Protocol REN-001-00: A Two-Year Follow-Up Study Comparing Sevelamer Hydrochloride (Renagel®) and Calcium-Based Binders in Hemodialysis Patients Treated According to Normal Clinical Practice.

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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 multicenter extension study conducted at 8 sites in Europe (7 in Germany and 1 in Austria).

Studied Period

First patient entered: 29 September 2000
Last patient completed: 31 December 2001

Phase of Development

Phase 3

Objectives

The objectives of this study were to assess the long-term effects of Renagel® and calcium-based binders on serum phosphorus, calcium-phosphorus product and serum intact parathyroid hormone (iPTH) in hemodialysis patients in a chronic "real life" environment by treatment according to normal clinical practice and to determine the long-term changes in cardiovascular calcification as measured by EBCT (coronary arteries, aortic valve, mitral valve, aortic arch, and myocardium).

Methodology

This was a phase 3, two-year, follow-up, multi-center, randomized, open label, parallel design study with dosing according to normal clinical practice conducted to compare the long-term effects of Renagel® and calcium-based binders on changes in cardiovascular calcification. European patients who completed 52 weeks of treatment on Genzyme Protocol GTC-49-301 were invited to continue the phosphate binder to which they had been randomized to in Protocol GTC-49-301. Patients were treated according to normal clinical practice and had an EBCT scan at months 12 and 24. Laboratory samples were drawn per usual clinical practice.

Number of Patients (Planned and Analyzed)

No. Enrolled / Treated: 72
No. Completed: 54

Diagnosis and Main Criteria for Inclusion

Patients included in the study were European hemodialysis patients who had completed 52 weeks of treatment in Genzyme study GTC-49-301.

Test Product, Dose, and Mode of Administration

Sevelamer hydrochloride (Renagel®): 800 mg tablets
Administered orally with meals

Duration of Treatment

The study was planned to last 24 months; however, it was terminated after approximately 14 months by the sponsor (Genzyme) after the analysis of GTC-49-301 demonstrated significant differences in arterial calcification.

Reference Therapy, Dose and Mode of Administration

Calcium carbonate (Sertuerner®): 500 mg tablets
Administered according to the package insert

CRITERIA FOR EVALUATION
Efficacy

The primary focus of this study was to present a descriptive evaluation of the long-term effects of Renagel® and calcium carbonate in hemodialysis patients in a chronic "real life" environment treated according to normal clinical practice. This study consisted of a two-year extension period that followed the original GTC-49-301 study, and considered laboratory measures and cardiovascular calcification.

The laboratory analysis focused on serum phosphorus, calcium, calcium-phosphorus product and intact parathyroid hormone (iPTH) obtained by local laboratories quarterly. The effects of Renagel® and calcium carbonate on tissue calcification (coronary arteries, aortic valve, mitral valve, aortic arch, and myocardium) as measured by EBCT was also assessed.

Safety

Safety endpoints included reporting of serious, related adverse events.

STATISTICAL METHODS
Efficacy

Laboratory measures were summarized and Wilcoxon signed rank tests were used to assess the changes within treatment groups while the Wilcoxon rank sum test was used to compare changes between treatment groups.

Volume and Agatston score at Day 0, Week 26, Week 52 (carried from GTC-49-301) and Month 24/final visit were summarized by location (coronary arteries, aortic valve, aortic arch, mitral valve, and myocardium). Nominal changes were presented for all patients while both nominal and percent changes for coronary arteries and aortic arch were presented for patients with a score of at least 30 at baseline. Wilcoxon signed rank tests were used to assess the changes within treatment groups and the Wilcoxon rank sum test was used to compare changes between the treatments. Additionally, to quantify the EBCT findings in a clinically meaningful way while using all data for all patients, the linear slopes of calcification over time (based on actual dates of EBCT assessment) for each patient were summarized. These slopes represent the average weekly change in calcification for a patient during the two year observation periods (data from Day 0 and Weeks 26 and 52 carried over from the GTC-49-301 study).

Safety

Related serious adverse events were summarized.

SUMMARY – CONCLUSIONS
Demographics and Renal History

The mean age of the patients was 57 years. Sixty-nine percent of the patients were male and 31% were female. The majority of patients were Caucasian (99%) The primary causes of ESRD included glomerulonephritis (26%), other (19%), polycystic kidneys (19%), hypertension (17%), and diabetes (11%).

Efficacy

There was no statistically significant difference between the Renagel® and calcium groups in change of serum phosphorus from baseline to end of treatment. Renagel® provided control of phosphorus levels that was comparable to calcium. Mean

serum phosphorus levels and mean serum calcium-phosphorus product were similar between the two treatment groups at both the baseline and end of treatment measurements. Uncorrected serum calcium levels at the baseline measure were significantly lower in the Renagel® treated group (uncorrected calcium, p-value = 0.0004). Serum calcium levels at the final measure were also significantly lowered in the Renagel® treated group (corrected calcium, p-value = 0.0006; uncorrected calcium p-value = 0.0010). There were also significant differences in serum intact parathyroid hormone levels at both the baseline and final measures, with calcium treated patients demonstrating lower levels (baseline, p-value = 0.0049; final, p-value = 0.0008).

In the aortic valve, mitral valve, and myocardium there was no clinically meaningful progression during the study.

Changes in tissue calcification in the coronary arteries and aortic arch, consistently favored Renagel® treated patients. Significantly less progression of calcification in these two anatomical areas were observed in the Renagel® group. Measurements were not normally distributed and therefore all results are presented as medians.

There was a statistically significant difference in nominal change in tissue calcification in the coronary arteries, as measured by Agatston score. This indicates less progression of calcification for Renagel® treated patients during the two year study period (Renagel® 37.4, calcium 484.0; p-value = 0.0178). This difference was further supported by the weekly rates of change for the two treatment groups. The weekly rate of change in tissue calcification, as measured by Agatston score was significantly less for patients in the Renagel® group (Renagel® 1.2, calcium 4.5; p-value = 0.0416). Among the subset of patients with baseline scores of at least 30, nominal change in tissue calcification from baseline to final, measured by Agatston score, indicated less progression in the coronary arteries for Renagel® patients (Renagel® 123.8, calcium 621.7; p-value = 0.0271). The percent change in Agatston score from baseline to final in the coronary arteries (for patients with a score of at least 30 at baseline) was statistically significantly different between the treatment groups (Renagel® 20%, calcium 83%; p-value 0.0310). Similar differences between treatment groups were observed when measuring calcification on the volumetric scale.

In the aortic arch, Renagel® treated patients experienced less progression in calcification as well. The nominal change (from baseline?) in tissue calcification in the aortic arch, as measured by Agatston score, indicated no change in calcification among Renagel® treated patients while calcium treated patients progressed substantially (Renagel® 0.0, calcium 609.8; p-value = 0.0039). This finding was confirmed when analyzing the weekly change in tissue calcification from baseline to final in the aortic arch. The weekly change in tissue calcification as measured by Agatston score indicated a statistically significant difference favoring the Renagel® treated patients over the calcium group (Renagel® 0.0, calcium 6.7; p-value = 0.0046). Among the subset of patients with a calcification score of at least 30, the Renagel® group has statistically significantly lower scores: Renagel® 385.2, calcium 864.5; p-value = 0.0223). Percent change in tissue calcification from baseline to final in the aortic arch, for patients with at least 30 at baseline, also indicated less progression for Renagel® patients (Renagel® 7%, calcium 66%; p-value = 0.0125). Similar findings were observed when measuring calcification on the volumetric scale.

Safety Results

Only treatment related, serious adverse events were collected during this study. Two patients receiving Renagel® experienced related, serious events during this Extension study. One patient experienced a sub-ileus, which was judged by the investigator to be moderate in intensity and probably related to study treatment. The second patient experienced three serious adverse events: bowel obstruction, intestinal perforation secondary to an enema, and sudden death. The timing of this patient's serious adverse events was such that the events were reported during the GTC-49-301 study as well as in this study report. All three of these events were judged by the investigator to be severe in intensity and possibly related to study treatment.

Three patients in the calcium treated group and two in the Renagel® treated group died during the Extension study. All of the deaths, except for the patient described above, were considered unrelated to study treatment.

Laboratory measurements included serum albumin, serum calcium, serum intact parathyroid hormone, and serum phosphorus. Laboratory measures indicated by the investigator as clinically significant were noted for all patients. These values did not demonstrate any notable differences between treatment groups. A greater number of calcium treatment patients, however, had calcium levels that were out of normal range.

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