CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20839

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20,839

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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:

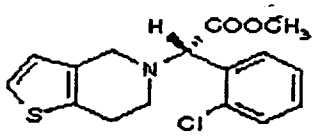
I. BACKGROUND

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.

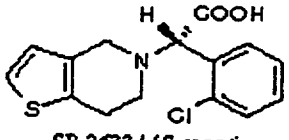
Due to the antiplatelet activity, this drug has potential for prevention of ischemic stroke, myocardial infarction and vascular death in patients with increased risk of such outcomes, including those with established atherosclerosis or history of atherosclerosis. The sponsor has proposed to market the 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.

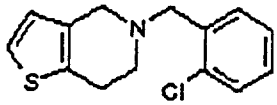
Figure:



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

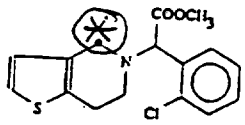
STUDY P1644: MASS BALANCE STUDY

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

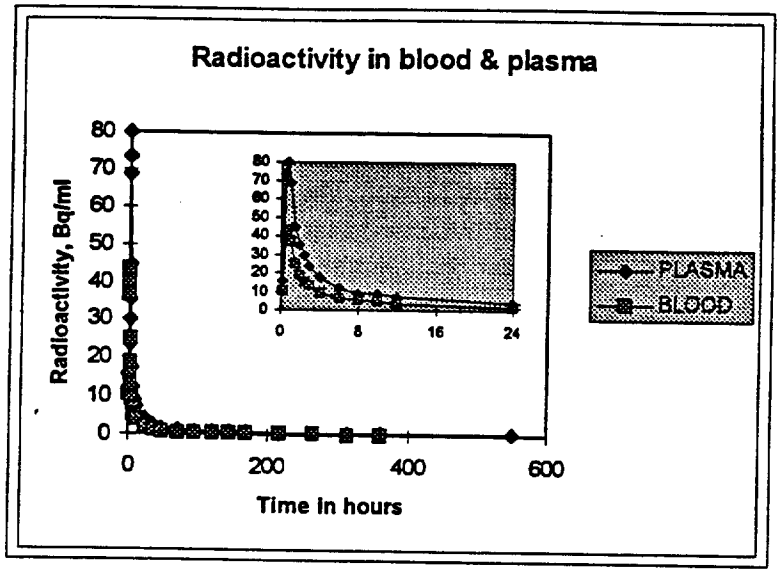
* incomplete stool collection

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

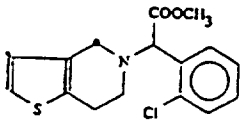
COMPARISON OF THE PHARMACOKINETIC PROPERTIES OF RADIOCARBON WHEN [^{14}C]-LABELED SR25990C (S-ENANTIOMER OF CLOPIDOGREL) IS GIVEN DURING STEADY-STATE AND IN CLOPIDOGREL-FREE HEALTHY VOLUNTEERS

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:

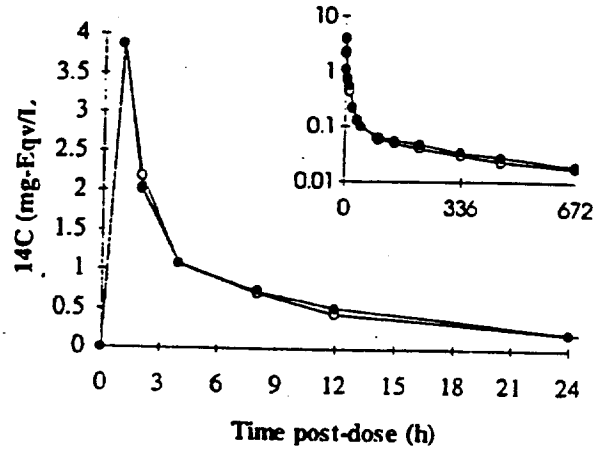


Fig. : Average radiocarbon plasma concentration after administration of 75 mg ^{14}C clopidogrel given as single dose (period I) or during steady-state (period II) in healthy subjects.
Values are means (N=6)
Inset: semi-logarithmic coordinates.
Period I (-O-); period II (-●-).

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:

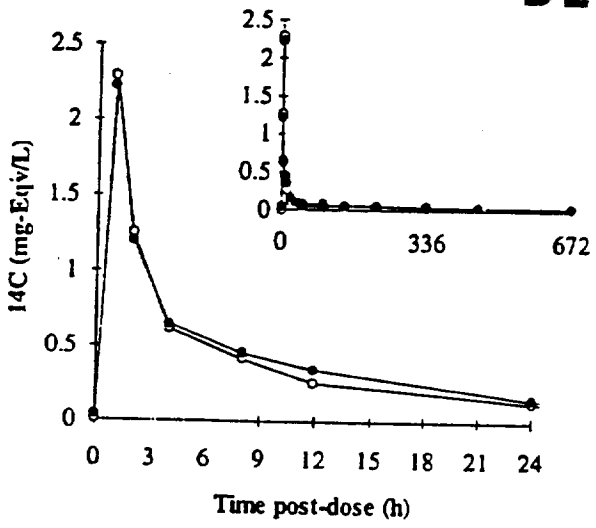


Fig. .: Average radiocarbon whole blood concentration after administration of 75 mg ^{14}C clopidogrel given as single dose (period I) or during steady-state (period II) in healthy subjects. Values are means (N=6) Inset: semi-logarithmic coordinates. Period I (-O-); period II (-●-).

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.

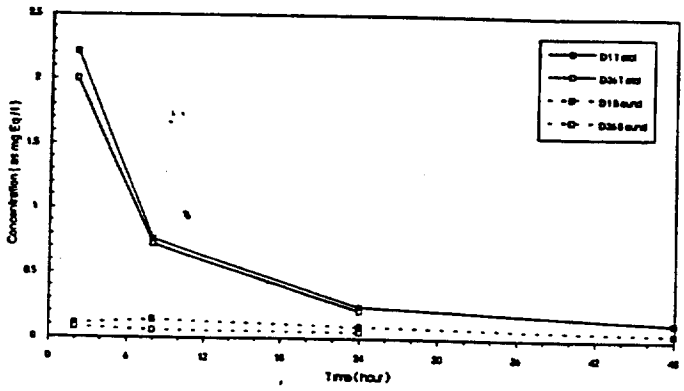
Bleeding time was prolonged by about 2.4 times after repeated administration of clopidogrel. ADP-induced maximum platelet aggregation decreased by about 74% after repeated administration of clopidogrel.

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.

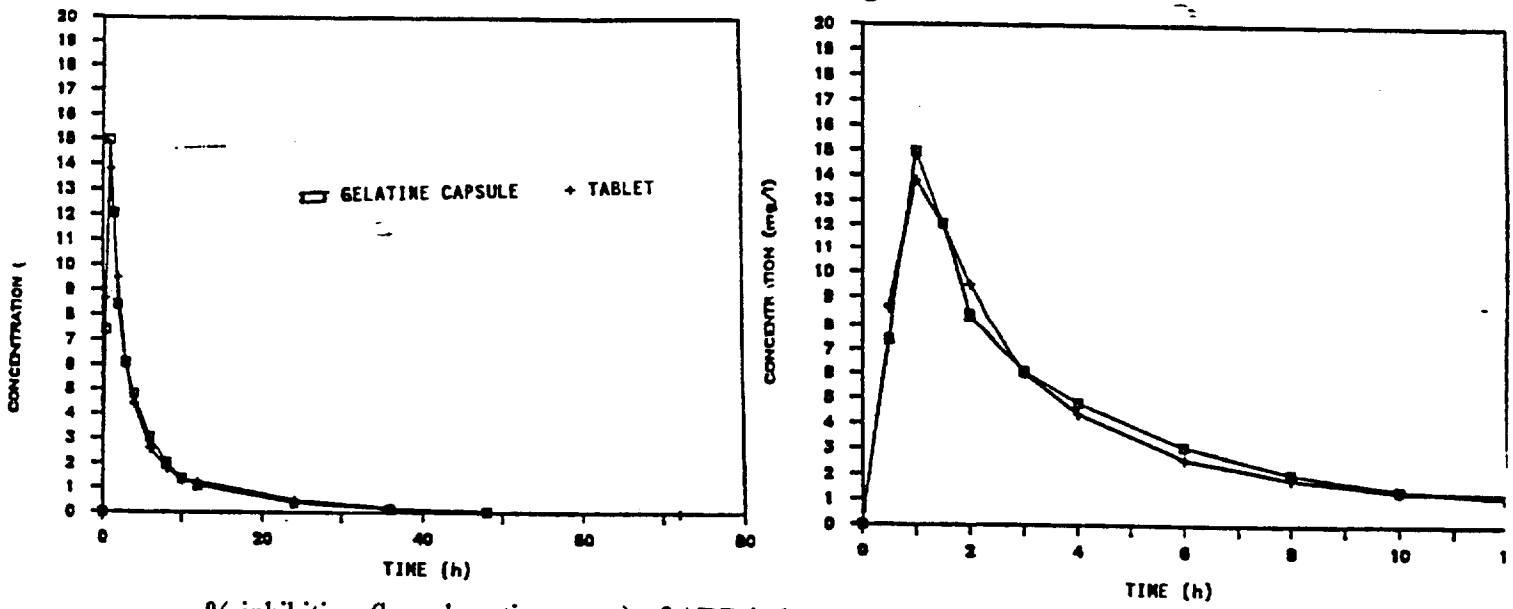
Results:

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.

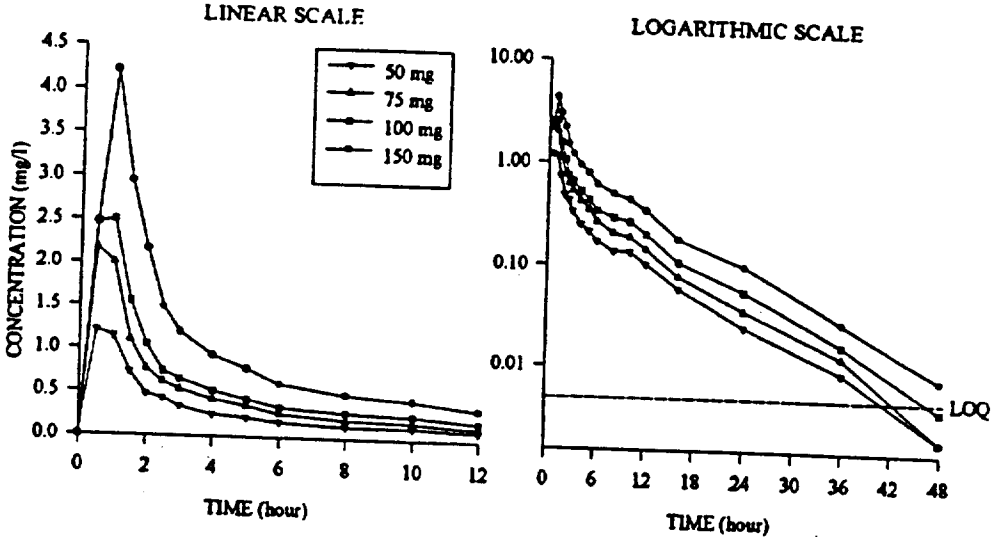
Blood was drawn from the subjects at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours after dosing for each period. Plasma samples were kept frozen until analyzed for SR26334 concentrations. Urine samples were collected at 0, 0-12 hours, 12 - 24 hours and 24 - 48 hours after dosing. 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:

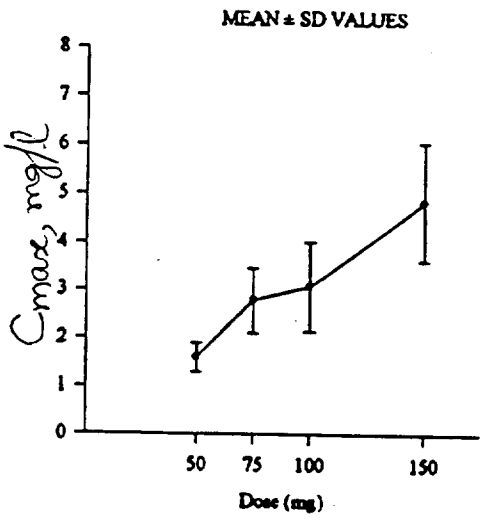


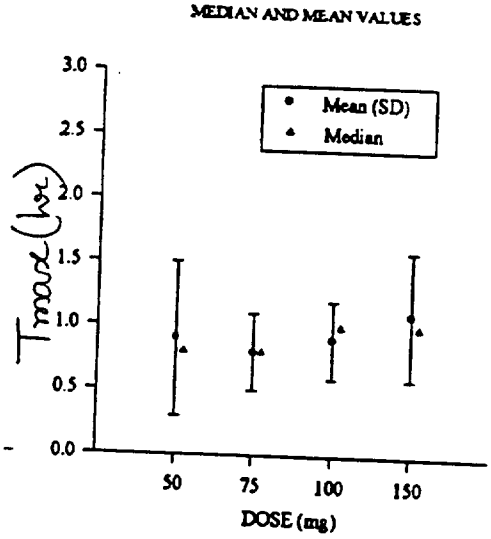
The table below shows the means (and standard deviations) for the SR26334 (clopidogrel acid metabolite) PK parameters.

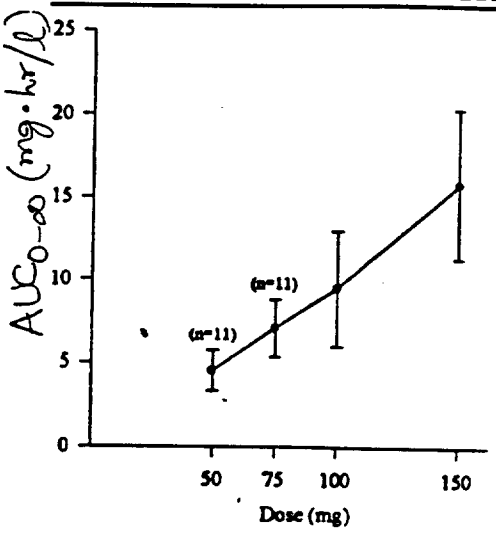
Parameter	50 mg	75 mg	100 mg	150 mg
C_{max}, mg/l	1.59 (0.30)	2.78 (0.68)	3.08 (0.94)	4.85 (1.22)
T_{max}, hr	0.9 (0.6)	0.8 (0.3)	0.8 (0.3)	1.1 (0.5)
AUC_{0-t}, mg.hr/l	4.56 (1.22)	7.12 (1.76)	9.33 (3.49)	15.60 (4.51)
$AUC_{0-\infty}$, mg.hr/l	4.51(1.20)*	7.05 (1.71)*	9.45 (3.47)	15.76 (4.52)
$t_{1/2}$, 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)

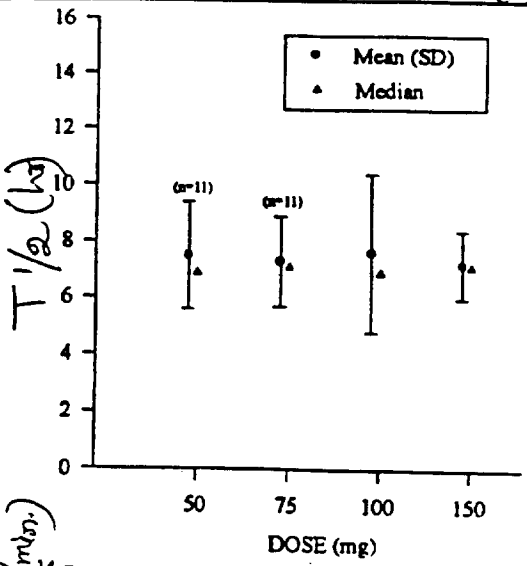
* n = 11

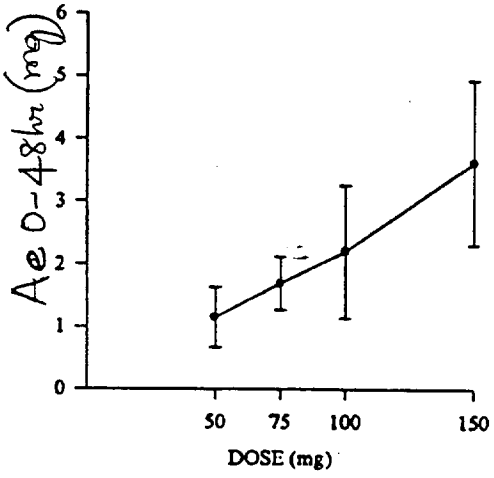
Plots to show dose proportionality in pharmacokinetics of SR 26334 are shown in 6 figures below:

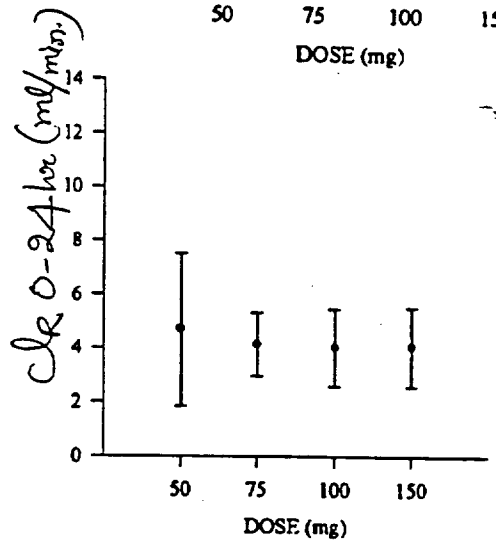












No dose-dependent changes in C_{max}, AUC, T_{max}, renal clearance and half-life were observed (non-significant treatment effects on dose-normalized parameters).

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)

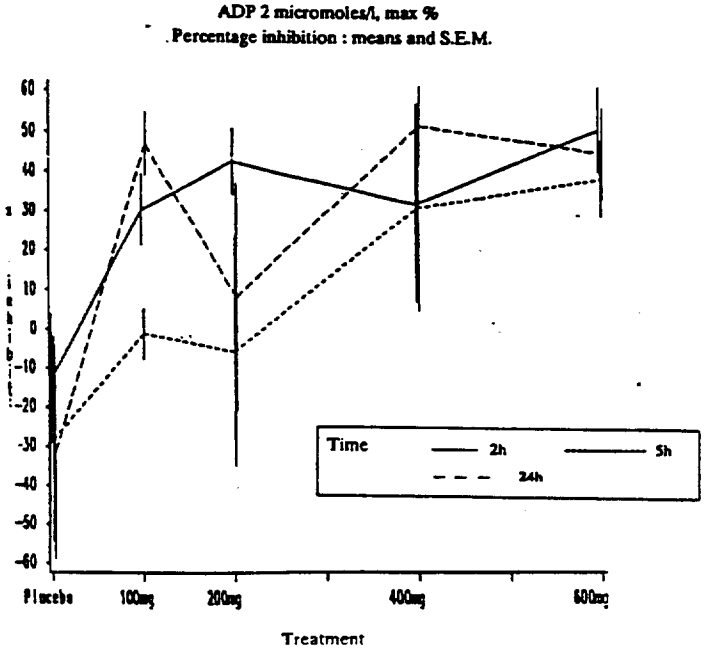
Blood samples were collected for determination of clopidogrel and its carboxy metabolite plasma concentrations at 0, 2, 5, 12 and 24 hours after drug administration. ADP-induced platelet aggregation was measured at 0, 2, 5 and 24 hours after drug administration in each period.

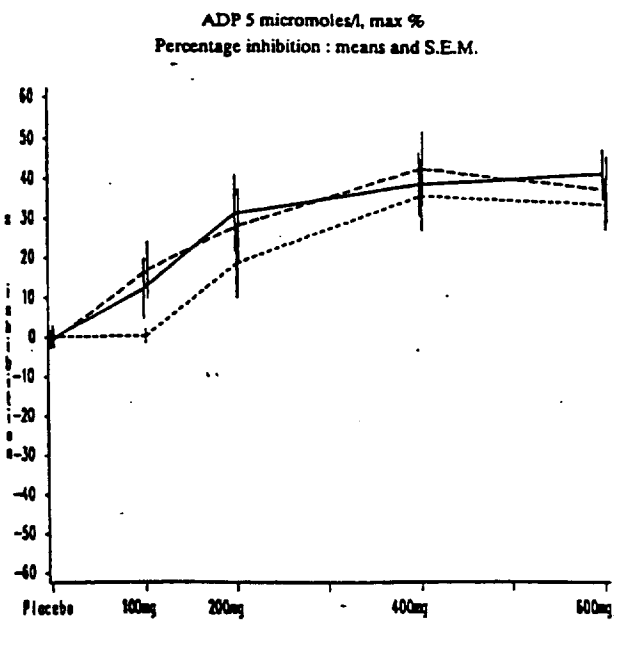
Bleeding time was measured at 0, and 5 hours after each treatment administration.

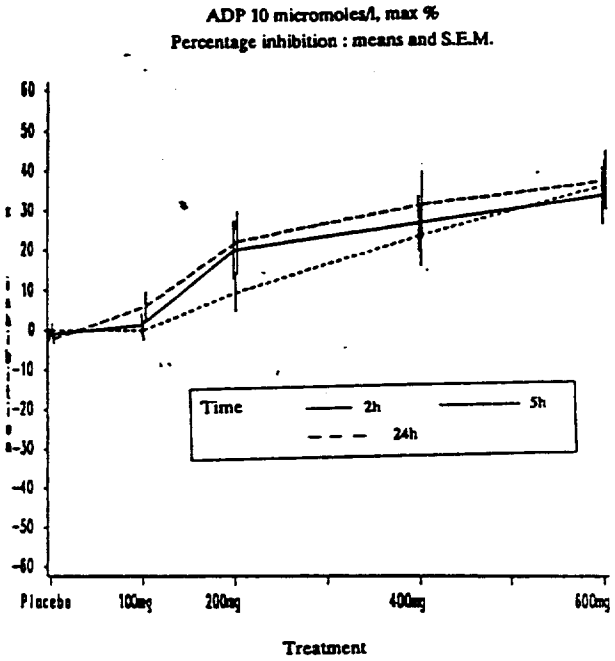
Data Analysis:
Plasma concentrations at each time were compared across doses using ANOVA. ANOVA was also used for analysis of results of aggregation and bleeding time.

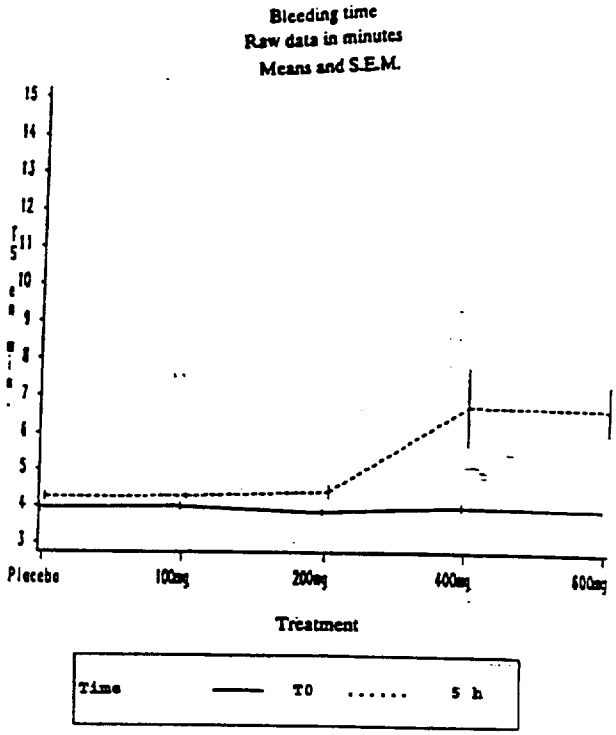
Assay was found to be acceptable with respect to calibration of assay. However, quality control data has not been provided.

% 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:

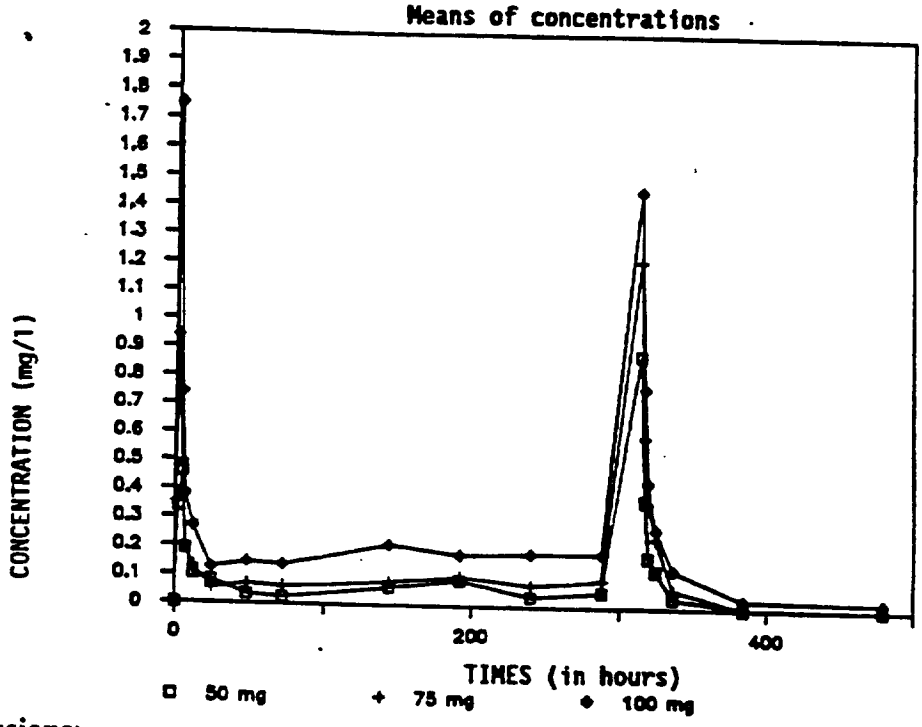
Day	Placebo	50 mg qd clopidogrel	75 mg qd clopidogrel	100 mg qd clopidogrel	500 mg/day ticlopidine
PERIOD OF TREATMENT					
D3	0.90 ± 0.05	1.13 ± 0.09	1.42 ± 0.06*	1.44 ± 0.14*	1.19 ± 0.07*
D4	0.98 ± 0.05	1.34 ± 0.12*	1.58 ± 0.14*	1.41 ± 0.12*	1.32 ± 0.08*
D7	0.92 ± 0.05	1.24 ± 0.10*	1.81 ± 0.22*	1.93 ± 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.

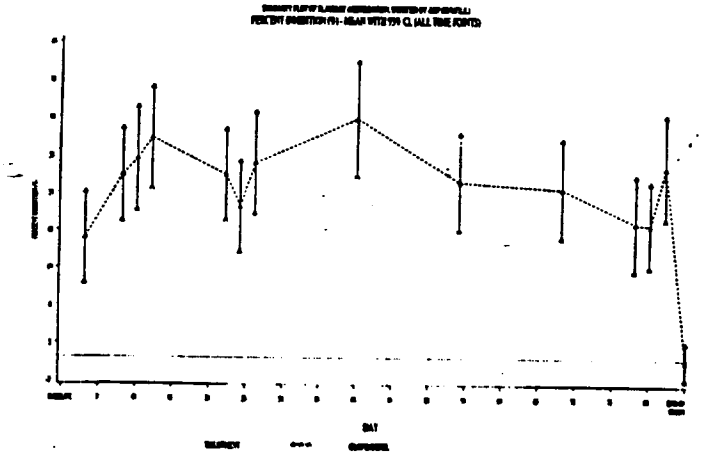
Blood samples were collected for determination of clopidogrel carboxy metabolite plasma concentrations at 0 hour on day 1 and at 0 hour (trough, pre-dose) and 1 hour after drug administration on days 3, 10, 24, 54 and 80. ADP-induced platelet aggregation was measured at 0 hour (pre-dose) on days 3, 8, 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.

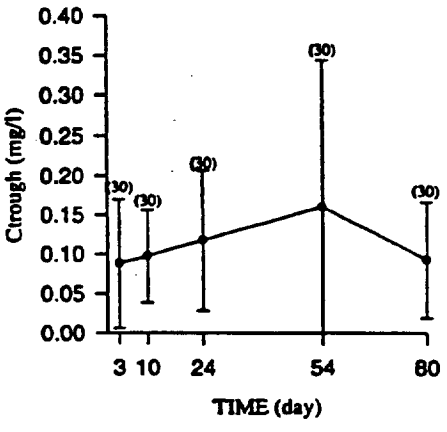
Assay was found to be acceptable.

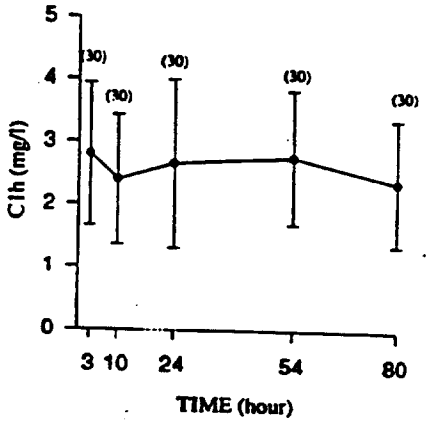
Of the 35 enrolled subjects, six were withdrawn from the study (one due to non-compliance, one due to lack of pharmacological response and four due to adverse events of rash, urticaria, bleeding time increase and mild hepatic enzyme elevations).

% 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.

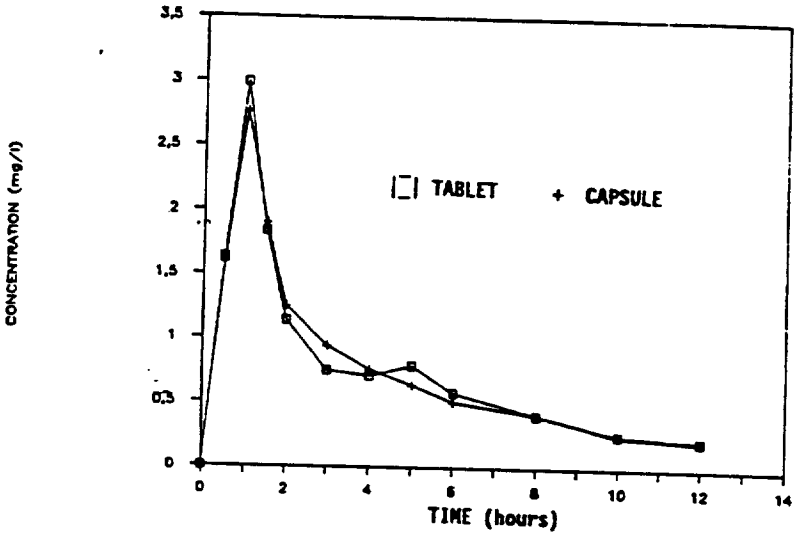
Batch #s: Clopidogrel 50 mg tablet: 2J1/RGG13
Clopidogrel 100 mg capsule: 1A1/RGE29

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.

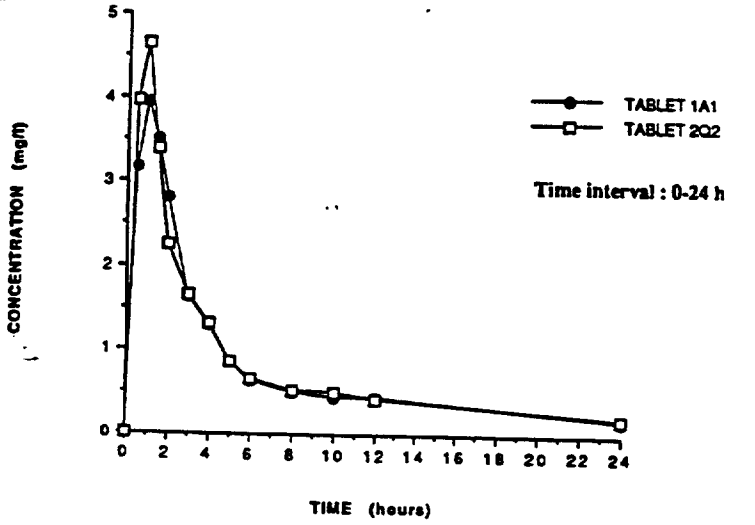
Batch #s: Clopidogrel 75 mg tablet: 2Q2/RHL19
Clopidogrel 75 mg tablet: 1A1/RHG08

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.

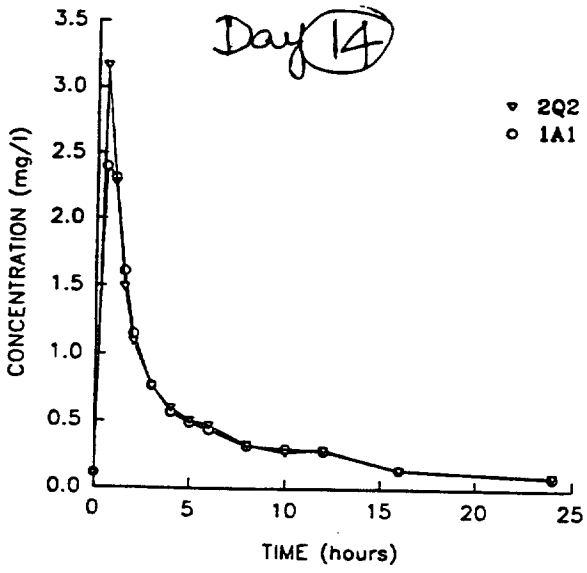
Mean (SD) PK parameters on day 14 are provided in the following table:

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.

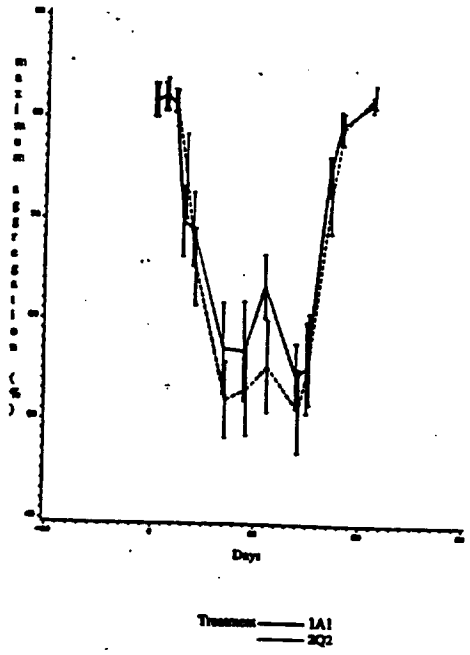
PHARMACODYNAMICS:

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		

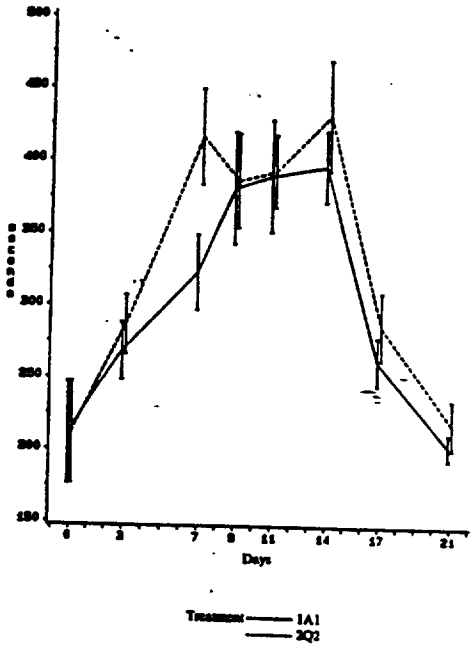
(1) significance based on the difference



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

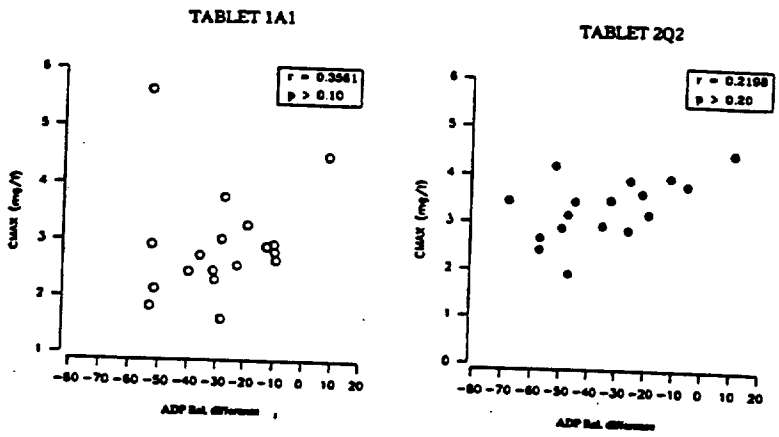
Bleeding time (s) and logarithm (subjects who completed the study n =18)

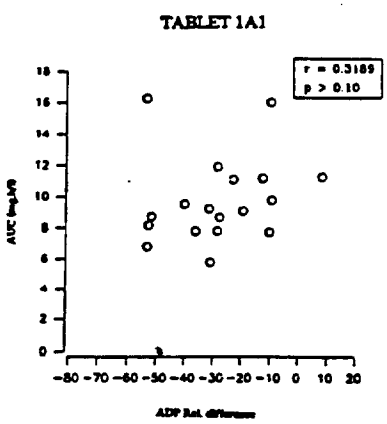
		Form.	m±sem	min-max	
Inclusion	BT (sec)	1A1-2Q2	178±11		
	log(BT)	1A1-2Q2	5.23±0.10		Treatment effect
Steady state	BT (sec)	1A1	373±24		NS
		2Q2	407±21		
	log(BT)	1A1	5.86±0.07		NS
		2Q2	5.96±0.05		

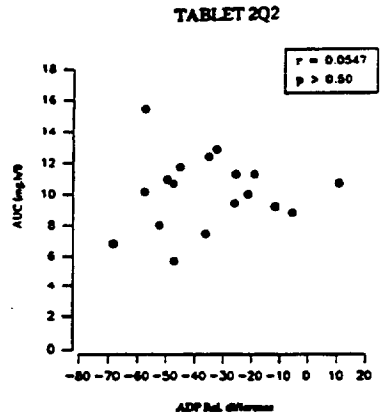


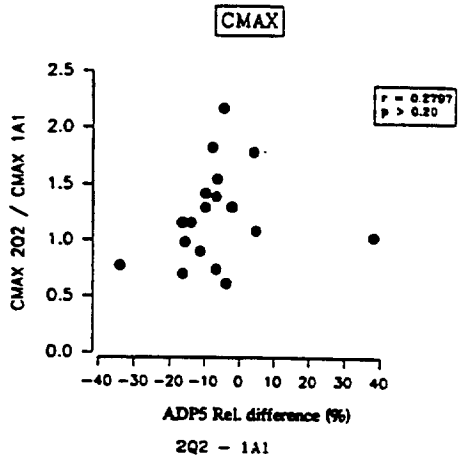
The study of bioequipotency using the Deheuvels method demonstrated equipotency for the 1A1 and 2Q2 formulations for ADP-related aggregation parameters and for bleeding time. Equipotency ± 15% can be confirmed for maximum aggregation induced by ADP 5 µmol/l.

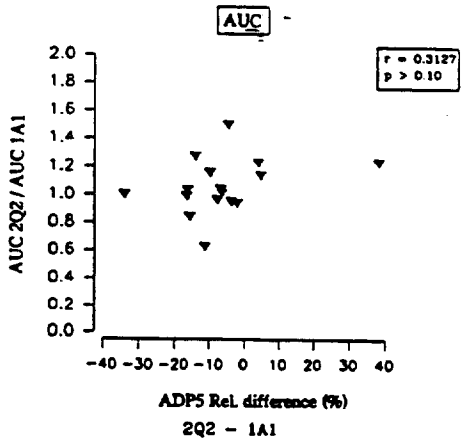
It was also shown that the C_{max} and AUC have no relationship to the ADP induced aggregation as shown in the following figures.











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.

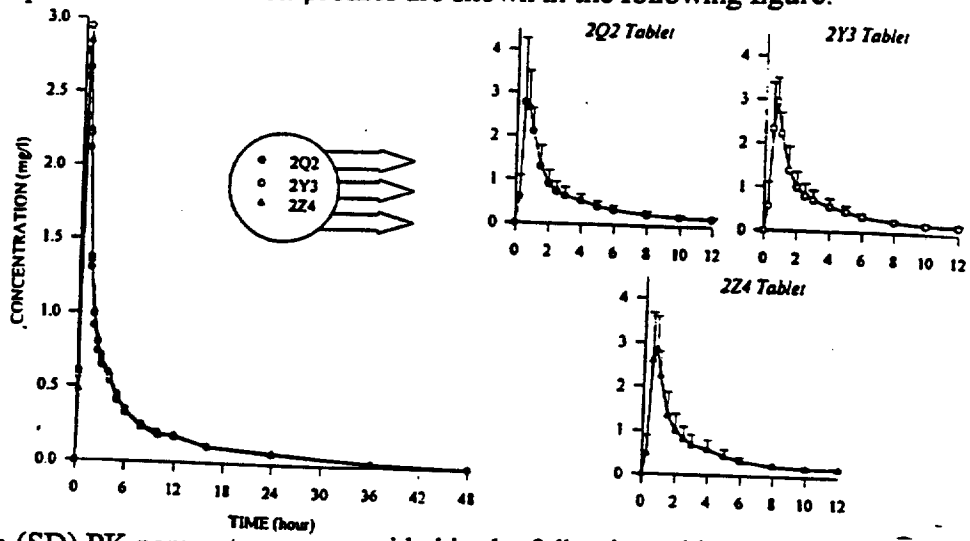
Study design:

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:

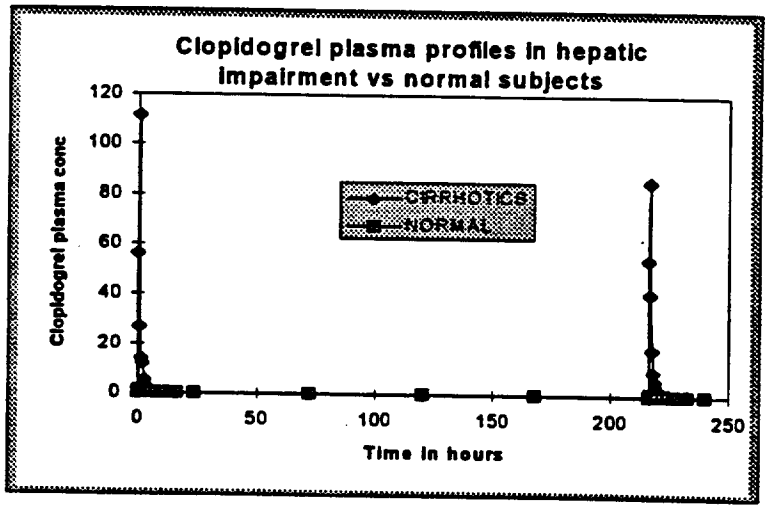
$$\text{BT prolongation factor} = \text{BT at a given point} / \text{BT at baseline}$$

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:



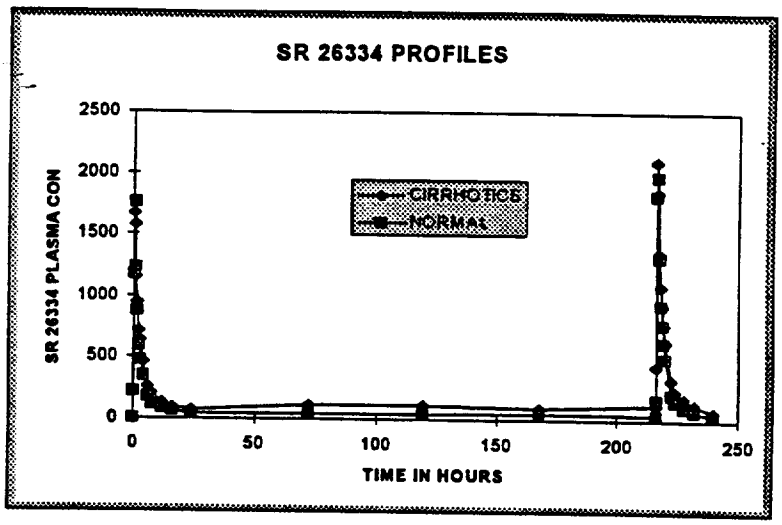
The pharmacokinetic parameters of clopidogrel carboxy metabolite (SR26334) for each group of subjects are shown in table below:

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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