CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020926

MEDICAL REVIEW(S)

20926NRenaGel

Review Completed October 16, 1998

NDA 20926

GelTex Pharmaceuticals
RenaGel (Sevelamer hydrochloride)
For phosphate binding
UFGD 11/3/98

Clinical Team Leader Review

Comments: Efficacy.

1. The placebo-controlled studies 201 and 301 indicate that RenaGel is effective in decreasing phosphorus in patients with end-stage renal failure.
2. Although these uncontrolled studies show changes in the right direction and provide much more exposure to RenaGel than the 2 controlled studies, the lack of adequate controls means that the studies cannot contribute much to the efficacy evaluation.
3. In study 10-201, the alteration in serum phosphorus was significant when a one-sided t test was used. When normophosphatemic patients were omitted from the analysis, the difference was significant at p=0.01. This indicates a very minimal difference between RenaGel and placebo.
4. The other controlled study (301) showed no significant difference in phosphorus decrease between RenaGel and calcium acetate. Non-inferiority apparently was not tested. Actual difference was very slight but favored calcium.

Comments: Safety.

1. There is some information on RenaGel interference with absorption of essential nutrients (especially fat-soluble vitamins)
2. There is inadequate information on absorption of drugs. Drug interactions will be addressed in phase 4 studies.
3. The primary safety concern is hypercalcemia; in that, RenaGel seems to have a clear advantage over calcium.

Recommendation: Approve NDA AP

/S/ 10/16/98
Gloria Troendle

/S/ 10/18/98

Cc:NDA 20926
Division File/HFD-510/GTroendle/BSchneider/RHedin

RenaGel is hydrophilic, but insoluble in water. It is sold in hard gelatin capsules containing 403 mg of anhydrous sevelamer HCl plus colloidal silicon dioxide and stearic acid. It is intended to reduce uptake of dietary phosphate by binding the phosphate so that it remains in the gut and is excreted in the stool. It appears from studies in animals and in normal humans that sevelamer is not absorbed, but absorption studies in humans with renal failure have not been done. Standard therapy for hyperphosphatemia in patients with renal failure at present is administration of calcium salts, which carries a risk of hypercalcemia.

The effectiveness of RenaGel in binding dietary phosphate and reducing serum phosphate levels was demonstrated in two controlled (placebo in one and calcium salt in the other) clinical trials, GTC-10-201 and GTC-36-301. There were also 4 open studies controlled only by baseline values.

GTC-10-201 was randomized, double-blind, and placebo-controlled. The primary endpoint was serum phosphorus concentrations. 36 end-stage renal failure patients were kept on their calcium regimen for 2 weeks; calcium was discontinued for 2 weeks to establish baseline phosphorus concentrations; and then, patients were randomized to placebo (12 patients) or RenaGel (24 patients) for 2 weeks at a dose based on the previous dose of calcium phosphate binder. All 36 of the randomized patients completed the study. Serum phosphorus decreased 0.68mg/dL in RenaGel and increased 0.32 mg/dL in placebo patients ($p = 0.0367$, one-sided unpaired t-test). I am told that the preferred test in this situation would be a 2-sample, paired, 2-sided t test. 11/12 placebo and 21/24 RenaGel patients had serum phosphorus >4.5 mg/dL; serum phosphorus decreased 1.36 mg/dL in these hyperphosphatemic RenaGel patients and increased 0.26 mg/dL in the placebo patients ($p=0.01$). Total cholesterol decreased 20.48 mg/dL in RenaGel and increased 0.45 in placebo patients ($p=0.0127$), and LDL cholesterol decreased 17.6 mg/dL in patients on RenaGel and increased 7.3mg/dL on placebo ($p=0.0026$).

GTC-36-301 was an **open-label cross-over** study comparing RenaGel and **Calcium acetate** in 84 patients on renal dialysis. 75 completed the study. The primary endpoint was serum phosphorus concentrations. Secondary endpoints were safety of RenaGel and comparison of **lipid levels** and

parathyroid hormone levels in RenaGel vs Calcium acetate patients. Phosphate binders were discontinued during a 2-week washout period, followed by two treatment periods with patients randomized to RenaGel first then calcium acetate or vise versa. The treatment periods were separated by another 2-week washout. During the baseline washout, patients who developed a serum phosphorus >6.0 mg/dL received drug treatment (randomly assigned RenaGel or calcium acetate). Initial RenaGel dose was based on phosphorus levels during the washout. At the **end of each of three 2-week periods the dose of RenaGel was increased** 1 capsule or 1 tablet per meal (3/day) to achieve serum phosphorus 2.5 to 5.5 mg/dL. The average final dose of RenaGel was 5.2g, and of calcium acetate was 5.0g. Total treatment periods were 8 weeks. Serum phosphorus decreased an average of 2.1 mg/dL on calcium acetate and 2.2 mg/dL on RenaGel. The decrease for each drug was significant compared to baseline, but decreases were **not different between RenaGel and calcium acetate.** Calcium acetate treatment increased serum calcium, but RenaGel had a "minimal effect." There were episodes of serum calcium 11 or more mg/dL in 4 patients (5%) during RenaGel treatment and in 18 (22%) during calcium acetate treatment. [The changes listed from here down on this study were generally not significant, but were consistent.] **Phosphorus calcium product** was greater than 66 at least once in 74% of patients when on RenaGel and in 64% when on calcium; it was greater than 66 at 2 or more times in 50% of patients when on RenaGel and in 39% when on calcium. There were 14 patients who had an **episode of hypercalcemia** when on calcium and one (or more) when on RenaGel, 22 who had an episode on calcium and no episode on RenaGel, and none who had an episode on RenaGel but no episodes on calcium. 44 had no episode on either drug. **LDL cholesterol** decreased (from 107 and 98 mg/dL) 28 and 23 mg/dL in the two groups when on RenaGel. Serum **iPTH** decreased on both drugs, but more on calcium than on RenaGel. LDL decreased 28 and 23 mg/dL from 107 and 98 on RenaGel, 8 and 0.2 mg/dL (from 107 and 104) on calcium. HDL, and TG did not change much.
Comments: This is the only study that provides evidence of relative efficacy. Calcium seems to have a little edge over RenaGel in each determination, except for levels of LDL cholesterol and episodes of hypercalcemia. See Dr. Schneider's comments on criteria for responders. Certainly, there should be a minimum reduction that is considered to be a response.

Four uncontrolled studies were done and were supportive of the findings in the above studies. There are no controls for assessing 1) the effect that entering a trial has on diet compliance and 2) regression to the mean.

GTC-10-202 studied the effect of RenaGel (dose titrated as in GTC-36-301 above) on serum phosphorus, lipids and intact PTH. Comparison to baseline washout was determined. Of 48 patients entered, 5 withdrew because of AEs and one withdrew consent. Only 28 were compliant and had a week 10 phosphorus. Mean serum phosphorus decreased 1.4 mg/dL from screening value of 8.1 between end of washout and end of treatment in ITT population (48 pts).

Comments: High, medium and low doses (tertiles of 16 patients each) did not produce significantly different serum phosphorus levels.

GTC-36-203 was a **randomized, but open comparison of RenaGel alone with RenaGel plus calcium carbonate** in 55 renal dialysis patients (75 patients entered, 20 dropped out). The study thus provides an evaluation of the value of **adding calcium to RenaGel**, but does not address, in a controlled way, the efficacy of RenaGel. Dose was titrated as in GTC-36-301 above with treatment continued to 12 weeks. Serum **phosphorus decreased** 2.4 mg/dL in RenaGel only patients and 2.3 mg in the group with added calcium. **LDL cholesterol** decreased similarly in both groups from about _____ during treatment. **Nausea** was more common in the combination group than in the group treated with RenaGel alone. The incidence of **hypercalcemic episodes** (before vs after washout) was 22.9% vs 2.9% for RenaGel alone and 36.1 vs 11.1 for the group with added calcium carbonate. It is postulated that this decrease in hypercalcemic episodes is due to discontinuing the calcium binders. **Phosphorus calcium product** decreased from 82.5 to 60.1 at week 14 and from 75.5 to 55.9 in the group given calcium. The **incidence of hypercalcemia** at the end of treatment was 5.7% in the RenaGel only group and 25% in the combination group, not statistically different from the incidence at end of washout for either group. **Intact PTH** decreased significantly in the RenaGel group but not in the combination group.

GTC-36-302 was an open label study in **172 patients** (144 completed) on hemodialysis to determine the effect of RenaGel on serum phosphorus, lipid levels,and iPTH. Dose was titrated as above (q 2 wk) to a serum phosphorus _____ Washouts of 2 weeks duration preceded and followed the treatment. **Phosphorus was reduced** during treatment compared to end of first washout by 2.5 mg/dL.

29 patients reported 33 serious adverse events, and there were 3 deaths. Total and **LDL cholesterol** and **iPTH** were significantly reduced (baseline control).
GTC-36-901 enrolled any patient who completed one of these dose titration studies. An **interim report** as of 5/1/97 was submitted. 192 patients entered; 25 terminated early. Dose was titrated by investigators to achieve a serum phosphorus level of 2.5 to 5.5 mg/dL. **Evening supplement of Calcium** was given. Serum **phosphorus decreased** from end of first washout and the change was associated with dose of RenaGel. The change was sustained during this extension. There was a dose trend for dyspepsia, hypochromic anemia and cough increase. 41 patients reported 68 AEs and 6 patients died. Total and LDL cholesterol decreased. This study showed that efficacy changes seen in studies 301 and 302 continued during the extension to 44 weeks.

Evaluation: Although efficacy of RenaGel in phosphate binding may be a little less than that obtained from calcium binders, the clear advantage to preventing hypercalcemia tips the benefit to risk decision to favor approval of RenaGel for patients on dialysis for end-stage renal failure.

Hedin

OCT 16 1998

MEDICAL OFFICER'S REVIEW

NDA # 20-926
SUBMISSION:

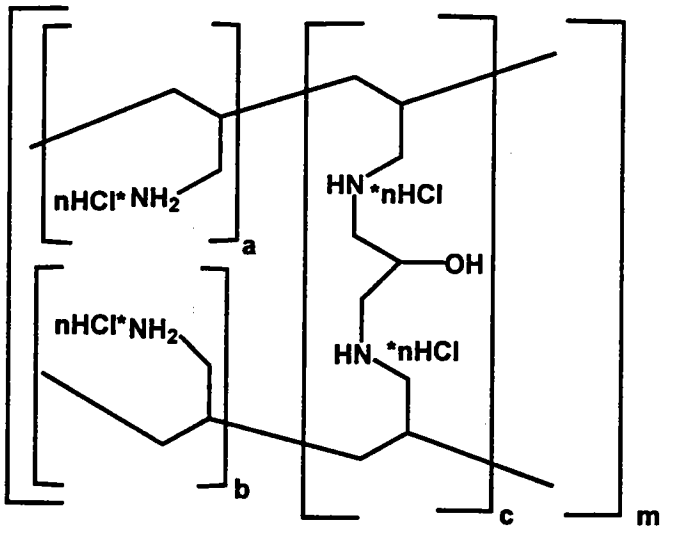
REVIEW COMPLETE:

DRUG NAME: RenaGel® Capsules

GENERIC NAME: Sevelamer Hydrochloride

PROPOSED TRADE NAME: RenaGel Capsules

CHEMICAL STRUCTURE:



Sevelamer Hydrochloride

a, b = number of primary amine groups a + b = 9
c = number of cross-linking groups c = 1
n = fraction of protonated amines n = 0.4
m = large number to indicate extended polymer network

1.3 SPONSOR: GelTex Pharmaceuticals, Inc., Waltham, MA 02154

1.4 PHARMACOLOGIC CATEGORY: RenaGel (sevelamer hydrochloride) is a cross-linked poly(allylamine), a non-absorbed phosphate binding polymer. RenaGel is free of calcium and aluminum.

1.5 PROPOSED INDICATION: Control of hyperphosphatemia in end stage renal failure.

1.6 DOSAGE FORM AND ROUTE OF ADMINISTRATION: Capsules, oral.

1.7 NDA DRUG CLASSIFICATION:

1.8 IMPORTANT RELATED DRUGS:

1.9 RELATED REVIEWS:

a) Statistics Review
b) Clinical Pharmacology and Biopharmaceutics Review
c) Pharmacology Review
d) Consultation from Division of Cardio-Renal Drug Products
Drug Products

APPEARS THIS WAY
ON ORIGINAL

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ON ORIGINAL

3 **MATERIAL REVIEWED** This review was based on a CANDA submitted by the sponsor. The following sections (volumes) of the CANDA were reviewed: #1, Index; #2, draft labeling; #3summary; #5, Nonclinical Pharmacology and Toxicology; #6,human pharmacokinetics and bioavailability; #8 Clinical data section. Of these, the clinical data section was reviewed in its entirety. The primary data from all the clinical trials were reviewed, and the analysis of this review is dependent on these data. Extensive discussions were held with reviewers from Statistics, Clinical Pharmacology, and Preclinical Pharmacology.

4 **CHEMISTRY/MANUFACTURING CONTROLS:** There are no outstanding issues.

5 **PRE-CLINICAL PHARMACOLOGY/TOXICOLOGY:**

Preclinical studies (*in vitro* and *in vivo*) have been carried out to address key issues of efficacy and safety. *In vitro* studies have demonstrated that RenaGel is capable of binding phosphate. In studies that measured the amount of phosphate bound to the RenaGel polymer as a function of the ambient phosphate concentration, it was determined that the polymer has the required binding capacity to absorb amounts of dietary phosphate required for therapeutic response.

Administration of RenaGel to normal rats produced 90 and 77% increases in fecal excretion of phosphorus. By comparison, these same experiments showed that calcium carbonate produced a 23% increase in fecal phosphorus excretion. Decreased urinary phosphorus, indicating decreased absorption was observed in a dose-dependant manner with RenaGel administration. In a partially nephrectomized rat model, RenaGel produced a statistically significant ($p < 0.05$) decrease in PTH levels on days 40 and 49 of the study. These results indicate that RenaGel is capable of binding dietary phosphorus and increasing fecal phosphorus in normal rats,and suppressing PTH secretion in partially nephrectomized rats.

In drug interaction studies in beagle dogs, RenaGel, 100 mg/kg, was administered with digoxin, estrone, propranolol, thyroxine, tetracycline, verapamil, valproic acid, dihydroxyvitamin D_3 or warfarin. All of the drugs were _____ serum concentrations were assayed by _____ except for dihydroxyvitamin D_3, which was assayed by _____. C_{max}, t_{max}, and AUC_{0-48} were calculated. RenaGel had no effect bioavailability when administered in combination with each of these drugs, and there were no statistically significant differences in Cmax or AUC. However, there was a delay in tmax. for estrone, propranolol, and thyroxine. These data have been reviewed in detail by Pharmacology.

PK studies in rats utilized _____ sevelamer. The polymer was radiolabeled in three different positions (the backbone, the cross-linker, and the

final cross-linked aminopolymer). Nearly 100% of the radioactivity was recovered in the feces, with a small residual amount of material in the GI lumen. There was no significant amount of radioactivity in the urine. The highest amount of radioactivity observed in any tissue was 0.05% of the total administered dose. This was found in the GI tract and was most likely due to incomplete rinsing of the GI lumen. There was a small amount of radioactivity observed in the blood, liver and skeletal muscle (≤ 0.1%). This may have been due to due to soluble radioactivity present in all [redacted] were not done on the tissue radioactivity.

Nonclinical toxicity studies were performed in rats and beagle dogs. RenaGel was adminstered orally to Sprague-Dawley rats for 1, 3 and 6 months at doses up to 10 g/kg/day and to Beagle dogs for 1, 3 and 12 months at doses up to 2 g/kg/day (see Section 5.4.3). Minimal toxicities were observed in both species. Of clinical concern, RenaGel produced a dose-dependent decrease in serum levels of vitamins D, E, and K, at doses greater than 6-10X the indicated human dose, on a body weight basis. The decrease in vitamin E observed may be due to the reductions in LDL cholesterol, since vitamin E circulates mainly in low-density lipoproteins. These high doses of RenaGel produced anemia and focal hemorrhages in rats. In one study, RenaGel produced an increased incidence of submucosal edema of the stomach in female rats; the etiology of this finding is still unclear. In dogs, RenaGel produced minimal signs of toxicity, which included decreased red blood cell indices and decreased levels of vitamins D and E; these findings were observed in animals administered 2 g/kg/day. No overt signs of clinical toxicity and no drug-associated histopathological findings were observed at doses up to 2 g/kg/day. These doses are about 5x the maximum intended clinical dose, on a weight basis.

Reproductive toxicity studies in rats and rabbits showed that RenaGel had no adverse effects upon male and female fertility or early embryonic development at doses up to 4.5 g/kg/day. There was also no evidence that RenaGel induced embryolethality, fetotoxicity or teratogenicity at doses up to 1.0 g/kg/day in rabbits and up to 4.5 g/kg/day in rats.

Genotoxicity studies revealed the following: In the *Salmonella typhimurium* reverse mutation assay, RenaGel produced the same mean number of revertants as the negative control, with and without metabolic activation. All positive controls were active, increasing the mean number of colonies threefold over that of the negative control article. Thus the test system was functional with known mutagens.

In the *in vitro* mammalian cytogenetics test, RenaGel, at 5 mg/mL, was weakly positive for the induction of structural chromosome aberrations and negative for the induction of numerical chromosome aberrations. The weakly positive effects of RenaGel may have been due to RenaGel's ability to absorb the culture medium and not the direct action of the test article. To confirm these results,

RenaGel was tested in the *in vivo* mouse micronucleus assay, using intraperitoneally injected drug (RenaGel is not absorbed) in doses up to 5 g/kg/day for 2 consecutive days. Under the conditions of this study, RenaGel was concluded to be nonclastogenic.

6. CLINICAL BACKGROUND:

6.1 Relevant Human Experience

In renal failure, the system for maintaining phosphorus balance is perturbed. As the glomerular filtration rate (GFR) falls, hyperphosphatemia, and hypocalcemia (secondary to 1,25-dihydroxyvitamin D deficiency) develop. The combination of hypocalcemia, low vitamin D levels, and hyperphosphatemia stimulate parathyroid hormone (PTH) secretion. As a result, osteoclastic bone resorption is increased. Continued exposure to elevated PTH levels leads to osteitis fibrosa, or renal osteodystrophy. In individuals with normal renal function, parathyroid hormone promotes the excretion of phosphate by decreasing its tubular reabsorption. However, with reduction of GFR to less than 25% of normal, PTH, even at substantially elevated levels, cannot further increase phosphorus excretion. Consequently, hyperphosphatemia develops. Hyperphosphatemia elevates the CaXP ion product in blood. When this product exceeds the solubility point, calcium phosphate precipitates in soft tissues, causing significant morbidity in ESRD patients. In addition, the hyperphosphatemia itself is important in the development of secondary hyperparathyroidism.

RenaGel was developed for the treatment of hyperphosphatemia in end stage renal disease (ESRD). The drug acts by binding dietary phosphate, which is the major source of the elevated phosphorus in ESRD patients. Phosphate binder therapy has been based on aluminum- or calcium-based drugs. Use of aluminum-based products in ESRD patients causes aluminum toxicity (in brain, bone, and muscle). Calcium acetate (PhosLo®) is currently the only FDA-approved drug for use as an oral phosphate binder. Calcium acetate can increase the serum calcium concentration, often to unacceptably high levels. RenaGel is free of calcium and aluminum, and thus has the potential to reduce the serum phosphorus without causing aluminum toxicity or hypercalcemia.

6.2 Related Drugs

There are no related phosphate binders currently available. Bile acid binding resins (e.g., cholestyramine) have the potential to decrease bioavailabilty of concomitantly administered drugs.

6.3 Foreign experience: RenaGel is not marketed outside the USA.

6.4 Human Pharmacology, pk, and pd.

A complete review of human pharmacology and biopharmaceutics has been received. There are two issues of direct clinical importance:

1) RenaGel was not systemically absorbed in a study in normal volunteers given C-RenaGel. Systemic absorption studies have not been done in patients with ESRD. RenaGel is thought to act entirely within the gastrointestinal lumen.

2) Of note, no drug-drug interaction studies have been done in humans. Thus the ability of RenaGel to decrease the bioavailability of concomitantly administered drugs, vitamins, and other nutrients is not known.

These issues are discussed in detail in the review of clinical trials. As indicated in the Recommendations section, the issues will be addressed in the labeling.

6.5 Other relevant background information

The clinical program was developed with consultation from the DMEDP.

6.6 Directions for use

To be effective, RenaGel must be taken with meals. A dosing schedule is provided in the label. The label also includes a suggested dose titration schedule, whereby the dose of the drug can be adjusted according to the serum phosphate concentration. RenaGel may bind to drugs, vitamins, and other nutrients within the GI tract. Therefore, if reduced bioavailability of a concomitant medication would be of clinical concern, that medication should be given at least one hour before, or three hours after, the administration of RenaGel.

7 Description of Clinical Data Sources

The clinical data sources derive exclusively from all the studies submitted by the sponsor to the NDA. Eight clinical studies were submitted, and these are each reviewed separately below. Tables describing the types of studies, number of patients, demographics doses, extent of exposure, endpoints (safety and efficacy) are provided in section 9 of this review.

The total database includes 408 patients with ESRD on hemodialysis. No renal transplant patients, peritoneal dialysis patients, or non-dialyzed patients were studied. Patients were adult males and females. The demographics and medical histories were representative of the intended treatment population.

Only two of the studies were controlled. One was a double-blind placebo-controlled study that exposed a small number of patients to RenaGel for two weeks. This study was conducted in phase 2 of development. The other was a larger phase 3 trial that used a crossover design to compare RenaGel with

calcium acetate, in terms of both safety and efficacy. In the remainder of the studies, all patients were given RenaGel, and within-group comparisons were made. The weaknesses of this study design are well known and are discussed in detail in individual sections below, as well as in the overview section (section 9). The rationale for the use of uncontrolled studies was that patients should not be kept off phosphate binder therapy for more than a few weeks, for medical and ethical reasons. Although all trials are reviewed in depth here, particular attention is given to the two trails in which between-group safety and efficacy comparisons can be made. A description of the studies submitted to the NDA is provided in tabular form below:

PHASE I	**DESIGN**	**OBJECTIVE**	**NUMBER TREATED WITH RENAGEL**
GTC-02-101	Randomized, placebo controlled Normal volunteer	Safety and pd	24
GTC-02-801	Open-label, normal volunteer	RenaGel absorption	20
PHASE II			
GTC-10-201	Randomized, placebo-controlled	Efficacy and safety	24
GTC-10-202	Open-label, dose titration	Efficacy and safety	48
GTC-36-203	Randomized, open-label dose titration	Efficacy, safety, and effects of calcium supplementation	75
PHASE III			
GTC-36-301	Randomized, open-label, cross-over comparison with calcium acetate	Efficacy and safety	82
GTC-36-302	Open label dose titration	Efficacy and safety	172
GTC-36-901	Open label extension study	Long-term safety and efficacy	192 (TAKEN FROM ABOVE STUDIES)

8 CLINICAL STUDIES:

Rationale and Overview of Clinical Development Program

As described above (section 6), oral phosphate binder therapy for treatment of hyperphosphatemia in ESRD can result in systemic aluminum toxicity or hypercalcemia, depending on the phosphate binder preparation. Currently, PhosLo (calcium acetate) is the only available, FDA-approved oral medication for hyperphosphatemia in ESRD. However, approximately 30-40% of orally administered calcium acetate is systemically absorbed. Therefore, ESRD patients are at risk of developing hypercalcemia during calcium acetate therapy. The goal of RenaGel therapy is to reduce the serum phosphorus concentration without elevating the serum calcium level. Avoidance of hypercalcemia will not only decrease the incidence of clinically significant hypercalcemia, but it will also decrease the consequences of chronic calcium overload which are associated with elevations in the Ca X P ion product.

Thus in all clinical studies which the sponsor carried out in ESRD patients, the primary efficacy endpoint was a reduction in serum phosphorus concentration. Changes in serum calcium, PTH, and CaXP ion product were also monitored in clinical trials. Occasionally, one or more of these parameters became efficacy endpoints as well. Serum calcium changes were always analyzed as safety endpoints. All patient studies submitted to this NDA have involved subjects who have ESRD and are currently receiving hemodialysis treatment. The clinical development plan evolved with input from the Division of Metabolic and Endocrine Drug Products at FDA.

The sponsor has conducted two studies in normal healthy volunteers and six clinical studies in hemodialysis patients. During the course of these studies, a total of 44 normal healthy volunteers and 408 ESRD patients received RenaGel. The demographics and medical histories of the ESRD patient population were broadly representative of the intended treatment population.

In the initial studies conducted on healthy volunteers, (studies GTC-02-101 and GTC-10-801) the sponsor evaluated the phosphate binding efficacy of RenaGel (using urine and fecal phosphorus measurements), as well as the degree of systemic absorption of the drug _____.

Following completion of these studies, the sponsor conducted the following six clinical trials in hemodialysis patients (two controlled and four uncontrolled); the primary efficacy endpoint in these studies was reduction in serum phosphorus concentration:

1) A controlled study (GTC-10-201) comparing RenaGel with placebo for 2 weeks, the maximum period that the sponsor and investigators deemed ethical to use a placebo.

2) An uncontrolled single arm trial (GTC-10-202) that titrated the RenaGel dose every two weeks based on serum phosphorus concentrations.
3) An uncontrolled dose titration study (no placebo) that compared RenaGel with RenaGel plus an evening calcium supplement (GTC-36-203).
4) A controlled dose titration study (GTC-36-301), comparing RenaGel with calcium acetate (PhosLo).
5) An uncontrolled dose titration study (GTC-36-302) in which the RenaGel dose was titrated every two weeks based on serum phosphorus concentrations.
6) An extended treatment study (GTC-36-901) in which ongoing therapy with RenaGel was offered to patients who had participated in any previous RenaGel study.

The following is a description and review of each of the eight clinical studies/clinical trials (two studies in normal volunteers and six trials in hemodialysis patients) reported to the NDA. Throughout the following section, I have inserted reviewer's comments in bold type, as required.

8.1.1 Reviewer's Trial # 1 Sponsor's Protocol # GTC-02-101

8.1.1.1 Objective:

1)To determine the safety and tolerability of single oral doses of RenaGel (1 g, 2.5 g, and 5 g) in normal subjects.

2)To determine the safety, tolerability, and efficacy of multiple oral doses of RenaGel (1 g, 2.5 g, and 5 g) administered 3 times daily to normal individuals for 8 consecutive days.

8.1.1.2 Study Design

This was a randomized, double-blind, placebo-controlled, parallel-design evaluation of the safety and tolerability of single and multiple oral doses (1, 2.5, or 5 grams) of RenaGel in 24 healthy volunteers. The study was carried out at a single site. Patients remained in the research unit (on controlled, constant 24-hour oral phosphate intakes) for the duration of the study.

Comments: The size of the population, length of exposure to the drug, and close monitoring of the patients in a controlled environment were adequate for an initial study of safety and tolerability. In addition, the design of this initial study was appropriate and adequate to perform the metabolic studies in normal volunteers and meet the objectives of this initial phase 1 trial. Measurements of urinary and fecal phosphorus are appropriate in a population with intact kidney function, since renal adjustments for deviations in phosphate intake are generally sufficient to maintain normal serum phosphate levels in such individuals, thus preventing hyperphosphatemia. In addition, measurements of fecal phosphate, if reliable, should confirm the mechanism of action of the drug in humans. If

positive, this study should demonstrate an increase in fecal phosphorus and a decrease in urinary phosphorus. The serum phosphate concentration would most likely remain unchanged.

8.1.1.3 Protocol

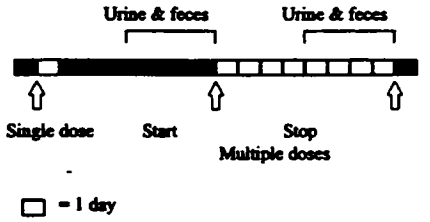
8.1.1.3.1 Population and Procedures:

Population: This study was conducted in 24 healthy volunteers (17 men and 7 women) 18 to 40 years of age. Inclusion/exclusion criteria were appropriate and comprehensive. These are given in adequate detail in the NDA submission (Appendix 8-1). Important entry criteria were: normal body weight; absence of overt evidence of substance or ethanol abuse, as well as negative urine drug screen; normal battery of hematology and chemistry tests; normal PE; negative HCG; and no history of GI, renal, or hepatic disease.

Procedures: After screening, eligible subjects were randomized into 3 groups of 8 subjects each and admitted to the study unit. Six of the 8 subjects in each group were then randomized to receive a specific dose of active drug; the remaining two subjects received placebo. During the entire period (18 days) in the clinical study unit, the subjects consumed a phosphate-controlled diet which provided 1200 mg elemental phosphorus per day (3 meals plus 1 snack).

On Day 1, the subjects received a single oral dose of RenaGel or placebo (Group 1, 1g RenaGel; Group 2, 2.5g RenaGel; Group 3, 5g RenaGel). In each group, 6 subjects received the specified dose of RenaGel, and the remaining 2 subjects received placebo. For the next 7 days (days 2-8), subjects received no drug. From the morning of Day 5 to the morning of Day 9, 24-hour urine and feces were collected. On Days 9-16, all subjects received either RenaGel or placebo three times daily. 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. All doses of RenaGel (or placebo) were administered t.i.d., just before (within 5 minutes) each meal.

The study design is summarized in the following figure:



Design of Study #1: Patients were maintained on 1200 mg of phosphorus/day throughout the study. The design included baseline and treatment periods of 8 days each. Fecal and urine collections occurred on the 5th through 8th days of both the baseline and treatment periods.

Safety was evaluated on the basis of reported and/or observed adverse experiences, and on changes in laboratory values. A complete listing of measured laboratory parameters is provided in the NDA. Among these parameters are basic hematology, clinical chemistry panel, PT, serum vitamin levels, serum iron, and urinalysis.

Efficacy was evaluated using stool and urine phosphorus concentrations and content. In addition, the ratio of stool/urine phosphorus was measured. This ratio (normally in the range _____) should increase in normal individuals who are given an oral phosphate binder.

During the two periods of serial 24-hour urine and feces collections (Days 5-9 and 13-17), samples were collected at each voiding and pooled in urine or stool collection containers (for each 24-hour period). At the end of each 24-hour collection interval, the total volume of urine and the total weight of feces was recorded. One-hundred-ml aliquots were taken from each 24-hour urine collection and frozen at -20°C. until assayed for creatinine, elemental phosphorus, sodium, potassium, calcium, and chloride concentrations. The 24-hour feces collected during the two 4-day collection periods were weighed and homogenized _____ The feces were then frozen at -20°C. Aliquots (10 mg) of the pooled 4-day fecal samples were packed in dry ice and shipped to the analytical laboratory for determination of elemental phosphorus concentrations.

Comment: The analytical methodology is straightforward, well-established, and appropriate for this type of metabolic study. The dose of drug, dosage schedule, and protocol for urine and fecal phosphorus collections are all reasonable and appropriate to the goals of the study. The timing of drug administration (just prior to meals) is important, because the drug works by binding dietary phosphate.

The efficacy analysis compared the phosphorus concentrations and content in the stool and urine collected on Days 13-17 with the baseline concentrations in the stool and urine collected on Days 5-9; The analysis also compared changes from baseline in phosphorus concentrations among the groups. ANOVA was used to detect an overall difference in the treatment groups (1 g, 2.5 g, 5 g and placebo). If the overall test was significant, pairwise tests were to be performed to determine a possible dose response. The ratio of stool to urine phosphorus was similarly examined.

In addition, analyses were performed to explore the influence of outliers. A 98% confidence interval was determined for each subject based on mean and standard deviation of the 6 middle observed urine creatinine values (eliminating the highest and the lowest of 8 urine creatinine values). If a subject's urine creatinine value at any time point was above or below the thus-determined confidence interval limits, that value (and the corresponding urine phosphorus

value) was considered an outlier and excluded.

Comments on Protocol: There apparently was some inconsistency on the part of the sponsor in designating whether the efficacy analysis was to measure the *concentration* or *content* of phosphorus in stool and feces. The sponsor states:

"Although the protocol specified that phosphorus excretion was to be evaluated on the basis of urine and fecal phosphorus concentrations, the intent was to examine total urine and fecal phosphorus contents. Urine phosphorus content is a better measure of absorbed phosphorus than concentration, as it is independent of urine volume, which varies depending on fluid consumption. Fecal phosphorus content is a better measure of nonabsorbed phosphorus than concentration, as it is independent of stool volume (weight), which is influenced by the amount of water and nondigestible fiber in the stools. Thus additional analyses of total urine and fecal phosphorus contents were carried out. Total phosphorus content in the urine was calculated from the concentration in the aliquot multiplied by the total volume. Total phosphorus content in the feces was determined from the concentration in the aliquot multiplied by the total weight and then dividing by the number of collection days

Comments (cont.): In reviewing the protocol, neither "concentration" nor "content" is mentioned in the Objectives section. The efficacy analysis in the protocol uses the term "concentration." However, it seems that the sponsor intended to determine total content, as this is a more meaningful quantity. Furthermore, the concentrations of phosphorus in individual aliquots would be highly variable, for reasons cited above by the sponsor. It is important to note that, in the chemical analyses, the determination of 24-hour phosphorus content represented an *actual* measurement (i.e., the phosphorus concentration in an aliquot taken from the 24-hour urine collection, multiplied by the total volume of that collection), rather than a derived value. Thus I do not feel that this "additional analysis" represents a *"post-hoc"* evaluation.

8.1.1.3.2 Endpoints

The designated efficacy endpoints are described in detail above.

Comments: The efficacy endpoints were objective and clearly stated. As indicated above, the measurement of urine and stool phosphorus content is, on theoretical grounds, appropriate in a population with normal renal function in whom the serum phosphate levels would not be expected to change. The primary laboratory analysis, determination of phosphate in biological materials, is easily performed using standard chemical assays. The methodology should be sufficient to enable detection of changes in phosphorus metabolism during the time period of the study. However, it

should be noted that, by themselves, changes in urine phosphate excretion can only suggest that the drug altered intestinal phosphate absorption. Conclusions about drug effects on intestinal absorption depend upon the fecal phosphate data. Unfortunately, fecal balance studies often yield highly variable data. Sample recovery represents a large part of the difficulties encountered in these balance studies.

As described above (8.1.1.3.2), it is my opinion that the "additional analysis" provided by the sponsor is not a *"post-hoc"* analysis. The primary objectives and endpoints were in no way altered or modified during or after the study.

8.1.1.3.2 Statistical Considerations

The statistical analyses are straightforward, and no special techniques are employed.

8.1.1.4 Results

8.1.1.4.1 Populations enrolled

As shown in the table below, the demographic characteristics of the population were equally divided among all 4 treatment arms.

Demographic characteristics of Study Subjects in Clinical Trial #1

Variable	Placebo (N = 6)	RenaStat 1 g (N = 6)	RenaStat 2.5 g (N = 6)	RenaStat 5 g (N = 6)	p value
Sex					
Male	5 (83.3%)	4 (66.7%)	4 (66.7%)	4 (66.7%)	1.000
Female	1 (16.7%)	2 (33.3%)	2 (33.3%)	2 (33.3%)	
Race					
Caucasian	6 (100.0%)	6 (100.0%)	3 (50.0%)	4 (66.7%)	
Black	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	0.131
Hispanic	0 (0.0%)	0 (0.0%)	1 (16.7%)	2 (33.3%)	
Native American	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	
Age (years)					
Mean ± SD	27.7 ± 5.5	31.0 ± 8.1	25.2 ± 4.9	28.5 ± 5.1	0.433
Range	24-38	22-39	20-31	25-36	
Height (cm)					
Mean ± SD	174.3 ± 6.9	177.0 ± 11.3	177.0 ± 7.3	177.8 ± 10.0	0.915
Range	165-183	163-193	163-183	168-193	
Weight (kg)					
Mean ± SD	68.6 ± 6.6	75.4 ± 18.0	74.7 ± 9.3	75.8 ± 10.1	0.690
Range	60-75	56-99	61-82	62-86	

Comments: In this initial study in normal volunteers the population size was appropriate for the metabolic balance studies, as well as for a first study of safety and tolerability. All subjects met all inclusion/exclusion criteria. During the trial, there were no protocol violations, dropouts from the trial, or reports of significant concomitant medications or illnesses. All subjects consumed sufficient amounts of their prescribed diet. All subjects received all 25 doses of RenaGel (food and drug intake data provided in appendix 2 0f NDA).

It should be noted, however, that the study population was almost exclusively Caucasian and in late 20's. This will differ somewhat from the demographic composition of the intended treatment population. There is no clear *a priori* reason why this consideration limits the efficacy portion of the study. However, the drug may have adverse effects and/or altered efficacy in older individuals or possibly in other populations.

8.1.1.4.2 Efficacy endpoint outcomes

The primary efficacy outcome, the effect of RenaGel on the absorption of dietary phosphorus, was evaluated by comparing fecal and urinary phosphorus concentrations collected on Days 13-17, the baseline concentrations in the stool and urine collected on Days 5-9, and the changes from baseline in phosphorus concentrations among the treatment groups.

The data set was derived from urine and fecal samples taken from the entire study population. Because this study addresses mechanism, I have included considerable detail in the efficacy analysis.

Urine Phosphorus

As shown in the table below, the urine phosphorus concentrations did not differ statistically among the 4 treatment groups at baseline ($p = 0.90$). There was a statistically significant difference, between the groups, in average urine phosphorus concentrations on Days 13-16: 50.46 mg/dL for placebo *vs* 44.18 mg/dL, 37.63 mg/dL, and 27.97 mg/dL for RenaStat 1 g, 2.5 g, and 5 g, respectively, ($p = 0.013$, ANOVA comparing the 4 treatment groups). Pairwise comparisons revealed statistically significant differences between placebo and RenaStat 5 g ($p = 0.0019$) and between RenaStat 1 g and RenaStat 5 g ($p = 0.0183$). The change from baseline was smallest in the placebo group and greatest in the RenaStat 5 g group: –18.96 mg/dL for placebo, –29.13 mg/dL for RenaStat 1 g, –29.18 mg/dL for RenaStat 2.5 g, –34.70 mg/dL for RenaStat 5 g ($p = 0.504$). The data are summarized in the table below.

Table 5. Urine phosphorus concentrations (mg/dL) mean±standard deviation (SD)

	Placebo (N = 6)	RenaStat 1 g (N = 6)	RenaStat 2.5 g (N = 6)	RenaStat 5 g (N = 6)	Overall p value*
Baseline (Average, Days 5-8)	69.42±6.46	73.30±32.55	66.82±23.11	62.67±29.05	0.900
Treatment (Average, Days 13-16)	50.46±8.97	44.18±15.18	37.63±11.85	27.97±5.15	0.013
Change from baseline	-18.96±8.68	-29.13±20.73	-29.18±12.56	-34.70±24.86	0.504

Reference: Appendix 5, Tables 8A-8B

- ANOVA comparing the 4 treatment groups

Comments: The ANOVA demonstrates that the 4 groups are not identical on days 13-16. Pairwise comparisons of the values during this period show statistically significant differences in the expected direction. However, all groups reduced urinary phosphorus concentrations from baseline, and the changes from baseline were not statistically significant. It is my opinion that these results are due to small n's plus variability in phosphorus concentrations. More meaningful data are derived from analysis of phosphorus content (see below).

Fecal Phosphorus

Results of the analyses of fecal phosphorus concentrations failed to show any changes in any of the treatment groups, either in mean concentrations or in change from baseline. This appears to be the result of the large standard deviations around the mean phosphorus concentrations.

Table 6. Fecal phosphorus concentrations (mg/g) mean±SD

	Placebo (N = 6)	RenaStat 1 g (N = 6)	RenaStat 2.5 g (N = 6)	RenaStat 5 g (N = 6)	Overall p value
Baseline (Average, Days 5-8)	0.97±0.48	0.84±0.40	0.98±0.43	1.06±0.51	0.870
Treatment (Average, Days 13-16)	0.76±0.33	0.99±0.33	0.95±0.54	0.97±0.50	0.802
Change from baseline	-0.21±0.18	0.15±0.21	-0.04±0.53	-0.09±0.37	0.393

Reference: Appendix 5, Tables 9A-9B

- ANOVA comparing the 4 treatment groups

Ratio of Stool to Urine Phosphorus

As shown in the table below, there was a statistically significant difference between the groups for fecal/urine phosphorus ratios on Days 13-16 (0.44 for placebo *vs* 0.38, 0.58, and 1.22 for RenaStat 1 g, 2.5 g, and 5 g, respectively ($p = 0.006$). Pairwise comparisons revealed statistically significant differences between placebo and RenaStat 5 g ($p = 0.0030$), RenaStat 1 g and RenaStat 5 g ($p = 0.0015$), and RenaStat 2.5 g and RenaStat 5 g ($p = 0.0111$). There was also a statistically significant difference between the groups in change from baseline ($p=0.005$). Pairwise comparisons revealed statistically significant differences between placebo and RenaStat 5 g ($p = 0.0024$); between RenaStat 1 g and RenaStat 5 g ($p = 0.0012$); and between RenaStat 2.5 g and RenaStat 5 g ($p = 0.0100$).

Table 7. Ratios of stool to urine phosphorus mean±SD

	Placebo (N = 6)	RenaStat 1 g (N = 6)	RenaStat 2.5 g (N = 6)	RenaStat 5 g (N = 6)	Overa p valu
Baseline (Average, Days 5-8)	0.39±0.14	0.37±0.32	0.40±0.22	0.50±0.20	0.743
Treatment (Average, Days 13-16)	0.44±0.19	0.38±0.16	0.58±0.27	1.22±0.71	0.006
Change from baseline	0.06±0.13	0.01±0.22	0.18±0.22	0.72±0.56	0.005

Reference: Appendix 5, Tables 10A-10B

- ANOVA comparing the 4 treatment groups

Comments: The changes in ratios are in the anticipated direction and are statistically significant.

Analysis of Urine and Fecal Phosphorus Content: The total daily urine phosphorus for each group is shown in table 8 below. The 24-hr urine phosphorus content was similar in all treatment groups at baseline ($p = 0.578$). With treatment (Days 13-16), the urine phosphorus content fell in a dose-dependent manner. Pairwise comparisons revealed statistically significant differences between placebo and RenaStat 2.5 g ($p = 0.0025$); placebo and RenaStat 5 g ($p = 0.0001$); and between RenaStat 1 g and RenaStat 5 g ($p = 0.0038$). Changes from baseline were also statistically significant ($p = 0.001$). Pairwise comparisons revealed statistically significant differences between placebo and RenaStat 2.5 g ($p = 0.0382$); placebo and RenaStat 5 g ($p = 0.0001$); RenaStat 1 g and RenaStat 5 g ($p = 0.0023$); and between RenaStat 2.5 g and RenaStat 5 g ($p = 0.0106$).

Mean Total Daily Urine Phosphorus (mg)

ASSESSMENT TIME	PLACEBO (N=6)	RENAGEL 1 G (N=6)	RENAGEL 2.5 G (N=6)	RENAGEL 5 G (N=6)	P-VALUE*
Baseline (Ave. Days 5-8)	831.57	814.13	716.67	786.14	0.578
Treatment (Ave. Days 13-16)	869.88	761.65	625.34	530.23	0.001
Change from baseline	38.31	-52.48	-91.34	-255.91	0.001

- ANOVA used to test overall treatment group difference.

Total Fecal Phosphorus Content

At baseline, the total fecal phosphorus content was indistinguishable among the 4 treatment groups. The total daily phosphorus rose more in the RenaGel 5 g group than in the other 3 treatment groups, but the overall inter-group difference was not statistically significant (p=0.071) Change from baseline was also higher in the 5 g group than in the other 3 groups, but the difference was not statistically significant (p= 0.184). The data are shown in the table below.

Mean Total Daily Fecal Phosphorus (mg)

ASSESSMENT TIME	PLACEBO (N=6)	RENAGEL 1 G (N=6)	RENAGEL 2.5 G (N=6)	RENAGEL 5 G (N=6)	P-VALUE*
Baseline (Ave. Days 5-8)	309.80	273.96	299.63	384.76	0.669
Treatment (Ave. Days 13-16)	372.51	290.45	343.64	612.23	0.071
Change from baseline	62.71	16.50	44.01	227.47	0.184

*ANOVA used to test overall treatment group difference.

Comments: Again, the measurements of fecal phosphorus have proven unreliable, in view of the large standard deviations. There is a trend in the expected direction in the 5 gram treatment group. Overall comments on efficacy appear below in 8.1.1.5.

8.1.1.4.3 Safety Outcomes

Each subject received all 25 doses of RenaGel or placebo. There were no dropouts from the study. There were no serious adverse events during the study.

All adverse experiences occurring after the single dose of RenaGel are presented in the NDA in Tables 6A.1, 6B.1, 6B.1.2, 6C.1, 6D.1, and 6D.1.2 (Appendix 5, Study Summary Tables); these experienced are summarized in the table below.

There were no statistically significant differences among the 4 treatment groups in: overall incidence of adverse events, incidence of adverse events by body system, severity of event; or relationship of event to study drug. There was a statistically significant inter-group difference in the incidence of events related to the digestive system. The incidence of adverse GI events was higher in the RenaGel 2.5 g group (p = 0.04), but was no higher than placebo in the 1g or 5g dose groups:

Number of subjects with adverse experiences after a single dose of RenaStat or placebo (Days 1-8)

Adverse experiences		Placebo (N = 6)	RenaStat 1 g (N = 6)	RenaStat 2.5 g (N = 6)	RenaStat 5 g (N = 6)
None		5 (83.3%)	2 (33.3%)	2 (33.3%)	5 (83.3%)
At least one		1 (16.7%)	4 (66.7%)	4 (66.7%)	1 (16.7%)
Body as a whole	Asthenia	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)
	Headache	1 (16.7%)	2 (33.3%)	1 (16.7%)	0 (0.0%)
	Back pain	0 (0.0%)	2 (33.3%)	0 (0.0%)	0 (0.0%)
Digestive system	Diarrhea	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)
	Dyspepsia	0 (0.0%)	0 (0.0%)	2 (33.3%)	0 (0.0%)
Nervous system	Somnolence	0 (0.0%)	1 (16.7%)	0 (0.0%)	1 (16.7%)
	Vasodilation	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)
Urogenital system	Dysmenorrhea	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)

Reference: Appendix 5, Study Summary Tables, Tables 6A.1 and 6B.1

- A subject may be included in more than one body system

Adverse experiences by body system are presented in Appendix 5 of the NDA. There were 14 adverse experiences (1 in the placebo group, 5 in the RenaStat 1 g group, 7 in the RenaStat 2.5 g group, and 1 in the RenaStat 5 g group) in 10 subjects. As mentioned above, the incidence of GI adverse experiences was significantly higher in the RenaStat 2.5 g group: 50% *vs* 0% in the other 3 groups ($p = 0.040$). The three subjects with these events reported upset stomach, loose stools, and heartburn. Pairwise comparison revealed no statistically significant difference between the groups in adverse experiences by body system (Appendix 5, Table 6B.1.2). All of the events resolved with no concomitant treatment.

Multiple Dose Phase

The adverse events occurring during the multiple dosing phase (drug given t.i.d for each of days 9-16) through the follow-up visit (Day 24) are presented in the NDA in Tables 6A.2, 6B.2, 6B.2.2, 6C.2, 6C.2.2, 6D.2, and 6D.2.2 (Appendix 5, Study Summary Tables). A summary of these events is given in the table below.

There were no statistically significant differences between placebo and the active treatment groups or between the 3 RenaStat dose groups in adverse events (overall incidence, incidence by body system, severity, or relation to study drug).

Number of subjects with adverse experiences during the multiple-dose phase of RenaStat or placebo (Days 9-24)*

Adverse experiences		Placebo (N = 6)	RenaStat 1 g (N = 6)	RenaStat 2.5 g (N = 6)	RenaStat 5 g (N = 6)	p value
None		1 (16.7%)	2 (33.3%)	2 (33.3%)3	3 (50.0%)	0.931
At least one		5 (83.3%)	4 (66.7%)	4 (66.7%)	3 (50.0%)	
Body as a whole	Asthenia	1 (16.7%)	1 (16.7%)	2 (33.3%)	1 (16.7%)	1.000
	Fever	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000
	Headache	1 (16.7%)	2 (33.3%)	2 (33.3%)	0 (0.0%)	0.695
	Abdominal pain	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	1.000
	Back pain	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	1.000
Digestive system	Diarrhea	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000
	Dyspepsia	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	1.000
	Nausea	1 (16.7%)	1 (16.7%)	2 (33.3%)	1 (16.7%)	1.000
	Abdominal pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	1.000
Hemic and lymphatic system	Lymphadenopathy	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	1.000
Musculoskeletal System	Twitch	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	1.000
Nervous system	Somnolence	0 (0.0%)	2 (33.3%)	1 (16.7%)	0 (0.0%)	0.573
	Vasodilation	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000

Respiratory system	Dyspnea	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	1.000
	Epistaxis	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	1.000
	Pharyngitis	1 (16.7%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	1.000
	Rhinitis	1 (16.7%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	1.000
Special senses	Abnormal vision	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	1.000
	Amblyopia	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	1.000
	Conjunctivitis	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	1.000
	Dry mouth	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (33.3%)	0.217
	Lacrimation disorder	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	1.000
	Pain eye	0 (0.0%)	1 (16.7%)	2 (33.3%)	0 (0.0%)	0.573
	Taste loss	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	1.000
Urogenital system	Metrorrhagia	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000
	Urinary frequency	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000

Reference: Appendix 5, Study Summary Tables, Tables 6A.2 and 6B.2

- A subject may be included in more than one body system

Ten events (in 9 subjects) were thought to be possibly or probably related to treatment. These 10 events are summarized in the table below:

Number of subjects with adverse experiences judged possibly or probably relate to treatment (multiple-dose phase)

Body system	Adverse experience	Placebo (N = 6)	RenaStat 1 g (N = 6)	RenaStat 2.5 g (N = 6)	RenaStat 5 g (N = 6)	p value
Body as a whole	Abdominal pain	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	1.000
Digestive system	Diarrhea	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000
	Dyspepsia	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	1.000
	Nausea	0 (0.0%)	1 (16.7%)	2 (33.3%)	1 (16.7%)	0.878
	Abdominal pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	1.000
Special senses	Taste loss	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	1.000
Subjects with experiences possibly or probably related to treatment		2 (33.3%)	2 (33.3%)	2 (33.3%)	3 (50.0%)*	1.000

Reference: Appendix 5, Study Summary Tables, Table 6C.2

- Nausea and abdominal pain were recorded in the same subject (#19)

All adverse events resolved without treatment except for one subject whose swollen glands and sore throat persisted for 1 week after the Day 24 follow-up visit.

Physical Examinations and Vital Signs

Physical examinations at discharge (Day 17 and at Day 24 during the follow-up visit were unremarkable (Appendices 2 and 5 in NDA). Similarly, there were no clinically significant changes in vital signs after single or multiple dosing (data in Appendices 2 and 5 of NDA).

Laboratory Values

Complete laboratory values are presented in Appendix 2 of the NDA. Following a single dose of RenaGel (baseline to Day 3), the mean laboratory values were unremarkable in all treatment groups.

For the multiple dose phase of the study, the laboratory values are presented in Appendix 5.

Hematology (multiple-dose phase)

No statistically significant changes from baseline to Day 17 were detected among hematology values, except for hematocrit and some isolated values (RBC and WBC). These were evenly distributed among the treatment groups and were not clinically significant.

Changes from baseline in hematocrit were statistically significant for the placebo group (–1.30%, p = 0.004) and the RenaStat 1 g group (–2.80%, p = 0.003). This produced a statistically significant difference between the groups (p = 0.0229). Pairwise comparisons revealed statistically significant differences in change from baseline hematocrit (Appendix 5, Table 7G) for RenaStat 1 g *vs* RenaStat 2.5 g (p = 0.0231) and for RenaStat 1 g *vs* RenaStat 5 g (p = 0.0036). None of these changes were clinically significant. There was no decline in average hematocrit in the 2.5 or 5 g group.

Chemistry (multiple-dose phase)

Chemistry values are provided in Appendix 5. No statistically significant changes from baseline to Day 17 were detected except for cholesterol (see below) and some isolated values (sodium, CO_2 and glucose), which were not clinically significant and were evenly distributed among the treatment groups. Pairwise comparison revealed statistically significant differences between placebo and some RenaStat groups or between the RenaStat dose groups for calcium, CO_2, sodium, and uric acid (see Appendix 5, Table 7H). As shown in the table below, these changes were not clinically significant or dose-related.

Cholesterol values were statistically significantly lower relative to baseline in all 3 RenaStat groups (–27.50 mg/dL, –21.17 mg/dL, and –41.83 mg/dL for RenaStat 1 g, 2.5 g, and 5 g, p = 0.006, p = 0.006, and p = 0.002, respectively), resulting in a statistically significant inter-group difference (p = 0.0001). These changes

from baseline in cholesterol were clinically significant in magnitude. Pairwise comparisons for change from baseline for cholesterol revealed statistically significant differences for placebo and all RenaStat groups (placebo *vs* RenaStat 1 g, p = 0.0005; placebo *vs* RenaStat 2.5 g, p = 0.0036; placebo *vs* RenaStat 5 g, p = 0.0001) and between the RenaStat 2.5 g group and the RenaStat 5 g group (p = 0.0141).

Comments: The reduction in LDL cholesterol was an unanticipated finding. Presumably, the mechanism involves sequestration of bile acids in the intestine. Cholesterol reduction, particularly in the intended patient population, would provide an added benefit of RenaGel therapy. Reduction in cholesterol became an efficacy endpoint in subsequent clinical trials.

Renal function (multiple-dose phase):

Renal function values are presented in Appendix 5. There were no statistically significant changes from baseline and no statistically significant inter-group differences in creatinine values. For BUN, the change from baseline was statistically significant in the RenaStat 5 g group (–1.67 mg/dL, p = 0.0199), resulting in a statistically significant inter-group difference (p = 0.0124). These changes were not clinically significant.

Hepatic function (multiple-dose phase)

Hepatic function values are presented in Appendix 5. GGT was statistically significantly decreased from baseline in the placebo group (–1.33 uL, p = 0.0250). LDH was statistically significantly decreased in the RenaStat 1 g group (–9.00 uL, p = 0.0332), resulting in a statistically significant inter-group difference (p = 0.0058). These changes were not clinically significant.

In the RenaStat 5 g group, AST was statistically significantly increased relative to baseline (5.33 uL, p = 0.0050), as was alkaline phosphatase (11.00 uL, p = 0.0063), resulting in a statistically significant intergroup difference (p = 0.0076 for alkaline phosphatase). These changes were not clinically significant.

Pairwise comparisons revealed the following statistically significant differences between the individual treatment groups in terms of changes from baseline:

- Alkaline phosphatase — placebo *vs* RenaStat 5 g: 1.83 uL *vs* 11.00 uL (p = 0.0087); and RenaStat 1 g *vs* 5 g: –0.83 uL *vs* 11.00 uL (p = 0.0013).
- LDH — placebo *vs* RenaStat 5 g: 0.67 uL *vs* 12.17 uL (p = 0.0494); RenaStat 1 g *vs* 2.5 g: –9.00 uL *vs* 7.67 uL (p = 0.0066); and RenaStat 1 g *vs* 5 g: –9.00 uL *vs* 12.17 uL (p = 0.0010).

Urinalysis (multiple-dose phase)

There were no significant findings in the urinalysis results (see Table 7E.1, Appendix 5, Study Summary Tables).

24-hour urine collections (multiple-dose phase)

Values for 24-hour urine collections are presented in Appendix 5. There were no statistically significant differences between the groups in terms of change from baseline. There were isolated statistically significant changes from baseline in the RenaStat dose groups (calcium, chloride, creatinine, and potassium) *vs* none in the placebo group. There were no statistically significant inter-group differences and none of these changes were clinically significant.

PT, vitamins, and iron (multiple-dose phase):

These values are presented in Appendix 5 of the NDA.

On Day 14, iron levels were markedly lowered relative to baseline in all groups (–38% for placebo, –33%, –31%, and –50% for RenaStat 1 g, 2.5 g, and 5 g, respectively). These changes were not statistically significant and iron values returned to baseline by Day 17 in all groups (Table 7F, Appendix 5).

Statistically significant changes from baseline were found for some of the vitamins in all RenaStat dose groups *vs* none for placebo. None of these were clinically significant. Pairwise comparison revealed a statistically significant difference between the RenaStat 1 g group and the RenaStat 5 g group for change from baseline in 25-hydroxy vitamin D ($p = 0.0051$). PT was significantly decreased relative to baseline in all RenaStat dose groups (–0.40 sec, –0.40 sec, and –0.80 sec for RenaStat 1 g, 2.5 g, and 5 g, $p = 0.0021$, $p = 0.0117$, and $p = 0.0030$, respectively), resulting in a statistically significant inter-group difference ($p = 0.0001$). These changes, however, were not clinically significant. Pairwise comparisons revealed statistically significant differences in change from baseline in PT for placebo *vs* all RenaStat groups ($p = 0.0021$, $p = 0.0021$, and $p = 0.0001$, for placebo *vs* RenaStat 1 g, 2.5 g, and 5 g, respectively) as well as between RenaStat dose groups, namely RenaStat 1 g *vs* RenaStat 5 g and RenaStat 2.5 g *vs* RenaStat 5 g ($p = 0.0292$ in both cases).

Abnormal laboratory values: Out-of-range laboratory values are listed in Appendix 2, Listing 14h. There were abnormal values in all treatment groups and no trend was discernible.

8.1.1.5 Conclusions Regarding Efficacy and Safety Data

This Phase 1 study adequately demonstrated that RenaGel can significantly reduce urinary phosphate excretion in normal individuals consuming a phosphorus-controlled diet. The urinary phosphorus content

increased in the placebo group (+38.33 mg), and decreased in dose-dependent fashion in the 3 RenaStat groups (–52.48 mg, –91.34 mg, and –255.91 mg, for RenaStat 1 g, 2.5 g, and 5 g, respectively). The changes from baseline were statistically significant (placebo vs RenaStat 2.5 g; placebo vs RenaStat 5 g; and RenaStat 1 g vs RenaStat 5 g).

The results of the fecal phosphorus studies were not as conclusive. Fecal phosphorus concentration was essentially unchanged in all 4 treatment groups. Fecal phosphorus content is a better measure of nonabsorbed phosphorus than is concentration, because the former parameter is independent of stool volume or weight. Fecal phosphorus content appeared to be higher in the RenaStat 5 g group. However, this result was not statistically significant.

When the data were expressed as ratios of stool to urine phosphorus, there were statistically significant increases all 3 RenaStat groups: placebo vs RenaStat 5 g, RenaStat 1 g vs RenaStat 5 g, and RenaStat 2.5 g vs RenaStat 5 g.

Taken together, the data strongly indicate that RenaGel can significantly reduce urine phosphate excretion, most likely by binding dietary phosphorus in the GI tract.

The reduction in LDL cholesterol was an unanticipated finding. Since this could provide an additional benefit advantages to Renagel therapy, reduction in cholesterol became an efficacy endpoint in subsequent patient trials.

Comments on Safety: In this study in normal volunteers, the data show no increase in clinical adverse events attributable to RenaGel. There were no clinically significant changes in laboratory values after multiple dosing of the drug, with the exception of serum cholesterol, which decreased in a dose-related fashion. There was an unexplained fluctuation in the serum iron level in all groups, including placebo. This may have been the result of the phosphate-controlled diet, but there was no proof of this. There were no clinically significant changes in levels of fat-soluble vitamins. There was no imbalance in incidence of any abnormal laboratory values in any of the treatment groups (including placebo). Within the limitations of this study (mainly young, Caucasian, healthy individuals exposed to 25 doses of drug over a period of 17 days), RenaGel appeared to be safe and well-tolerated.

8.1.2 Reviewer's Trial #2 Sponsor's Protocol # GTC-10-801 Absorption of ^{14}C-RenaGel (500 μCi) in Healthy Young and Old, Male and Female Volunteers