8.1.2.1 Objective:
to determine whether RenaGel is systemically absorbed following oral administration in healthy young and old, male and female subjects.

8.1.2.2 Design:

This was an open label, parallel design study of 20 healthy subjects, with 5 subjects in each of 4 groups: young (age 20-40) males, young females, old (age 65 years or older) males, and old females. This study employed [redacted] RenaGel administered orally to human volunteers. Blood, fecal, and urinary levels of radioactivity were monitored for several days after administration of the radiolabeled drug. If detectable plasma concentrations of [redacted] RenaGel® were detected, the sponsor planned to calculate standard non-compartmental pharmacokinetic parameters. If detectable radioactivity appeared in the urine, the total amount of radioactivity excreted, excretion rate and renal clearance were to be calculated.

Comments on design: This approach is ideally suited to fulfill the stated goals of the study. Further comments on suitability of the study population and experimental protocol appear below.

8.1.2.3 Protocol

8.1.2.3.1 Population and Procedures

Population: The sponsor recruited 20 healthy subjects, divided into four groups of 5 subjects each:

Group 1:	Young Females (19-40 inclusive)
Group 2:	Young Males (19-40 inclusive)
Group 3:	Old Males (65+ years)
Group 4:	Old Females (65+ years).

The subjects were screened within 21 days prior to study enrollment. The screening procedure included a medical history, physical examination and a series of standard clinical laboratory tests. Four subjects from each group were then selected to receive the [redacted] RenaGel. The remaining subject was retained as an alternate. The inclusion/exclusion criteria are outlined in the protocol (Appendix 1).

Comments on study population: The inclusion/exclusion criteria employed are comprehensive and adequately designed to provide a normal, healthy study population. Importantly, patients had normal histories, physical exams, and laboratory tests and had no evidence of any gastrointestinal, endocrine, or renal disorder.

However, it should be noted that this study was carried out in subjects with normal renal function. The intended treatment population consists of patients with end stage renal disease. Such patients are not only uremic, but they also often have other diseases that caused the renal failure (e.g., diabetes mellitus). Gastrointestinal function in these patients differs from that in normal individuals, and it is possible that these differences may affect the dynamics of RenaGel absorption. The conduct of a RenaGel absorption study in uremic patients would be feasible even though urinary excretion data would not be available. I have raised this issue with the sponsor during a teleconference, but they have insisted that an absorption study in uremic individuals is "not feasible."

I suggest that the labeling of the drug inform the reader that the absorption study was conducted only in normals and that no absorption studies were carried out in patients with ESRD.

Protocol: For the first 28 days (study Day -28 through study Day –1), each subject received 2.325 g of non-radiolabeled RenaGel p.o. three times daily. On the morning of Day 1 of the study, following a 10 hour fast (time 0), the subjects received a single oral dose of 2.325 g of RenaGel At 1200 and 1800 hours, subjects then received RenaGel, 2.325 g per dose. On Study Days 2-4, the subjects received 2.325 g of RenaGel t.i.d. Blood samples were collected at 0, 4, 8, 12, 24, 48, 72, and 96 hours post-dose. All urine and feces voided were collected separately during the following intervals: 0-24, 24-48, 48-72, 72-96 hours post-dose. Each blood sample was approximately 10ml. All urine voided was collected during the following intervals; 0 hour, 0-24, 24-48, 48-72, 72-96 hours post-dose. Fecal samples were collected pre-dose and post-dose over 24-hour periods at 0-24, 24-48, 48-72, 72-96 hours.

Comments on protocol and methodology: The dosing schedule is appropriate for this type of study and certainly adequate to achieve the stated goals. The timing of sample collection (blood, urine, and feces) is appropriate.

The analytical methods for sample preparation and counting of radioactivity are standard for this type of balance study. However, the fecal recovery study employed 3 known doses of RenaGel to calculate recovery. A standard curve is probably preferable, in case the recovery (or loss) is non-linear over the range. On the other hand, since the initial dose is known provided the quench corrections are working properly. This number can then be compared to the administered and the recovery calculated as the ratio of the two

values. If radioactivity is lost during the oxidation process, and this loss in not detected, this should result in under-reporting of fecal _____ which would work against the sponsor's hypothesis. The analytical methodology for measuring radioactivity in blood leaves open the question of loss during oxidation. The text of the NDA states that the whole blood samples were dried and oxidized prior to counting, but does not mention generation of a standard curve or the addition of ____ spiking experiments for the blood samples. It is not clear whether such recovery experiments were performed. If not, and if radioactivity were lost from the blood sample during the oxidation phase, this would result in under-reporting of RenaGel in blood. It is possible that the sponsor used the results of the _____ experiments conducted in the fecal recovery studies as a standard for blood. It is not clear to me why the sponsor did not count radioactivity in an additional aliquot of blood directly. The possible limitations imposed by counting a smaller sample volume could be overcome by increasing the counting time.

8.1.2.3.2 Endpoints:
Comments: The endpoints are clearly stated (measurement of radioactivity in blood, feces, and urine) and appropriate, as described above.

8.1.2.4 Results

8.1.2.4.1 Population: The demographics of the population, given in Appendix 2.1 of the NDA, are within the expected distribution for the defined characteristics, in terms of age, sex, height, and weight. Of note, all but one of the subjects were Caucasian. There were no serious protocol deviations. There were no serious adverse events, with the exception of one patient who was diagnosed with colon cancer at the termination of the study. This was judged to be unrelated to the study.

Comments: It should be noted that, in both of the clinical pharmacology studies, nearly all the subjects were Caucasian.

8.1.2.4.2 Efficacy/endpoint results: No ____ radioactivity was detected in the blood of any subject at any time during the study. In seven of the subjects, a small fraction of the total administered radioactivity (0.02% or less) was recovered in the urine (100000- 200000 dpm were recovered on day 2 in all 7 subjects. This = 1-2 x 10^5 dpm / 1.1 x 10^9 dpm = 0.01-0.02% of the administered dose). All of the subjects except for Subject 6 had at least 90% of the administered dose recovered in the feces within seven days of drug administration. More than 80% of the total dose of RenaGel was recovered in the feces of Subject 6. Typically, radioactivity began to appear in the stool by day 3, with a peak in radioactivity by days 3-4 (Appendix 3 Table 3 of NDA. This pattern held true for all the subjects. The mean percent of dose eliminated in the

feces by day seven for all subjects was 99.57%. Some subjects eliminated more than 100% of their dose, a result that was most likely due to analytical variability.

Comments: The results are highly consistent and demonstrate that essentially none of the administered RenaGel is systemically absorbed. The small amount of radioactivity present in urine (less than 0.02 % of the administered dose) may well have been a radioactive contaminant present in the original preparation.

found in urine.

to determine how much administered RenaGel is degraded in the intestine.

8.1.2.4.3 Safety issues: Safety was evaluated on the basis of adverse experiences (reported and/or observed), and changes in laboratory values, vital signs, and physical examination. No serious or unexpected adverse events were reported, with the exception of one subject who was diagnosed with colon cancer shortly after completion of the study. This event is presumed to be unrelated to RenaGel.

No serious changes in laboratory values were observed, with the exception of two subjects (Subjects 16 and 20) who had abormal serum chemistry results at study day 6 (including alkaline phosphatase, ALT, AST, CO_2, LDH, and potassium). Serum chemistry values returned to normal for both subjects within 1 to 2 months. These results appear in Table 2.9, Appendix 2.

Conclusions: This study convincingly demonstrates that RenaGel is not systemically absorbed, when given to a normal population. Since this study was not carried out in patients with ESRD (the intended treatment population), the labeling should be amended to state that absorption studies have been carried out only in normal volunteers. In addition, it should be re-emphasized that both clinical pharmacology studies were carried out almost exclusively in a Caucasian population.

CLINICAL TRIALS IN HEMODIALYSIS PATIENTS

Comments: Two of the six clinical trials in ESRD patients were controlled (one was placebo controlled and the other involved comparison with calcium acetate therapy). The Division has had considerable discussion with the sponsor regarding medical and ethical problems involved in conducting placebo-controlled trials of phosphate binders in this patient population. It is the strong opinion of the sponsor, as well as of the nephrologists at the numerous study sites, that studies which include a prolonged placebo treatment group would pose serious ethical problems. I believe that this view is valid. However, although important information can be derived from alternative study designs, as described below, safety and

efficacy data are certainly more convincing when they are obtained from controlled studies. The use of an active drug comparison arm, as in study #301, provides safety and efficacy data over longer periods of exposure to RenaGel.

The two controlled studies will be reviewed first.

8.2 Indication:
Reduction of serum phosphate concentration in ESRD patients undergoing hemodialysis.

8.2.1.1 Reviewer's trial # 3 Sponsor's Protocol # GTC-10-201
Objectives:
This study had three objectives:

1. Compare the efficacy of RenaGel with calcium-based phosphate binders in lowering serum phosphorus in hemodialysis patients.
2. Compare RenaGel and placebo for adverse events and laboratory parameters.
3. Compare RenaGel with placebo for ability to lower serum cholesterol in hemodialysis patients.

8.2.1.2 Design:

This was a phase 2, randomized, double-blind, placebo-controlled, parallel-design multi-center study involving 38 patients with ESRD. The duration of the study was 8 weeks. For the first 2 weeks, patients were treated with their own calcium-based phosphate binder regimen. During the second two-week period, the patients discontinued their calcium-based binders (washout period). During the third two-week period, patients were treated with either RenaGel or placebo, with the dose determined for each patient by the amount calcium phosphate binder previously taken. The study ended with a two-week follow-up period. Serum phosphorus concentrations were monitored throughout all phases of the study.

Safety was evaluated on the basis of reported and/or observed adverse experiences, and on the basis of changes in laboratory values (chemistry, hematology, PT, and serum level of vitamin E).
Efficacy was evaluated on the basis of changes in serum phosphorus concentration.
Bioequivalence was tested using the 80%-125% rule on a log scale:

$$\log(0.80) < \Delta(\log RG - \log CB) < \log(1.25),$$

where RG = serum phosphorus concentration during RenaGel treatment and CB = serum phosphorus concentration during calcium binder treatment.

Comments on Design: This design permits a comparison of efficacy of RenaGel with placebo for a two-week period. Given the lability of the serum phosphate concentration, this time period is adequate to show an acute effect of the drug. For ethical reasons (above), extension of the placebo-controlled study would have been problematic. It should be noted that, owing to the prior washout period, placebo patients were drug-free for 4 consecutive weeks. The design also permits a comparison of the efficacy of a patient's usual calcium-based therapy with that of 2 weeks of treatment with RenaGel. However, this comparison will be within-group and will not contain a concurrent control.

Given the rapidity and magnitude of the reduction in cholesterol that were associated with RenaGel in Trial #1, this study should also permit comparison of the lipid-lowering effects of RenaGel with those of placebo. The study would have gained additional power if it had included a cross-over phase, preceded by a second washout period. However, since this was the first controlled clinical trial of RenaGel in ESRD patients, the size and duration were appropriate.

8.2.1.3 Protocol

Population: The study population consisted of male and female patients, 18 years of age or older, on a stable three times/week dialysis regimen for at least 3 months. Other relevant inclusion criteria were: 1)stable dose of calcium acetate or calcium carbonate for at least 1 month prior to screening; 2) if patient received vitamin D, the dose had to be stable for at least 1 month prior to screening; 3)other criteria are listed in appendix 4.1. Exclusion criteria: 1) poorly controlled diabetes, hypertension, vasculitis or other unstable cond;ition; 2) history of dysphagia or other swallowing disorders; 3) history of GI motility disorder or major GI surgery; 4) abnormal or irregular bowel function; 5) other, listed in appendix 4.2.

Comments: The target population and exclusion/inclusion criteria are appropriate. The use of GI exclusionary criteria is consistent throughout the NDA. It is important to note that RenaGel will not have been studied in this group of patients.

Procedures: The format of the study is diagrammed below:

Week -1	Weeks 1-2	Weeks 3-4	Weeks 5-6	Weeks 7-8
Screening	Treatment with calcium-based phosphate binders	Washout	RenaGel/placebo	Follow-up

During the first 2 weeks of the study (Weeks 1 and 2), the patients maintained their previous calcium-based phosphate binder regimen. During the washout

phase, (Weeks 3 and 4), patients discontinued all phosphate binders. The patients then were randomized to either RenaGel or placebo. To determine the individual dosage of RenaGel, the dose (mg) of calcium binder taken during week 2 and divided by 500 mg to calculate the daily number of RenaGel or placebo capsules. The number of RenaGel or placebo capsules to be taken each day was divided into 3 daily doses, to be taken with meals. In the follow-up period (Weeks 7 and 8), the patients returned to their original calcium –binder regimens. Treatment compliance was determined by capsule-counting.

Special precautions were taken for patients receiving coumadin and cardiac glycosides. For patients taking coumadin, PT was determined after 1 week of study drug therapy, in addition to the PT determinations specified in the protocol. In patients receiving cardiac glycosides (digoxin, digitoxin), digoxin levels were to be determined just prior to treatment with the study drug, after 1 week of treatment with the study drug (i.e, at the end of Week 5), at the end of randomized treatment (i.e, at the end of Week 6), and at the final follow-up visit (end of Week 8). The investigator was to adjust coumadin or cardiac glycoside dosages as appropriate.

Any concomitant drug was to be administered at least 2 hours before or 4 hours after the study drug, if fluctuation in serum levels of the drug would have a significant effect on safety or efficacy profile.

Comment: This instruction regarding concomitant medication remained in operation throughout the NDA. However, the dosing of any concomitant drug and/or vitamin was left to the discretion of the individual investigator. This consideration is important in assessing the possible interference with absorption of concomitant medications.

Efficacy evaluation was based on changes in serum phosphorus concentrations. The mean serum phosphorus in the last week of each of the treatment phases (the calcium binder treatment phase, the washout phase, and the randomized treatment phases) were calculated by averaging the final 2 measurements of that week. Thrice-weekly dialysis regimens were maintained throughout. For patients on a Monday-Wednesday-Friday dialysis schedule, the final 2 measurements of each week were taken on Wednesday and Friday, while for patients on a Tuesday-Thursday-Saturday dialysis schedule, the final 2 measurements were those taken on Thursday and Saturday.

Safety was evaluated on the basis of reported and/or observed clinical adverse experiences, as well as on the basis of changes in laboratory values (chemistry, hematology, PT, and vitamin E).

In clinical practice, the dose of calcium-based phosphate binder therapy is typically adjusted to meet the requirements of the individual patient. Thus it would have been unrealistic and probably not very useful to investigate the efficacy of fixed dose levels of calcium-based binder therapy. The sponsor

designed efficacy analysis in the comparison phase of the study according to the following rationale: "The first analytical goal was to assess the equivalence of RenaGel and the calcium binder regimen in terms of controlling hyperphosphatemia (based on equal doses of RenaGel and calcium binders). There is the possibility, however, that equivalent efficacy of equal dosing (on a weight-to-weight basis) of calcium binder and RenaGel does not exist but equivalence on a proportional-dose basis does. In this case, a given daily dose of RenaGel may be more or less efficacious as the same dose (by weight) of calcium binder." Therefore, additional analyses were to be performed in order to determine the relative dose- response of RenaGel to calcium binder. Additionally, dietary or demographic factors were to be explored to determine their influence on equivalence and dose-response" (NDA section 9, statistical analysis plan).

The primary analysis of treatment equivalence was based on the intent-to-treat population. Additional efficacy analyses were performed on the evaluable population: those patients who took at least 80% of their assigned treatment and who did not take medications that could interfere with the assessment of serum phosphorus.

All patients who received at least one dose of RenaGel or placebo were included in the safety analysis.

All statistical tests were performed using two-tailed tests, with a level of significance of 0.05, unless otherwise noted.

For analysis of efficacy in lowering serum cholesterol, RenaGel was compared with placebo in terms of changes in serum cholesterol observed between the washout and RenaGel/placebo treatment periods. Per-patient differences were calculated for (cholesterol value at the end of the washout period) – (cholesterol value at the end of the RenaGel/placebo period). Differences between RenaGel and placebo were measured using an ANOVA on the intent-to-treat population.

Diet was analyzed by recall diaries. A detailed analysis was conducted on changes in dietary calcium and phosphorus in the calcium binder, washout, and RenaGel/placebo periods. Regression analyses were performed on serum phosphorus reduction, using dietary levels of phosphorus and calcium as covariates.

Compliance with drug and/or placebo was analyzed in detail and expressed as the ratio of # pills taken/ # prescribed.

Comments: The efficacy endpoints are clear, objective, and easily measured. The two efficacy endpoints, reduction in serum phosphate and in serum cholesterol, were to be analyzed independently. The primary endpoint remained a reduction in serum phosphate concentration, with no change in relative importance assigned to either one. The study design and

analyses are appropriate and comprehensive. The design of this study was adequate to achievement of the first of the primary goals, to compare RenaGel with placebo, because this part of the study had a concurrent control. The other primary goal, to compare RenaGel with calcium-based phosphate binder therapy, is based on within-group comparison of concurrent with prior therapy. This comparison will yield less conclusive information.

8.2.1.4 Results

8.2.1.4.1 Populations: Thirty-eight patients were enrolled. Two were dropped from the study during the first phase, one because of laboratory abnormalities and the other to receive a kidney transplant. All of the remaining 36 patients completed the study and were included in the intent-to-treat efficacy analyses and in the safety analyses (12 in the placebo group and 24 in the RenaGel group). Of these 36 patients, 11 (5 in the placebo group and 6 in the RenaGel group) took less than 80% of the prescribed treatment and were thus excluded from the fully evaluable analyses. One patient was dropped from analysis because no serum phosphorus levels were available during the 2 weeks on RenaGel. The remaining 24 patients were fully evaluable (7 in the placebo group and 17 in the RenaGel group).

The baseline demographic characteristics of the patient population are given in the table below:

Variable	Placebo (N = 12)	RenaGel (N = 24)	p value
Sex			
Male	2 (16.7%)	11 (45.8%)	0.143
Female	10 (83.3%)	13 (54.2%)	
Race			
Caucasian	3 (25.0%)	5 (20.8%)	
Black	9 (75.0%)	16 (66.7%)	0.903
Hispanic	0 (0.0%)	2 (8.3%)	
Asian	0 (0.0%)	1 (4.2%)	
Age (years)			
Mean ± SD	53.7 ± 13.9	58.8 ± 17.1	0.375
Range	29-76	27-82	
Height (cm)			
Mean ± SD	160.6 ± 7.9	166.6 ± 9.9	0.076
Range	152-180	152-185	
Weight (kg)			
Mean ± SD	70.6 ± 14.3	76.4 ± 15.7	0.292
Range	52-101	55-132	

The groups did not differ in mean initial calcium binder dose or type (calcium acetate vs calcium phosphate).

Comments: The inclusion of greater proportion of minorities in this study population (approximately 70% of the study population was black) than appeared in the earlier studies lends additional importance to the conclusions.

There were no statistically significant differences between groups in terms of compliance with any of the treatment regimens. All 36 patients (12 in the placebo group and 24 in the RenaGel group) completed the study. These 36 were included in the intent-to-treat analyses. Eleven patients (5 in the placebo group and 6 in the RenaGel group) took less than 80% of the prescribed treatment and were thus excluded from the fully evaluable population.

8.2.1.4.2 Efficacy outcomes

The primary efficacy outcome was a change in the serum phosphorus concentration. Analysis of the entire intent-to-treat population demonstrated that the mean serum phosphorus levels at the end of the washout period were, as expected, higher than at the end of the calcium binder period (mean increase, 1.63 mg/dl, p=0.0001). At the end of the 2-week randomized treatment period, the serum phosphorus levels in the placebo group increased by a mean of 0.32 mg/dl over the value at the end of the washout period (p=.4275), while the phosphate levels in the RenaGel group decreased by a mean of 0.68 mg/dl (p=0.0503). The difference between RenaGel and placebo was statistically significant (p=0.0367). The results are summarized in the table below:

Changes in serum phosphorus (intent-to-treat population)

	Change in serum phosphorus (mg/dL)		
Variable	**Mean±SD**	**Range**	**p value**
Washout–calcium binder (N = 36)	1.63 ± 1.32	–0.25-5.45	0.0001a
Washout-RenaGel (N = 24)	0.68 ± 1.60	–2.50-4.00	0.0503[b]
Washout-placebo (N = 12)	–0.32 ± 1.35	–2.15-2.70	0.4275[b]

[a] *Paired t-test for difference in serum phosphorus (washout-calcium binder)*
[b] *Paired t-test for difference in serum phosphorus (washout-randomized treatment period)*

T-test for difference in serum phosphorus (washout-RenaGel) > difference in serum phosphorus (washout-placebo), p = 0.0367

Similarly, for the 24 fully evaluable patients (those who had taken at least 80% of the prescribed treatment), the mean serum phosphorus levels at the end of the washout period were higher (mean increase: 1.87 mg/dL, p = 0.0001) than at the end of the calcium binder period. At the end of the randomized treatment period,

serum phosphorus levels had decreased by a mean of 0.79 mg/dL from end of washout period (p = 0.0621) in the 17 patients receiving RenaGel and had increased by a mean of 0.79 mg/dL in the 7 patients receiving placebo (p = 0.0963). The difference between RenaGel and placebo was statistically significant (p = 0.0278). The data are summarized in the table below:

Changes in serum phosphorus (evaluable population)

	Change in serum phosphorus (mgdL)		
Variable	**Mean±SD**	**Range**	**p value**
Washout–calcium binder (N = 24)	1.87 ± 1.40	–0.05-5.45	0.0001a
Washout-RenaGel (N = 17)	0.79 ± 1.62	–1.20-4.00	0.0621[b]
Washout-placebo (N = 7)	–0.79 ± 1.06	–2.15-0.45	0.0963[b]

[a] Paired t-test for difference in serum phosphorus (washout-calcium binder)

[b] Paired t-test for difference in serum phosphorus (washout-randomized **treatment period)**

T-test for difference in serum phosphorus (washout-RenaGel) > difference in serum phosphorus (washout-placebo), p = 0.0278

Reference: Appendix 16.9, Study Summary Tables, Table 11B.2

APPEARS THIS WAY
ON ORIGINAL

An additional efficacy analysis was performed on a sub-group of 32 patients (11 in the placebo group and 21 in the RenaGel group) in whom mean serum phosphorus levels at the end of the washout period were statistically significantly higher (mean increase: 2.18 mg/dL, p < 0.0001) than at the end of the calcium binder period. In this analysis, the washout serum phosphorus was also statistically significantly higher than at the end of the randomized treatment period for the 21 patients in the RenaGel group (mean difference: 1.36 mg/dL, p = 0.0005), while they remained almost unchanged in the 11 patients in the placebo group (mean decrease relative to washout: –0.26 mgdL, p = 0.6282). The difference between RenaGel and placebo was statistically significant (p = 0.0101).

Change in serum phosphorus in hyperphosphatemic patients

	Change in serum phosphorus (mgdL)		
Variable	**Mean±SD**	**Range**	**p value**
Washout–calcium binder (N = 32)	2.18 ± 1.68	–0.30-6.35	<0.0001[a]
Washout-RenaGel[b] (N = 21)	1.36 ± 1.50	–1.15-4.80	0.0005[c]
Washout-placebo[b] (N = 11)	–0.26 ± 1.75	–2.15-2.75	0.6282[c]

Reference: Appendix 16.9, Study Summary Tables, Table 11B.3

[a] Paired t-test for difference in serum phosphorus (washout-calcium binder)
[b] T-test for difference in serum phosphorus (washout-RenaGel) > difference in serum phosphorus (washout-placebo), p = 0.0101
[c] Paired t-test for difference in serum phosphorus (washout-randomized treatment period)

Comments: A categorical analysis (number of patients who responded to the drug in a pre-defined manner) was not included in this trial because hyperphosphatemia was not an inclusion criterion for this study and because the study did not alter the dose titration. Analysis of responder rates is included in subsequent studies.

Bioequivalence analysis (RenaGel vs calcium binders): Bioequivalence between RenaGel and calcium-based phosphate binders was tested using the "80-125 rule," as described above, on a log scale:

log (0.80) < Δ (log RG - log CB) < log (1.25).

The sponsor conducted an analysis of the intent-to-treat population in the 24 patients who received RenaGel. The 90% confidence interval for **log (serum phosphorus concentration with RenaGel) – log (serum phosphorus concentration with calcium binders)** was 0.0201, 0.0927, which is contained within the 80%, 125% log-limits of [–0.0969, 0.0969]. Thus, RenaGel and the calcium binders were bioequivalent in the intent- to-treat population of this study, using this method of analysis. The data are presented in Appendix 16.9, Table 11C.1 of the NDA.

A similar analysis was conducted in the 17 fully evaluable patients who received RenaGel. The 90% confidence interval for **log (serum phosphorus concentration with RenaGel) – log (serum phosphorus concentration with calcium binders)** was 0.0131, 0.0928, which is contained within the 80%, 125% log-limits of –0.0969, 0.0969. Thus, RenaGel and the calcium binders were also bioequivalent in the fully evaluable population, using this method of analysis.. The data are presented in Appendix 16.9, Table 11C.2.

Finally, an additional analysis was conducted in the 21 patients receiving RenaGel, as pre-defined in the protocol as being hyperphosphatemic at the end of the washout period. In this subgroup, the 90% confidence interval for **log**

(serum phosphorus concentration with RenaGel) – log (serum phosphorus concentration with calcium binders) was 0.0085, 0.0937, which is contained within the 80%, 125% log-limits of –0.0969, 0.0969. Thus, RenaGel and the calcium binders were bioequivalent in this sub-population as well.

Serum cholesterol: As shown in the table below, there was a statistically significant reduction in both total and LDL cholesterol, associated with RenaGel therapy. From the end of the washout period to the end of the randomized treatment period, mean total cholesterol decreased by 20.48 mg/dL with RenaGel and increased by 0.45 mg/dL in the placebo group (p = 0.0127). Mean LDL cholesterol decreased by 17.6 mg/dL with RenaGel and increased by 7.3 mg/dL in the placebo group (p = 0.0026). HDL cholesterol was essentially unaffected (mean increase of 0.81 mg/dL with RenaGel *vs* a mean increase of 1.09 mg/dL with placebo, p = 0.9324).

	Change in serum cholesterol (washout – treatment)		
Variable	**Mean±SD**	**Range**	**p value**
Total cholesterol (mg/dL)			
RenaGel (N = 21)	20.48 ± 21.73	–6.00-65.00	0.0127
Placebo (N = 11)	–0.45 ± 20.15	–30.00-34.00	
LDL cholesterol (mg/dL)			
RenaGel (N = 21)	17.59 ± 21.90	–15.00-59.40	0.0026
Placebo (N = 11)	–7.31 ± 16.94	–39.20-16.20	
HDL cholesterol (mg/dL)			
RenaGel (N = 21)	–0.81 ± 10.00	–32.00-13.00	0.9324
Placebo (N = 11)	–1.09 ± 5.89	–15.00- 7.00	

Reference: Appendix 16.9, Study Summary Tables, Table 11E

APPEARS THIS WAY
ON ORIGINAL

Dietary Data Analysis:

Dietary intakes of calories, fat, calcium, and phosphorus during the 3 main study periods were assessed by the 24-hour recall method, as described in Appendix 16.5, Dietary Recall Methodology. The analyses demonstrated that dietary intake remained stable throughout the study. An analysis of variance was performed on the changes in dietary intake of calcium and phosphorus in the calcium binder and randomized treatment period (RenaGel/placebo) relative to the washout period. As shown in the table below, there was no statistically significant

difference between the RenaGel and the placebo groups in terms of change in dietary intake of calcium and phosphorus relative to the washout period.

Variable	Change in dietary intake (from washout) Mean±SD	Range	p value
Calcium (mgdL)			
Calcium binder (N = 20)	31.03 ± 221.74		
RenaGel (N = 15)	26.67 ± 240.23		0.8924
Placebo (N = 7)	42.09 ± 258.64		
Phosphorus (mgdL)			
Calcium binder (N = 20)	20.51 ± 242.99		
RenaGel (N = 15)	7.80 ± 217.60		0.9917
Placebo (N = 7)	6.71 ± 247.14		

Reference: Appendix 16.9, Study Summary Tables, Table 13A

To investigate further whether changes in serum phosphorus were due to changes in dietary calcium of phosphorus, regression analyses were performed on serum phosphorus reduction, using dietary levels of phosphorus and calcium as covariates. This analysis, which involved the evaluable population only, revealed that changes in dietary calcium and phosphorus between the washout and the RenaGel period were not significant as explanatory variables(Appendix 16.9, Table 13B).

Comments: It is important to know whether drug effects are confounded by changes in dietary phosphorus. The sponsor has carried out extensive dietary intake analyses of which demonstrate that the changes in serum phosphorus concentrations which were observed during the trial were not due to alterations in diet. This was repeatedly demonstrated in subsequent studies, described below.

8.2.1.4.3 Safety outcomes

The safety analysis was based on data derived from all 36 randomized patients. In this trial, 24 patients took RenaGel (average 7 capsules, or about 3.5 g, per day) for an average of 13.5 days.

During the 8-week trial period, the placebo and the RenaGel groups had identical incidences of adverse experiences. 33.3% of the placebo group and 33.3% of the RenaGel group had no adverse experiences, while 66.7% of each group had at least one adverse experience (Appendix 16.9). Similarly 50% of the

patients in each treatment group had no treatment-emergent events (weeks 5-8), while 50% of patients in each group had at least one treatment emergent event (Appendix 16.9)

There were no statistically significant differences between placebo and RenaGel, in terms of the numbers of adverse experiences by body system and preferred term (COSTART dictionary, data presented in Appendix 16.9).

Similarly, as the table below shows, there were no statistically significant differences between placebo and RenaGel in terms of the numbers of adverse experiences by body system and COSTART preferred term during the randomized treatment and follow-up phase (Weeks 5-8).

Treatment-emergent events by body system and preferred term

Adverse events by body system	Placebo (N = 12)	RenaGel (N = 24)	p value
Body as a whole			
Ascites	0 (0.0%)	1 (4.2%)	1.000
Chills	0 (0.0%)	1 (4.2%)	1.000
Flu	0 (0.0%)	1 (4.2%)	1.000
Headache	2 (16.7%)	0 (0.0%)	1.000
Pain	1 (8.3%)	0 (0.0%)	1.000
Abdominal pain	1 (8.3%)	0 (0.0%)	1.000
Chest pain	0 (0.0%)	1 (4.2%)	1.000
Pain neck	0 (0.0%)	1 (4.2%)	1.000
Cardiovascular system			
Hypotension	1 (8.3%)	2 (8.3%)	1.000
Syncope	0 (0.0%)	1 (4.2%)	1.000
Thrombosis	0 (0.0%	1 (4.2%)	1.000
Thrombosis, arterial	2 (16.7%)	4 (16.7%)	1.000
Digestive system			
Diarrhea	2 (16.7%)	0 (0.0%)	1.000
Dyspepsia	0 (0.0%)	2 (8.3%)	1.000
Nausea	1 (8.3%)	0 (0.0%)	1.000
Vomiting	0 (0.0%)	1 (4.2%)	1.000
Metabolic and nutrition			
Edema	0 (0.0%)	1 (4.2%)	1.000
Edema, peripheral	1 (8.3%)	1 (4.2%)	1.000

APPEARS THIS WAY ON ORIGINAL

Musculoskeletal system			
Myasthenia	1 (8.3%)	0 (0.0%)	1.000
Respiratory system			
Dyspnea	1 (8.3%)	2 (8.3%)	1.000
Edema, lung	0 (0.0%)	1 (4.2%)	1.000
Respiratory disorder	1 (8.3%)	1 (4.2%)	1.000
Rhinitis	0 (0.0%)	1 (4.2%)	1.000
Dermatological system			
Pruritus	1 (8.3%)	0 (0.0%)	1.000
Sweat	1 (8.3%)	0 (0.0%)	1.000
Special senses			
Amblyopia	0 (0.0%)	1 (4.2%)	1.000
Cataract	0 (0.0%)	1 (4.2%)	1.000
Urogenital system			
Dysmenorrhea	1 (8.3%)	0 (0.0%)	1.000

APPEARS THIS WAY
ON ORIGINAL

Reference: Appendix 16.9, Study Summary Tables, Table 8B.2

The table below summarizes those adverse events that were judged possibly or probably related to the study drug, categorized by body system and COSTART preferred term. There was no statistically significant difference in adverse events judged possibly or probably related to treatment between placebo and RenaGel (p = 1.000).

APPEARS THIS WAY
ON ORIGINAL

Adverse experiences judged related to treatment

Adverse events by body system	Placebo (N = 12)	RenaGel (N = 24)	p value
Body as a whole			
Abdominal pain	1 (8.3%)	0 (0.0%)	1.000
Digestive system			
Diarrhea	1 (8.3%)	0 (0.0%)	1.000
Dyspepsia	0 (0.0%)	2 (8.3%)	1.000
Nausea	1 (8.3%)	0 (0.0%)	1.000
Vomiting	0 (0.0%)	1 (4.2%)	1.000
Special senses			
Amblyopia	0 (0.0%)	1 (4.2%)	1.000

APPEARS THIS WAY
ON ORIGINAL

Reference: Appendix 16.9, Study Summary Tables, Table 8C

APPEARS THIS WAY
ON ORIGINAL

Other safety parameters: There was no association of intensity of adverse events with RenaGel treatment. There was no statistically significant difference, by dose, in the incidence of adverse experiences, treatment-emergent events, treatment-emergent body-system-specific events, or events judged related to treatment.

Laboratory values:There were no inter-group changes from baseline in hematology or clinical chemistry that were statistically and clinically significant. In six patients receiving cardiac glycosides, the digoxin levels remained within the normal levels in three (two RenaGel and one placebo) and were high in three (two RenaGel and one placebo). There were no changes in PT or Vitamin E levels. Out-of-range laboratory values, listed in Appendix 16.8, were mainly not clinically significant. No changes in physical examination were reported, except for procedures related to dialysis access.

Comments: In this study, there were no unanticipated adverse events or laboratory abnormalities following two weeks' exposure to RenaGel in 24

patients with ESRD on hemodialysis. These safety data are important, because the study allowed comparison between drug-treated and placebo-controlled groups. The conclusions that can be drawn from these data are restricted to two weeks' exposure to the drug.

8.2.1.4 Conclusions regarding efficacy/safety data:

1) Reduction of serum phosphorus: In this study of 36 hemodialysis patients, the data presented by the sponsor showed that RenaGel was effective in reducing the mean serum phosphate levels, when compared to placebo, during two weeks of therapy. In addition, RenaGel was as effective as calcium-based phosphate binders in lowering and normalizing serum phosphorus, based on the bioequivalence analysis. The bioequivalence of RenaGel and calcium-based phosphate binders was demonstrated in the intent-to-treat and the efficacy-evaluable populations (which included patients who were not hyperphosphatemic) and in a subset of patients who were hyperphosphatemic.

2) Reduction of serum cholesterol: This study demonstrated that, following two weeks of therapy, RenaGel was capable of significantly lowering serum total and LDL cholesterol without affecting HDL cholesterol. The comparison with a placebo group lends cogency to this conclusion.

1) Safety: The study raised no safety concerns in the 24 patients who were exposed to the drug for 2 weeks.

8.2 Indication: hyperphosphatemia

8.2.2 Reviewer's trial # 4 Sponsor's protocol # GTC-36-301

An Open Label, Cross Over Study of RenaGel and Calcium Acetate in Hemodialysis Patients

8.2.2.1 Objectives:

Primary objectives were:

1. Determine the efficacy of RenaGel in lowering serum phosphorus in hemodialysis patients.

2. Determine the safety of RenaGel in lowering serum phosphorus in hemodialysis patients.

Secondary objectives were:

1. Compare the efficacy of RenaGel and PhosLo (calcium acetate) in lowering serum phosphorus in hemodialysis patients.

2. Compare the safety of RenaGel and calcium acetate in hemodialysis patients.

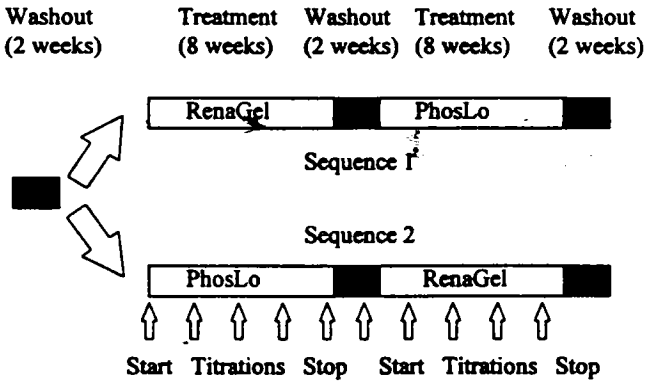
3. Compare the effects of RenaGel and calcium acetate on lipid profiles in hemodialysis patients.

4. Determine the effect of RenaGel and calcium acetate on intact parathyroid hormone levels in hemodialysis patients.

8.2.2.2 Design

This phase 3, multicenter, 22-week study of over 100 hemodialysis patients employed an open-label, crossover design. Following screening and a 2-week washout period (during which patients were free of calcium binder therapy), hyperphosphatemic patients (serum P>6.0 mg/dl) were eligible to enter the study. Eligible patients were randomized to receive either RenaGel or calcium acetate for 8 weeks. Following this, they underwent a second washout period of 2 weeks and were then crossed over to the alternate phosphate binder for a second eight week treatment period. Following the second treatment period, patients underwent a third two-week phosphate binder washout period (Weeks 21-22) during which the crossover treatment was discontinued. Serum phosphorus levels were measured to determine if serum phosphorus reductions were due to the alternate treatment or other factors.

A diagram of the study design is shown below:



Comments on design: This was a pivotal phase 3 study, which enrolled 109 hemodialysis patients and ultimately randomized 84 patients. The study design exposed patients to RenaGel for 8 weeks, following a 2-week washout period. Therefore, a placebo-controlled trial design would have

denied phosphate binder therapy to the placebo patient group for a total of 10 weeks. This was felt to be unethical and medically unsound by the sponsor and by many of the nephrologists conducting the trials. In discussions with FDA (at end of phase 2 meetings and earlier in drug development), the Division concurred with this approach. I believe that the design of the present study allowed for an adequate comparison between RenaGel and calcium acetate, in terms of efficacy and safety.

8.2.2.3 Protocol

Population: Patients meeting inclusion/exclusion criteria and developing hyperphosphatemia (serum P > 6.0 mg/dl) during the first washout period were eligible for randomization.

The major Inclusion criteria were:

1. Men or women 18 years of age or older.
2. On three times per week hemodialysis for three months or longer.
3. On a phosphate binder (calcium or aluminum) at a stable dose for at least one month prior to screening.
4. If on vitamin D replacement therapy, the dose must have been stable for at least one month prior to screening.
5. Were willing to avoid any intentional changes in diet such as fasting or dieting.
5. If women of child bearing potential (pre-menopausal and not-surgically sterilized) were on an effective contraceptive method including barrier methods, hormones, or IUDs.

Major exclusion criteria were:

1. Poorly controlled diabetes mellitus or hypertension, active vasculitis, HIV infection, or any clinically significant unstable medical condition (defined by investigator).

2. History of dysphagia or swallowing disorders.

3. History of an intestinal motility disorder, including but not limited to ileus, pseudoobstruction, megacolon, or mechanical obstruction. Active gastroparesis as evidenced by nausea and/or vomiting was an exclusionary criterion. However, treated gastroparesis was not an exclusionary criterion. Abnormal or irregular bowel function was an exclusionary criterion.

4.History of gastrointestinal tract surgery, such as gastrectomy or intestinal resection. Uncomplicated appendectomy or polypectomy or non-intestinal tract abdominal surgery such as cholycystectomy or nephrectomy were not exclusions.

5. Participation in a study of an investigational drug during the 30 days preceding the start of the screening period.

6. Current use of antiarrhythmic medications (e.g., quinidine, procainamide, tocainide, or amiodarone) or a medication for the control of a seizure disorder (phenytoin, phenobarbital, valproate, or carbamazepine).

7. Active ethanol or drug dependence or abuse, excluding tobacco use.

8. Any other condition which, in the investigator's opinion, would prohibit the patient's participation in the study.

9. Pregnancy or breast-feeding.

10. Any of the following laboratory abnormalities on the screening blood tests: hemoglobin < 8.0 g/dL or ALT > the upper limit of normal.

11. Previous treatment with RenaGel.

Comments: the exclusion of patients with a variety of GI disorders (2,3, and 4) is understandable, given the nature of this drug. These exclusionary criteria appear in all the clinical studies, however; consequently, prescribing physicians should be made aware that the safety and efficacy of RenaGel have not been evaluated in patients with these disorders. GI motility disorders are not uncommon in this population, especially in the subset of patients whose ESRD has been caused by diabetes.

APPEARS THIS WAY
ON ORIGINAL

During the study, patients were prohibited from consuming antacids containing aluminum or magnesium, or calcium salts except for bedtime calcium supplements as prescribed. If a patient was taking a drug "in which altered serum levels might adversely affect safety or efficacy," the drug was to be taken at least one hour before or three hours after treatment. These drugs are not specified in the protocol.

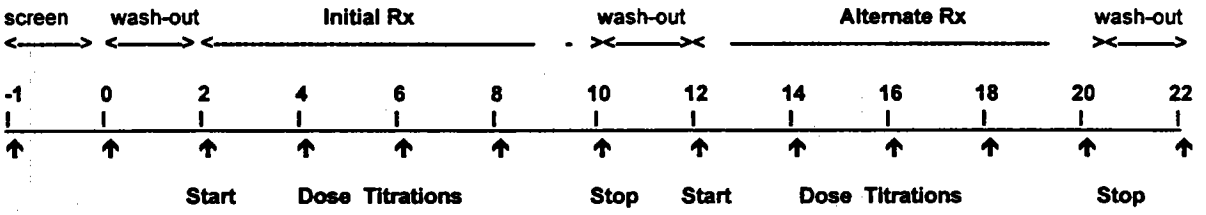
Vitamin D replacement therapy regimens were to be maintained unless the dosage needed to be reduced or stopped for safety reasons.

In patients receiving cardiac glycosides, digoxin levels were to be measured at the end of week 2 and then every 2 weeks for the remainder of the study.

Comments: Apparently, the dosing of concomitant medications was left to the discretion of the individual investigators. It is not clear, from the protocol or from the results, when in relation to RenaGel administration, concomitant medications were given.

Procedures: A schematic of the design of this 22- week study is shown below.

APPEARS THIS WAY
ON ORIGINAL



During the initial washout period off phosphate binders (weeks 1-2), serum phosphorus was monitored, and only patients whose phosphorus levels were > 6.0 mg/dl were eligible to enter the treatment period. Eligible patients were then randomized to receive either RenaGel or calcium acetate for the next 8 weeks (Weeks 3-10). Depending on the serum phosphate levels, starting doses for RenaGel were two (0.93 g), three (1.4 g), or four (1.86 g) capsules, three times a day with meals; starting doses of calcium acetate were one (0.667), two (1.33 g), or three (2.0 g), tablets, three times a day with meals. Serum phosphorus and calcium were monitored weekly, PTH was monitored biweekly, and lipids were monitored every fourth week. At the end of each 2-week period, the investigator would adjust the dose of RenaGel or calcium acetate in an attempt to achieve a serum phosphorus level between 2.5 and 5.5 mg/dL.

Following the initial 8-week treatment period, patients underwent a second washout period (Weeks 11-12) during which either phosphate binder was discontinued. The patients were then crossed over to the alternate phosphate binder for a second 8-week treatment period (Weeks 13-20). Starting doses of either drug were again based on the serum phosphorus level. During the second 8-week period, the investigators titrated the dose of drug every two weeks as necessary to achieve a serum phosphorus level between 2.5 and 5.5 mg/dL.

Low serum calcium levels were treated by addition of up to 1000 mg of elemental calcium (as calcium carbonate) po. in the evening. For patients on calcium acetate, elevations of serum calcium above 11.0 mg/dl were treated by reducing the dose of calcium acetate.

A diary was maintained by each patient to record treatment, in order to ensure patient compliance and proper dosing. The investigator inquired if the patient

experienced any adverse events or had changes in medication that might indicate adverse events.

The weekly laboratory schedule during the study is presented in the table below:

First Washout Period

Week	Tests
1	Phosphorus and calcium
2	Chemistry profile PTH Hematology profile PTPTT Vitamins A, D, and E

First Treatment Period

Week	Tests
3	Phosphorus and calcium
4	Phosphorus and calcium PTH
5	Phosphorus and calcium
6	Chemistry profile PTH Hematology profile PTPTT
7	Phosphorus and calcium
8	Phosphorus and calcium PTH
9	Phosphorus and calcium
10	Chemistry profile PTH Hematology profile PTPTT Vitamins A, D, and E
	Physical Examination

APPEARS THIS WAY ON ORIGINAL

Second Washout Period

Week	Tests
11	Phosphorus and calcium

12	Chemistry profile PTH Hematology profile PT/PTT Vitamins A, D, and E

Alternate Treatment Period

Week	Tests
13	Phosphorus and calcium
14	Phosphorus and calcium PTH
15	Phosphorus and calcium
16	Chemistry profile PTH Hematology profile PT/PTT
17	Phosphorus and calcium
18	Phosphorus and calcium PTH
19	Phosphorus and calcium
20	Chemistry profile PTH Hematology profile PT/PTT Vitamins A, D, and E Physical Examination

APPEARS THIS WAY
ON ORIGINAL

Follow-up Period

Week	Tests
21	Phosphorus and calcium
22	Chemistry profile PTH Hematology profile, PT/PTT Vitamins A, D, and E

Diet: Dietary intake was assessed by a trained dietary interviewer, using the 24-hour recall method. Patients were contacted by telephone on three random days during each of the following periods: the first wash-out, initial treatment, second wash-out, alternative treatment, and follow-up. The calls were made on one dialysis day, one non-dialysis day, and a weekend day for each of the five study periods. The data were analyzed using the _____

_____

Comments: This study design is appropriate and adequate for the assessment of effects of RenaGel on serum phosphate concentrations in this patient population. The efficacy and safety parameters (clinical and laboratory) are measured at the appropriate intervals. The periods of exposure to the drug are sufficient to establish efficacy and short-term safety.

APPEARS THIS WAY
ON ORIGINAL

8.2.2.3.2 Endpoints:

Analysis of the primary efficacy outcome (changes in serum phosphorus concentration) is based on the change in serum phosphorus from the last week of a wash-out period (baseline) to the end of a treatment period (final) during the RenaGel treatment period. Analysis of secondary efficacy outcomes were: 1) comparison of the change in serum phosphorus observed during RenaGel with that found during calcium acetate treatment; 2) comparative analyses of the changes in intact PTH, serum lipid levels (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) during both treatment periods; and comparative analysis of the change in serum calcium during both treatment periods.

For analysis of changes in serum phosphorus, descriptive statistics are used for overall changes, by sequence, and by vitamin D use. The Wilcoxon signed rank test was used to compare baseline values within a sequence to indicate whether there is a significant carry-over effect within a sequence. An ANOVA model was used to assess sequence, treatment, and sequence-by-treatment interactions. Linear regression models were also used to estimate dose effects on changes in serum phosphorus.

In determination of responder rate, the response to treatment is pre-defined as returning to either pre-washout serum phosphorus levels or 5.5 mg/dL, whichever level is attained first.

Similar statistical approaches were used to analyze changes in serum calcium levels, changes in PTH levels, and alterations in lipids. ANOVA models were used to analyze sequence, treatment, and sequence-by-treatment interactions.

Comments: the use of the sponsor's definition of response can be misleading, as discussed below.

Safety analysis:

Safety evaluation was conducted on all enrolled patients who received any study medication. The analysis was based on reported and/or observed adverse experiences, changes in laboratory values (chemistry; hematology; PT and PTT; and vitamins A, D, and E) and changes in physical examinations.

Data were collected during the washout, treatment and follow-up phases of the study. The data were coded using the 4th quarter 1995 COSTART dictionary. Treatment-emergent adverse events are defined as newly occurring or worsening events following the start of RenaGel or PhosLo treatment. The schedule of laboratory testing and physical examinations are provided in the previous table.

All statistical analyses used two-tailed hypothesis tests, with a significance level of $p \leq 0.05$.

Comments: The efficacy outcomes are appropriate, objective, and easily measured. The planned comparisons and statistical analyses are straightforward and appropriate.

The safety outcomes are comprehensive and also focus on problems that might be expected with 8 weeks of RenaGel therapy: alterations in absorption of fat-soluble vitamins (including vitamin K), changes in serum calcium concentrations, and changes in digoxin levels in patients receiving cardiac glycosides.

APPEARS THIS WAY
ON ORIGINAL

8.2.2.4 Results

8.2.2.4.1 Populations enrolled/analyzed:

A total of 109 patients were enrolled. Of these, 84 patients were randomized. Sixteen patients were dropped from the study because they were not hyperphosphatemic at the end of the washout. Four left for reasons of protocol violations, and the remainder left because of an adverse event, non-compliance, or withdrawal of consent (9). Forty-two patients were randomized to sequence 1 (RenaGel) and 42 patients began sequence 2 (calcium acetate). Of the 84 patients randomized to treatment, four patients discontinued prior to starting the second treatment period 2 in each sequence arm. Therefore, 40 patients in sequence 1 were crossed over to calcium acetate treatment and 40 patients in sequence 2 were crossed over to RenaGel treatment. Of the 80 patients who crossed over to the alternate treatment, 75 completed the study.

Demographic data are provided by the sponsor for the safety population, the intent-to-treat population, and the per-protocol population. In the safety population (84 patients), the mean age was 54.6 years

53.6% were male and 46.4% were female. Fifty-six percent of the patients were African-American, 31% were Caucasian, 9.5% were Hispanic, 2.4% were Asian, and 1.2% were classified as "other" race. The demographics for the intent-to-treat and per-protocol populations were comparable to those of the safety population, with minor differences in gender and race. There were no demographic differences between the two treatment sequences (Appendix 8.6, section 9.4).

Comments: The patient population of this pivotal phase 3 study adequately represents African-Americans, but under-represents Asian-Americans. The demographic characteristics are equally balanced between the two treatment sequence arms.

Details regarding patient medical history are provided in Appendix 8.6, section 9.4, table 3.1.). In the safety population, the primary cause of ESRD included hypertension (35.7%), diabetes (28.6%), nephritis (14.3%), polycystic kidney disease (3.6%), and "other" (17.9%). The mean duration of dialysis was 4.3 years, ranging from less than 1 year to 21 years. There were only minor differences in renal-related medical histories among the intent-to-treat, per-protocol, and safety populations. Vitamin D use did not differ among the groups. The use of concomitant medications within 30 days prior to study also did not differ among the groups.

Dietary intake of nutrients and vitamins could affect efficacy and safety outcomes in this study. Therefore, the sponsor collected extensive data (via 24-hour recall) on relevant nutrients and vitamins and analyzed these data by groups. The intakes of phosphorus, calcium, vitamin D, total energy, protein, fat, carbohydrate, iron, sodium, potassium, total vitamin A, and total alpha-tocopherol were recorded (Appendix 14.5). For both sequence 1 and sequence 2 groups, there were no changes in directions that would have affected the efficacy outcomes of the study. For example, for the sequence 1 group, mean dietary phosphorus intake increased 151.4 mg/d during RenaGel treatment and increased 28.0 mg/d during calcium acetate treatment; mean dietary calcium intake increased 170.9 mg/d (from 347.0 mg/d) during RenaGel treatment and increased 194.2 mg/d (from 463.9 mgd) during calcium acetate treatment; mean dietary vitamin D intake increased negligibly during both RenaGel and calcium acetate treatment phases.

However, the mean total vitamin A intake increased 330.4 mcg/d (from 654.1 mcg/d) during RenaGel treatment and also increased 454.1 mcg/d (from 1040.0 mcgd) during calcium acetate treatment. The mean total alpha-tocopherol intake increased 13.3 mg/d (from 5.6 mg/d) during RenaGel treatment and increased 7.3 mg/d (from 13.1 mgd) during calcium acetate treatment.

Comment: The recorded changes in all dietary nutrients would not affect the efficacy outcomes, particularly since the phosphorus intakes rose

during treatment. However, the vitamin A and alpha-tocopherol intakes increased during both treatment phases, and it is possible that this increase is partially responsible for the maintenance of vitamin A levels in blood of the treated patients (see below under safety outcomes).

8.2.2.4.2 Efficacy endpoint outcomes

Serum phosphorus: The primary efficacy endpoint was a change in the serum phosphorus concentration. Eighty patients (40 in each sequence arm) had valid post-baseline serum phosphorus data. When compared to post-washout baseline values, the serum phosphorus levels significantly changed in both the RenaGel and calcium acetate treated patients. In the intent-to-treat population, the mean baseline (Week 2) serum phosphorus level was 8.4 mg/dL for RenaGel treatment and 8.0 mg/dL for calcium acetate treatment. At the end of the eight-week treatment period, the mean serum phosphorus level was 6.4 mg/dL for RenaGel and 5.9 mg/dL for calcium acetate. Overall, the mean change in serum phosphorus over the 8 week treatment was -2.0 mg/dL (std=2.3 mg/dL, $p<0.0001$) for RenaGel treatment period and -2.1 mg/dL (std=1.9 mg/dL, $p<0.0001$) for calcium acetate treatment.

An ANOVA model for serum phosphorus changes showed that there was no treatment difference between RenaGel and calcium acetate ($p=0.7098$), no sequence difference ($p=0.8712$), and no sequence by treatment interaction ($p=0.4907$). Essentially the same results obtained for the per-protocol population (Appendix, table 6.2.1).

A linear regression model showed that higher doses of either RenaGel or calcium acetate were associated with a greater serum phosphorus lowering effect (for the intent-to-treat population: $p=0.0141$ for RenaGel; $p<0.0001$ for calcium acetate) with similar results for the per-protocol population.

APPEARS THIS WAY
ON ORIGINAL

Within the sequence 1 group, there were statistically significant differences in serum phosphorus levels between treatment groups both at baseline (Week 2) and final (Week 10). Mean serum phosphorus at baseline was 8.3 mg/dL (std=1.7) for those who would receive RenaGel treatment and 7.4 mg/dL (std=1.9) for calcium acetate treatment ($p=0.0067$), while the final mean serum phosphorus was 6.2 mg/dL (std=1.4) after RenaGel treatment and 5.5 mgdL (std=1.5) after calcium acetate ($p=0.0051$). This difference was not observed within the sequence 2 group. These data are shown below:

	Sequence 1 RenaGel ⇒ Calcium Acetate			Sequence 2 Calcium Acetate⇒ RenaGel		
	RenaGel Mean	Calcium Acetate Mean	p-value*	RenaGel Mean	Calcium Acetate Mean	p-value*
Baseline	8.3	7.4	0.0067	8.6	8.6	0.8372
Final	6.2	5.5	0.0051	6.7	6.3	0.0926
Change	-2.0	-2.0	0.7527	-1.9	-2.2	0.3890

* Wilcoxon signed rank test used to test changes between treatment groups within sequence.

Comment: The data show no statistically significant differences, between calcium acetate and RenaGel, in absolute reduction in phosphate concentrations. The lower final level of phosphate in the sequence 1 calcium acetate group was due to a lower washout phosphate level in that group.

Extensive data are provided on serum phosphorus levels over time, on a per-visit basis for the duration of the study. This analysis demonstrated that the mean phosphorus levels changed in the anticipated direction over time in both RenaGel and calcium acetate treated patients, in both sequence groups. For the intent-to treat population, in sequence 1, the data are summarized in the table below: