Protocol GTC-02-101: A Randomized Double-Blind Placebo-Controlled Parallel-Design Evaluation of the Safety and Tolerance of Single and Multiple Oral Doses of 1, 2.5, and 5 Grams of Renagel® (Sevelamer Hydrochloride) in Normal Subjects

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Prescribing decisions should be made based on the approved package insert in the country of prescription.

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 the United States.

Studied Period

First Patient Enrolled: 04 January 1995
Last Subject Visit: 03 February 1995

Phase of Development

Phase I (first in-human study)

Objectives

To determine the safety and tolerance of single oral doses of sevelamer 1, 2.5, or 5 g in healthy volunteers.

To determine the safety, tolerance, and efficacy of multiple oral doses of sevelamer 1, 2.5, or 5 g administered three times daily (t.i.d.) for 8 consecutive days to healthy volunteers.

Methodology

This was a randomized, double-blind, placebo-controlled, parallel-group study. Eligible subjects were admitted to the clinical study unit. The subjects remained in the clinical study unit from the day of admission until discharge on Day 17 and returned for a follow-up visit on Day 24. After admission, 6 of the 8 subjects in each group were randomized to receive active drug while the other two received matching placebo.

During the clinic confinement, subjects were prescribed a phosphate-controlled diet designed to provide 1.2 g elemental phosphorus as phosphate per day. On Day 1, subjects received a single oral dose of 1, 2.5 or 5 g of sevelamer or placebo. From the morning of Day 5 to the morning of Day 9, 24-hour urine and feces were collected. On Days 9-16, subjects received 1, 2.5 or 5 g of sevelamer or placebo t.i.d. orally. From the morning of Day 13 to the morning of Day 17, 24-hour urine and feces were collected. The subjects were discharged on Day 17 and returned for a follow-up visit on Day 24.

Number of Patients (Planned and Analyzed)

As planned, 24 subjects were enrolled, randomized, and received study drug. All subjects completed the study and were included in the analyses.

Diagnosis and Main Criteria For Inclusion:

Healthy male and female volunteers between 18 and 40 years of age.

Test Product, Dose, and Mode of Administration

Sevelamer hydrochloride (500 mg capsules) for oral administration at dose levels of 1, 2.5, and 5 g.

Reference Therapy, Dose and Mode of Administration

Placebo (capsules containing 300 mg microcrystalline cellulose) for oral administration.

Duration of Treatment

The total study duration for a subject was 24 days.

CRITERIA FOR EVALUATION

Criteria for Evaluation – Efficacy

The primary efficacy variables were: urine phosphorus (to determine absorbed phosphorus), stool phosphorus (to determine non-absorbed phosphorus) and the ratio of total stool phosphorus to total urine phosphorus (to assess the effect of sevelamer on dietary phosphorus absorption).

Criteria for Evaluation – Safety

Adverse events, changes in laboratory results (hematology, chemistry, prothrombin time, vitamins, iron, and urinalysis), vital signs (blood pressure, pulse, temperature, and respiratory rate), and physical examinations.

STATISTICAL METHODS

Data from the placebo subjects were pooled into one group for analyses. All statistical tests were 2-tailed with a 0.05 level of significance.

Statistical Methods – Efficacy

The efficacy analysis compared the phosphorus concentrations in the stool and urine collected on Day 13-17, the baseline concentrations in the stool and urine collected on Day 5-9, and the changes from baseline in phosphorus concentrations. ANOVA was used to detect an overall difference in the treatment groups (placebo, sevelamer 1, 2.5 or 5 g). If the overall comparison yielded a statistically significant difference, pairwise tests were to be performed to determine a possible dose response. The ratio of stool to urine phosphorus and the total phosphorus concentration was analyzed in a similar fashion.

Statistical Methods – Safety

The overall incidence of adverse events, adverse events by preferred term, and adverse events by organ class were analyzed using Fisher's exact test. If the overall test comparing the treatments was significant, pairwise comparisons were to be performed. The single and multiple dosing periods were analyzed separately.

Laboratory results were summarized using descriptive statistics. Intragroup and intergroup changes from Day 9 to Day 17 were analyzed. Vital signs were summarized using descriptive statistics. Results of physical examinations were tabulated.

SUMMARY – CONCLUSIONS

Summary – Conclusions (Subjects)

There were no statistically significant differences across the dose groups in terms of demographic characteristics. Seventeen subjects were male and 7 were female; 19 of 24 subjects (79%) were Caucasian, 3 of 24 (13%) were Hispanic, 1 of 24 (4%) was Black, and 1 of 24 (4%) was Native American. The mean age in each group was 28 years (placebo), 31 years (sevelamer 1 g), 25 years (sevelamer 2.5 g), and 29 years (sevelamer 5 g).

Summary – Conclusions (Efficacy)

All subjects consumed sufficient amounts of the prescribed diet to be included in the efficacy analyses (n=24).

The effect of sevelamer was clearly apparent in total urine phosphorus content. Urinary phosphorus content increased in the placebo group (+38.31 mg) and decreased in a dose-dependent fashion in the three sevelamer groups (-52.48 mg, -91.34 mg, and -255.91 mg for the sevelamer 1 g, sevelamer 2.5 and sevelamer 5 g groups, respectively). There were statistically significant differences in change from baseline between placebo and the sevelamer 2.5 and sevelamer 5 g groups. There was also a statistically significant difference between the sevelamer 1 g and sevelamer 5 g groups. Urine phosphorus concentration also decreased in a dose-dependent fashion, with statistically significant differences between the placebo and sevelamer 5 g groups; and the sevelamer 1 g and sevelamer 5 g groups.

Fecal phosphorus concentration was essentially unchanged in all four groups. Fecal phosphorus content was markedly higher in the sevelamer 5 g group, but not statistically significant.

Ratios of stool to urine phosphorus concentration increased in all three sevelamer groups showing statistically significant differences between placebo and sevelamer 5 g; sevelamer 1 g and sevelamer 5 g; and sevelamer 2.5 g and sevelamer 5 g groups.

Summary – Conclusions (Safety Results)

All subjects were included in the safety analyses (n=24).

Each subject received all 25 doses of study drug as specified in the protocol.

During the single dose period, ten subjects had 14 adverse events (1 event in 1 subject in the placebo group, 5 events in 4 subjects in the sevelamer 1 g group, 7 events in 4 subjects in the sevelamer 2.5 g group, and 1 event in 1 subject in the sevelamer 5 g group). There were no statistically significant differences among the 4 treatment groups in incidence of the following: adverse events overall by preferred term, by severity and preferred term, or by relationship to study drug. However, there was a statistically significant intergroup difference in the incidence of adverse events affecting the digestive system that was higher in the sevelamer 2.5 g group than in the other three groups (50% vs. 0%). Three subjects in the sevelamer 2.5 g group reported upset stomach, loose stools and heartburn (one event in total for each patient). Except for heartburn, these events occurred 5 days or more after dosing. Pairwise comparison revealed no statistically significant difference between the groups in adverse events by body system. There were no severe adverse events in any group. No adverse events occurring between administration of the single dose and Day 8 were assessed as related to study medication.

During the multiple dose period, 16 patients experienced 46 adverse events (11 events in 5 patients in the placebo group, 15 events in 4 patients in the sevelamer 1 g group, 12 events in 4 patients in the sevelamer 2.5 g group, and 8 events in 3 patients in the sevelamer 5 g group). There were no statistically significant differences between placebo and the active treatment groups or between the three active treatment groups in adverse events (overall, by body system, by preferred term, by severity, or by relationship to study drug). Most of the adverse events were mild to moderate in intensity. One event (headache) occurring on the first day of multiple dosing was assessed as severe intensity; however was considered not related to the study drug by the Investigator. Ten events in 9 patients were judged possibly related to the study drug: 2 events in 2 subjects in the placebo group (diarrhea, dyspepsia), 2 events in 2 subjects in the sevelamer 1 g group (abdominal pain, nausea), 2 events in 2 subjects in the sevelamer 2.5 g group (2 instances of nausea), and 4 events in 3 subjects in the sevelamer 5 g group (dyspepsia, nausea, abdominal pain, and taste loss).

No serious adverse events occurred during the study.

Laboratory values revealed no clinically significant changes. The notable exception was cholesterol, which decreased in a dose-related fashion in all three sevelamer groups (by 27.5, 21.2, and 41.8 mg/dL for the sevelamer 1, 2.5 and 5 g groups, respectively). Vital signs and physical examinations results did not change during the course of the study.

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