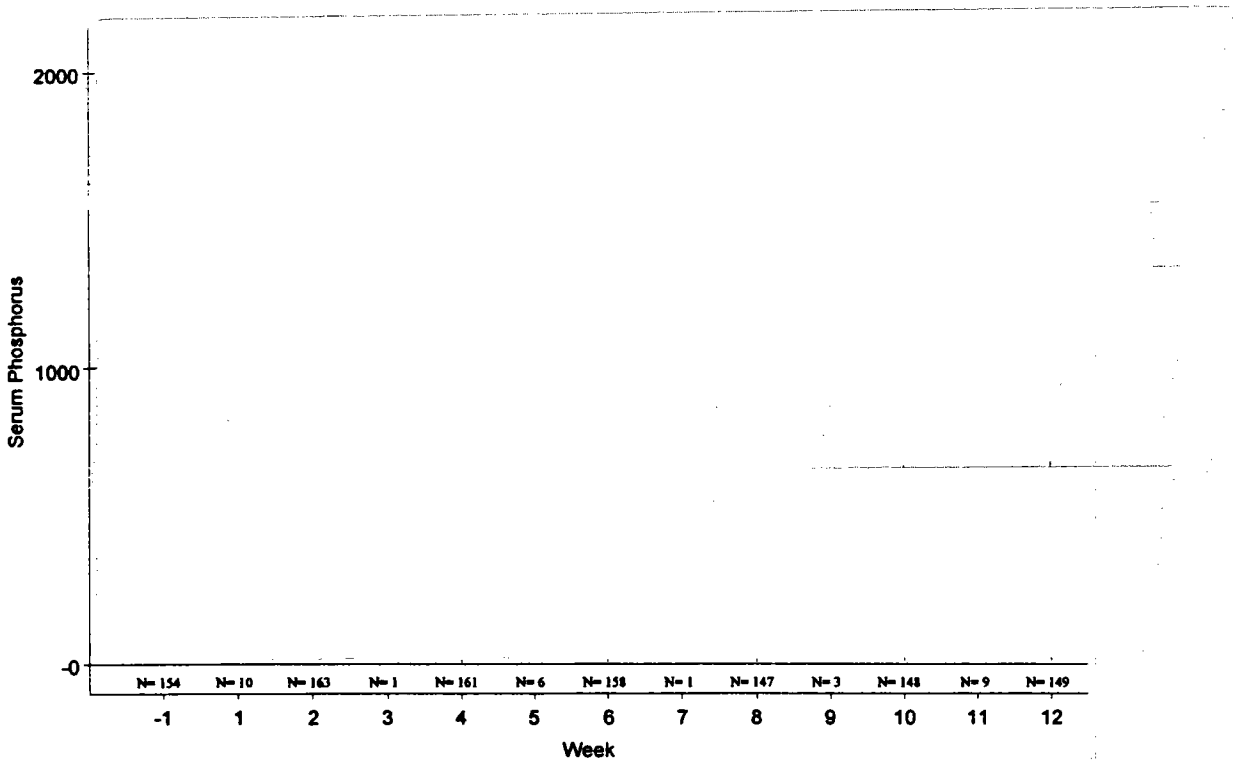
We have presented the PTH data as boxplots of PTH levels in the entire study group over the time of the trial:



Again, the data show a large spread in PTH values, with PTH levels in most of the patients remaining elevated. The upper limit of normal for iPTH assays is usually 65 pg/ml.

Lipids: Mean total and LDL cholesterol changed significantly during RenaGel treatment. In the intent-to-treat population, mean total cholesterol changed -25.9 mg/dL (from 171.0 mg/dL, $p<0.0001$), a drop of 13.9%. Cessation of RenaGel treatment at Week 10 was followed by a rise of 23.8 mg/dL, $p<0.0001$) by end of the second washout. These results were similar in the per-protocol population.

Mean LDL cholesterol was 102.0 mg/dL (std=34.9) at baseline and 75.6 mg/dL (std=29.4) at the end of RenaGel treatment, a mean reduction of 26.4 mg/dL (std=26.4 mg/dL, p-value<0.0001). At the end of the second washout (Week 12), mean LDL cholesterol returned to baseline levels: 101.1 mg/dL (std=31.5 mg/dL).

A linear regression model examined the relationships between cholesterol changes and a multiplicity of factors present at baseline. The model found that race was a significant predictor of change in LDL cholesterol ($p=0.0361$).

African-American patients exhibited a lower reduction in LDL compared to non-African-American patients. For African-American patients, mean change in LDL cholesterol was -22.8 mg/dL (std=24.1 mg/dL), while mean change in LDL cholesterol for non-African-American patients was -30.3 mg/dL (std=28.5 mg/dL).

Mean change in LDL cholesterol was generally greater for patients with baseline LDL level ≥ 100 mg/dL.

HDL cholesterol and triglycerides: There was no change in either of these lipid moieties during the study.

Comments: The changes in lipids are consistent with changes found during the previous pivotal trial (#4). The changes are prompt and of clinically significant magnitude. All the above changes were consistent across intent-to-treat and per-protocol populations.

8.2.3.4.3 Safety outcomes

The population for the safety analysis consisted of all patients who received at least one dose of RenaGel. All adverse events occurring during the treatment and washout periods are presented by body system and by patient (Appendix of NDA). For the safety population (n=172 patients), during the RenaGel treatment period, a total of 499 adverse events occurred among 130 patients. During the first washout period, a total of 120 events occurred among 67 patients, and a total of 128 adverse events occurred among 51 patients during the second washout period.

The digestive system was associated with the most frequent occurrence of AE's, when grouped by system, accounting for 135 events among 74 patients during RenaGel treatment. These AE's included diarrhea (12.8%), nausea (11.6%), dyspepsia (9.3%), vomiting (7%), and constipation (7.0%).

There were 2 events of hypercalcemia in 1 patient and 6 hypocalcemic events in 6 patients.

Overall, there were 159 treatment-emergent events among 56 patients in patients receiving low doses (<8 capsules/day) of RenaGel, 156 events among 66 patients in the medium dose (8-12 capsules/day) group, and 184 events among 54 patients in the high dose (>12 capsules/day) group. Although there was a statistically significant difference in patient-based incidence rates across dose groups for "any adverse event" (p=0.0005), the incidence of events appeared to decrease with higher doses of RenaGel. There were no statistically significant differences in incidence rates by dose level for any body system or

individual adverse event, except for insomnia and pneumonia, which appeared to decrease with higher doses of RenaGel.

The digestive system was the site of the most frequent treatment-emergent adverse events: 43 digestive events among 29 patients in the low dose group, 47 events among 32 patients in the medium dose group, and 45 events among 26 patients in the high dose group. The most common events were: nausea (27 events among 20 patients), diarrhea (22 events among 22 patients), dyspepsia (20 events among 16 patients), vomiting (16 events among 12 patients), and constipation (13 events among 12 patients). These differences across RenaGel dose groups were not statistically significant.

Neither hyper-nor hypocalcemia were associated with RenaGel dose.

Overall, there were 81 treatment-emergent adverse events that were possibly or probably related-related adverse events among 43 patients. In the low dose group, there were 26 events related to study treatment among 14 patients; in the medium dose group, 35 events among 23 patients; and in the high dose group, 20 events among 14 patients. There was no statistically significant difference in these incidence rates across dose levels overall, by body system, or by individual adverse events.

The digestive system had the most frequent treatment-related adverse events: 60 events among 39 patients. There was no dose relationship. In the low dose group, there were 21 treatment-related digestive events among 13 patients; in the medium dose group there were 25 events among 19 patients, while in the high dose group there were 14 events among 12 patients. The most frequent treatment-related digestive disorders included: diarrhea (11 events among 11 patients), dyspepsia (10 events among 10 patients), vomiting (11 events among 8 patients), nausea (7 events among 6 patients), and constipation (8 events among 7 patients).

Most of the treatment-related adverse events were of mild intensity: 26 patients (15.1%) had a mild treatment-related adverse event, 19 patients (11.0%) had a moderate event, and no patient had a severe treatment-related adverse event.

At the low dose level 10 patients had a mild adverse event, while 4 had a moderate adverse event. At the medium dose level 13 patients had a mild adverse event, while 10 had a moderate adverse event. At the high dose level, 6 patients had a mild adverse event, while 8 had a moderate adverse event.

Within the digestive system, 27 patients (15.7%) had a mild treatment-related adverse event and 14 patients (8.1%) had a moderate treatment-related adverse event. The most common digestive disorders included: nausea (3 mild, 4 moderate), diarrhea (7 mild, 4 moderate), vomiting (5 mild, 3 moderate), dyspepsia (8 mild, 2 moderate), and constipation (6 mild, 2 moderate).

Two of the hypocalcemic events were of mild intensity, and one was of moderate intensity. The one episode of pruritis was mild in intensity.

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Serious adverse events: During the first washout period there were 2 serious adverse events among 2 patients (1.2%). During the RenaGel treatment period, 33 serious AE's occurred among 29 patients (16.9%), and during the second washout period, 9 serious adverse events occurred among 8 patients (4.7%).

During the first washout period, there was one death, which was due to pancreatitis and sepsis. One patient died due to acute myocardial infarction one month following discontinuation of RenaGel. A third patient died due to cardiac arrest during the second washout period. These events were judged not related to RenaGel treatment.

During the treatment period, 11 patients had a serious cardiovascular event (6.4%), including 3 patients with thrombosis and two patients with congestive heart failure. Other frequent serious adverse events during the treatment period included: 3 patients with chest pain, 3 with sepsis, and 3 with pneumonia.

Instances of serious hypercalcemia and hyperphosphatemia were infrequent. One patient had serious hypervolemia during the treatment period, and one patient had serious hypocalcemia during RenaGel treatment.

Serum chemistries: Changes in levels of phosphate, calcium CaXP ion product, lipids, and PTH are described above, in the efficacy section.

No clinically significant changes in serum sodium or potassium were observed during treatment.

The mean chloride concentration increased significantly by 2.4 mEq/L (from 99.1 mEq/L, $p<0.0001$) during treatment. The elevation in chloride did not appear to increase with increasing dose levels: the low dose group increased 1.5 mEq/L (from 99.9 mEq/L), the moderate dose group increased 1.1 mEq/L (from 100.3 mEq/L), and the high dose group increased 3.2 mEq/L (from 98.4 mEq/L). Cessation of RenaGel treatment at Week 10 was followed by a statistically significant decrease in chloride of 2.6 mEq/L (from 101.5 mEq/L, $p<0.0001$) at the end of the second washout period. The increases in chloride observed during the treatment period were well within the normal range and thus were not considered clinically significant.

The CO2 content did not significantly change during treatment, but rose significantly during the second washout, by 2.1 meq/l (from 16.2, p<0.0001).

No clinically significant changes were seen in serum glucose, uric acid, magnesium, total iron, TIBC, folate, or ferritin.

Hepatic function tests : No clinically significant changes were seen in ALT, AST, total bilirubin, LDH, total protein, albumin, pre-albumin, or globulin. There was an increase in mean alkaline phosphatase, during treatment (Week 2 to Week 10). The mean level of the enzyme rose by 19.6 UL (from 88.6 UL, p<0.0001). There was a significant difference among the three dose groups (p<0.0001). The low dose group increased 5.0 UL (from 98.0 UL), the moderate dose group increased 15.1 UL (from 70.3 UL), and the high dose group increased 27.4 UL (from 90.7 UL). Following the cessation of RenaGel, alkaline phosphatase isoenzyme did not significantly change by the end of the second washout period. The increase seen during the treatment period was within the normal range and, therefore, was not considered clinically significant. Individual alkaline phosphatase isoenzymes were analyzed. The intestinal and bone isoenzymes did not change. However the liver isoenzyme decreased by 2.4%, p=0.0043. Thus the meaning or source of the increase in total alkaline phasphatase is not clear.

Renal function: No clinically significant changes were observed in mean BUN or creatinine levels over the treatment period.

Hematology: no clinically significant changes were seen, during the treatment period, in hematocrit, hemoglobin, red cell count, MCV, MCH, MCHC, white cell count, neutrophils-segmented, lymphocytes, monocytes, eosinophils, basophils, and platelet count. Individual patient data for hematology measures are listed in Listings 7.6.A to 7.6.C of the appendix of the NDA.

PT, PTT, INR, vitamins A, D, E, and levels of digoxin: During treatment, the PT decreased fy 0.3 seconds (from 13.1 sec, p=0.0003). There ws no dose effect. There ws no change in PTT, and no clinically significant change in INR. Vitamin A levels decreased by 10.8 mcg/dl during treatment, from 182.6 mcg/dl (p=0.0145), with no differences among dose groups. The levels of vitamin A throughout the study were above the normal laboratory range of 30 – 95 mcg/dl.

Vitamin D: Mean levels of 25-hydroxy vitamin D decreased by 4.4 ng/mL (from 37.6 ng/mL, p<0.0001). There was no significant dose effect, and the levels of this vitamin did not change after the second washout. The decrease during treatment was not considered a clinically significant change because the levels remained well within the normal range. When the data were analyzed by vitamin D usage, the reduction in vitamin D levels was statistically significant for patients not taking vitamin D supplements (decrease of 5.8 ng/mL (from 37.7 ng/mL, p=0.0008), and also for patients receiving intravenous vitamin D supplementation (3.3 ng/mL, from 37.8 ng/mL, p=0.0149). There were not

enough patients to assess a change in vitamin D 25-hydroxy levels among those using an oral vitamin D supplement.

Levels of 1,25-dihydroxyvitamin D did not significantly change during treatment.

Vitamin E did not significantly change during treatment.

Digoxin : There were no significant changes in digoxin levels among the Five of ten patients receiving cardiac glycoside therapy had digoxin levels measured during treatment. There were no significant changes in digoxin levels among these five patients.

Physical examination disclosed no clinically significant changes during treatment with RenaGel.

Comments: there were no safety issue raised as a result of this clinical trial. However, there was no control group in this study, and again there was the expected high background level of adverse events in this patient population. The lack of change in serum vitamin levels would be more reassuring if the dose regimens were clarified. Again, the lack of drug-drug interaction studies keeps this issue at the forefront of safety concerns.

8.2.3.5 Conclusions Regarding Efficacy Data

This trial was one of the two pivotal phase 3 studies that were submitted to the NDA. The study met its primary efficacy objective, in that the mean serum phosphorus was significantly reduced from baseline during RenaGel treatment in both the intent-to-treat and per-protocol populations. The two secondary objectives were also met. Statistically and clinically significant reductions in total and LDL cholesterol were demonstrated during RenaGel therapy. It should be emphasized that this study was uncontrolled, andlefficacy results are derived from within-group analyses.

RenaGel treatment was associated with a statistically significant reduction in mean and median PTH levels, although the magnitude of the PTH reduction was small and probably not clinically meaningful. There was no clinically significant elevation in mean calcium levels; and, as shown above, the serum calcium remained stable throughout the eight weeks of RenaGel treatment. This stability in serum calcium concentrations was independent of vitamin D use, although the calcium levels were consistently higher among vitamin D users. In addition, there was a clinically significant reduction in CaXP ion product during the RenaGel treatment period.

Although the responder rate in this study was 81%, this figure is based on the sponsor's definition of response. As described in the review of trial #4 above, this definition can be misleading. However, the sponsor makes no claims about responder rates in the proposed labeling.

In this study, eight weeks' exposure to RenaGel appeared to be safe and tolerable, although the lack of a comparison group limits the value of the safety analysis.

The patient population, which consisted of 172 hyperphosphatemic hemodialysis patients, was large for a study of ESRD patients and representative of the intended treatment population, in terms of demography and medical history.

8.2.4 Reviewer's Trial # 6 Sponsor's Protocol # GTC-10-202

8.2.4.1 Objectives

The objectives of this trial were to:

1) determine the efficacy of RenaGel in lowering the serum phosphorus in hemodialysis patients,
2) determine the safety of RenaGel in hemodialysis patients,
3) determine the effect of RenaGel treatment on lipid profiles in hemodialysis patients, and
4) determine the effect of RenaGel on intact PTH levels in hemodialysis patients.

8.2.4.2 Design

This was a phase 2, uncontrolled, open-label, dose titration study of 48 patients with ESRD on hemodialysis. Patients whose serum phosphorus levels were > 6.0 mg/dl during a two-week phosphate binder washout period were eligible to enter as 8-week RenaGel treatment phase. The starting dose of RenaGel was based on the degree of hyperphosphatemia. At the end of each of three subsequent two-week periods, the dose of RenaGel was titrated in an attempt to achieve a serum phosphorus level between Blood chemistries, including serum phosphorus, calcium, and PTH, were monitored weekly. The study design is diagrammed below. The investigators maintained the serum calcium level within the normal range by supplementing with oral calcium carbonate at bedtime or by increasing the dialysate calcium concentration. Throughout the study, patients maintained their regular dialysis schedule and normal eating habits. Phosphorus intake was monitored frequently using 24-hour dietary recall methodology.

The following is a schematic of the study design:

Week -1	Weeks 1-2	Weeks 3-10	Weeks 11-12
Screening	Washout	RenaGel treatment	Washout

Safety was evaluated on the basis of adverse experiences as well as on the basis of changes in standard laboratory values.

Efficacy was evaluated on the basis of changes in serum phosphorus from the end of the first washout to the end of the treatment period.

Comments: This phase 2 uncontrolled trial used the "off-on-off" design that is characteristic of most of the studies submitted to this NDA. The strength of the conclusions is again limited by the lack of placebo control (discussed above) or an active comparison arm.

8.2.4.3 Protocol

8.2.4.3.2 Population, procedures

Patients were male and female adults with ESRD on hemodialysis thrice weekly for 3 months or longer. They also were on a phosphate binder (calcium or aluminum) at stable dose for at least one month prior to screening. If they were on vitamin D, the dose must have been stable for at least one month prior to screening. The inclusion/exclusion criteria for this study were essentially the same as in the studies reviewed above. It is worth emphasizing again that patients with the following GI disorders were excluded from the study: a history of dysphagia or swallowing disorders; a history of a motility disorder of the intestines including but not limited to gastroparesis, ileus, pseudoobstruction, megacolon, or mechanical obstruction; a history of such major gastrointestinal tract surgery as gastrectomy or intestinal resection; a history of abnormal or irregular bowel function (more than 4 bowel movements/day or less than 1 bowel movement/week).

Comments: These are reasonable exclusionary criteria; however, the safety, tolerability, and efficacy of RenaGel cannot be assured in patients with these GI disorders.

At the screening visit, eligibility was determined, informed consent was obtained, and the patients received a medical history, and physical examination. Blood was obtained for basic laboratory tests: hematology, chemistry, vitamin A and E, PT, PTT, and parathyroid hormone. Patients were to continue their usual diet and phosphate binder therapy.

During the first phosphate binder washout period, serum phosphorus, calcium and parathyroid hormone were measured weekly. Blood was drawn prior to the

dialysis that followed the longest inter-dialysis period (generally on Monday or Tuesday). In week 2, blood was also taken for chemistry and hematology, vitamins A and E, PT and PTT, and hCG (women only).

Patients whose serum phosphorus concentration was > 6.0 mg/dl entered the treatment period. The starting dose of RenaGel was based on the highest phosphorus level achieved during the washout period, according to a pre-determined schedule. During this period, nutritional data were collected from the patients via phone calls on three random days. Patients were to continue their usual diets, take the study medication as prescribed by the investigator, and record RenaGel use in the diary.

During the treatment period blood was obtained weekly for phosphorus, calcium, and parathyroid hormone levels. In addition, blood was obtained every two weeks for chemistry and hematology profiles, vitamins A and E, PT and PTT. Based on the serum phosphorus levels, the dose of RenaGel was titrated, on weeks 4, 6, and 8, to attempt to achieve a serum phosphorus level between 4.0 and 5.5 mg/dL. Patients kept a drug diary, as in the other clinical studies, and if the dose was changed, the diary was to reflect this. The diary was reviewed to ensure compliance and proper dosing.

Patients were asked about adverse experiences and/or changes in concomitant medications during the dialysis sessions. The investigator was to drop any patients who developed signs or symptoms suggesting metastatic calcification: these included, but were not limited to, severe pruritus, conjunctivitis, iritis, episcleritis, or painful, swollen cutaneous masses which the investigator determined were caused by calcium-phosphate precipitation. These signs or symptoms were considered to be adverse experiences.

Comments: The population, inclusion/exclusion criteria, procedures, dose regimens, and timing of blood drawings are all appropriate and consistent with other studies in the NDA.

8.2.4.3.2 Endpoints

The primary efficacy variable was a change in the serum phosphorus from week 2 to week10, the end of the RenaGel treatment period. The secondary efficacy variables were changes in PTH and serum cholesterol during this period. The safety variables were: incidence of adverse experiences; changes in laboratory values (chemistry and hematology profiles, vitamins A and E, PT and PTT); and changes in physical examination findings determined at screening and during treatment periods. Analyses were planned for the intent-to-treat populations and the evaluable populations. In addition, patients were grouped into tertiles, based on the level of the baseline (post-washout) serum phosphorus. Compliance was determined by capsule counting. Standard statistical analyses were designed to detect changes in serum phosphorus from baseline (week 2) to end of RenaGel treatment (week 10) using paired t-tests and ANOVA with treatment group and

study site as factors. The proportion of responders to RenaGel therapy was compared overall and by treatment group using Fisher's exact test. In addition, regression analyses were used to determine the influence of parathyroid hormone, calcium, dietary intake of phosphorus and calcium, and the use of Vitamin D, on the reduction of serum phosphorus.

Comments: The planned analyses are appropriate for this study. The efficacy endpoint variables are clear, objective, and easily measured. They are also consistent with those used in other studies. The safety endpoints are consistent with those used in other studies within the NDA. They are clear, focused, and objective. The statistical analyses are clearly presented and appropriate.

Of note is that the definition of responder is different from that used in the two pivotal phase 3 studies (discussed above). In this study there were 5 definitions of response:

1) **Serum phosphorus at endpoint (week 10) < 6.0 mg/dl.**
2) **Serum phosphorus at endpoint ≤ 6.0, or a 20% reduction in phosphorus from baseline to endpoint**
3) **Serum phosphorus at endpoint ≤ the screening serum phosphorus**
4) **Meet either definition 1 or definition 3**
5) **Meet at least one of the definitions 1, 2, or 3.**

It should be emphasized that only definitions 1 or 2 meet criteria that a patient must have reduced his/her phosphorus from baseline in order to be classified as a responder. The other 3 definitions are clinically meaningless, for reasons discussed above.

8.2.4.4 Results

8.2.4.4.1 Populations enrolled/analyzed

Forty-eight patients were enrolled in the study and received at least one dose of RenaGel. Thus these 48 individuals comprised the safety population. Each of these patients had a baseline and at least one post-baseline serum phosphorus evaluation, and therefore also comprised the intention-to-treat (ITT) population. Of these, 28 patients were at least 80% compliant with the medication and had a week 10 efficacy evaluation. These patients comprised the evaluable population.

Of the 20 dropouts, 15 were excluded because they were less than 80% compliant over the course of the study. Another 5 patients did not have an

efficacy evaluation at week 10, and were thus excluded. Four of these patients discontinued due to an adverse event, while one patient withdrew consent.

Of the enrollment population (48 patients), 30 patients were male (62.5%) and 18 were female (37.5%). Thirteen of the female patients were post-menopausal (72.2%) and two were using hormone supplements (11.1%). Twenty-four of the patients were Caucasian (50.0%), 20 were African-American (41.7%), three were Hispanic (6.3%) and one was East Indian. Continuous demographic data are summarized by washout serum phosphorus group in Appendix 16.9, Study Summary Tables Table 2B and in Table 2 of the NDA. The mean age was 52 years, the mean height was 171.1 cm, and the mean weight was 78.0 kg. The primary cause of ESRD was diabetes in 35.4% of the patients, hypertension in 29.2%, nephritis in 10.4%, polycystic kidneys in 6.3%, pyelonephritis in 4.2%, and other reasons in14.6%. Phosphate binders used by the patients: calcium carbonate in 41.7%, calcium acetate in 50.0%, and the remaining 8.3% were using aluminum. Nine patients had a kidney transplant (18.8%), while only one patient had a parathyroidectomy. Twenty-nine patients reported Vitamin D analogue use (60.4%).

There were a few minor protocol violations/deviations during the study. These are described in the Appendix, section 10.3. Overall, the % compliance (defined by the sponsor as 100 X [# capsules taken /# capsules prescribed]) was 80%. When grouped by the washout serum phosphorus level, there was no difference in compliance rates across groups.

Comments: The demographics of the enrolled population are again representative of the intended treatment population. In this relatively small, phase 2 study, the dropout rate was quite high: 20 out of the original 48 who were enrolled. The reasons for most of the dropouts was < 80% compliance with the medication. It would be of interest to see a distribution of compliance rates—e.g., how many were 70% compliant. The reasons for non-compliance may possibly be of importance in assessing tolerability. Nonetheless, this was a small study and the intent-to-treat population is analyzed independently of the evaluable population.

8.2.4.4.2 Efficacy endpoint outcomes

Serum phosphorus : For the intent-to treat population, the serum phosphorus significantly decreased from baseline (week 2) to the end of the treatment period, at week 10. The mean baseline serum phosphorus for ITT population was 8.1 mg/dL. By week 10, the mean serum phosphorus had decreased by 1.4 mg/dl ($p=0.0001$). A carry-forward analysis of the change in serum phosphorus from baseline to endpoint (the last serum phosphorus determination while on RenaGel) yielded results that were similar to the ITT population. When the results were analyzed by washout serum phosphorus values, the greatest

decrease was found in the group with baseline phosphorus >8.0 mg/dl. The results of the analysis on the intent-to-treat population and the carry-forward analysis are shown in the table below. The results are also displayed according to the baseline phosphorus concentrations.

		Total	Washout Serum Phosphorus (mg/dL)		
			> 6.0 to < 7.0	≥7.0 to < 8.0	≥8.0
Baseline[1]	N	48	12	8	28
	Mean ± SD	8.1± 2.0	6.2± 0.5	7.1± 0.5	9.3± 1.8
Change from baseline to final[2]	N	42	12	6	24
	Mean ± SD	-1.4± 1.9	-0.4± 1.0	-1.3± 1.7	-1.9± 2.1
	p* value	0.0001	0.2381	0.1072	0.0002
Change from final to washout[3]	N	41	12	6	23
	Mean ± SD	1.5± 2.2	0.8± 1.1	0.8± 1.4	2.1± 2.7
	p* value	0.0001	0.0331	0.2175	0.0011
Change from baseline to endpoint[4]	N	48	12	8	28
	Mean ± SD	-1.4± 2.0	-0.4± 1.0	-0.8± 1.7	-1.9± 2.2
	p* value	0.0001	0.2381	0.2020	0.0001

*A p-value less than 0.05 indicates that the stated change was statistically significant.
[1]Baseline is defined as the serum phosphorus level from the second week of the first washout (week 2).
[2]Final serum phosphorus is defined as the week 10 value.
[3]Washout serum phosphorus is defined as the week 12 value.
[4]Endpoint serum phosphorus is defined as the last serum phosphorus level on active treatment

Comments: the carry-forward analysis yielded essentially the same results as the analysis on the ITT population.

Results for the evaluable population were similar. The mean baseline serum phosphorus was 8.0 mg/dL overall. For the overall evaluable population the serum phosphorus significantly decreased by 1.5 mg/dl from baseline to the end of the RenaGel treatment period, at week 10 (p=0.0002). Within the washout serum phosphorus groups, serum phosphorus decreased 0.5 mg/dL from 6.2 mg/dL for the <7.0 group, 1.3 mg/dL from 7.2 mg/dL for the ≥7.0 to <8.0 group,

and 2.0 mg/dL from 9.0 mg/dL for the ≥8.0 group. The mean decrease in serum phosphorus for the ≥8.0 group was statistically significant (p-value=0.0011). The data are displayed in the table below:

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		Total	Washout Serum Phosphorus (mg/dL)		
			> 6.0 to < 7.0	≥7.0 to < 8.0	≥8.0
Baseline[1]	N	28	7	5	16
	Mean ± SD	8.0± 1.8	6.2± 0.4	7.2± 0.6	9.0± 1.7
Change from baseline to final[2]	N	28	7	5	16
	Mean ± SD	-1.5± 1.8	-0.5± 0.9	-1.3± 1.9	-2.0± 2.0
	p* value	0.0002	0.1847	0.1829	0.0011
Change from final to washout[3]	N	28	7	5	16
	Mean ± SD	1.8± 2.2	1.2± 0.5	0.6± 1.5	2.5± 2.6
	p* value	0.0002	0.0012	0.4251	0.0017

*A p-value less than 0.05 indicates that the stated change was statistically significant.
[1]Baseline is defined as the serum phosphorus level from the second week of the first washout (week 2).
[2]Final serum phosphorus is defined as the week 10 value.
[3]Washout serum phosphorus is defined as the week 12 value.

Comments: Again, the greatest reduction occurred in the group with the highest baseline phosphorus concentration. Lack of statistical significance in the two other groups was likely due to small n's.

Responder analysis:The table below displays the % of patients responding to RenaGel according to the definition of response (for the ITT population):

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Responder Definition:	Responder		Non-Responder		95% Confidence Limits	
	n	%	n	%	Lower	Upper
(1) Less than 6.0 Endpt	20	41.7	28	58.3	0.277	0.556
(2) <6.0 or 20% Decrease	26	54.2	22	45.8	0.401	0.683
(3) EndPt ≤ Screening	26	54.2	22	45.8	0.401	0.683
(4) <6.0 or Endpt≤Scr	29	60.4	19	39.6	0.466	0.743
(5) <6.0, E≤S, 20% Decr	32	66.7	16	33.3	0.533	0.800

95% Confidence interval based on the normal approximation to the binomial distribution

1. Less than 6.0 mg/dL serum phosphorus at endpoint (protocol-defined criterion)
2. Less than 6.0 md/dL serum phosphorus at endpoint or 20% decrease in phosphorus from baseline
3. Endpoint serum phosphorus ≤ screening phosphorus
4. Less than 6.0 mg/dL serum phosphorus at endpoint or endpoint serum phosphorus ≤ screening serum phosphorus
5. Less than 6.0 serum phosphorus at endpoint or endpoint serum phosphorus ≤ screening phosphorus or at least 20% decrease from baseline

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A similar analysis done for the evaluable population showed that the responder rates went from 42.9% according to definition 1 to 60.7% using definition 2, to 71.4% using definition 5.

Comments: not surprisingly, the responder rate increases as the response definition broadens. Using clinically meaningful definition of serum P<6.0, the response rate in the ITT population is only 41%. Using definition 2, the rate increases to 54.2%. These data are consistent with the results from our analysis in the 301 crossover study. These considerations should be taken into account when interpreting responder rates in the other clinical trials.

PTH levels: For the intent-to-treat population, changes in PTH levels from baseline to end of treatment were highly variable and not statistically significant. Using responder definition 1 (phosphorus <6.0), the mean PTH level declined by 95.2 pg/ml, from 667.5 pg/ml for responders and increased 31.0 pg/ml (from 452.9 pg/ml) for non-responders. Neither change was statistically significant. For the evaluable population, the mean PTH declined by 185.2 pg/ml (from 607

pg/ml) for responders and increased by 42 pg/ml for the non-responders. The difference in PTH changes between the two groups was statistically significant (p=0.027).

Comments: mean changes in PTH levels of this magnitude are not clinically significant, since the mean levels of the hormone remain around 400 pg/ml in the responders.

Lipid profiles: For the ITT population, the total cholesterol decreased by 24.7 mg/dL (from 176.9 mg/dL, p=0.0001). The LDL decreased 23.4 mg/dL (from 97.7 mg/dL, p=0.0001). HDL cholesterol and triglycerides did not significantly change from Week 2 to endpoint.

Safety outcomes

Safety analysis was done on all patients who received at least one dose of RenaGel. This included all 48 patients who completed washout and received at least one dose of RenaGel. Adverse events were grouped by RenaGel dose (calculated from the mean daily dose of RenaGel: low=<6.4 caps/day, medium= between 6.4 and 10 caps/day, and high=10 or more caps/day) The incidence of all AE's in the safety population is shown below:

	RenaGel Dose Level*		
	Low	Medium	High
	n(%)	n(%)	n(%)
No adverse experiences	4 (25.0%)	3 (18.8%)	2 (12.5%)
At least one adverse experience	12 (75.0%)	13(81.3%)	14 (87.5%)
Total patients	16 (100%)	16 (100%)	16 (100%)

The incidence of treatment-emergent AE's (those that began or worsened during the treatment period) was 68%, across dose groups, as shown below:

	RenaGel Dose Level*		
	Low	Medium	High
	n(%)	n(%)	n(%)
No adverse experiences	5 (31.3%)	5 (31.3%)	5 (31.3%)
At least one adverse experience	11 (68.8%)	11 (68.8%)	11 (68.8%)
Total patients	16 (100%)	16 (100%)	16 (100%)

Adverse events are presented in the Appendix by body system. Common treatment-emergent adverse events included: diarrhea in six patients (12.5%), and constipation, vomiting, and peripheral edema, each in five patients (10.4%). There were more episodes of nausea and vomiting in the medium and high dose groups than in the low-dose group. However, this dose relationship was not replicated in the analysis of treatment-emergent AE's judged possibly/probably related to the study drug, as shown below:

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Adverse experiences by body system	RenaGel Dose Level***			Total
	Low	Medium	High	
Digestive system				
Constipation	1 (6.3%)	3 (18.8%)	0 (0%)	4 (8.3%)
Diarrhea	2 (12.5%)	2 (12.5%)	0 (0%)	4 (8.3%)
Dyspepsia	1 (6.3%)	0 (0%)	0 (0%)	1 (2.1%)
Nausea and vomiting	1 (6.3%)	1 (6.3%)	0 (0%)	2 (4.2%)
Vomiting	0 (0%)	1 (6.3%)	1 (6.3%)	2 (4.2%)
Abnormal stools	0 (0%)	0 (0%)	1 (6.3%)	1 (2.1%)
Flatulence	0 (0%)	0 (0%)	1 (6.3%)	1 (2.1%)
Nausea	0 (0%)	0 (0%)	1 (6.3%)	1 (2.1%)
Body as a whole				
Abdomen enlarged	0 (0%)	1 (6.3%)	0 (0%)	1 (2.1%)
Abdominal pain	0 (0%)	0 (0%)	1 (6.3%)	1 (2.1%)
Hemic and Lymphatic				
Ecchymosis	0 (0%)	0 (0%)	1 (6.3%)	1 (2.1%)
Nervous				
Insomnia	0 (0%)	0 (0%)	1 (6.3%)	1 (2.1%)
Nervousness	0 (0%)	0 (0%)	1 (6.3%)	1 (2.1%)

* Treatment emergent adverse experiences include those which began or worsened during the treatment period.
** Related = possible or probable relationship as determined by the investigator
*** Dose categories were calculated from the mean daily dose as follows: < 6.4 caps/day = "Low", ≥6.4 to < 10 caps/day = "Medium", and ≥10 caps/day = "High"

Most adverse experiences were judged mild or moderate in intensity. Eleven experiences were judged severe. Two out of the 11 experiences occurred in the low dose group, 5 of the 11 occurred in the medium dose group, and the remaining 4 experiences occurred in the high dose group. None of these severe adverse experiences were judged treatment related. The one death that occurred during the study was judged not to be treatment-related.

Laboratory tests:

Hematology: There were no clinically significant changes noted in hematology parameters during the study.

Chemistry: The mean potassium level increased during the treatment period by 0.3 mEq/L (from 4.9 mEq/L, p-value=0.0105). There was no statistically significant difference among the three groups with respect to change in potassium, and no dose-relationship was apparent.

The mean chloride increased 2.7 mEq/L (from 98.8 mEq/L, p-value=0.0001). There was no statistically significant difference among the three groups with respect to change in chloride. However, there was a trend toward greater increases in chloride as the RenaGel mean dose level increased, with the low dose group increasing 1.6 mEq/L (from 100.5 mEq/L), the medium dose increasing 2.7 mEq/L (from 99.3 mEq/L), and the high dose increasing 3.7 mEq/L (from 96.7 mEq/L).

The mean carbon dioxide decreased 1.6 mEq/L (from 18.8 mEq/L, p=0.0353). There was no statistically significant difference among the three groups with respect to change in carbon dioxide, but change increased as the RenaGel mean dose level increased, with the low dose increasing 0.1 mEq/L (from 16.4 mEqL), the medium dose decreasing 1.4 mEqL (from 18.5 mEq/L), and the high dose decreasing 3.6 mEq/L (from 21.7 mEqL).

Comments: the changes in CO2 and chloride noted in other studies are also seen here. RenaGel may possibly cause some increase in GI bicarbonate loss. These effects appear not to cause clinically significant changes in blood chemistries over an 8-week period.

Renal function: There were no statistically significant changes in BUN or creatinine during the treatment period.

Hepatic function: AST, ALT, bilirubin, and LDH did not change during the treatment period. Alkaline phosphatase levels increased 30.7 UL (from 105.4 UL, p=0.0386). There was no apparent dose-response relationship, and there was no statistically significant difference among or within the three dose groups.

PT, PTT, vitamins A and E: did not change during the treatment period.

Physical examination: No notable changes were found in physical examination from screening to end of treatment.

Comments: The lack of a control or comparison group weakens safety outcome data. However, there were no serious treatment-emergent,

treatment-related adverse events. Furthermore, there was no dose effect on the incidence of clinically significant AE's.

8.2.4.5 Conclusions Regarding Efficacy Data

In this relatively small uncontrolled open-label study, RenaGel showed very modest efficacy in reducing the serum phosphorus level. Overall, there was a statistically significant reduction in mean phosphorus concentrations. However, it should be noted that statistical significance was achieved only for the high washout phosphate group. This was true for the ITT population, the evaluable population, and the LOCF–analyzed population.

Calcium levels did not change significantly during the study.

In addition, the responder rate was less than 50%, using definitions 1 or 2; and these are the only clinically meaningful responder definitions among the five options.

There were no clinically significant changes in PTH levels.

The declines in total and LDL cholesterol were statistically and clinically significant, and are consistent with the findings in other trials within the NDA.

8.2.5 Reviewer's Trial # 7 Sponsor's Protocol # GTC-36-203

8.2.5.1 Objectives: The objectives of this study were:

1. Determine the efficacy of RenaGel and RenaGel with evening calcium carbonate supplements in lowering serum phosphorus in hemodialysis patients.

2. Determine the effect of RenaGel and RenaGel with evening calcium carbonate supplements on intact parathyroid hormone levels in hemodialysis patients.

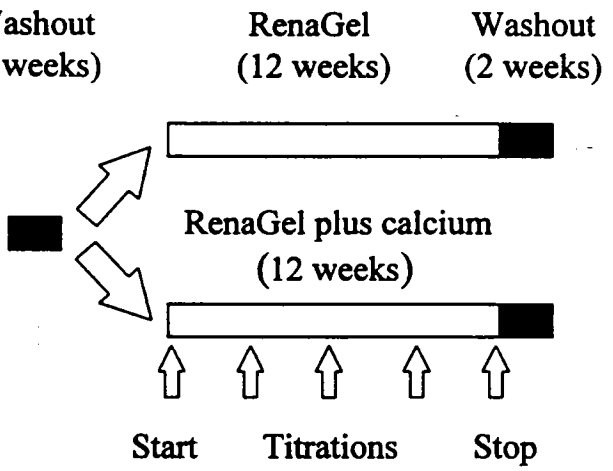
3. Determine the effect of RenaGel and RenaGel with evening calcium carbonate supplements on lipid profiles in hemodialysis patients.

4. Determine the safety of RenaGel and RenaGel with evening calcium carbonate supplements in hemodialysis patients.

8.2.5.2 Design

This uncontrolled phase 2 trial was a randomized, open-label, dose titration study in which RenaGel was compared to RenaGel plus an evening dose of

calcium carbonate, in terms of the above four outcome measurements. The design of the study is diagrammed below:



This phase 2 trial was designed as a pilot study. The magnitude of the effect of a calcium supplement on the efficacy of RenaGel was unknown, and no formal power analysis of sample size was made prior to the study. Ninety-four ESRD hemodialysis patients were enrolled and 75 patients were randomized to one of the two treatment arms shown above. Patients discontinued phosphate binder therapy during the 2-week washout period. Those patients developing a serum phosphorus > 6.0 mg/dl during the washout were eligible for RenaGel treatment. Patients were randomized to RenaGel alone or RenaGel plus an evening calcium supplement of 3 TUMS EX tablets, each containing 300 mg of elemental calcium as calcium carbonate. The initial dose of RenaGel was determined by the washout serum phosphorus level, according to a pre-determined schedule. The treatment period lasted 12 weeks. At 3-week intervals during the treatment period, the RenaGel dose was titrated, to try to achieve a serum phosphorus level between 2.5 and 5.5 mg/dl. Following the 12-week treatment period, patients entered a second 2-week washout period, following which repeat laboratory studies were obtained. Patients then returned to their original phosphate binders.

Efficacy was evaluated on the basis of changes in serum phosphorus from the end of the first washout to the end of the treatment period. An intent-to-treat analysis was performed with the last observation carried forward for patients who terminated early.

Safety was evaluated on the basis of reported and/or observed adverse experiences, and changes in laboratory values (chemistry, hematology, PT and PTT, and serum levels of vitamins A, D and E).

Comments: Again, the lack of concurrent controls limits the strength of conclusions regarding the efficacy and safety of RenaGel alone. However, the study was designed to compare RenaGel with RenaGel plus calcium, and this design should permit this comparison, provided that there is adequate power to detect differences between the two treatment groups.

8.2.5.3 Protocol

8.2.5.3.1 Population and Procedures

Six centers participated in this study. Patients were adult men or women, 18 years of age or older, with ESRD on hemodialysis 3 times weekly for 3 months or longer. The inclusion/exclusion criteria were the same as in the other clinical trials, and again included the following:

- history of dysphagia or swallowing disorders.
- history of a motility disorder of the intestines including but not limited to ileus, pseudoobstruction, megacolon, or mechanical obstruction. Active gastroparesis as evidenced by nausea and/or vomiting was an exclusion. However, treated gastroparesis was not an exclusion.
- history of gastrointestinal tract surgery, including gastrectomy or intestinal resection. Uncomplicated appendectomy or polypectomy or non-intestinal tract abdominal surgery such as cholycystectomy or nephrectomy were not exclusions.
- abnormal or irregular bowel function (> 4 bowel movements/day or < 1 bowel movement per week).

Comments: as noted above, the consistent exclusion of patients with a variety of GI disorders is understandable, given the nature of this drug. However, 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. Otherwise, the planned population for the study is appropriate. As intended by the sponsor, the population should resemble the other study populations.

Procedures: Following screening and enrollment into the study, patients remained on their usual diets (assessed by dietary recall). During the study, patients were prohibited from consuming antacids containing aluminum or magnesium. The patients who were randomized to RenaGel with an evening calcium supplement were not to take additional or substitute calcium salts.

Patients randomized to the RenaGel only group were not to consume calcium salts after the screening period except for the bedtime calcium supplement, if prescribed by the investigator as described earlier. Unless medically necessary, the investigators were asked to refrain from prescribing new medications to the patients during the study.

For patients on vitamin D replacement therapy, the original dose of the vitamin was to be maintained, unless it needed to be stopped or reduced for safety reasons.

Digoxin levels were to be measured at the end of week 2 and every three weeks during the treatment and washout periods in those patients receiving cardiac glycosides.

Comments: it is again not clear when, in relation to meals and RenaGel dosing, other vitamin supplements were given. The statement, " Drugs administered that could potentially alter serum levels and impact the safety and efficacy profile of the study treatment were prescribed to be taken at least one hour before or three hours after treatment," **appears in the protocol sections of other clinical trial in the NDA. Presumably the statement means that any drug whose absorption could be impeded by RenaGel was not to be given concomitantly with RenaGel. However, the statement is unclear, and it is not known whether these guidelines were adhered to during the study.**

At the time of screening, a battery of laboratory tests was obtained. These tests included: hematology, chemistry, PT, PTT, and parathyroid hormone levels. The scheduling of laboratory tests and drug dosing during the study was as follows:

Week	**Tests**
1 (washout period)	Phosphorus and calcium
2	Chemistry profile PTH Hematology profile PT, PTT Vitamins A, D (1,25 dihydroxy and 25-hydroxy), and E

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Those patients whose serum phosphorus was > 6.0 mg/dl at any time during the washout period were eligible to enter the treatment phase. Patients were randomized into the RenaGel or the RenaGel plus calcium treatment groups.

The starting dose of RenaGel depended on the highest serum phosphorus achieved during the washout period:

Serum Phosphorus	Starting Dose
> 6.0 and < 7.5 mgdL	6 capsules (2.79 g) daily
≥ 7.5 and < 9.0 mgdL	9 capsules (4.2 g) daily
≥ 9.0 mgdL	12 capsules (5.58 g) daily

At the end of each three week period within the 12-week treatment phase, the investigator would titrate the RenaGel dose by one capsule per meal as necessary in an attempt to achieve a serum phosphorus level between [redacted] If the serum phosphorus fell to less than 2.5 mg/dL, the investigator would decrease the RenaGel dose by one to three capsules per day. The maximum anticipated daily dose in the study was 21 capsules (9.8 g). Patients assigned to take RenaGel with an evening calcium supplement were instructed to take three TUMS EX® 750 mg tablets (a total of 900 mg of elemental calcium) on an empty stomach at bedtime.

The weekly laboratory schedule during the treatment period is presented below:

Week	Tests
3	Phosphorus and calcium
4	Phosphorus and calcium
5	Chemistry profile PTH
6	Phosphorus and calcium
7	Phosphorus and calcium
8	Chemistry profile PTH Hematology profile PT/PTT Vitamins A, D (1,25 dihydroxy and 25-hydroxy), and E
9	Phosphorus and calcium
10	Phosphorus and calcium
11	Chemistry profile PTH

12	Phosphorus and calcium
13	Phosphorus and calcium
14	Chemistry profile PTH Hematology profile PTPTT Vitamins A, D (1,25 dihydroxy and 25-hydroxy), and E

At the final visit of the treatment period, the investigator performed a physical examination, documenting changes from the physical examination performed at screening.

During the second washout period (weeks 15 and 16), RenaGel was discontinued and unused study drug was retrieved by the investigator. The laboratory schedule during this period is presented below:

Week	Tests
15	Phosphorus and calcium
16	Chemistry profile PTH Hematology profile PTPTT Vitamins A, D(1,25 dihydroxy and 25-hydroxy), and E

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Comments: the scheduling of laboratory tests and procedures is appropriate. The laboratory testing is comprehensive and also focused on the relevant parameters. The RenaGel dose regimen is consistent throughout all clinical trials in the NDA.

Dietary assessment procedures were the same as in the other clinical trials. A trained dietary interviewer assessed each patient's dietary phosphate intake using the 24-hour recall method. Patients were called on three random days during each of the following periods: the first washout, treatment, and second washout. The calls included one dialysis day, one non-dialysis day, and a

weekend day for each of the study periods. The data were analyzed using the Minnesota Nutrient Data System, Version 2.7.

The investigator kept a drug inventory using a drug dispensing log. Compliance with medication was assessed by counting the remaining capsules in the bottles at study weeks 5, 8, 11, and 14.

8.2.5.3.2 Endpoints

The primary efficacy analyses was based on the change in serum phosphorus from the last week of the first washout period (Week 2) to the end of the RenaGel treatment period (Week 14). Secondary efficacy parameters included changes in serum PTH and lipid levels (total, LDL, and HDL cholesterol, and triglycerides) during the RenaGel treatment period.

Safety was evaluated on the basis of adverse experiences (reported and/or observed), as well as changes in laboratory values (chemistry, hematology, PT/PTT, and vitamins A, D, and E) and changes in physical examinations.

Statistical analysis was done on the safety, intent-to-treat, and per-protocol populations. The safety population is defined as all enrolled patients who received any study medication. The intent-to-treat population is defined as all treated patients who had any valid post-baseline efficacy lab data. The per-protocol population consists of those ITT patients who completed the 12-week treatment period with no significant protocol violations.

For the ITT population, a carry-forward approach was used to fill in missing and invalid data, within each washout and treatment period independently. A carry-forward approach was also used in the analysis of the per-protocol population, when there were missing or invalid data.

Patients were excluded if they had received aluminum, magnesium-containing antacids, or calcium salts other than bedtime calcium supplementation, or changed their vitamin D supplementation during the study. Patients were also excluded from the per-protocol population if they were less than 70% compliant.

Statistical comparisons were made within groups over time, as well as between groups. All efficacy analyses were conducted on the intent-to-treat and per-protocol populations. Descriptive statistics are presented for serum phosphorus by treatment group, by vitamin D use and overall. Analyses are given for the changes in serum phosphorus between pre-washout and baseline, baseline and final, and final and the end of second washout. The Wilcoxon signed rank test was used to assess changes in serum phosphorus levels. The Wilcoxon rank sum test was used to compare changes between the treatment groups.

Response to treatment was again defined as returning to either pre-washout serum phosphorus levels or 5.5 mg/dL, whichever level is attained first.

Similar statistics are used to assess and compare changes in calcium, PTH, and lipids.

Comments: the planned comparisons and statistical approach are appropriate. The efficacy endpoints are consistent across studies, objective, and easily measured. The safety endpoints are comprehensive, but also focused on anticipated side effects of the drug. These endpoints are consistent across studies.

This study uses a treatment response definition that can be misleading, as discussed above.

8.2.5.4 Results

8.2.5.4.1 Populations enrolled/analyzed

A total of 94 patients were enrolled. Eight patients were discontinued during the first washout period because their serum phosphorus remained <6.0 mg/dl. One discontinued because of an adverse event, seven discontinued due to a protocol violation, one withdrew consent, and two discontinued during the first washout period for reason "other." A total of 75 patients were randomized into the treatment phase: 37 to RenaGel 38 patients to RenaGel with an evening calcium carbonate supplement.

Of these 75, 55 completed the study. In the RenaGel group, one died (cardiac arrest), eight discontinued due to an adverse event, one patient withdrew consent, and two patients were discontinued for reason "other." Total dropouts=12.

In the RenaGel with calcium carbonate treatment group, five patients discontinued due to an adverse event, two patients withdrew consent, and one patient was discontinued for reason "other." Total dropouts=8.

For the safety population, the mean age was 58.7 years
66.7% were male and 33.3% were female. 80% of the females were post-menopausal and 4% used hormone replacement. The mean weight was 76.9 kg, ranging

The population was 57.3% Caucasian, 38.7% African-American, 2.7% Hispanic, and 1.3% Asian. There were no differences between the two treatment groups for these patient demographics factors. Demographics for the intent-to-treat and per-protocol populations were comparable to those of the safety population.

In the safety population, the primary causes of ESRD were:

Diabetes 37.3%

Hypertension 29.3%

Nephritis 13.3%

Polycystic disease 5.3%

Pyelonephritis 1.3%

Other 13.3%.

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There were no differences between the 2 treatment groups in these parameters. There were also no differences between groups in history of kidney transplantation (8%) or vitamin D use (50.7%). Renal and general medical histories for the ITT and per-protocol populations were comparable to those of the safety population.

The dietary intake data showed small decreases in phosphorus during the treatment period in both treatment groups. The mean dietary calcium intake increased negligibly in both groups (this does not include the supplemental calcium). The mean vitamin A intake increased by 44.3 mcg/day in the RenaGel group (from 1176 mcg/day) and decreased by 256 mcg/day (from 1060.9 mcg) in the RenaGel plus calcium group. There were negligible decreases in vitamin E intakes in both treatment groups, and essentially the same intakes of vitamin D in both these groups.

8.2.5.4.2 Efficacy endpoint outcomes

Serum phosphorus: The primary efficacy endpoint was a change in the serum phosphorus. For the intent-to-treat population, the mean serum phosphorus levels found in both treatment groups throughout the course of the study are graphed below. At screening, the mean serum phosphorus levels in both treatment groups were the same (6.8 mg/dl). However, the post-washout serum phosphorus levels differed between the groups (8.9 for RenaGel vs 8.1 for RenaGel with calcium). This imbalance between the two groups persisted throughout the study, as shown in the graph below. By the end of the treatment period the phosphorus levels were 6.4 (a decline of 2.4 mg/dl from baseline, $p<0.0001$) for the RenaGel group and 5.8 mg/dl (a decline of 2.3 mg/dl, $p<0.0001$) for the RenaGel plus calcium group. The results in the per-protocol population were similar.

Vitamin D user status had no effect on the magnitude of the phosphorus response in either treatment group. The magnitude of the change in phosphorus was also the same between groups, irrespective of vitamin D use.

Using the sponsor's definition of response, the response rate was 94.3%, CI 86.6%-102.0% for RenaGel and 94.4% (CI 86.9%-101.9%) for RenaGel plus

calcium. The response rate was even higher and occurred sooner among patients using vitamin D supplements, compared to non-users.

Comments: Again, the definition of response is achievement of pre-washout serum phosphorus or a phosphorus level of 5.5 or less, whichever occurs sooner. This definition can be misleading and/or clinically meaningless, for reasons described above.

A graph of the serum phosphorus over time in both treatment groups is presented below:

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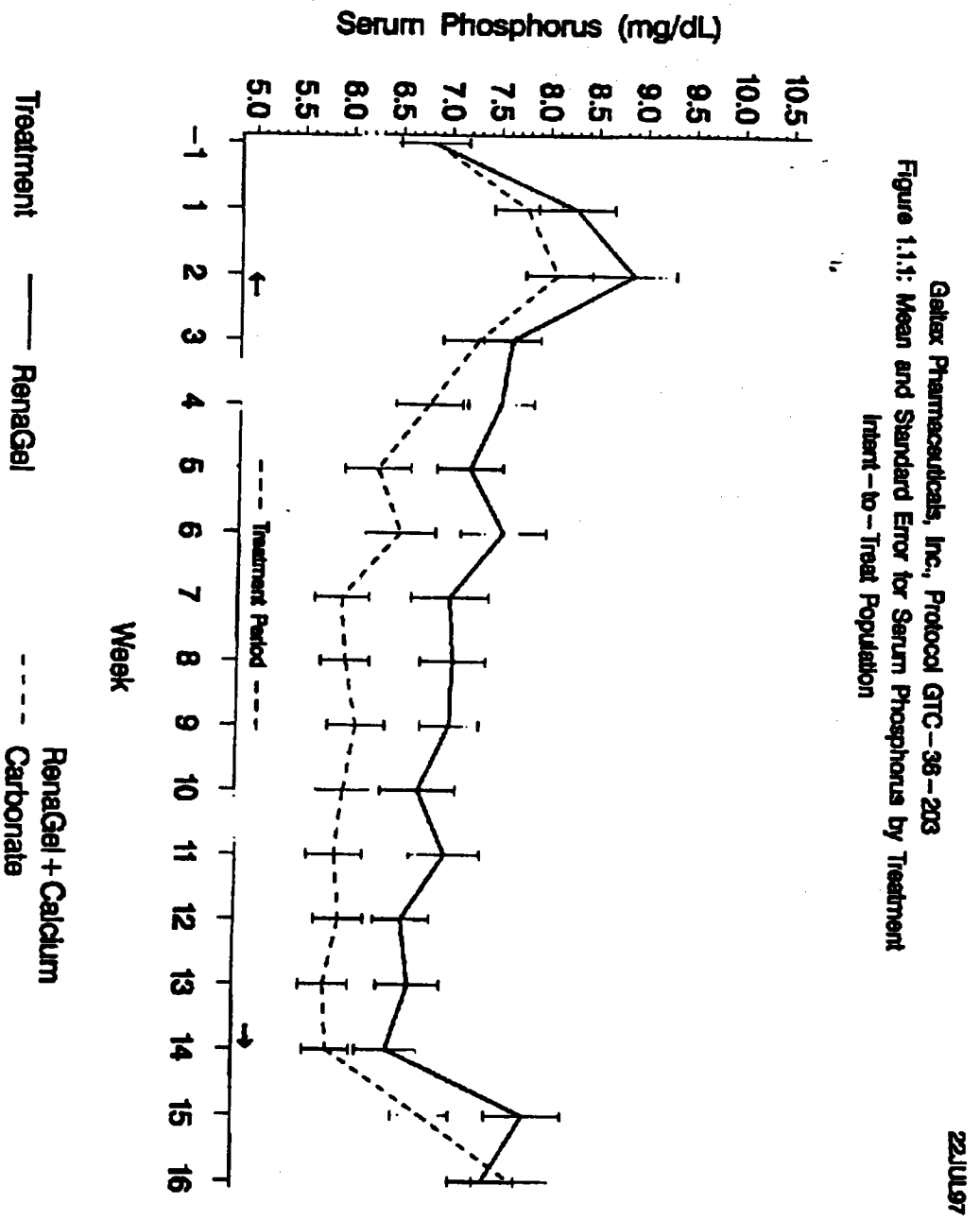

Geltex Pharmaceuticals, Inc., Protocol GTC-36-203

Figure 1.1.1: Mean and Standard Error for Serum Phosphorus by Treatment
Intent-to-Treat Population

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Serum calcium: The serum calcium levels did not change from baseline in the RenaGel treatment group (9.4 mg/dl at baseline and at end of treatment). However, the serum calcium levels increased from 9.4 at baseline to 9.7 at the