Protocol ICR013769: An Open Label Study to Assess the Potential Pharmacokinetic Interaction of Single Doses of Renagel® (Sevelamer Hydrochloride) with Digoxin 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: 25 March 1999
Last subject dosed: 23 April 1999

Phase of Development

Phase I

Objectives

Primary: To determine the effect of sevelamer on the pharmacokinetics of digoxin.

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

Methodology

This study was an open-label, randomized, crossover comparison of the pharmacokinetics of digoxin alone with digoxin plus sevelamer. The subjects were confined to the clinical research unit for 3 nights and participated in 2 outpatient visits following each drug administration session. In one session, subjects received a single dose (1 mg) of digoxin. In the other session, the subjects were dosed concomitantly with digoxin (1 mg) and sevelamer (2418 mg). This concomitant dose was followed by five additional doses of 2418 mg of sevelamer over the next two days. A 96-hour digoxin 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 18 subjects was planned. Twenty subjects were enrolled and 19 subjects completed the study. One subject withdrew from the study because of personal reasons.

Diagnosis and Main Criteria For Inclusion:

Healthy male and female volunteers between 18 and 50 years of age.

Test Product, Dose, and Mode of Administration

Digoxin/Sevelamer: Sevelamer hydrochloride 6 x 403 mg capsules (2418 mg) plus digoxin 1 mg tablet; both drugs were administered orally

Reference Therapy, Dose and Mode of Administration

Digoxin alone: Digoxin 1 mg tablet administered orally

Duration of Treatment

The total study duration for a subject was approximately 3 weeks including 2 dosing sessions separated by a washout of at least two weeks.

Criteria for Evaluation – Pharmacokinetics

During each study session, blood samples for the analyses of plasma for digoxin were collected from each subject predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72 and 96 hours after dosing. Standard pharmacokinetic parameters were calculated and compared between treatments.

Criteria for Evaluation – Safety

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

Statistical Methods – Subjects

Race, sex, age, height, and weight 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., digoxin/sevelamer minus digoxin 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 digoxin/sevelamer relative to digoxin 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 ECG were summarized by treatment group using descriptive statistics at each timepoint, along with changes from the predose value. No hypothesis testing was carried out on safety parameters.

Summary – Conclusions (Patients)

All subjects were Caucasian and 17 of 20 (85%) were male. The mean age of all subjects was 34.7 ± 7.1 years. The mean height was 171.4 ± 6.6 cm and the mean weight was 71.89 ± 9.39 kg

Summary – Conclusions (Pharmacokinetics)

All except the subject who withdrew from the study after the first session were included in the pharmacokinetic analyses (n=19).

The overall shape of the mean digoxin concentration–time profiles resulting from co-administration of digoxin with sevelamer is similar to that resulting from the administration of digoxin alone. Individual C_{max} concentrations were observed within 0.5 to 2.0 hours for digoxin alone (C_{max} range 2.97 to 5.50 ng/mL) and within 0.5 to 4.0 hours for digoxin with sevelamer (C_{max} range 2.73 to 6.55 ng/mL). The mean ratios of log-transformed C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ for the comparison of the two treatments were 1.02, 1.03, and 0.98, 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 digoxin absorption.

Summary – Conclusions (Safety)

All subjects who received study drug were included in the safety analyses (n=20).

All but one subject (who withdrew due to personal reasons) received the study drug in accordance with the protocol: a total of 2 mg digoxin and 14508 mg sevelamer.

A total of 7 post dose adverse events occurred following dosing with digoxin/sevelamer compared with no adverse events for patients taking digoxin only. Four adverse events were considered to be related to study medication (3 events of headache and one event of dyspepsia). All adverse events were reported as mild. There were no serious adverse events.

There were no clinically significant changes in laboratory results, ECGs, or physical examinations. Several subjects had reductions in supine blood pressure after dosing, but all episodes were asymptomatic.

Based on Report Prepared on: 28 May 1999
Synopsis Prepared on: 30 May 2006