Protocol ICR013821: An Open Label Study to Assess the Potential Pharmacokinetic Interaction of Single Doses of Renagel® (Sevelamer Hydrochloride) with Warfarin in Healthy Volunteers

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Name of Sponsor/Company

Genzyme Corporation, 500 Kendall Street, Cambridge, MA 02142
Geltex Pharmaceuticals, Inc., Waltham, MA 02451, (Geltex Pharmaceuticals, Inc. was acquired by Genzyme Corporation December 2000)

Investigators and Study Center(s)

This was a single-center study conducted in Scotland.

Studied Period

First subject dosed: 23 March 1999
Last subject completed: 18 April 1999

Phase of Development

Phase I

Objectives

Primary: To investigate any pharmacokinetic interaction between sevelamer and warfarin.

Secondary: To assess the safety and tolerability of combining sevelamer and warfarin.

Methodology

This study was an open-label, randomized, crossover comparison of the pharmacokinetics of warfarin alone with warfarin plus sevelamer. For each dosing session, the subjects were confined to the clinical research unit for three nights. They were discharged 48 hours after dosing. Subjects were required to return to the clinic as outpatients 60, 72, 84, 96, 120, and 144 hours post dose. In one session, subjects received a single dose (30 mg) of warfarin. In the other session, the subjects were dosed concomitantly with warfarin (30 mg) and sevelamer (2418 mg). This concomitant dose was followed by 5 additional doses of 2418 mg of sevelamer over 2 days. A 144-hour warfarin pharmacokinetic profile was performed following each dose. There was a washout of 2 weeks between dosing sessions.

Number of Patients (Planned and Analyzed)

A sample size of 14 subjects was planned, and 14 subjects completed the study.

Diagnosis and Main Criteria For Inclusion:

Healthy male volunteers between 18 and 50 years of age.

Test Product, Dose, and Mode of Administration

Warfarin/Sevelamer: Sevelamer hydrochloride 6 x 403 mg capsules (2418 mg) plus warfarin 6 x 5 mg tablets (30 mg); both drugs were administered orally

Reference Therapy, Dose and Mode of Administration

Warfarin alone: Warfarin 6 x 5 mg tablets (30 mg) administered orally

Duration of Treatment

The total study duration for a subject was approximately 4 weeks including 2 dosing sessions separated by 2 weeks.

CRITERIA FOR EVALUATION

Criteria for Evaluation – Pharmacokinetics

During each study session, blood samples for the analysis of plasma for warfarin were collected from each subject: predose, 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, and 144 hours post dose. Standard pharmacokinetic parameters were calculated and compared between treatments.

Criteria for Evaluation – Safety

Adverse events, laboratory results (chemistry, hematology, urinalysis, INR), vital signs (blood pressure and heart rate), electrocardiogram (ECG), and physical examination.

STATISTICAL METHODS

Statistical Methods – Subjects

Race, sex, age, height, weight, and physical examination (normal/abnormal by body system) were summarized by treatment sequence. No significance testing was performed.

Statistical Methods – Pharmacokinetics

Following logarithmic transformation, AUC and C_{max} (obs) values were subjected to analysis of variance (ANOVA) techniques including terms for subject, period, and treatment. Point estimates and 90% confidence intervals (CIs) for the difference between the 2 treatments (i.e., warfarin/sevelamer minus warfarin alone) were constructed using the error variance obtained from the ANOVA. The point and interval estimates were then back transformed to give estimates of the ratio of warfarin/sevelamer relative to warfarin alone. If the 90% CI for this ratio lay within the acceptable range of 0.80-1.25, then this demonstrated the lack of a relevant interaction.

Statistical Methods – Safety

Adverse events, drug-related adverse events and adverse events by intensity were summarized by treatment group. Laboratory parameters were summarized by treatment group at each timepoint, along with changes from the predose result on Day 1. Vital signs and ECGs were summarized by treatment group using descriptive statistics at each timepoint, along with changes from the predose value of the relevant session. No hypothesis testing was carried out on safety parameters.

SUMMARY – CONCLUSIONS

Summary – Conclusions (Patients)

All subjects were Caucasian males. The mean age was 34.1 ± 6.6 years. Overall subjects, the mean height was 174.3 ± 7.5 cm , and the mean weight was 71.76 ± 8.2 kg .

Summary – Conclusions (Pharmacokinetics)

All subjects who completed the study were included in the pharmacokinetic analyses (n=14).

The overall shape of the mean warfarin concentration–time profiles resulting from co-administration of warfarin with sevelamer was similar to that resulting from the administration of warfarin alone. Individual C_{max} concentrations were observed within 1 to 4 hours for warfarin alone (C_{max} range 1894.2 to 3431.9 ng/mL^{-1}) and within 1 to 4 hours for warfarin with sevelamer (C_{max} range 1926.2 to 3946.2 ng/mL^{-1}). The mean ratios of log-transformed C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ for the comparison of the two treatments were 1.01, 0.96, and 0.95, respectively. The 90% confidence intervals for log-transformed C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ were all within the 0.80-1.25 range, indicating that sevelamer had no detectable effect on the rate and extent of warfarin absorption.

Summary – Conclusions (Safety)

All subjects who completed the study were included in the safety analyses (n=14).

All subjects received the study drug in accordance with the protocol: a total of 60 mg warfarin and 14508 mg sevelamer.

A total of 17 post-dose AEs were reported. Five adverse events occurred in four patients (28.6%) after dosing with warfarin only and twelve adverse events occurred in 8 patients (57.1%) after dosing with warfarin/sevelamer. All adverse events recorded during the study were mild. Six patients experienced nine adverse events (diarrhea, nausea, abdominal pain, headache, dyspepsia, bad taste in mouth, headache, rash, and nose bleeds) that were considered by the Investigator to be related to warfarin/sevelamer dosing. No AEs were considered related to warfarin alone. There were no serious adverse events.

There were no clinically significant changes in laboratory results, vital signs, ECGs, or physical examinations. As expected, international normalized ratio (INR) was prolonged after each dose of warfarin for all subjects in each session. On one occasion, a single subject remained in the clinic after 48 hours because of prolonged INR, which returned to normal several hours later.

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Synopsis Prepared on: 30 May 2006