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Link to drug label

Proprietary Drug Name	INN	Therapeutic area and FDA approved indications
Celebrex	Celecoxib	Relief of signs and symptoms of osteoarthritis Relief of signs and symptoms of rheumatoid arthritis in adults Management of acute pain in adults Treatment of primary dysmenorrhea Reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis as an adjunct to usual care

Name of Sponsor/Company: Pfizer Pharmaceuticals Inc.

Title of Study: Study E49-02-12-146

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center, Multiple-Dose Study to Assess the Interaction of Celecoxib 200 mg BID on Prothrombin Time (PT) With Acenocoumarol or Phenprocoumon

Study centre(s): 3 European study centers (2 Netherlands; 1 Germany)

Publication: None

Studied period	Phase of development: Phase 3, Commitment Study (Switzerland)
18 July 2002 - 19 March 2003	

Objectives:

Primary: The primary objective of the study was to assess the effects of celecoxib on prothrombin time (PT) compared to placebo treatment in subjects with a stable medical condition that required use of chronic treatment with acenocoumarol or phenprocoumon.

Secondary: The secondary objective was to assess changes in the maximal plasma concentrations of acenocoumarol, phenprocoumon, and celecoxib.

Methodology: This was a double-blind, randomized, multicenter, placebo-controlled, parallel-group, multiple- dose study. The study assessed the effect of celecoxib 200 mg BID administration with either acenocoumarol ≥1.0 mg/day or phenprocoumon 0.5 to 3.0 mg/day on PT in subjects with a stable medical condition that required use of chronic treatment with either acenocoumarol or phenprocoumon, stabilized at their maximum anticoagulant dose. Subjects were assigned to 1 of the 2 anticoagulant strata and randomly assigned 1 of the 2 study treatments: celecoxib plus concurrent anticoagulant or placebo plus concurrent anticoagulant. Subjects in the acenocoumarol stratum received ≥1.0 mg/day acenocoumarol and 200 mg BID celecoxib (or placebo) for 14 days. Subjects in the phenprocoumon stratum received 0.5 - 3.0 mg/day phenprocoumon and 200 mg BID celecoxib (or placebo) for 21 days.

Number of patients (planned and analyzed): It was anticipated that a total of 54 subjects would be sufficient number of subjects for completing the study (27 subjects in each anticoagulant strata). A total of 56 subjects were enrolled in the study (18 subjects in the acenocoumarol stratum and 38 subjects in the phenprocoumon stratum) and 45 subjects (15 in the acenocoumarol stratum and 30 in the phenprocoumon stratum) completed the study.

Diagnosis and main criteria for inclusion: Eligible subjects were men or women of non reproductive potential (using adequate contraception, non lactating, and having a negative serum pregnancy test within 72 hours of receiving the first dose of study medication), between 18 and 75 years of age, having a stable medical condition that required use of chronic treatment with either acenocoumarol (≥1.0 mg/day) or phenprocoumon (0.5 - 3.0 mg/day) for at least 60 days prior to participation in this study. Eligible subjects were to achieve stabilized International Normalized Ratio (INR) values between 2.0 and 3.5 during the Lead-in Period.

Duration of treatment: 14 days for the acenocoumarol portion and 21 days for the phenprocoumon portion

Test product, dose and mode of administration: Celecoxib: 200 mg white capsules were manufactured by Pharmacia. Capsules were administered orally.

Reference therapy, dose and mode of administration Placebo: White capsules were manufactured by Pharmacia. Capsules were administered orally. Acenocoumarol (Sintrom®) 1 mg tablets, manufactured by Novartis Pharma; Phenprocoumon (Falithrom® or Marcoumar®) 3 mg tablets, manufactured by Hexal.

Criteria for evaluation:

Effect on PT: The primary endpoint of this study was the change in INR values pre- and postdose comparing celecoxib with placebo treatment in subjects with a stable medical condition that required use of chronic treatment with acenocoumarol or phenprocoumon.

Other Safety: Safety measures included the incidence of adverse events, physical examinations, vital signs, and clinical laboratory assessments.

Statistical methods: Separate analyses were presented for subjects in the acenocoumarol and phenprocoumon strata. All randomized subjects who received at least 1 dose of study medication were included in the tabulations of subject disposition and analysis of demographics and Baseline characteristics. Subject disposition and reasons for study termination were tabulated by treatment group. Subject demographic and Baseline characteristics (gender, race, weight, height and vital signs) were summarized for each treatment group. The 2 treatment groups were compared using the 2-sample t-test for continuous variables and the Pearson Chi-square test for categorical variables.

Prothrombin Time Determination: During the treatment period, (Days 0 to 13 for the acenocoumarol stratum and Days 0 to 20 for the phenprocoumon stratum), predose INR value was determined 15 minutes prior to study medication dosing on Day 0 (Baseline), 1, 2, 4, 6, 8, 10, 12 and 13 (acenocoumarol stratum) and on Days 0 (Baseline), 1, 3, 6, 9, 12, 15, 18, and 20 (phenprocoumon stratum). All PT assessments performed in the morning prior to subjects taking their anticoagulant dose were included in the analyses. The mean (+/- standard error of the mean [SEM]) and subject-specific INR values over time were plotted for each treatment group. Summary statistics (mean, standard deviation, median and range,) were tabulated by day for each treatment group. A repeated-measures analysis of variance was used to analyze the treatment difference in mean changes in PT from predose Day 0 (Baseline) to predose during treatment. The validity of the repeated measures model was assessed using the sphericity test and Huynh-Feldt adjusted p-values were used as appropriate. The model included the effects of treatment, time, and treatment-by-time interaction. In addition, the Wilcoxon nonparametric 2-sample test was used to compare daily differences. The changes from Baseline to the INR value assessments obtained at 4 hours after the morning dose (from Days 0 to 13 [acenocoumarol stratum] and from Days 0 to 20 for the [phenprocoumon stratum]) were compared using a 2-sample t-test. The proportion of subjects withdrawn due to treatment failure in each treatment group was compared using Fisher's Exact Test.

Pharmacokinetic Analyses: All statistical analyses involving area under the plasma concentration curve (AUC[0-24]) (acenocoumarol), the maximum plasma concentration (Cmax) (acenocoumarol), AUC(0-24) (phenprocoumon), and Cmax (phenprocoumon) were done using dose-adjusted AUC(0-24) and Cmax values. The dose adjustment was done by dividing the subject's AUC(0-24) and Cmax values with the subject's daily anticoagulant dose. Summary statistics for plasma concentrations (dose-adjusted for acenocoumarol and phenprocoumon), including mean, standard deviation, coefficient of variation (CV),

median, and range were presented for each time point. Dose-adjusted acenocoumarol and phenprocoumon concentrations for each subject and mean (+/- standard error) dose-adjusted concentrations were plotted for each treatment group. PK parameters were calculated using WinNonlin Pro Version 2.1A. AUC(0-24) was calculated using the trapezoidal rule. Summary statistics for dose-adjusted AUC(0-24), Cmax and the time to maximum plasma concentration (tmax) values for acenocoumarol, phenprocoumon, and celecoxib, including mean, standard deviation, CV, median, and range were presented. The confidence intervals for the ratios of the mean dose-adjusted AUC(0-24) and Cmax values were calculated using the logarithmic transformation and a linear model with treatment (celecoxib versus placebo) as a factor. The point estimates and the confidence interval endpoints of the differences on the logarithmic scale were exponentiated to obtain the ratios and the corresponding confidence interval endpoints on the natural scale. **Safety Analyses:** All randomized subjects who received at least 1 dose of study medication were included in the safety analyses. The safety analyses were completed separately for the subjects in the acenocoumarol stratum and subjects in the phenprocoumon stratum. Safety was assessed through the incidence of adverse events, mean change in laboratory and vital sign measurements, and the incidence of extreme laboratory and vital sign measurements.

Summary

Disposition of Subjects and Baseline Characteristics:

Fifty-six subjects were randomized to the study, 45 subjects completed the study, and 11 subjects withdrew from the study (3 subjects in the acenocoumarol stratum and 8 subjects in the phenprocoumon stratum). The majority of subjects (100% of subjects in the acenocoumarol stratum and 92% of subjects in the phenprocoumon stratum) enrolled in this study were Caucasian. Overall, there were 36 males and 20 females enrolled in this study. Subjects ranged from 30 to 74 years (32 to 74 years in the acenocoumarol stratum and 30 to 73 years in the phenprocoumon stratum). Baseline demographic characteristics were not significantly different between the 2 acenocoumarol treatment groups with regard to age, race, gender, height, and weight. Baseline demographic characteristics were significantly different between the 2 phenprocoumon treatment groups with regard to age and gender ($p = 0.038$).

Effect on PT: Acenocoumarol Stratum Among subjects in the acenocoumarol stratum, the mean change from Baseline in predose INR values at Days 1 to 13 was consistently greater among subjects who received 200 mg BID celecoxib treatment compared with subjects who received placebo treatment; statistical significance was observed at Days 4, 6, 8, and 10 ($p = 0.004$, 0.003, 0.003, and 0.007, respectively). The mean change from Baseline in predose INR value peaked at Day 6 for the 200 mg BID celecoxib treatment group. A decrease in the mean change from Baseline in predose INR value was observed among subjects in the acenocoumarol stratum who received placebo treatment. The maximum decrease in the mean change from Baseline in predose INR for the placebo treatment group occurred at Days 8 and 10. A Repeated Measures Analysis of Variance for the change from Baseline in predose INR value was performed including all data from Days 1 through 13. An overall treatment group effect ($p =0.006$) over time was observed between placebo and 200 mg BID celecoxib groups. No statistically significant differences ($p = 0.282$) were observed in the mean change from Day 0 (Baseline) to Day 13 in 4-hour postdose INR values between placebo and 200 mg BID celecoxib treatment groups in the acenocoumarol study stratum. A low and similar number of subjects in the 200 mg BID celecoxib (2 subjects) and placebo (1) treatment groups who received concurrent treatment with acenocoumarol, were withdrawn from the study due to treatment failure (INR values <1.5 or >3.5); a statistically significant difference was not observed between treatment groups in the acenocoumarol stratum.

Phenprocoumon Stratum Among subjects in the phenprocoumon stratum, the mean change from Baseline in INR values to Day 20 was generally similar among subjects who received 200 mg BID celecoxib treatment compared with subjects who received placebo treatment. A statistically significant difference between these treatment groups only occurred at Day 1 ($p = 0.029$). A Repeated Measures Analysis of Variance for the change from Baseline in predose INR value was performed including all data from Days 1 through 20. No overall treatment group effect ($p = 0.799$) was detected between placebo and 200 mg BID celecoxib treatment groups over time. No statistically significant differences ($p = 0.808$) were observed in the change from Day 0 (Baseline) to Day 20 in 4-hour postdose INR values between placebo and 200 mg BID celecoxib treatment groups in the phenprocoumon stratum. A similar number of subjects in the 200 mg BID celecoxib treatment group (3 subjects) and the placebo treatment group (1) were withdrawn due to

treatment failures (INR values <1.5 or >3.5); a statistically significant difference was not observed between treatment groups in the phenprocoumon stratum.

Pharmacokinetic Results: Based on R- and S-acenocoumarol tmax values, the rate of absorption following administration of acenocoumarol with celecoxib was similar to that observed without celecoxib. Differences in mean tmax values were less than 1 hour in each case. Mean R- and S-acenocoumarol dose-normalized Cmax values in subjects receiving concomitant treatment with celecoxib were approximately 16% to 40% lower than those in subjects without celecoxib. The 90% confidence intervals for the ratios of treatment geometric mean dose- normalized Cmax values were outside the 80% to 125% equivalence range. Mean R- and S-acenocoumarol dose-normalized AUC(0-24) values following administration with celecoxib were approximately 24% to 44% lower than those in subjects without celecoxib. The 90% confidence intervals for the ratios of treatment geometric mean values were outside of the 80% to 125% equivalence range. Failure to fall within the equivalence range reflects the large variability of Cmax and AUC(0-24) values in regard to the small number of subjects involved in the study.

Effect of Celecoxib on Phenprocoumon Based on both R- and S-phenprocoumon tmax values, the rate of absorption following administration of phenprocoumon with celecoxib was similar to that observed without celecoxib. Mean R- and S- phenprocoumon dose-normalized Cmax values following administration with celecoxib were approximately 21% to 36% lower than those in subjects without celecoxib. The 90% confidence intervals for the ratios of treatment geometric mean dose-normalized Cmax values were outside the 80% to 125% equivalence range and the range did not include 100%. Mean R- and S-phenprocoumon dose-normalized AUC(0-24) values following administration with celecoxib were approximately 24% to 30% lower than those in subjects without celecoxib. The 90% confidence intervals for the ratios of treatment geometric mean dose-normalized AUC(0-24) values were outside of the 80% to 125% equivalence range and the range did not include 100%.

Celecoxib Pharmacokinetics Based on the similarity of celecoxib plasma concentrations at 24 hours following 200-mg BID celecoxib administration on Day 1 and the concentrations prior to the celecoxib dose on Days 13 and 20, steady state concentrations of celecoxib were achieved by the second day of the BID-dosing schedule. Based on the ratio of AUC(0-8) at steady-state / AUC(0-8) on Day 1, the accumulation at steady state was approximately 1.7 which was expected during BID dosing of a drug having an elimination t½ of approximately 10-12 hours.

PHARMACOKINETIC DISCUSSION For both acenocoumarol and phenprocoumon strata, the ratios of treatment geometric mean dose-normalized Cmax and AUC(0-24) values were outside the 80% to 125% equivalence range. Mean dose-normalized Cmax and AUC(0-24) values following administration of either acenocoumarol or phenprocoumon with celecoxib were lower than those without celecoxib. Similar results were observed following the first celecoxib dose as well as during steady-state celecoxib dosing. It is expected that inhibition of metabolism of acenocoumarol and phenprocoumon by celecoxib would result in higher plasma concentrations. Examination of individual subject mg/kg body weight doses failed to rectify the apparent discrepancy in expected results. These unexpected observations could possibly have been avoided had individual acenocoumarol and phenprocoumon concentration values been obtained during the day prior to administration of celecoxib. These results preclude an estimate of the difference in acenocoumarol or phenprocoumon pharmacokinetics between concomitant treatment with celecoxib and with placebo. In the absence of control data, these results cannot be interpreted since these differences in Cmax and AUC(0-24) may still be present without concomitant administration of celecoxib in the active group.

Safety Results: The majority of subjects (40 of 56, 71%) experienced at least 1 treatment-emergent adverse event during the study. In the acenocoumarol stratum, 4 (80%) subjects who received placebo and 7 (54%) subjects who received 200 mg BID celecoxib reported at least one treatment emergent adverse event. In the phenprocoumon stratum, 11 (85%) subjects who received placebo and 18 (72%) subjects who received 200 mg BID celecoxib reported at least one treatment emergent adverse event. The most frequently occurring adverse events (occurred in >1 subject in any treatment group) were headache not otherwise specified (NOS), fatigue, nausea, flatulence, and nasopharyngitis. Six subjects (5 subjects in the phenpocoumon stratum and 1 subject in the acenocoumarol stratum) reported hemorrhagic or thromboembolic adverse events including rectal bleeding, haematuria present, injection site thrombosis, phlebitis NOS, anemia NOS, haematoma right arm, and haematoma NOS. All adverse events were mild or

moderate in maximum intensity. A total of 29 subjects had adverse events that were considered by the investigator to be attributed to study medication. In the acenocoumarol stratum, 3 (60%) subjects who received placebo and 4 (31%) subjects who received 200 mg BID celecoxib had treatment-related adverse events. In the phenprocoumon stratum, 7 (54%) subjects who received placebo and 15 (60%) who received 200 mg BID celecoxib had treatment-related adverse events. No subject died or experienced a serious adverse event in this study. Three subjects who received 200 mg BID celecoxib concurrently with phenprocoumon withdrew from the study due to adverse events.

CONCLUSIONS: Analysis of the change from Baseline in predose INR values indicated a statistically significant difference between the placebo and 200 mg BID celecoxib treatment groups within the acenocoumarol stratum, but not in the phenprocoumon stratum. The observed differences in INR did not lead to a greater number of patients withdrawing from the celecoxib treatment groups in either stratum because of INR treatment failure. It is not possible to exclude a drug-drug pharmacokinetic interaction with certainty, but the absence of change in anticoagulant pharmacokinetic parameters between the first and last doses of celecoxib, and the lower anticoagulant concentrations in the celecoxib groups compared to the placebo groups, are not suggestive of one. Celecoxib was well tolerated in patients taking oral coagulants who have stable INR parameters.

Based on report prepared on: 05 December 2003