibrillation. There were no interpretable events during the trial.

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* For all these results, see Volume 1.149, pages 26–32.

† See Study INT2240 in Volume 1.147.

- Study P2221 (pages 275–276), a 24-week, double-blind, parallel-group study of 25–75 mg of daily clopidogrel in 381 patients who had had strokes or transient ischemic attacks. There were no differences in the on-treatment incidences of new ischemic events.

- Study P2299 (pages 277–281), a 17-patient, open-label crossover trial consisting of two 4-week test periods. The patients were middle-aged adults with objectively verified peripheral arterial disease and reproducible claudication on treadmill exercise; they received placebo during one test period and clopidogrel 25–100 mg qd during the other. As measured by treadmill performance, patients dervived greater benefit from placebo than from clopidogrel.

- Study 2300 (pages 282–285), an open-label study in 49 hemodialysis patients who had problems with residual blood or clots in the dialyzer. The investigators thought that dialysis problems were less frequent as the clopidogrel dose was escalated.

CAPRIE

The Clopidogrel *vs.* Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial was a 19 185-patient, 1.6-year, 304-center, international, randomized, triple-blind, 2-armed, parallel-group study comparing clopidogrel to aspirin as secondary prevention of certain events related to atherosclerosis. Clopidogrel exposure in CAPRIE was 98% of all clopidogrel exposure reported in the application, and it was nearly 99% of the exposure in randomized, double-blind trials.

CAPRIE and its results were described in a paper in *The Lancet* (348: 1329–1339 (1996)); minor discrepancies between the paper and the study report are described on pages 331–332 of Volume 161.7.

The trial's protocol appears on pages 207–255 of Volume 161.2. Many details of the sort usually found in protocols are not included here, but they are instead found in the "Operations Manual"* that was produced on the same date (26 November 1991, about 4 months before the first patient was randomized). Although the study report states that the protocol was not amended,† the IND includes copies of the "bulletins" that were sent from the trial's coordinating center to its investigators.‡ Some of the bulletins dealt with pedestrian administrative matters, but others constituted what would normally be said to be amendments. For example, when it was decided to extend recruitment, effectively increasing the trial's patient population by about 30%, investigators got the news through bulletins from this series.

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* See Volume 161.3, pages 2–28.

† Volume 161.1, page 34.

‡ Volume 161.7, pages 296–322.

Eligibility for enrollment. A patient could become eligible for enrollment in any of three different ways.

- A patient could be enrolled if 1-26 weeks before randomization he or she had had an **ischemic stroke** (IS), thought likely to have been of atherosclerotic origin, confirmed by computerized tomography or magnetic resonance imaging,* and associated with residual neurological signs for at least a week.

- A patient could be enrolled because of a qualifying **myocardial infarction** (MI). Such an infarction was diagnosed if within the 35 days before randomization the patient had had at least two of (a) at least 20 minutes of characteristic pain; (b) elevation of CK, CK-MB, LDH, or AST to at least twice the laboratory's upper limit of normal, with no other explanation; and (c) development of new 40-ms Q waves in at least two adjacent electrocardiogram leads or development of a new dominant R wave of at least 1 mm in lead V_1.

- A patient could be enrolled because of **peripheral arterial disease** (PAD), manifest either as current claudication or as a history of major intervention for claudication. Current claudication was defined as leg pain of presumed atherosclerotic origin, induced by walking and relieved within 10 minutes after walking was stopped and the patient remained standing, with at least one ankle/arm systolic blood-pressure ratio less than 0.86 at rest on two assessments on separate days. The qualifying major interventions were amputations, reconstructive surgical procedures, and angioplasties of the legs, performed because of atherosclerotic disease and without persisting complications.

Each enrolled patient was counted as having been enrolled because of exactly one of the three conditions, even if the patient's history were sufficient for eligibility in one or both of the other categories too. In the application and in this review, there is continual mention of the three "diagnostic groups," referring to the three mutually-exclusive groups of patients who were *enrolled because of* the specified conditions, not the larger (and overlapping) groups of patients who *had* the specified conditions.

With very few exceptions, each investigator recruited patients in exactly one category: Neurologists recruited stroke patients, cardiologists recruited MI patients, and vascular surgeons recruited patients with PAD.

Qualification for randomization. Enrolled patients could be disqualified from randomization for most of the usual reasons (dementia, expected major surgery, contraindications to either test drug, short expected survival, concomi-

* Early in the course of the trial, the protocol was revised so that an otherwise-qualifying retinal infarction could be used as a qualifying IS event without tomographic imaging. See Volume 161.7, page 297.

tant use of other anticoagulants or antiplatelet agents, reasonable risk of pregnancy, and so on).* In addition, a patient was disqualified from randomization in the IS group if the qualifying stroke had been induced by carotid endarterectomy or angiography, or if he or she had had endarterectomy since the qualifying stroke.

Randomization of patients in the MI group was deferred, if necessary, until 48 hours after the completion of thrombolytic therapy.

Randomization. Randomization between clopidogrel and aspirin (1:1) was stratified by center and qualifying condition, and the treatment assignments are listed in Volumes 161.4 (pages 5–203), 161.5 (pages 1–350), 161.6 (pages 1–250), and 161.7 (pages 1–201). The randomization appears to have been generated in blocks of 4 patients at a time, but the procedure by which the codes were generated is not revealed in the application.

Randomization, drug packaging, and drug delivery were all performed by an outside vendor, independent of the sponsor, but the chairman of the Data Safety Monitoring Board (DSMB)† was also informed of treatment assignments as they were made, and the DSMB was provided with treatment-labeled data for its periodic safety assessments.‡

Patient Monitoring. Randomized patients were followed with routine examinations and laboratory studies. Because of concern that clopidogrel might turn out to be associated with myelotoxicity similar to that of ticlopidine, the protocol specified three different levels of monitoring. The first and most intensive level was to be followed for the first 500 patients. If blinded review of those patients' laboratory reports were reassuring, it was planned to relax monitoring to the middle level of intensity. Similarly, if no myelotoxic effect were evident on blinded review of the first 1000 patients' 3-month laboratory data, then it was planned to relax monitoring to the lowest level of intensity. The progressively-loosening monitoring scheme is described on pages 225–228 of Volume 161.2. At the least intensive level of monitoring, patients were seen every month for four months and every four months thereafter. There was no requirement for a final visit at the very end of the trial.

Drug regimens. Each patient was randomized to receive clopidogrel 75 mg or aspirin 325 mg, to be taken once daily with breakfast. A double-dummy technique was used, so each patient took two pills daily.

Trial duration. Whether or not still receiving blinded treatment, each patient was followed for three years or until the end of the trial, whichever came first. The trial was to continue until one year after the last patient had been randomized, so every patient's time on treatment was — unless the patient withdrew or an endpoint event intervened — at least one year.

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* Volume 161.2, pages 223–224.

† Throughout the application, the DSMB is consistently called the "External Safety and Efficacy Monitoring Committee," or "ESEMC."

‡ See Volume 161.3, page 17.

Planned analysis of results. The outcome events of interest were new ischemic events, including ischemic strokes, myocardial infarctions, and death from "other vascular causes."* Other events of interest included non-vascular deaths and above-ankle amputations not attributable to trauma or malignancy. Each reported event was to be evaluated by a blinded "Central Validation Committee" (CVC). The criteria that the CVC were to apply, and the procedures to be used for resolving disagreements, are described in considerable detail in the Operations Manual.† The criteria of ischemic stroke and myocardial infarction were similar to those used in determining eligibility for enrollment in the trial; the criteria for "vascular death" were inclusive rather than exclusive, so in the end "any . . . death that cannot be definitely ascribed to a nonvascular cause [was to be] classified as vascular death."

The primary test of efficacy was to be an unadjusted, intention-to-treat Mantel-Haenszel test of Kaplan-Meier survival curves, plotting the time to the first occurrence of ischemic stroke, myocardial infarction, or vascular death.

Secondary analyses were to include similar tests of survival curves showing the time to

- ischemic stroke, myocardial infarction, amputation, or vascular death;
- vascular death;
- any stroke, myocardial infarction, or death from any cause; and
- death from any cause.

The protocol specified that if *post hoc* analysis revealed "important prognostic imbalance" between the aspirin and clopidogrel groups, then the trial would be reanalyzed, using *post hoc* stratification or adjustment via a Cox proportional-hazards model. The primary analysis and each of the secondary analyses was also to be performed both using the intention-to-treat model and using an "efficacy" model in which patients were to be censored 4 weeks after they were known to have discontinued study drug. There were thus 20 different intended life-table analyses,‡ but the protocol makes plain that the primary analysis should be the unadjusted, intention-to-treat analysis described above.

Interim analyses were planned for the times at which 25%, 50%, and 75% of the events had accrued, using a Peto-Haybittle rule that allocated a two-sided type I error of 0.001 to each interim analysis and a two-sided type I error of 0.048 for the final analysis. In addition, the study was to be stopped early if the upper limit of a 95% confidence interval for the risk reduction fell below 14%.§

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* See Volume 161.2, page 224.

† See Volume 161.3, pages 9–15.

‡ (1 primary+4 secondary)×(adjust or not)×(intention-to-treat or efficacy); see Volume 161.2, page 235.

§ In April 1995, the DSMB decided that even if this threshhold were crossed, the Steering Committee would be encouraged *not* to stop the trial. See Volume 4.4, page 165.

In addition, the Operations Manual alludes to a variety of circumstances under which the trial might be aborted, generally when the safety and efficacy profiles of clopidogrel appeared insufficiently promising to justify continuing the trial. The Manual provides guidelines limiting communications between the DSMB and the Steering Committee, including the requirement that any such communications be in writing.

The planned analyses were intended to include patients from all three qualifying groups. The investigators believed that

> ... there is no prior evidence to suggest that over a long period of time the relative efficiency of clopidogrel and aspirin should differ among the separate diagnostic groups, and thus the primary analysis will combine the treatment-effect estimates for stroke, myocardial infarction, and peripheral arterial disease patients. The consistency of these treatment effects across the three clinical disorders will be investigated.

To increase the credibility of the trial's overall result, the investigators planned to compare the pooled results from the North American centers with the pooled results from the European and Australian Centers.

Course of the trial. The first patient was randomized on 20 March 1992, and it was expected that it would take three years to recruit the target population of 15 000 patients. In fact, recruitment was more successful than had been anticipated, and the overall event rate was slightly lower. After considering the option to stop after the original target enrollment had been achieved, the Steering Committee instead elected to hold to (roughly) the original schedule; in order to balance the final population among the three diagnostic groups, recruitment was continued

- until 31 October 1994 in the PAD group;
- until 31 December 1994 in the MI group; and
- until 28 February 1995 in the IS group*

with the last followup visits about a year later in each group.

Pursuant to the plan described under "Patient monitoring" on page 12, hematological testing was initially intensive, but then became progressively looser when myelotoxicity appeared to be absent.†

Patients enrolled. The three qualifying conditions were approximately equally represented among the 19 185 randomized patients. About 40% of the patients were from North America, and the remainder were from Europe, Australia, and New Zealand. As might have been expected in a study this size, with randomization stratified by center and qualifying condition, the clopidogrel and aspirin groups were tightly matched, with the same mean age to within a month or two, the same mean weight to within an ounce or two, and so on. Differences in the racial composition of the two groups were nominally significant

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* See Volume 161.7, pages 312 and 314–315.

† See Volume 161.7, pages 307–309.

($P=0.02$), but this result was driven by differences in the fractions of Black, Oriental, and Other Non-Caucasian patients, who together made up less than 6% of the total of either treatment group.

In contrast (but as might also have been expected), the three qualifying conditions were associated with patient populations that were sharply distinct from each other, at least in a statistical sense. As shown in table 2 below, the MI patients were generally younger than patients in the other two groups, they had fewer risk factors, and they had fewer signs of diffuse atherosclerosis. The PAD patients, although no older than the patients in the IS group, had more signs and risk factors.

Table 2
Characteristics of Patients
Recruited with Different
Qualifying Conditions

	Qualifying Condition		
	IS	MI	PAD
age <55	18.33%	37.59%	16.86%
55–64	28.11%	30.89%	29.49%
65–74	34.40%	23.48%	40.10%
>74	19.16%	8.03%	13.55%
(mean)	64.6	58.4	64.3
male	63.68%	80.78%	72.37%
white	90.95%	95.73%	97.57%
smoking current	22.19%	28.15%	38.24%
former	43.49%	50.34%	52.88%
never	34.32%	21.50%	8.88%
amaurosis fugax	2.33%	0.21%	2.06%
amputation	0.56%	0.17%	N/A
angioplasty	1.51%	2.05%	N/A
cardiac surgery	4.14%	8.25%	10.90%
cardiomegaly	5.89%	3.70%	4.23%
congestive failure	4.09%	7.03%	5.70%
claudication	7.79%	5.51%	N/A
diabetes	25.50%	14.39%	20.68%
hypercholesterolemia	37.96%	41.05%	44.62%
hypertension	65.29%	38.10%	50.91%
ischemic stroke	18.15%*	2.17%	5.97%
myocardial infarction	12.08%	16.84%*	21.19%
reconstructive surgery	2.04%	1.40%	N/A
stable angina	13.99%	24.79%	26.50%
TIA	15.53%	1.87%	6.46%
unstable angina	2.85%	17.14%	6.17%
digitalis glycosides	7.10%	9.10%	8.60%
antiepileptics	7.40%	1.50%	2.90%

* Before development of index condition.

from Volume 161.8, pp. 61–68, 71–76, and 80–82.

Patient retention. As of the end of the trial, 56 patients (0.3%) had been lost to followup; 1131 (5.9%) had died; 2460 (12.8%) had completed the maximum duration of randomized treatment (3 years); and 15538 (81%) were still assigned to treatment with study drug.* The two treatment groups did not significantly differ with respect to the number of patients lost to followup (30 and 26 for clopidogrel and aspirin, respectively) or the duration of time on study before these patients were lost (428±290 days and 475±284 days).†

The mean duration of participation in the trial was 23 months; because the three diagnostic groups completed recruitment at different times, the average durations of trial participation differed slightly from one group to another,‡ but average length of participation did *not* differ between the clopidogrel and aspirin groups (698.99±256.34 days and 698.91±256.35 days, respectively).§

About a quarter of the patients discontinued treatment with study drug before the end of the study or the assigned three-year point. Of these patients, about half discontinued because of adverse events, including outcome events;‖ about 20% withdrew consent; about 10% began to receive a prohibited concomitant medication; about 1% were belatedly found not to have met the trial's inclusion criteria;¶ and the remainder were simply noncompliant or lost to followup. The mean duration of drug treatment was about 20 months, so there were 15634 patient-years of exposure to clopidogrel and 15626 patient-years of exposure to aspirin.

The 86 patients (0.4%) who never received study drug were about evenly split between the two assigned treatments. The great majority of these patients (described on pages 10–14 of Volume 161.35) withdrew consent; there were scattered instances of forbidden concomitant medication; and there were a few patients who turned out, on reconsideration, not to have had the qualifying condition after all.

Similarly, there were 60 patients (0.3%) who for various short periods were inadvertently given the opposite study drug from the one to which they had been assigned. These patients were about equally split between the two assigned treatments.

Overall efficacy *vs.* aspirin. The prespecified **primary analysis** was, as noted above, an intention-to-treat analysis using the Mantel-Haenszel test, looking at the time to first occurrence of protocol-defined ischemic stroke, myocardial infarction, or vascular death. As shown in Table 3 on the next

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* See Volume 161.1, page 79.

† For more detail, see Table A1 in the Appendix.

‡ See Volume 161.1, page 73.

§ For more detail, see Table A2 in the Appendix.

‖ After an outcome event, withdrawal from study drug was *not* required by the protocol.

¶ Of the randomized patients, 392 (2%) were in retrospect improperly enrolled. Many of these patients had had events of atherothrombotic origin, but not events that met the trial's criteria. When these patients were identified, treatment with study drug was continued (352 patients) or discontinued (40 patients) at the discretion of the investigators following them. These patients were of course retained in the study for purposes of the intention-to-treat analyses. See Volume 161.1, pages 80–83, and Volume 161.35, pages 4–6.

Table 3
Outcome Events of the
Primary Analysis

	clopidogrel	aspirin
patients	9599	9586
IS (fatal or not)	438 (4.56%)	461 (4.81%)
MI (fatal or not)	275 (2.86%)	333 (3.47%)
other vascular death	226 (2.35%)	226 (2.36%)
total	939 (9.78%)	1020 (10.64%)

from Volume 161.1, page 94

page, the clopidogrel patients had a lower incidence of events in every category, with an overall relative risk reduction of 8.7% (95% confidence interval 0.2–16.4%, $P \doteq 0.045$ by the stratified* logrank test). These results are only slightly affected (RRR still 8.7%, $P=0.043$) when the calculations are revised so as to include the 14 patients who had been lost to followup but were located within a few days after the data lock.† Similarly, there is little change when the analysis uses the slightly different counts that appear when the investigators' reports are taken at face value, without endpoint adjudication by the CVC.‡ When non-first strokes and MIs are added, the pattern is slightly reinforced (1077 events in the clopidogrel group, 1182 in the aspirin group);§ when analysis is *limited* to non-first outcome events (that is, to new outcome events in patients who had survived an in-study IS or MI), the clopidogrel group again has lower rates of ischemic stroke (0.66% *vs.* 0.76%), myocardial infarction (0.29% *vs.* 0.44%), and vascular death (1.29% *vs.* 1.59%).‖ Even when the patients lost to followup are all treated as having had events at the time of their disappearances, the result is only slightly weakened (968 events *vs.* 1046, relative risk reduction 8.2% (-0.2–15.9%), $P=0.055$).

The overall primary result in the European, Australian, and New Zealand centers (relative risk reduction of 7.0%) was not significantly different from the overall primary result in the North American centers (relative risk reduction of 10.9%). Not surprisingly, inasmuch as the overall trial result was only barely significant, neither of these regional results was nominally significant.¶

All of the prespecified intention-to-treat **secondary analyses** also favored clopidogrel, as did a revised primary endpoint that included all-cause mortality in place of "vascular" mortality. These results are shown in Table 4 on the next page; none of the differences was nominally significant ($0.08 \le P \le 0.71$). In the primary analysis and in each of the four secondary analyses, the numerical

* The protocol is somewhat ambiguous as to whether the logrank test was to be stratified, but various historical trial documents, provided by the sponsor with the submission of 13 August, convince us that stratification was intended.

† See Volume 161.1, page 107.

‡ See Volume 161.1, pages 104–107.

§ See Volume 161.1, page 97.

‖ See Volume 161.1, page 104.

¶ See Volume 161.1, pages 107–111.

Table 4
Outcome Events of the
Secondary Analyses

	clopidogrel	aspirin	relative risk reduction
patients	9599	9586	
IS, MI, amputation, vascular death	979 (10.2%)	1050 (11.0%)	7.5%
vascular death	350 (3.6%)	378 (3.9%)	7.6%
any stroke, MI, any death	1133 (11.8%)	1206 (12.6%)	6.9%
any death	560 (5.8%)	571 (6.0%)	2.2%
IS, MI, any death*	1108 (11.5%)	1173 (12.2%)	6.4%

* Reviewers' analysis, *not* protocol-specified.

from Volume 161.1, page 98

advantage of clopidogrel was visible by six months and (with one exception) sustained at one, two, and three years.*

As noted under "Patient retention" on page 16, about a quarter of the patients discontinued study drug prematurely, and only a minority of these discontinuations were related to outcome events. In another protocol-specified analysis, the investigators reexamined the primary endpoint, excluding events that occurred more than 4 weeks after study drug had been discontinued. As shown in Table 5 on the next page, these results are extremely similar to those of the primary analysis; the new relative risk reduction is 9.4%, with $P=0.046$.

Efficacy and qualifying condition. When the primary analysis is separately repeated on each of the three diagnostic groups, the results are heterogeneous. The treatment×group interaction is significant at $P=0.043$, and (as shown in Table 6 on the next page and in the figure on page 20) the point estimates for relative risk reduction vary from 23.7% in the PAD group down to -4% (that is, a relative risk *increase*) in the MI group.† As shown in Table 7 on page 21, the same pattern was seen in selected combinations of the secondary analyses. If the effect were really uniform across the three groups, then the likelihoods of results as extreme as those seen in the extremal strata (the MI and PAD groups) would have been 0.067 and 0.13, respectively.‡

In the MI group, a plot of event-free survival reveals a slight edge for aspirin at most times, but a slight edge for clopidogrel at a few others. In the IS group, clopidogrel is superior at every time point, but never by much. In

* The one exception was for all-cause mortality at two years, which was slightly higher (5.83% *vs.* 5.82%) in the clopidogrel group. See Volume 161.1, pages 96–97 and 99.

† Not surprisingly, inasmuch as the overall trial result and the treatment×group interaction were each only barely significant, the clopidogrel-aspirin differences in the MI and IS groups were not statistically significant ($P=0.64$ and $P=0.26$, respectively).

‡ These probabilities can be derived using the formula given by Inglefinger, Mosteller, Thibodeau, and Ware in *Biostatistics in Clinical Medicine*, 2nd edition (New York: Macmillan, 1987), page 281 or by using percentiles of the *P*-value distribution based on the overall effect size, as given by Hung, O'Neill, Bauer, and Köhne in *Biometrics* **53**: 12 (1997).

Table 5
Outcome Events of the
Primary Analysis, Censored
4 Weeks After Study Drug Discontinued

	clopidogrel	aspirin
patients	9553	9546
IS (fatal or not)	385 (4.03%)	403 (4.22%)
MI (fatal or not)	225 (2.36%)	283 (2.96%)
other vascular death	165 (1.73%)	166 (1.74%)
total	775 (8.11%)	852 (8.93%)

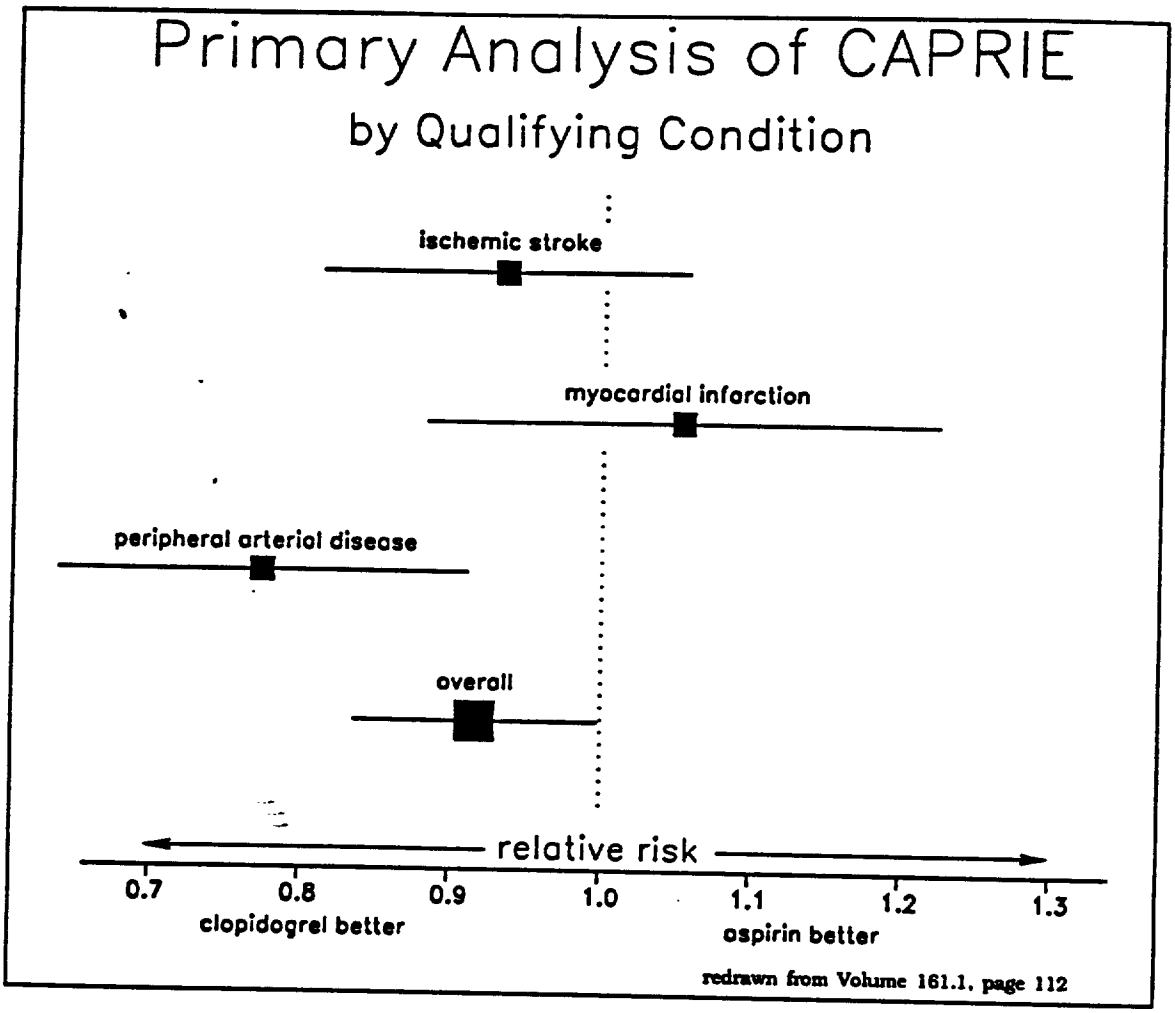
from Volume 161.1, page 101

IS group, clopidogrel is superior at every time point, but never by much. In the PAD group, the curves separate after two or three months, and they seem (see Volume 161.1, pages 113–115) to separate further over time.

Table 6
Outcome Events of the
Primary Analysis
by Diagnostic Group

	clopidogrel	aspirin	relative risk reduction (95% C.I.)
IS group			
patients	3233	3198	
IS (fatal or not)	315 (9.74%)	338 (10.57%)	
MI (fatal or not)	44 (1.36%)	51 (1.59%)	
other vascular death	74 (2.29%)	72 (2.25%)	
total	433 (13.39%)	461 (14.42%)	7.3% (-5.7, 18.7)
MI group			
patients	3143	3159	
IS (fatal or not)	42 (1.34%)	41 (1.30%)	
MI (fatal or not)	163 (5.19%)	174 (5.51%)	
other vascular death	86 (2.74%)	67 (2.12%)	
total	291 (9.26%)	282 (8.93%)	-4.0% (-22.5, 11.7)
PAD group			
patients	3223	3229	
IS (fatal or not)	81 (2.51%)	82 (2.54%)	
MI (fatal or not)	68 (2.11%)	108 (3.34%)	
other vascular death	66 (2.05%)	87 (2.69%)	
total	215 (6.67%)	277 (8.58%)	23.7% (8.9, 36.2)

from Volume 161.1, pages 73 and 111



Covariate Influence on Efficacy. Even though the heterogeneity among the three diagnostic groups is statistically significant, the point estimates cited above might not be the best estimates of the effect to be seen in patients like those who were recruited into the three respective diagnostic groups. Before the demonstrated heterogeneity can be turned into prediction, one must face difficult problems of estimation and of description.

Although CAPRIE was designed to detect heterogeneity in efficacy among the diagnostic groups, it was *not* designed to provide separate estimates of the effect size in each group. If the trial population had been (biologically) homogeneous, then the best estimates of effect for any subgroup would be obtained not from only the data pertaining to that subgroup, but rather from the parent population. Oppositely, when two or more subgroups are expected to experience totally unrelated effects of an intervention (for example, in an amantadine trial that recruited (a) patients with Parkinson's disease and (b) patients at risk of infection with influenza A virus), then the best statistics describing each group are of course computed from only the data obtained from that group. The situation here is intermediate, and there is no established procedure for weighting the group data against the overall data.

Table 7
Outcome Events of
Selected non-Primary Analyses
by Diagnostic Group

	clopidogrel	aspirin	relative risk reduction (95% C.I.)
IS group			
patients	3233	3198	
IS, MI, any death	511 (15.85%)	527 (16.48%)	4.3% (-8.1, 15.2)
any stroke, MI, any death	527 (16.30%)	550 (17.20%)	5.5% (-6.5, 16.1)
MI group			
patients	3143	3159	
IS, MI, any death	319 (10.15%)	312 (9.88%)	-3.0% (-20.4, 11.9)
any stroke, MI, any death	322 (10.24%)	315 (9.97%)	-3.0% (-20.3, 11.8)
PAD group			
patients	3223	3229	
IS, MI, any death	278 (8.63%)	334 (10.34%)	18.3% (4.2, 30.3)
any stroke, MI, any death	284 (8.81%)	341 (10.56%)	18.3% (4.3, 30.2)

In particular, it is difficult to decide whether the best estimate of effect in the MI group should really be adverse, as it is in Tables 6 and 7 and in the figure. From the test described by Gail and Simon,* the apparent adverse effect could easily be a result of chance ($P=0.71$), but our 10 000-run simulation shows that even if the point estimates of the tables and figure were correct, the Gail-Simon test would have only 5.5% power to detect the adverse effect. That is, the Gail-Simon test doesn't really help in deciding whether the apparent adverse effect was the result of chance.

Moreover, whatever estimate of within-group effect size one accepts, it is not clear which were the pivotal characteristics that caused the three groups to be associated with such different results. For example, as shown in Table 2 on page 15, many of the patients in the PAD and IS groups had had myocardial infarctions (although not necessarily within the qualifying time period). If the effect-determining characteristic of patients in the MI group were their histories of having had MIs, then one might expect the IS and PAD patients who had had infarctions to have derived less benefit from clopidogrel than infarction-free members of their respective cohorts.

Such was not the case. For patients in the IS and PAD groups, having had an MI was associated with a substantial increase in the incidence of primary outcome events during the trial, but (as shown in Table 8 on the next page) the relative benefit of clopidogrel over aspirin appeared to be *greater* in these patients than it was in their infarction-free colleagues.

* *Biometrics* 41: 361-372 (1985).

Table 8
Outcome Events of the Primary Analysis
by non-MI Diagnostic Group
and History of MI

	clopidogrel	aspirin	relative risk reduction
IS group			
history of MI	86/413 (20.8%)	87/364 (23.9%)	12.9%
no such history	347/2820 (12.3%)	374/2834 (13.2%)	6.8%
PAD group			
history of MI	78/686 (11.4%)	109/681 (16.0%)	28.8%
no such history	137/2537 (5.4%)	168/2548 (6.6%)	18.2%

Clopidogrel's relatively poor performance in the MI group might somehow be related to the fact that those patients had all had *recent* infarctions, probably more recent than those experienced by any but a very few of the patients in the other two groups. This possibility has not been investigated.

Because they were specifically defined by the inclusion criteria, the three diagnostic groups are natural targets of analysis, but they are not the targets of any preferred analysis prespecified by the CAPRIE protocol. For this reason, exploratory analysis that tries to account for the observed heterogeneity should be free to look for other cofactors (*i.e.*, other than qualifying condition) that might better account for the observed variance. We have tried to identify such cofactors, but without success.

Increasing age, for example, was strongly associated with an increasing incidence of outcome events ($P=0.0001$); the clopidogrel/aspirin relative risk ratio was heterogeneous across the age groups ($P=0.009$); and the MI group was substantially younger than either of the others ($\chi^2_3 = 1277$, $P<10^{-648}$). We anticipated that clopidogrel's advantage over aspirin would rise with age in every group, and that the relatively poor performance of clopidogrel in the MI group could arguably be better described as relatively poor performance in younger patients. As shown in Table 9 on the next page, however, this speculation is not borne out by the data. What is evident in Table 9 is that the clopidogrel/aspirin benefit actually *declines* with age in the IS and PAD groups, while its relation to age in the MI group is nonmonotonic.

A Cox regression analysis (which allowed age to be treated as a continuous, rather than categorical, variable) gave results that were consistent with those shown in Table 9. That is (as shown in Table A3 in the Appendix), age had some explanatory power in each of the three groups, but the effect varied from group to group.

As shown (in part) in Table 2 on page 15, the three diagnostic groups differed in many of their other pre-randomization characteristics. In a series of

Table 9
Outcome Events of the
Primary Analysis by
Diagnostic Group and Age

group and age	clopidogrel	aspirin
IS group		
<55	52 (8.6%)	60 (10.4%)
55–64	99 (10.7%)	111 (12.6%)
65–74	155 (14.2%)	167 (14.9%)
>75	127 (20.9%)	123 (19.7%)
MI group		
<55	65 (5.4%)	60 (5.1%)
55–64	69 (7.3%)	94 (9.4%)
65–74	94 (12.6%)	82 (11.2%)
>75	63 (24.5%)	46 (18.5%)
PAD group		
<55	15 (2.8%)	31 (5.7%)
55–64	54 (5.6%)	68 (7.2%)
65–74	93 (7.1%)	127 (9.9%)
>75	53 (12.7%)	51 (11.2%)

analyses shown in Tables A4–A20 in the Appendix, we attempted to identify one or more of these cofactors that might account for the apparent intergroup differences through a treatment×cofactor interaction. We examined smoking status, any concomitant disease reported to have been present in at least 10% of the population, and concomitant medications. With scattered small exceptions best attributed to chance, the performance of clopidogrel and aspirin in the identified subgroups (IS patients with/without hypertension, MI patients receiving/not receiving calcium antagonists, and so on) was similar to that seen in the larger groups.

Finally, we performed a series of multifactor Cox regression analyses, thinking that even though the treatment×qualifying-condition interaction could not be explained away by any single covariate, perhaps it would fall to an attack by many at once. Our ultimate analysis included 28 covariates; after all of that (as shown in Table 10 on the next page), the heterogeneity among the diagnostic groups was essentially unchanged.

Comparison to placebo. Because clopidogrel and placebo have never been compared in a single trial, any estimate of their relative efficacy must rest upon a combination of CAPRIE (clopidogrel/aspirin) and one or more other trials (aspirin/placebo).

The aspirin/placebo data have been exhaustively reviewed by the Oxford-based Antiplatelet Trialists' Collaboration ("the Trialists").* The work of the

* See, *inter alia*, their "Collaborative overview of randomised trials of antiplatelet therapy I" in *British Medical Journal* 308: 81–106 (1994).

Table 10
Risk Reduction by Qualifying Condition
After Adjustments for Various Cofactors

covariates included	Qualifying Condition IS	MI	PAD	overall*
none	7.3%	-4.1%	23.5%	8.5%
age, diabetes, smoking status	5.1%	-4.1%	22.7%	7.6%
everything except anchovies†	5.3%	-6.8%	19.2%	5.7%

* Adjusted for qualifying condition.

† Age, sex, diabetes, smoking status, cardiac surgery, congestive heart failure, hypercholesterolemia, hypertension, previous MI, cardiac arrhythmia, previous ischemic stroke, stable angina, unstable angina, transient ischemic attack, ACE inhibitors, antidiabetic therapy, anti-epileptic therapy, β-blockers, calcium-channel blockers, estrogens, anti-lipid products, coronary vasodilators, digitalis glycosides, diuretics, peripheral vasodilators, anti-inflammatory products, anti-thrombotic products, and peripheral surgical interventions.

Trialists has been reviewed by Dr. Ganley and one of us (JH), and we here include only the high points of that analysis.

The Trialists concluded that aspirin is more or less uniformly beneficial in patients at risk of atherothrombotic events. Their papers, however, are sufficiently data-rich that one may do one's own analysis and draw one's own conclusions.

Many of the trials analyzed by the Trialists (and by Ganley & Hung) recruited patients who were reasonably similar to the patients recruited into one or another of the diagnostic groups of CAPRIE. Other trials' patients were a looser fit to CAPRIE, notably those who had had TIAs as their only manifestation of cerebrovascular disease. As it turns out, the results of the Ganley-Hung analysis are not much affected by inclusion or exclusion of the TIA patients.

The results are also reasonably robust with respect to variation in meta-analytic technique. Our preferred technique is to compute overall results by weighting the individual study results by their sample sizes, but alternative schemes (weighting studies equally; pooling at the patient level) give results that are only trivially different. Similarly, we prefer to exclude studies in which no outcome events were observed, but inclusion of such studies has little effect here.

The results of our preferred analysis for the composite of stroke, MI, and cardiovascular death are shown in Table 11 on the next page. Table 12 on the next page is similar, with the endpoint expanded to include noncardiovascular death. In either table, one sees a strong protective effect of aspirin in the MI group and a slightly weaker effect in the IS/TIA group. In the PAD group, perhaps because of the much smaller population of patients studied, the results are equivocal. The best-estimate overall effect in a CAPRIE-like population is a risk reduction of 15–20%.

Table 11
Effect of Aspirin (*vs.* Placebo) on
Stroke, MI, and Cardiovascular Death

group	trials	patients ASA	patients placebo	odds ratio (95% C.I.)
MI	Cardiff I, Cardiff II Paris I, AMIS, CDP-A, GAMIS, Micristin	6286	5913	0.76 (0.68–0.84)
IS	AICLA, Britton, SALT	1127	1140	0.83 (0.68–1.01)
IS (& TIA)	AICLA, Britton, SALT, AITIA, UK-TIA, Canadian cooperative	3054	2250	0.84 (0.74–0.96)
PAD	Hess, Schoop-I, Munich-A, Munich-B	545	534	0.96 (0.48–1.92)

from Table 4 of the Ganley-Hung review

Moreover, the group-specific results are strangely complementary to those of CAPRIE. Where clopidogrel looks best against aspirin (that is, in the PAD group), aspirin is of unproved value *viz-à-viz* placebo. Where clopidogrel appears to be no better than aspirin (that is, in the MI group), aspirin is markedly superior to placebo.

In a report written for the sponsor (included in the submission of 20 August), Lloyd Fisher estimated that with respect to the primary composite endpoint of CAPRIE, the overall clopidogrel/placebo odds ratio was 70.5%. Dr. Fisher went on to compute confidence limits for this estimate of the

Table 12
Effect of Aspirin (*vs.* Placebo) on
Stroke, MI, and Death

group	trials	patients ASA	patients placebo	odds ratio (95% C.I.)
MI	Cardiff I, Cardiff II Paris I, AMIS, CDP-A, GAMIS, Micristin	6286	5913	0.78 (0.70–0.86)
IS	AICLA, Britton, SALT	1127	1140	0.81 (0.67–0.97)
IS (& TIA)	AICLA, Britton, SALT, AITIA, UK-TIA, Canadian cooperative	3054	2250	0.80 (0.70–0.90)
PAD	Hess, Schoop-I, Munich-A, Munich-B	545	534	1.07 (0.55–2.07)

from Table 5 of the Ganley-Hung review

clopidogrel/placebo odds ratio; the probability that this odds ratio could really be ≥100%; similar estimates, confidence limits, and *P*-values for components of the endpoint; similar estimates, confidence limits, and *P*-values for modified endpoints (*e.g.*, counting all-cause mortality instead of vascular mortality); and reanalyses by qualifying condition. We agree with Dr. Fisher that clopidogrel seems highly likely to be more effective than placebo in every identifiable subgroup.

We are unwilling to say more than that. As noted on page 3 of the Ganley-Hung review, the covariates that might influence the aspirin/placebo odds-ratio calculation include duration of treatment, duration of followup, secular changes in concomitant treatment, and many others. We believe that adequate adjustment for these covariates is not possible, so that while we do not quarrel with Dr. Fisher's calculations *per se*, we believe that any interpretation of his combined odds-ratio, confidence-limit, and *P*-value results is problematic.

Safety

Pre-CAPRIE trials. Exposure to clopidogrel in pre-CAPRIE trials was limited (about 270 patient-years, compared to almost 16 000 patient-years in CAPRIE), but the patients in the early trials were generally followed more closely than those of CAPRIE. Also, many of the early trials used ticlopidine and/or placebo controls, both of which were absent in CAPRIE.

All of the clopidogrel-exposed patients in CAPRIE received 75 mg daily, while dosing in the pre-CAPRIE trials included doses ranging from 10 to 600 mg. One might hope that subtle safety information might be teased out of dose-response observations, but the total exposure to doses other than 75 mg was only about 6 patient-years.

On pages 153–155 of Volume 1.173, the sponsor summarizes the data regarding each adverse event that occurred with frequency≥2% in the pre-CAPRIE studies; a more detailed listing appears on pages 17–29 of Volume 1.175. In an attempt to expose dose-response signals, the clopidogrel exposures are tabulated by separating doses less than 75 mg, equal to 75 mg, or greater than 75 mg. The other columns of these displays are for placebo and "other drug" (usually ticlopidine). These tables must be interpreted together with the tables of ADR-related dropouts on pages 168–171 of Volume 1.73.

Many of the apparent findings in this sort of tabulation are likely to be spurious. For example, abnormal pre-CAPRIE laboratory findings are listed and described on pages 172–180 of Volume 1.73. The hematocrit dropped below the normal range in fully 20% of the clopidogrel-exposed patients, but in only 9% of the patients exposed to placebo. That sounds bad, but 38% of the clopidogrel cases turn out to have been patients who underwent coronary bypass surgery in a trial (P1398, Volume 1.129) that had no placebo control. When examining the pooled pre-CAPRIE data, one must remember that the various treatment groups were not selected from the same population. Without keeping this consideration in mind, one might (for example) have difficulty understanding the finding that

the incidence of "any event" in the 75-mg clopidogrel group was 43%, but the incidence in the subjects who received *higher* doses was only 12%.

Of the tabulated varieties of adverse event, many were no more common with clopidogrel than with placebo. Table 13 below lists the ADRs of interest.

- Most of the "autonomic nervous system disorders" were cases of **flushing**. In addition, "hot flushes" are recorded under the Body As A Whole category, where there were 1 case on low-dose clopidogrel, 4 cases on 75 mg of clopidogrel, and 1 case on placebo, for an incidence of 0.6% in each group.

- There was only one case of **chest pain** that was reported to be substernal, but we can't tell whether "chest pain" and "substernal chest pain" were recorded as overlap-

Table 13
Number (%) of pre-CAPRIE Subjects
With Adverse Events Occurring
More Often with Clopidogrel than with Placebo and
(a) Associated with Discontinuation or
(b) Seen in at least 2% of Subjects

	clopidogrel 75 mg	placebo
autonomic nervous system disorders	16 (2.2%)	0
chest pain	20 (2.8%)	3 (1.9%)
headache	63 (8.7%)	10 (6.5%)
diarrhea	20 (2.8%)	1 (0.7%)
ulcerative stomatitis	5 (0.7%)*	0
bleeding, clotting, or platelet disorder	72 (10.0%)	6 (3.9%)
hematoma	25 (3.5%)	0
laboratory abnormalities	15 (2.1%)†	0
pharyngitis	9 (1.2%)‡	1 (0.6%)
purpura	10 (1.4%)§	4 (2.6%)
rhinitis	19 (2.6%)	2 (1.3%)
skin disorders	35 (4.9%)	4 (2.6%)
white-cell and reticuloendothelial disorders	15 (2.1%)	0

* Listed because stomatitis was also reported in 3 (2.5%) of subjects exposed to clopidogrel doses greater than 75 mg.

† These included 1 subject with SGPT increased, 1 with "hepatocellular damage," 12 with unspecified hepatic enzymes increased (1 of whom also had increased creatine phosphokinase), and 1 with hypercholesterolemia. Of these subjects, only the patient with CPK elevation withdrew from treatment.

‡ Listed because pharyngitis was also reported in 4 (2.4%) of subjects exposed to clopidogrel doses less than 75 mg. In addition, it may be pertinent that coughing was reported by 4 (0.6%) of subjects receiving clopidogrel 75 mg, 1 subject (0.8%) receiving a higher dose, and no subjects receiving placebo. Three patients with pharyngitis and/or coughing withdrew from trials.

§ Listed because purpura was also reported in 5 (4.1%) of subjects exposed to clopidogrel doses greater than 75 mg.

ping or as mutually exclusive categories. Events in this area were, in any case, better studied in CAPRIE.

- The **headache** and **diarrhea** cases speak for themselves.

- The **pharyngitis/rhinitis/cough** entries are a little implausible, but of course that's what we once thought about ACE-inhibitor-induced cough, too. Should the subject with angioedema (now listed with the dermatologic problems; see below) have been listed here? Not counting the subject with angioedema, 4 of these subjects withdrew from treatment.

- The hemostasis-related events seen in these trials should be ignored, inasmuch as the same phenomena were better studied in CAPRIE.

- The "skin disorders" category included **rashes** (bullous, erythematous, folliculitic, maculopapular, psoriaform, urticarial/dermatographic, and unspecified), **itching**, and one case of **angioedema**. The angioedema patient and 14 others withdrew from treatment. The incidence of events was low in each of the subcategories, but something is definitely going on. Could the **stomatitis** cases have been lichen planus?

- We don't know what to make of the "white-cell and reticuloendothelial disorders" category. The 15 patients were associated with 18 reported events, consisting of eosinophilia (2, one of whom withdrew from treatment), granulocytopenia (2), leukocytosis (4), lymphadenopathy (2), cervical lymphadenopathy (1), monocytosis (1, who withdrew from treatment), neutropenia (1), and an unspecified white-cell disorder (5). This is such a mixed bag that we are inclined to believe that there is no signal worth tracking, unless something shows up in CAPRIE.

Ignoring the most flagrantly uninterpretable categories, and ignoring disorders of hemostatic mechanism (better studied in CAPRIE), the laboratory values of note are shown in Table 14 on the next page. The implications of these findings will be discussed with the findings of CAPRIE.

Clopidogrel was compared to **ticlopidine** in four pre-CAPRIE trials, but the total ticlopidine exposure in these trials was about 30 patient-months, so stable comparative results could not be obtained.

Fourteen early **Japanese** clopidogrel studies are also described in the application (Volume 1.173, pages 205–224). The total clopidogrel exposure in these studies was less than 2 patient-years, and the tabulated events and abnormalities are not different, better described, or different in frequency from those described elsewhere.

Table 14
Number (%) of pre-CAPRIE Subjects
With Laboratory Abnormalities Occurring
More Often with Clopidogrel than with Placebo and
Seen in at least 2% of Subjects

	clopidogrel 75 mg	placebo
leukopenia	115 (17.0%)	7 (5.5%)
lymphopenia	14 (2.2%)	1 (0.8%)
monocytopenia	17 (2.7%)	0
neutropenia	44 (6.8%)	3 (2.5%)
ALT increased	41 (6.1%)	0
AST increased	66 (9.8%)	0
hypercholesterolemia	13 (2.1%)	1 (0.9%)
creatinine increased	26 (4.0%)	0
hypertriglyceridemia	35 (6.8%)	6 (6.1%)

Safety findings of CAPRIE. Some adverse events reported in CAPRIE were of significantly different incidence between the treatment groups, and others are of interest because of findings in the pre-CAPRIE studies discussed above. Adverse-event findings of these varieties are displayed in Table 15 on the next page. Most of Table 15 is taken from the sponsor's table on pages 66–67 of Volume 1.173, but some entries had to be obtained by interrogation of the database in the sponsor's CANDA.

Some concerns raised by the pre-CAPRIE database are alleviated, or at least put into context, by the larger-scale database from CAPRIE. For example, while **flushing** was significantly more commonly reported with clopidogrel than with placebo in the early studies, the incidence of flushing in CAPRIE was slightly greater among aspirin patients than among clopidogrel patients. Similarly, the data shown in Table 15 should dissipate concerns about **angioedema** and **stomatitis**, and although **headache** was weakly associated with clopidogrel in the earlier trials, in CAPRIE it was only slightly more frequent with clopidogrel than with the analgesic aspirin. The **pharyngitis/rhinitis/cough** cluster is also no longer impressive, although one might have a small nagging worry that some cough might arise as an asthma equivalent, so that with respect to this adverse effect aspirin might be an (adversely) active control.

Other findings from the pre-CAPRIE studies are reinforced by CAPRIE, notably the associations of clopidogrel with **diarrhea** and with a wide range of **skin problems.***

* The reported dermatopathology ranges from alopecia through xerosis. Acutely life-threatening conditions (Stevens-Johnson syndrome, epidermal necrolysis, *etc.*) were not reported; the clopidogrel group included 22 bullous eruptions, while the aspirin group included 15 bullous eruptions and one "pemphigoid reaction." Many of the CANDA-tabulated data appear nonspecifically as "rash" or "skin disorder."

Table 15
Number (%) of CAPRIE Patients
With Adverse Events Occurring
(a) Significantly More Often in One Treatment Group, or
(b) Otherwise of Interest

	clopidogrel	aspirin
abdominal pain	541 (5.64%)	684 (7.14%)‡
angibedema	8 (0.08%)	11 (0.11%)
constipation	228 (2.38%)	319 (3.33%)‡
cough	220 (2.29%)	175 (1.83%)*
diarrhea	428 (4.46%)	322 (3.36%)‡
dyspepsia	501 (5.22%)	585 (6.10%)†
flushing	21 (0.22%)	23 (0.24%)
headache	730 (7.60%)	694 (7.24%)
heart rate & rhythm disorders	409 (4.26%)	483 (5.04%)*
hypertension	415 (4.32%)	487 (5.08%)*
pharyngitis	22 (0.23%)	16 (0.17%)
purpura	506 (5.27%)	353 (3.68%)‡
rhinitis	403 (4.20%)	405 (4.22%)
skin disorders	1518 (15.81%)	1254 (13.08%)‡
stomatitis	31 (0.32%)	35 (0.37%)
bleeding, clotting, or platelet disorder	(see text)	
white-cell and reticuloendothelial disorders	(see text)	
other laboratory findings	(see text)	

* $P \leq 0.05$.
† $P \leq 0.01$.
‡ $P \leq 0.001$.

CAPRIE demonstrated that aspirin is associated with a slightly higher incidence of cardiac arrhythmias than is clopidogrel, but the reported arrhythmias ranged from extrasystoles to cardiac arrest, and these events seem to be hopelessly confounded with the outcome events. Table 15 also shows that aspirin is more likely than clopidogrel to cause **abdominal pain**, **constipation**, **dyspepsia**, and **hypertension**, but the differences in incidence are probably not sufficient to alter the behavior of clinicians. A number of other small differences in symptomatic endpoints are described on pages 68–80 of Volume 1.173; some of the differences were nominally statistically significant, but the comparisons are taken from among so many that they are not convincing.

Disorders of hemostasis were of course given special attention. Some of these (non-ischemic strokes) were scored as secondary outcome events, but many less serious events were also recorded. An intent-to-treat analysis of hemorrhage counted intracranial hemorrhages (fatal or not) and other hemorrhagic deaths. As shown in Table 16 on the next page, these events were infrequent, but consistently less frequent in the clopidogrel group than in the aspirin group. In addition, Table 17 on the next page lists all of the pertinent-seeming events we could find in the sponsor's CANDA. Incidence rates (percentages) are omitted to

Table 16
Major Hemorrhagic Events

	clopidogrel	aspirin
patients	9599	9586
nonfatal intracranial hemorrhage	14 (0.15%)	24 (0.25%)
fatal intracranial hemorrhage	16 (0.17%)	16 (0.17%)
other fatal hemorrhage	7 (0.07%)	11 (0.11%)

from Volume 161.1, page 100

conserve space, but the exposed groups were so nearly identical in size (9599 *vs.* 9586) that the raw counts are not misleading. As is seen Table 17, some events were much more common in one group than the other (more purpura with clopidogrel, $P<0.001$; more gastrointestinal bleeding with aspirin, $P<0.05$).

In clinical trials of the congener drug ticlopidine, 50/2048 patients (2.4%) developed **neutropenia** (counts less than 1.2 G/L), and a third of these patients had counts less than 0.45 G/L. As described under "Patient monitoring" on page 12, CAPRIE patients were (at least initially) intensively monitored in an attempt to detect any similar effect in association with clopidogrel. In the preplanned analysis, cases of apparent neutropenia were reviewed in blinded

Table 17
Number of CAPRIE Patients
With Bleeding-Related Adverse Events

	all events		events called serious	
	clop	ASA	clop	ASA
hemorrhagic duodenal ulcer	17	14	17	13
epistaxis	281	245	11	12
hemorrhagic gastric ulcer	8	12	7	11
rectal hemorrhage	52	75	5	15
hemorrhagic gastritis	4	4	4	4
peptic ulcer	6	13	3	5
purpura	506	353	3	0
hemothorax	4	1	2	1
perforated gastric ulcer	1	3	1	3
retroperitoneal hemorrhage	2	2	1	2
hyphema	16	9	1	0
hemorrhagic cystitis	3	0	1	0
respiratory tract hemorrhage	1	1	1	0
pulmonary hemorrhage	1	0	1	0
vaginal hemorrhage	18	15	0	4
hemopericardium	0	1	0	1
oral hemorrhage	2	5	0	1
aggravation of peptic ulcer	0	2	0	0
uterine hemorrhage	2	6	0	0

fashion by a hematologist; the hematologist, unlike the investigators, could reject some results as being laboratory errors or insignificant changes from low baseline values.

The reports of the investigators and the hematologist are summarized in Table 18 on the next page. In addition, capsule summaries of the 7 cases in which counts were below 0.45 G/L are tabulated on pages 84–85 of Volume 1.173. The aspirin patient rejected by the hematologist had a nadir neutrophil count of 0.397 G/L, but it had been only 0.866 G/L at baseline. In all 4 of the clopidogrel patients and one of the remaining aspirin patients, neutrophil counts returned to normal after the drug was discontinued; the other aspirin patient was an 81-year-old man who remained granulocytopenic despite withdrawal of aspirin.

Also, graphs on pages 102–112 of Volume 161.11 show that at almost every time of measurement, CAPRIE patients receiving clopidogrel had lower counts of basophils, eosinophils, lymphocytes, monocytes, platelets, and neutrophils than did the patients receiving aspirin. From the error bars and the values shown, the many differences are usually statistically significant, but never clinically so.*

Clopidogrel may have a weak neutropenic effect, and it may even be capable of causing agranulocytosis. CAPRIE clearly demonstrates, however, that this neutropenic effect (if it is real) is at least one or two orders of magnitude weaker than that of ticlopidine.

Clopidogrel and aspirin had statistically different effects on many different **laboratory values**, but most of the effects were clinically trivial. For example, total bilirubin was consistently significantly higher in the clopidogrel group, but the values at a typical time point were 0.570±0.005 mg/dL (clopidogrel) and 0.546±0.003 mg/dL (aspirin). Similar results were seen in measurements of albumin and calcium (trivially higher in the clopidogrel group) and of creatinine, cholesterol, sodium, alkaline phosphatase, uric acid,† and hepatocellular enzymes (trivially higher in the aspirin group). On some other tests (cholesterol, LDL cholesterol, triglycerides), the two treatment groups could not be distinguished statistically, let alone clinically.‡

Adverse events that led to **early discontinuation of therapy** are tabulated on page 94 of Volume 1.173. The overall rates of early discontinuation were almost identical (11.94% *vs.* 11.92%) in the two treatment groups. As grounds for withdrawal, categories of adverse events appeared in the two treatment groups in the same pattern as before: more gastrointestinal problems with aspirin, more dermatologic problems with clopidogrel, and so on.

---

* The opposite pattern was seen with hemoglobin and red-cell count. Both of these values rose steadily in both treatment groups, from 14.4 to 14.7 g/dL and 4.7 to 4.8 T/L, respectively. At almost every on-treatment time of measurement, each value in the clopidogrel group was statistically significantly higher than the corresponding value in the aspirin group, but these differences (and, for that matter, the overall differences from baseline) were all clinically meaningless.

† The incidence of frank gout was actually somewhat higher in the clopidogrel group than in the aspirin group (175 *vs.* 132, $P<0.025$).

‡ For all of these laboratory results, see pages 116–125 of Volume 1.173 and pages 89–101 of Volume 161.11.

Table 18
Number of CAPRIE Patients
With Certain Treatment-Emergent Neutrophil Counts

	per investigator		per hematologist	
	clop	ASA	clop	ASA
agranulocytosis	2	0	2	0
0 < count < 0.45 G/L	2	3	2	2
0.45 ≤ count < 1.2 G/L	22	20	4	12
count ≥ 1.2 G/L, but decreased	43	27	not done	

Conclusions

Biopharmaceutic issues. We do not frequently see applications for drugs whose active moiety is unidentified. Such a situation must always lead to concern that under one or another circumstance of metabolic derangement, the pharmacokinetics of the drug will be unpredictably altered, with corresponding unpredictable effects on pharmacodynamics.

Clopidogrel's high bioavailability provides some comfort. In addition, one can derive considerable reassurance from the results of Study PDY3079 (page 6 above). In that study, the pharmacodynamics of clopidogrel were essentially unchanged despite 50-fold increases in the peak levels of the parent compound.

Despite *in vitro* evidence that clopidogrel is a moderate inhibitor of P_{450} (2C9), there were no interpretable trials to estimate the magnitude of clopidogrel's effect upon the metabolism of drugs dependent upon this enzyme. The affected drugs include tamoxifen, tolbutamide, and warfarin.

Relative efficacy of clopidogrel and aspirin. Clopidogrel is probably more effective than aspirin in prevention of the secondary complications of atherosclerosis. We say that clopidogrel is only "probably" more effective because the data come from only a single trial (CAPRIE), and the results of that trial were only marginally significant. Even within CAPRIE, the results were heterogeneous, with clopidogrel showing no advantage in certain subpopulations.

In some other ways, however, CAPRIE demonstrated robust internal consistency. As described on pages 16–18 above, essentially all of the various efficacy results of CAPRIE supported the superiority of clopidogrel. Some of the results (*e.g.*, analysis using nonadjudicated endpoints) were so tightly correlated to the primary result that they could not possibly provide much additional information or comfort, but other results (*e.g.*, analyses of the separate components of the composite endpoint, or analysis of non-first outcome events) had a measure of confirmatory independence. When analyses excluded events that might have been expected to be unrelated to treatment (*e.g.*, non-vascular deaths, or any events occurring long after treatment was discontinued), the apparent benefit of clopidogrel was consistently increased.

Relative efficacy in various subpopulations. Over the population at risk as recruited into CAPRIE, the efficacy of clopidogrel relative to aspirin is heterogeneous. The heterogeneity is a robust finding, with the same sort of statistical significance and internal confirmation as is available for the primary result of the trial.

The benefit of clopidogrel appeared to be greatest in patients with peripheral vascular disease and additional risk factors, and weakest in patients whose sole major sign of vascular risk was a recent myocardial infarction. CAPRIE allows one to estimate the relative efficacy in these groups, but these estimates (as with any estimates of effect in extremal subgroups) are likely to overstate the expected value of the deviation from the overall observed relative efficacy.

Relative efficacy of clopidogrel and placebo. Clopidogrel seems highly likely to be more efficacious than placebo in reducing the incidence of secondary complications of atherosclerosis. In the CAPRIE subgroup in which clopidogrel's superiority to aspirin was equivocal, aspirin's superiority to placebo seems to be well established. Conversely, in the subgroup in which the efficacy of aspirin is not established, clopidogrel appeared to be strongly superior to aspirin, so that clopidogrel could fail to be superior to placebo only if aspirin turned out to be substantially *inferior* to placebo.

Safety of clopidogrel. At the doses used in CAPRIE (respectively 75 mg and 325 mg daily), clopidogrel was associated with significantly more dermatologic problems, and aspirin was associated with significantly more bleeding. Adverse reactions leading to withdrawal were equally common in the two groups.

Unlike the congener drug ticlopidine, clopidogrel does not appear to cause neutropenia or agranulocytosis.

Recommendations by RRF

● Clopidogrel should be approved, indicated for the reduction of atherosclerotic events in patients with atherosclerosis made evident by recent stroke, recent MI, or established peripheral arterial disease.

● The CAPRIE trial should be described in the **Clinical Pharmacology** section of the labeling in language similar to this:

> Essentially all of the clinical evidence of clopidogrel's efficacy is derived from the CAPRIE trial. This was a 19 185-patient, 304-center, international, randomized, triple-blind, parallel-group study comparing clopidogrel (75 mg daily) to aspirin (325 mg daily). The patients randomized had recent histories of myocardial infarction (within 35 days); recent histories of ischemic stroke (within 6 months) with at least of week of residual neurological signs; or objectively established peripheral arterial disease. Patients received randomized treatment for an average of 1.6 years (range 1–3 years).

> The trial's primary outcome metric was the time to first occurrence of new ischemic stroke (fatal or not), new myocardial infarction (fatal or not), or other vascular death. In general, deaths not easily attributable to nonvascular causes were all classified as vascular.
>
> As shown in the table [here would be a table similar to our Table 3], clopidogrel was associated with a lower incidence of outcome events of every kind. The overall risk reduction (9.78% *vs.* 10.64%) was 8.7%, $P=0.045$. Clopidogrel was also associated with somewhat lower rates of vascular deaths (3.6% *vs.* 3.9%); all-cause mortality (5.8% *vs.* 6.0%); composite endpoints that counted all-cause mortality and all-cause strokes instead of vascular mortality and ischemic strokes; and all types of non-first outcome events (that is, new outcome events in patients who had survived an in-study stroke or myocardial infarction).
>
> The efficacy of clopidogrel relative to aspirin was heterogeneous across the population studied ($P=0.043$). The relative benefit of clopidogrel appeared to be strongest in patients who were enrolled because of peripheral vascular disease and who had also experienced myocardial infarction; weaker in other peripheral-vascular-disease patients; and weaker still in stroke patients (especially those who had not experienced myocardial infarction). In patients who were enrolled in the trial on the sole basis of a recent myocardial infarction, clopidogrel did not appear to be superior to aspirin. Although groups of the recruited patients differed in many demographic variables (patients in the myocardial infarction group were younger, patients in the peripheral-vascular-disease group were heavier smokers, and so on), adjustment for these variables did not reduce the intergroup differences in the relative efficacy of clopidogrel and aspirin.

- The "Drug Interactions" subsection of the **Precautions** section of the labeling should note that

> *In vitro*, clopidogrel inhibits P_{450} (2C9), and accordingly may be expected to interfere with the metabolism of **tamoxifen, tolbutamide, warfarin,** some **HMG CoA reductase inhibitors,** and many **non-steroidal anti-inflammatory agents.** 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 clopidogrel.

- Other parts of the labeling should be noncontentious.

Robert R. Fenichel, M.D., Ph.D.

H. M. James Hung, Ph.D.

Concur: Dr. Mahjoob
Dr. Chi 9/22/97

cc: NDA 20-839
HFD-110/RFenichel
HFD-110/SFredd
HFD-110/CGanley
HFD-111/DRoeder

Appendix

Detailed Statistical Tables

Table A1
Time to censoring (days) of the
56 CAPRIE Patients Lost to Followup

	clopidogrel	aspirin
patients	30	26
Percentile		
99th	1119	943
95th	1071	943
90th	823	882
75th	545	712
50th	420	520.5
25th	246	244
10th	48.5	46
5th	25	42
1st	22	29
Max		
Min		
Mean	428.3	474.6
s.d.	290.1	284.5

Table A2
Time in trial (days) of CAPRIE's
Intention-to-Treat Population

	clopidogrel	aspirin
Percentile		
99th	1109	1109
95th	1098	1098
90th	1092	1092
75th	873	881
50th	726	725
25th	488	488
10th	364	364
5th	358	358
1st	120	121
Max		
Min		
Mean	698.99	698.91
s.d.	256.34	256.35

Table A3
Cox Regression Analyses of Primary Endpoint by Age and Treatment (T) for Each Qualifying Condition

QC	model	deviance
IS	T	15113.56
	T, age* **	15035.11
	T, age, age²†	15031.98
	T, age***, T×age	15033.48
	T, age, age²†, T×age	15030.46
	T, age, age², T×age, T×age²	15029.92
MI	T	9775.61
	T, age***	9635.56
	T, age, age²**	9628.09
	T†, age***, T×age*	9631.58
	T†, age, age², T×age†**	9624.84
	T, age, age², T×age, T×age²	9623.11
PAD	T**	8274.59
	T**, age***	8207.36
	T**, age, age²	8207.09
	T*, age*, T×age***	8203.46
	T*, age, age², T×age†	8203.26
	T, age, age², T×age, T×age²	8202.79

The "best" models are shown in boldface.
† $0.05<P<0.10$; * $P<0.05$; ** $P<0.01$; *** $P<0.001$.

Table A4
Primary Outcome Event Rate by Qualifying Condition and Smoking Status

Qualifying Condition	smoking status	patients (%) with event clop	ASA
IS	current	99 (14.0)	116 (16.1)
	former	199 (14.4)	184 (13.1)
	never	135 (11.9)	161 (15.1)
MI	current	64 (7.4)	79 (8.7)
	former	157 (9.8)	133 (8.5)
	never	69 (10.4)	70 (10.2)
PAD	current	70 (5.7)	113 (9.2)
	former	122 (7.1)	126 (7.5)
	never	23 (8.5)	38 (12.6)

Table A5
Primary Outcome Event Rate by Qualifying Condition and Diabetes Mellitus

Qualifying Condition	diabetes mellitus	patients (%) with event clop	ASA
IS	yes	147 (18.3)	163 (19.5)
	no	286 (11.8)	298 (12.6)
MI	yes	59 (13.2)	57 (12.4)
	no	232 (8.6)	225 (8.3)
PAD	yes	84 (12.6)	91 (13.7)
	no	131 (5.1)	186 (7.3)

Table A6
Primary Outcome Event Rate
by Qualifying Condition
and Hypertension

Qualifying Condition	hypertension	patients (%) with event clop	ASA
IS	yes	286 (13.5)	305 (14.6)
	no	147 (13.2)	156 (14.0)
MI	yes	128 (10.6)	130 (10.9)
	no	163 (8.5)	152 (7.7)
PAD	yes	135 (8.2)	158 (9.7)
	no	80 (5.1)	119 (7.5)

Table A7
Primary Outcome Event Rate
by Qualifying Condition
and Unstable Angina

Qualifying Condition	unstable angina	patients (%) with event clop	ASA
IS	yes	23 (24.0)	23 (26.4)
	no	410 (13.1)	438 (14.1)
MI	yes	62 (11.6)	62 (11.3)
	no	229 (8.8)	220 (8.4)
PAD	yes	25 (12.0)	26 (13.7)
	no	190 (6.3)	251 (8.3)

Table A8
Primary Outcome Event Rate
by Qualifying Condition
and Stable Angina

Qualifying Condition	stable angina	patients (%) with event clop	ASA
IS	yes	89 (19.1)	85 (19.6)
	no	344 (12.4)	376 (13.6)
MI	yes	111 (14.1)	97 (12.5)
	no	180 (7.6)	185 (7.8)
PAD	yes	98 (11.6)	120 (13.9)
	no	117 (4.9)	157 (6.6)

Table A9
Primary Outcome Event Rate
by Qualifying Condition
and History of Cardiac Surgery

Qualifying Condition	cardiac surgery	patients (%) with event clop	ASA
IS	yes	25 (18.1)	31 (24.2)
	no	408 (13.2)	430 (14.0)
MI	yes	30 (10.9)	29 (11.8)
	no	261 (9.1)	253 (8.7)
PAD	yes	40 (10.9)	62 (18.5)
	no	173 (6.1)	215 (7.4)

Table A10
Primary Outcome Event Rate
by Qualifying Condition
and Use of Coronary Vasodilators

Qualifying Condition	coronary dilators	patients (%) with event clop	ASA
IS	yes	127 (23.5)	126 (23.7)
	no	306 (11.4)	335 (12.6)
MI	yes	237 (11.6)	216 (10.5)
	no	54 (4.9)	66 (6.0)
PAD	yes	110 (14.3)	148 (18.1)
	no	105 (4.3)	129 (5.4)

Table A11
Primary Outcome Event Rate
by Qualifying Condition
and Use of β-Blockers

Qualifying Condition	β-blockers	patients (%) with event clop	ASA
IS	yes	130 (16.8)	141 (18.2)
	no	303 (12.3)	320 (13.2)
MI	yes	186 (8.2)	204 (8.7)
	no	105 (12.0)	78 (9.5)
PAD	yes	68 (9.6)	91 (12.5)
	no	147 (5.9)	186 (7.4)

Table A12
Primary Outcome Event Rate
by Qualifying Condition
and Use of Calcium Antagonists

Qualifying Condition	calcium antagonists	patients (%) with event clop	ASA
IS	yes	197 (15.0)	210 (16.6)
	no	236 (12.3)	251 (13.0)
MI	yes	143 (11.5)	128 (10.1)
	no	148 (7.8)	154 (8.1)
PAD	yes	112 (9.8)	153 (12.7)
	no	103 (5.0)	124 (6.1)

Table A13
Primary Outcome Event Rate
by Qualifying Condition
and Use of ACE Inhibitors

Qualifying Condition	ACE inhibitors	patients (%) with event clop	ASA
IS	yes	150 (14.5)	177 (16.3)
	no	283 (12.9)	284 (13.5)
MI	yes	142 (14.3)	143 (13.6)
	no	149 (6.9)	139 (6.6)
PAD	yes	82 (10.6)	105 (13.4)
	no	133 (5.4)	172 (7.0)

Table A14
Primary Outcome Event Rate
by Qualifying Condition
and Use of Diuretics

Qualifying Condition	diuretics	patients (%) with event clop	ASA
IS	yes	173 (17.2)	185 (17.6)
	no	260 (11.7)	276 (12.9)
MI	yes	161 (19.4)	144 (17.3)
	no	130 (5.6)	138 (5.9)
PAD	yes	99 (10.6)	143 (15.1)
	no	116 (5.1)	134 (5.9)

Table A15
Primary Outcome Event Rate
by Qualifying Condition
and Use of Any Antilipid Therapy

Qualifying Condition	antilipid therapy	patients (%) with event clop	ASA
IS	yes	61 (10.8)	64 (11.4)
	no	372 (13.9)	397 (15.1)
MI	yes	66 (6.0)	66 (5.8)
	no	225 (11.0)	216 (10.7)
PAD	yes	42 (5.4)	64 (8.6)
	no	173 (7.1)	213 (8.6)

Table A16
Primary Outcome Event Rate
by Qualifying Condition
and Use of HMG-CoA Reductase Inhibitors

Qualifying Condition	reductase inhibitors	patients (%) with event clop	ASA
IS	yes	41 (10.7)	38 (10.3)
	no	392 (13.8)	423 (15.0)
MI	yes	57 (6.3)	53 (5.7)
	no	234 (10.5)	229 (10.3)
PAD	yes	32 (5.7)	49 (8.8)
	no	183 (6.9)	228 (8.5)

Table A17
Primary Outcome Event Rate
by Qualifying Condition
and Use of Antidiabetic Therapy

Qualifying Condition	antidiabetic therapy	patients (%) with event clop	ASA
IS	yes	138 (19.6)	150 (21.0)
	no	295 (11.7)	311 (12.5)
MI	yes	51 (13.9)	63 (15.7)
	no	240 (8.7)	219 (7.9)
PAD	yes	75 (12.3)	83 (14.1)
	no	140 (5.4)	194 (7.4)

Table A18
Primary Outcome Event Rate
by Qualifying Condition
and Use of Anti-inflammatory Products

Qualifying Condition	anti-inflammatories	patients (%) with event clop	ASA
IS	yes	49 (12.5)	58 (16.3)
	no	384 (13.5)	403 (14.2)
MI	yes	28 (7.7)	30 (8.5)
	no	263 (9.5)	252 (9.0)
PAD	yes	28 (6.9)	37 (9.8)
	no	187 (6.7)	240 (8.4)

Table A19
Primary Outcome Event Rate
by Qualifying Condition
and Use of Antithrombotic Products

Qualifying Condition	anti-thrombotics	patients (%) with event clop	ASA
IS	yes	179 (33.0)	204 (38.2)
	no	254 (9.4)	257 (9.7)
MI	yes	174 (19.4)	180 (20.2)
	no	117 (5.2)	102 (4.5)
PAD	yes	88 (16.6)	134 (21.6)
	no	127 (4.7)	143 (5.5)

Table A20
Primary Outcome Event Rate
by Qualifying Condition
and Use of Estrogens

Qualifying Condition	estrogens	patients (%) with event clop	ASA
IS	yes	14 (9.7)	17 (11.6)
	no	419 (13.6)	444 (14.6)
MI	yes	7 (6.3)	3 (3.4)
	no	284 (9.4)	279 (9.1)
PAD	yes	3 (2.8)	6 (5.2)
	no	212 (6.8)	271 (8.7)

NDEL

JUL 9 1997

Memo to the File

Date: June 30, 1997

Application: NDA 20-839
Plavix (clopidogrel bisulfate) Tablets

Sponsor: Sanofi

Subject: Trade Name Review

Sanofi's proposed trade name "Plavix" was found to be unacceptable by the FDA's nomenclature committee in their review of February 11, 1997. I informed the sponsor of their recommendation on April 30, 1997. The sponsor responded with an argument in favor of the Plavix name in a submission dated June 16, 1997. I forwarded Sanofi's response and all related documents to Dr. Lipicky for his review. He concluded that the trade name "Plavix" is acceptable (see attachment). I call Ms. Terrie Maloney at Sanofi and conveyed this information to her.

David Roeder
Regulatory Health Project Manager

Attachment

cc: ~~Orig~~ NDA 20-839
HFD-110
HFD-110/CSO

Dr. Lipicky,

Sanofi proposed the trade name "Plavix" for clopidogrel prior to the NDA submission (when it was still with Dr. Fredd). The nomenclature committee didn't like it because it sounds too much like Lasix. The firm was anxious to get a ruling on the issue, so I suggested that they submit an argument in support of "Plavix" and that I would send it up to you for a decision. So, here it is.

I've included the report from the Nomenclature committee. They are anxious to get a decision as soon as possible since this is a "P" application and they wouldn't have much time if they have to find a new name. Let me know if you have any questions.

Dave

Plavix sounds fine to me. If it is only my call, I say O.K. Plavix it is.

Lipicky

PLAVIX
(clopidogrel bisulfate)
Tablets
75 mg once daily

Note: In a recent submission (Serial number 175), the applicant states that they just got the name PLAVIX registered.

Indication: The prevention of vascular ischemic events (myocardial infarction, stroke, vascular death) in patients with a history of symptomatic atherosclerotic disease.

Description: pink, round, biconvex, engraved with "75" film coated tablet

Conflicting name	dosage form & dosage size	drug class	NDA approved
FLAREX	Ophthalmic suspension [HFD-550]	ophth-corticosteroid	19-079 2/11/86
FLAVINE (acriflavine)	a topical antiseptic used primarily in veterinary medicine. Dan Boring has stated in the April 18 e-mail that there is little potential for confusion with this product. NOTE: this was incorrectly spelled as FLAVIN in the consult response.		
LASIX	Round, White Tablet 20, 40, & 80 mg Injection & Oral Solution 20-80 mg once or twice daily. [HFD-110]	a potent diuretic	16-273 7/1/66 (Tablet)

OPG

REQUEST FOR TRADEMARK REVIEW

757

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Gastrointestinal and Coagulation Drug Products	**HFD-180**
Attention: Michael Folkendt, Project Manager	**Phone:** (301) 443-0487
Date: February 11, 1997 2/11/97	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: **PLAVIX**	**NDA/ANDA#** IND 34,663 (future NDA 20-839)
Established name, including dosage form: clopidogrel bisulfate	
Other trademarks by the same firm for companion products: -none-	
Indications for Use (may be a summary if proposed statement is lengthy): This drug is an antiplatelet agent for the reduction of the incidence of stroke, myocardial infraction, or vascular death in patients at risk.	
Initial Comments from the submitter (concerns, observations, etc.): -none-	

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original IND 34,663; HFD-180/division file; HFD-180/M.Folkendt; HFD-180/J.Sieczkowski

Rev. December 95

Consult #757 (HFD-180)

PLAVIX clopidogrel bisulfate

The following look-alike/sound-alike conflicts were noted: FLAREX, FLAVIN, LASIX. The Committee believes there is a significant potential for mix-up between these products and the proposed name. There were no misleading aspects found in the proposed proprietary name.

The Committee finds the proposed proprietary name unacceptable.

D Boring 3/27/97, Chair
CDER Labeling and Nomenclature Committee