

**Comments: The reductions in total and LDL cholesterol are statistically and clinically significant and appear to be consistent across studies.**

#### **8.2.5.4.3 Safety outcomes**

In the safety population, the incidence and nature of treatment-emergent adverse events was similar to those that have been reported in the other clinical trials submitted to the NDA. The sponsor has made statistical comparisons of the incidence of specific AE's between the two treatment arms of this trial.

Overall most of the AE's encountered in this trial affected the digestive system, with 36 adverse events among 20 patients (54.1%) in the RenaGel treatment group and 50 adverse events among 25 patients (65.8%) in the RenaGel with calcium carbonate treatment group ( $p=0.3506$ ). There was an increased incidence of nausea in the RenaGel with calcium carbonate treatment group compared to the RenaGel group (12 AE's in 10 patients, compared with 2AE's in 2 patients,  $p=0.0245$ ). Other treatment-emergent GI events with no difference in incidence between groups were: vomiting, dyspepsia, constipation, and diarrhea. The incidence of these events was similar to that found in other trials within the NDA, and ranged from 5% to approximately 20% of patients. The digestive AE's were mostly mild in intensity. Nausea was severe for only one patient (2.6%), in the RenaGel with calcium carbonate group.

There were no hypercalcemic events in the RenaGel treatment group, and there were 2 hypercalcemic events among one patient (2.6%, both judged to be of mild intensity) in the RenaGel with calcium carbonate group ( $p=1.0000$ ). These results are different from those presented in the efficacy analysis, because there was no carry-forward approach used in the safety analysis.

During treatment there were 9 serious AE's occurring among 5 patients in the RenaGel group and 14 serious AE's among 9 patients in the RenaGel with calcium treatment group. None of the serious AE's was judged to be related to treatment.

**Laboratory values:** Throughout the study, there were no clinically significant changes in means of any of the battery of laboratory tests. In particular, the serum chloride, CO<sub>2</sub>, magnesium, iron, IBC, BUN, creatinine, AST, ALT, LDH, bilirubin, alkaline phosphatase, albumin, or globulin.

**Hematology:** Throughout the study, there were no changes in mean hematocrit, hemoglobin, or indices. The WBC fell by 0.7 thousand/ mL (from 7.7 thousand,  $p=0.0300$ ) during treatment with RenaGel. Cessation of treatment at week 14 was followed by an increase of 0.4 thousand/mL. For the RenaGel plus calcium treatment arm, there was no change in the WBC during treatment. Within the WBC series, there was no change in neutrophil, lymphocyte, monocyte, or eosinophil count in either treatment arm. There was a slight fall in basophil count

in the RenaGel treatment group, but the change was within the normal range. Platelet count did not change significantly during treatment in either treatment group.

PT, PTT, Vitamins A, D, and E: There were no changes in PT or PTT during treatment, in either arm of the study. There was a small, significant increase in Vitamin A, but only in the RenaGel group. In the other group, the mean vitamin A level did not change during treatment. In both groups, the mean vitamin A levels were well above the normal range.

The levels of 25-hydroxy vitamin D did not change in patients who were using oral vitamin D supplementation. However, for patients not using a vitamin D supplement and for patients using an intravenous vitamin D supplement, there were statistically significant declines in levels of 25-hydroxy vitamin D in both treatment groups during the treatment period (Week 2 to 14). In the RenaGel treatment group, mean levels decreased 14.5 ng/mL (from 31.7 ng/mL,  $p=0.0059$ ) for patients not using a vitamin D supplementation and decreased 8.1 ng/mL (from 30.9 ng/mL,  $p=0.0391$ ) for patients using an intravenous vitamin D supplementation. In the RenaGel with calcium carbonate treatment group, mean vitamin D 25-hydroxy levels decreased 11.9 ng/mL (from 33.6 ng/mL,  $p=0.0156$ ) for patients not using vitamin D supplementation and decreased 9.9 ng/mL (from 27.7 ng/mL,  $p=0.0020$ ) for patients using an intravenous vitamin D supplementation.

Levels of 1,25-dihydroxy vitamin D did not significantly change during treatment with RenaGel or with RenaGel plus calcium carbonate. Levels of 1,25-dihydroxy vitamin D did not significantly change by vitamin D usage.

Levels of vitamin E declined during RenaGel treatment ( decrease of 2.0 mcg/mL  $p=0.0366$ ), but not during RenaGel with calcium treatment.

Digoxin levels were measured during treatment in 5 of the 7 concurrent users of cardiac glycosides. There were no changes in digoxin levels for any of these patients.

Individual listings of laboratory data and all adverse events are provided in the Appendix of the NDA. In addition, summary tables are displayed in the Appendix.

**Comments:** There were no safety issues raised during this study. The serious adverse events appeared to be unrelated to RenaGel use. The small changes seen in chloride and CO<sub>2</sub> concentrations in other trials were not seen in this study. There were no significant changes in levels of fat-soluble vitamins, with the exception of 25-hydroxy vitamin D in patients who were not using oral vitamin D supplementation. These declines in 25-hydroxy vitamin D levels were not reflected in reductions in 1,25-dihydroxy vitamin D levels, however. This may have been due to

concurrent use of oral 1,25-dihydroxy vitamin D or possibly to increased renal 1 $\alpha$ -hydroxylase activity caused by the reduction in serum phosphorus.

#### **8.2.5.5 Conclusions regarding efficacy data**

The primary efficacy endpoint was reduction in serum phosphorus. In this uncontrolled study, both treatment groups, RenaGel and RenaGel plus an evening dose of calcium carbonate, experienced significant reductions in mean serum phosphorus during the 12-week treatment period. The mean reduction in serum phosphorus, approximately 2.0 mg/dl, was consistent with that which was observed throughout all the clinical trials. In this study, patients treated with RenaGel plus calcium reached pre-washout levels earlier than did those treated with RenaGel alone. This is consistent with the known effects of calcium. Following treatment, there was a statistically significant increase in serum phosphorus in both treatment groups, supporting the conclusion that the reductions in serum phosphorus were due to treatment with RenaGel.

For unexplained reasons, the serum phosphorus levels were lower in the RenaGel with calcium carbonate group compared to the RenaGel group at baseline. However, the magnitude of the reductions in serum phosphorus was the same with both treatments. After 12 weeks of treatment, RenaGel reduced serum phosphorus levels 2.4 mg/dL from 8.9 mg/dL and RenaGel with calcium reduced serum phosphorus 2.3 mg/dL from 8.1 mg/dL.

Using the sponsor's definition (achieving either the patient's pre-washout serum phosphorus level or to 5.5 mg/dL), 94.3% of the patients in the RenaGel treatment group and 94.4% of the patients in the RenaGel with calcium carbonate treatment group responded to therapy. However, as indicated repeatedly above, this definition of response is clinically meaningless and potentially misleading.

The calciumXphosphorus ion product was reduced significantly in both treatment groups. There were no differences in the reductions in ion product between treatment groups.

RenaGel alone did not significantly reduce the mean PTH levels. Patients receiving RenaGel plus calcium had a mean reduction in serum PTH of 89.7 pg/ml, from 377.4 pg/ml. While this reduction was statistically significant, the clinical significance of the change is doubtful.

In summary, the mean phosphorus levels were statistically significantly reduced, in both RenaGel treatment arms, from baseline.

The secondary efficacy goal of the study was a change in serum lipids. As in other studies in the NDA, RenaGel treatment was associated with a

significant decline in total and LDL cholesterol. The magnitude of the reductions in these lipid moieties was essentially the same as those found in other trials submitted to the NDA. There was no effect of treatment on mean HDL cholesterol or triglyceride concentrations. The addition of calcium carbonate to the RenaGel regimen did not alter the observed changes in serum lipids.

## **8.2.6 Reviewer's trial # 8 Sponsor's protocol # GTC-36-901**

### **8.2.6.1 Objectives**

This was an extended use study of 48 weeks' duration.

The primary objectives were to:

1. confirm the safety of extended treatment with RenaGel in hemodialysis patients, and
2. confirm the efficacy of extended treatment with RenaGel in lowering serum phosphorus in hemodialysis patients.

The secondary objectives were to:

1. determine the effect of extended treatment with RenaGel on lipid profiles in hemodialysis patients, and
2. determine the effect of extended treatment with RenaGel on intact parathyroid hormone levels in hemodialysis patients.

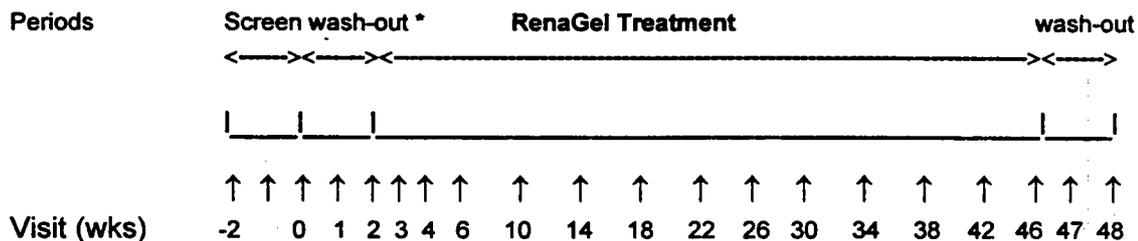
### **8.2.6.2 Design**

This was an open-label, uncontrolled, extended use, multi-center (24 centers) study of RenaGel in hemodialysis patients who had completed a prior RenaGel dose-titration study. Following screening, patients underwent a 2-week washout period to ensure that they were hyperphosphatemic without the use of phosphate binders. The post-washout phosphorus concentration was used as a baseline for comparison. The starting dose of RenaGel was based on the patient's previous RenaGel experience, dietary phosphorus intake, and the investigator's clinical judgement. During the study, the dose of RenaGel could be titrated to maintain a serum phosphorus level between 2.5 mg/dL and 5.5 mg/dL. An evening dose of calcium (900-1500 mg of elemental calcium was suggested; calcium carbonate or acetate were used) was added at the discretion of the investigator, or if the serum calcium level declined.

Safety was evaluated as previously described for the other trials. Adverse experiences (reported and/or observed), changes in physical examination, and changes in laboratory test values were all closely and repeatedly monitored

(laboratory values included serum chemistry, hematology, PT and PTT, and serum levels of vitamins A, D and E). Baseline was defined as the assessment on, or immediately before the RenaGel start date in the prior RenaGel study, while the final assessment was defined as the assessment on or immediately before the RenaGel stop date in this study. For patients who did not terminate early, the RenaGel stop date was defined as May 1, 1997 for the interim analysis.

The primary efficacy outcome was based on change 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. A schematic of the study design is presented below:



\* The initial wash-out may represent the final two weeks of the prior RenaGel study. In that case, the final physical examination and blood test from the prior study may serve as the baseline for the current study.

**Comments:** The study paradigm is the same as that which is found in most of the clinical trials submitted to this NDA, except that the treatment period is 44 weeks. The safety and efficacy outcome variables are essentially the same as in the other trials. Since there is no control arm in this study, the overall interpretation of the safety data is based on analysis of dose effects to some extent on clinical judgement. Separate analyses of the safety, intent-to-treat, and per-protocol populations constitute an important aspect of interpretation of the outcomes in this long-term study. It is important to characterize the nature of the population that was recruited into the study, in order to determine whether selection bias played a role in the outcomes (these were patients who had successfully completed one of three protocols).

### 8.2.6.3 Protocol

#### 8.2.6.3.1 Population/procedures

Patients were eligible for inclusion in the study if they had completed one of the following 4 protocols: GTC-10-202, GTC-36-203, GTC-36-301, or GTC-36-302.

Exclusion/exclusion criteria are presented by the sponsor and are essentially the same as for the other protocols.

**Comments:** Patients with a history of several gastrointestinal disorders (detailed above in the other clinical trials), including GI motility disorders, were excluded from the four prior trials. Although GI disorders are not specifically mentioned as exclusionary criteria for this study, it is assumed that the study admitted no patients with such histories. This is important, because the safety and efficacy of RenaGel in patients with GI motility disorders will not be established in this clinical trial.

**Procedures:** The procedures for this trial were essentially the same as in the other clinical studies. Following screening physical examinations and baseline laboratory tests, patients entered the first 2-week phosphate binder washout period. Hyperphosphatemic patients then entered the 44-week RenaGel treatment period. The starting dose of RenaGel was based on the serum phosphorus level. Throughout the remainder of the study (roughly every 4 weeks) the RenaGel dose was adjusted by the investigator to try to achieve a target serum phosphorus level of 2.5-5.5 mg/dl. A schedule of the laboratory procedures throughout the entire study is shown in the table below.

#### First Washout Period

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

#### Treatment Period

Week	Tests
3	Phosphorus and calcium
4	Phosphorus and calcium
6	Phosphorus and calcium
10	Chemistry profile PTH Hematology profile PT/PTT Vitamins A, D, and E
14	Phosphorus and calcium

18	Chemistry profile PTH Hematology profile PT/PTT Vitamins A, D, and E
22	Phosphorus and calcium
26	Chemistry profile PTH Hematology profile PT/PTT Vitamins A, D, and E
30	Phosphorus and calcium
34	Chemistry profile PTH Hematology profile PT/PTT Vitamins A, D, and E
38	Phosphorus and calcium
42	Phosphorus and calcium
46	Chemistry profile PTH Hematology profile PT/PTT Vitamins A, D, and E

APPEARS THIS WAY  
ON ORIGINAL

**Second Washout Period**

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

APPEARS THIS WAY  
ON ORIGINAL

As in the other studies, RenaGel was administered with meals. The patients maintained their normal dialysis schedules and diets. If patients were receiving vitamin D, the dose of the vitamin was to remain stable throughout the study, if possible.

**Comments:** The laboratory parameters are essentially the same as in the prior clinical studies. The scheduling of laboratory examinations, as well

as the tests themselves, are appropriate for the safety and efficacy analyses.

#### **8.2.6.3.2 Endpoints**

The safety and efficacy endpoints were the same as in the prior studies. For safety and efficacy outcomes, the effects of RenaGel dose were analyzed separately. The definitions of populations to be analyzed, the parameters measured, and the planned statistical comparisons remain unchanged from those employed in the earlier clinical trials and will not be reiterated here.

**Comments: The endpoints are clear, easily measured, and appropriate. As in other studies, analysis and presentation of individual safety and efficacy data (as opposed to means) would give a clearer picture of the clinical utility of this drug. This issue is discussed in further detail below.**

#### **8.2.6.3.3 Statistical considerations**

In keeping with the above comments, the Statistics review has focused on analysis of individual efficacy and safety data. This analysis appears in the Statistics review, but selected portions are presented in the Medical review because of clinical importance.

#### **8.2.6.4 Results**

##### **8.2.6.4.1 Populations enrolled/analyzed**

A total of 195 patients were enrolled, and 3 were dropped during the first washout period (one protocol violation, one withdrawn consent, one lost to follow-up). One hundred ninety-two patients entered RenaGel treatment, and 123 completed the study. Of the 69 who terminated from the study early, 25 discontinued due to adverse events, 3 of which were judged to be possibly related to RenaGel: nausea, rash, and diarrhea. There were 12 deaths, judged unrelated to RenaGel. The remainder were dropped because of withdrawn consent, protocol violations, and "other" reasons.

For the safety population, the demographics were representative of the patients in other clinical trials: the mean age was 56.1 years. 62.5% of the patients were male and 37.5% were female. 54.2% were African-American; 35.4% were Caucasian, 7.3% were Hispanic, 2.1% were Asian, and 1.0% were classified as "other" race.

The primary causes of ESRD were hypertension (33.9%), diabetes (29.7%), nephritis (14.1%) polycystic kidney disease (2.6%) and "other (19.8%).

**Comments: As expected, the demographics and medical histories are essentially the same as in the earlier studies. The completion rate of this 48-week study was over 60%, and the withdrawals do not appear to be due to an ill-effect of the drug. Judging from the numbers enrolled, it appears**

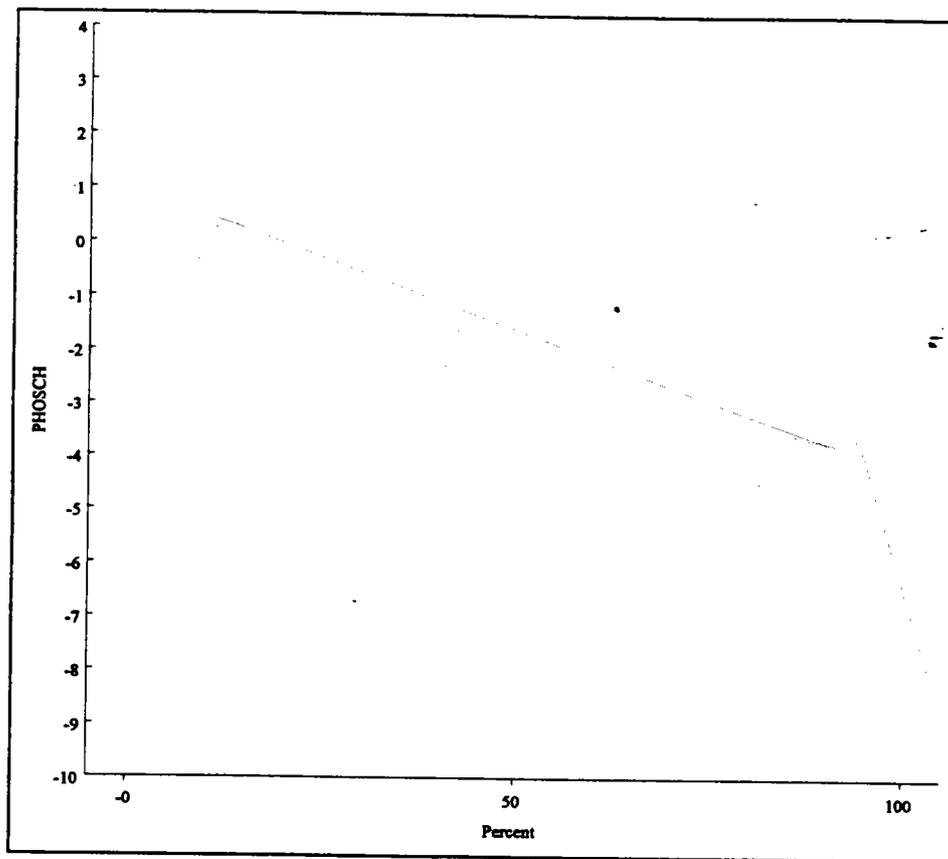
that the preponderance of patients who were offered entry into the trial accepted. However, it is unclear whether there was any subtle selection bias in the direction of more compliant patients or patients who had experienced fewer side effects of the drug in earlier studies.

#### 8.2.6.4.2 Efficacy endpoint outcomes

Serum phosphorus: decreased 2.2 mg/dL (from 8.7 mg/dL,  $p < 0.0001$ ) from 6.5 mg/dL. Among the 3 RenaGel dose groups, there was a significant trend ( $p = 0.0460$ ) toward greater serum phosphorus reductions at the highest dose. Cessation of RenaGel treatment at Week 46 was followed by an increase in mean serum phosphorus of 1.7 mg/dL ( $p < 0.0001$ ) at the end of the second washout.

**Comments:** The mean changes in serum phosphorus levels are entirely consistent with the results of the earlier clinical trials. The data show that this effect is not diminished in magnitude after 44 weeks of therapy with RenaGel. However, it should be emphasized that these data represent the mean for the population. When analyzed individually or categorically, the results appear somewhat less impressive. As shown below, only 50% of the evaluable population achieved a decline in serum phosphorus  $\geq 2.0$  mg/dl by the end of the study. Of interest, the distribution of response at 44 weeks appears to be the same as that found at 8 weeks in the 301 crossover study (shown in our figure in the analysis of the 301 study above), suggesting that the response rate within the population remains stable over 44 weeks.

APPEARS THIS WAY  
ON ORIGINAL



**GTC-36-901** Cumulative per cent of patients (x-axis) who attained a phosphorus change, from baseline to final, that was at least as great as the corresponding point on the y-axis. Data points represent individual patients. 50% of patients achieved a change of -2 mg/dl. About \_\_\_\_\_ had no change or an increase, and approximately the same percent had a decrease of 6mg/dl or more.

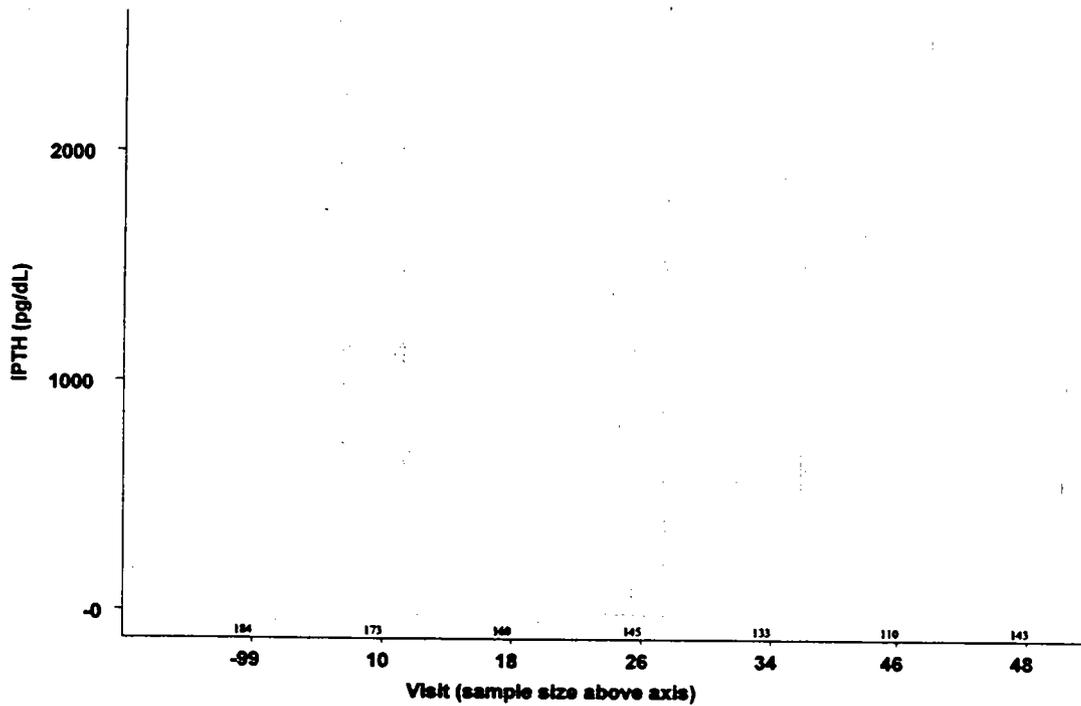
**Serum calcium:** During the study, there was a statistically significant increase in the mean serum calcium from baseline to final, of 0.3 mg/dl (from 9.1 mg/dl,  $p < 0.0001$ ). There was no significant trend among the 3 RenaGel dose groups.

**PTH:** There was no significant change overall in mean serum PTH concentrations from baseline to final assessment. There was a statistically significant trend among the 3 dose groups. However, the greatest decline, in the low dose group, was 53 pg/ml (from 293 pg/ml), and the high dose group experienced an increase in PTH levels of 71.2 pg/ml, from 491 pg/ml.

The overall median PTH levels decreased by 18 pg/ml (from 286 pg/ml). The greatest decrease was in the low dose group (55 pg/ml, from 216 pg/ml). The

medium dose group decreased by 16.5 pg/ml, and the high dose group increased by 10 pg/ml, from 343 pg/ml.

A boxplot depicting the median and inter-quartile ranges for PTH levels throughout the course of the study is shown below.



Boxplots for the same data grouped by RenaGel dose group (D level) are shown below:

APPEARS THIS WAY  
ON ORIGINAL



Calcium x phosphorus ion product: decreased significantly overall, from baseline to the final assessment, by 18.1. (from 78.4 p<0.0001). There was no significant trend among the three dose groups. Cessation of RenaGel at Week 46 was followed by a statistically significant increase of 15.4 (p<0.0001) at the end of the second washout.

Lipids: There were significant reductions in total and LDL cholesterol, from baseline to the final assessment. The overall mean total cholesterol decreased 27.9 mg/dL (from 175.3 mg/dL, p<0.0001). There was no significant trend among the three dose groups. Cessation of RenaGel treatment at Week 46 was followed by a statistically significant increase in total cholesterol of 24.6 mg/dL (p<0.0001). LDL cholesterol decreased 31.5 mg/dl (from 106.5 mg/dl, p<0.0001). There was no significant trend among the 3 dose groups. Following cessation of RenaGel at Week 46, the LDL cholesterol increased significantly by 26.8 mg/dl (p<0.0001).

The HDL cholesterol increased significantly during this period, by 5.9 mg/dl overall (from 36.4 mg/dl, p<0.0001). There were no significant changes in triglycerides.

**Comments: The reductions in total and LDL cholesterol are statistically and clinically significant and replicate the data from earlier trials. This study shows that these reductions are maintained over a 44-week period.**

#### **8.2.6.4.3 Safety outcomes**

An extensive analysis of all adverse events is provided in the Appendix of the NDA. For the safety population of 192 patients, there were 1006 treatment-emergent adverse events among 55 patients (96.5%) in the low dose group, 826 events among 48 patients (100.0%) in the medium dose group, and 1,423 events among 84 patients (96.6%) in the high dose group. There was no statistically significant linear trend across dose levels in the proportion of patients experiencing any treatment emergent adverse event (p=0.9074).

The following treatment-emergent adverse events showed significant linear dose trends, in which a higher incidence of events was observed at higher doses of RenaGel: hypochromic anemia, (2 medium dose and 8 high dose patients), cough (9 low dose, 10 medium dose, and 27 high dose), and cardiovascular disorder (1 low dose, 1 medium dose, and 10 high dose).

The number of patients with treatment-emergent adverse events judged by the investigator to be possibly or probably related to treatment is shown in the table below (data taken from the Appendix):

## NUMBER OF PATIENTS

INTENSITY	LOW DOSE	MEDIUM DOSE	HIGH DOSE
mild	4	8	8
moderate	5	7	13
severe	0	1	3

The 4 severe events were: pulmonary embolism, flatulence, a "gastrointestinal disorder" and hypercalcemia.

As in other studies, the digestive system had the greatest number of adverse events: 15 patients (7.8%) had a mild treatment related adverse event, 16 patients (8.3%) had a moderate event, and 2 patients (1.0%) had a severe treatment related adverse event. The most common treatment-related digestive system adverse events were: diarrhea (5 mild and 3 moderate), dyspepsia (6 mild and 3 moderate), flatulence (4 mild, 3 moderate, and 1 severe), nausea (6 mild and 8 moderate), and vomiting (2 mild and 5 moderate).

Serious adverse events: Overall, there were 164 serious adverse events observed among 84 patients (44.8%) during the RenaGel treatment period. However, no serious adverse event was judged by the investigators to be possibly or probably related to treatment. The most frequent serious events occurred in the cardiovascular system; myocardial infarction (9 patients, 4.7%), angina pectoris (4 patients, 2.1%), congestive heart failure (4 patients, 2.1%), and thrombosis (4 patients, 2.1%). Other serious adverse events occurred mainly in the "body as a whole" category: 49 such events occurred among 38 patients (19.8%) during the treatment period. These included: sepsis in 9 patients (4.7%), infection in 8 patients (4.2%), accidental injury in 7 patients (3.6%), and chest pain in 5 patients (2.6%).

No patients had serious hypercalcemia, hypocalcemia, or hyperphosphatemia during the treatment period.

There were 16 deaths during the entire treatment period. All were judged unrelated to RenaGel. The causes of death were sepsis, myocardial infarction, stabbing, renal carcinoma, necrosis of the foot, and "natural causes." One patient died of pneumonia, atrial fibrillation, GI hemorrhage, and intestinal obstruction.

**Comments:** This 86-year-old male had a history of arteriosclerotic heart disease, congestive failure, and cerebrovascular accident. The nature of

the GI complications is not given in detail in the Appendix. GI bleeding accompanied two other deaths in this group of patients; however, the bleeding occurred in the setting of failure of other organ systems (cardiovascular and respiratory). GI bleeding also accompanied other serious, mainly cardiovascular, adverse events. However, GI bleeding is common in this patient population, and it is unlikely that these events were due to RenaGel.

**Overall comments on adverse events:** It is not possible to compare the adverse event numbers with a concurrent group of patients, since the study lacked a control. The overall mortality rate for the RenaGel-treated patients (16 deaths per 192 patients = approx. 8 %) is lower than that which is commonly found in hemodialysis patients. In reviewing the case histories of the serious adverse events and deaths, it does not appear likely that RenaGel exposure was a contributing factor.

Laboratory values:

Phosphorus, calcium, CaXP ion product, lipids and PTH: changes are described above, in the efficacy outcomes section.

No clinically significant changes were seen in mean sodium or potassium concentrations.

The mean serum chloride concentration increased by 1.3 meq/L, from 99.5. There was no trend among the 3 dose groups. Cessation of RenaGel at Week 46 resulted in a decrease in chloride of 1.8 meq/L. The CO<sub>2</sub> content increased 1.3 meq/L (from 17.1 meq/L). There was a significant trend among the 3 dose groups. Cessation of RenaGel treatment at Week 46 resulted in an increase in CO<sub>2</sub> content of 0.8 meq/L.

Total iron, TIBC, Iron saturation, and ferritin: Mean total iron increased by 16.9 mcg/dL (from 75.8 mcg/dL,  $p=0.0030$ ) from baseline to final, with no significant trend among the three dose groups. The TIBC did not change significantly. There was a small increase in iron saturation (mean increase of 5.7%, from 26.6%,  $p=0.0001$ ). The mean ferritin increased 139.8 ng/mL (from 275.0 ng/mL,  $p<0.0001$ ). The mean final ferritin level was above the normal range.

**Comments:** the few cases of hypochromic anemia alluded to above in the linear dose trend effect are not reflected in similar changes in mean iron-related parameters.

Hepatic function: There were no changes in mean levels of ALT, AST, LDH, bilirubin, protein globulin, or albumin. The mean alkaline phosphatase level increased by 32.3 U/L, from 93.1. Cessation of RenaGel at Week 46 was

followed by a decrease of 4 U/L. The mean levels were within normal limits, and there was no trend among the 3 treatment groups.

Renal function: The BUN and creatinine levels both decreased slightly during RenaGel treatment.

Hematology: The mean hematocrit did not change. The hemoglobin decreased by 0.2 g/dL (from 10.8,  $p=0.0315$ ). There was no significant trend among the 3 treatment groups. The RBC count did not change during the study. The MCV increased slightly, the MCH did not change, and the MCHC decreased by 0.4%, from 33.1%,  $p<0.0001$ . These levels were within normal limits, and there was no trend among the 3 treatment groups.

No clinically significant changes in any of the leukocyte series were seen.

There were significant changes in mean platelet counts, with the following decreases seen: Mean platelet count decreased by 17328 per cu mm (from 221104,  $p<0.0001$ ). There was a significant trend among the 3 dose groups ( $p=0.0239$ ): low dose group fell by 8245/cu mm; medium dose, by 14791; and the high dose group, by 24678. These values were all within the normal range and were not considered clinically significant by the sponsor.

**Comments: This represents nearly a 10% drop in overall platelet count, with a significant trend among the 3 dose groups. There are no individual reports of thrombocytopenia, however, in this or in any of the other clinical trials.**

PT, PTT, Vitamins A, D, and E: The mean PT and PTT did not change during RenaGel treatment. Overall, mean vitamin A decreased by 14.6 mcg/dL (from 171,  $p=0.0085$ ). The means were above the normal range for vitamin A, and there was no significant trend among the 3 dose groups.

25-hydroxy vitamin D levels decreased by 6.5 ng/ml (from 32.7 ng/ml,  $p<0.0001$ ). These levels were within the normal range. The sponsor suggests that this change was secondary to seasonal effects, but provides no supporting evidence for this. However, a table, provided by the sponsor, shows that the mean 25-hydroxy vitamin D levels fell early in the study and appeared to increase slightly over time:

APPEARS THIS WAY  
ON ORIGINAL

**25-hydroxy vitamin D levels, ng/ml**

VISIT	N	MEAN	STD DEV
-1	52	31.3	23.0
2	60	29.8	20.2
10	172	23.7	17.6
18	154	25.5	18.0
26	143	27.4	18.8
34	131	29.0	18.4
46	111	28.0	19.2
Baseline*	156	32.7	20.2
Final*	192	26.9	18.7
Change**	156	-6.5	16.2

\*Baseline and final lab assessments were taken on or immediately before the original RenaGel start date and GTC-45-901 stop dates, respectively.

\*\*p-value < 0.0001

1,25-dihydroxy vitamin D levels: increased 6.9 pg/mL (from 11.6 pg/mL, p<0.0001). There was a significant trend among the three dose groups (p=0.0473) with greater elevations found at lower doses of RenaGel. These values are below the normal range for 1,25-dihydroxy vitamin D. Greater increases in levels of the vitamin were associated with an increase in use of 1,25-dihydroxy vitamin D.

Vitamin E levels decreased by 1.0 mcg/ml (from 14.6, p<0.0001). Cessation of RenaGel treatment was followed by a further decrease of 1.3 mcg/mL. There was no significant trend among the 3 dose groups.

**Comments: a small reduction in vitamin E may accompany the decreases in LDL cholesterol. The increases in 1,25-dihydroxy vitamin D may have been due to increased supplementation. However, the values at baseline and after 44 weeks of treatment remained below the normal range. Low values of 1,25-dihydroxy vitamin D are found in renal failure, unless the patients are given vitamin supplementation. It is not clear how many of this cohort of patients had been supplemented with 1,25-dihydroxy vitamin D prior to the extension study, and/or whether the prior RenaGel therapy may have interfered with the absorption of the vitamin supplement.**

**8.2.6.5 Conclusions regarding efficacy and safety outcomes of extension study**

This extension study demonstrated that the hypophosphatemic effect of RenaGel, as determined by the changes in mean phosphate levels from baseline to final, persisted over 44 weeks of treatment. In addition, the favorable effects on total and LDL cholesterol also persisted for the duration of the study. The declines in serum total cholesterol, LDL cholesterol, and phosphate levels were similar in magnitude to those observed in prior clinical trials.

As discussed above, a decline in mean phosphate level does not mean that all patients responded to the drug. A realistic assessment of the response rate is given by the cumulative frequency distribution presented in the figure that we have included in the efficacy analysis above.

It is difficult, if not impossible, to assess clinical and laboratory-related adverse events in an uncontrolled study using a population that has a high background of serious illness and multiple medication use. In this study, there were no obvious clusters of adverse events that could plausibly be related to RenaGel treatment, nor were there any statistically significant linear dose trends for individual treatment-related adverse events or for adverse events affecting any body system category. The only adverse events that were probably or possibly related to RenaGel were mild and in the gastrointestinal system.

APPEARS THIS WAY  
ON ORIGINAL

### OVERALL SUMMARY

#### 9 Overview of efficacy

Eight studies have been submitted to this NDA in support of the use of RenaGel in ESRD patients on hemodialysis. Two studies were conducted in healthy volunteers and six clinical trials have been concluded in ESRD patients. The eight studies are tabulated below:

APPEARS THIS WAY  
ON ORIGINAL

PHASE I	DESIGN	OBJECTIVE	NUMBER TREATED WITH RENAGEL
GTC-02-101	Randomized, placebo controlled Normal volunteer	Safety and pd	24

GTC-02-801	Open-label, normal volunteer	RenaGel absorption	20
<b>PHASE II</b>			
GTC-10-201	Randomized, placebo-controlled	Efficacy and safety	24
GTC-10-202	Open-label, dose titration	Efficacy and safety	48
GTC-36-203	Randomized, open-label dose titration	Efficacy, safety, and effects of calcium supplementation	75
<b>PHASE III</b>			
GTC-36-301	Randomized, open-label, cross-over comparison with calcium acetate	Efficacy and safety	82
GTC-36-302	Open label dose titration	Efficacy and safety	172
GTC-36-901	Open label extension study	Long-term safety and efficacy	192 (TAKEN FROM ABOVE STUDIES)

**Phase I studies:**

The first two (phase I) studies demonstrated that RenaGel is not systemically absorbed and that the drug is capable of reducing urinary phosphorus excretion (presumably by binding dietary phosphate in the intestine) in normal volunteers.

GTC-02-101 was a randomized, double-blind, placebo-controlled parallel-design, multiple dose study in normal subjects. Subjects were randomized to receive either RenaGel or placebo. All subjects were kept on a phosphate-controlled diet designed to provide 1.2 g of elemental phosphate/day. Blood, urine, and feces were collected during baseline and treatment periods. The data showed that RenaGel significantly reduced the mean 24-hour urinary phosphate excretion in a dose-related manner. There was a trend toward increased fecal phosphate excretion during treatment (indicating decreased dietary phosphate absorption), but this did not reach statistical significance. There was no clinically significant increase in clinical or laboratory adverse events in this study. An unanticipated result of this study was a reduction in total and LDL cholesterol in the RenaGel-treated group. This became an efficacy outcome in subsequent clinical trials.

GTC-02-801 was conducted to determine whether RenaGel is systemically absorbed. In this study \_\_\_\_\_ RenaGel was given to normal volunteers. Subjects were given \_\_\_\_\_ RenaGel for 28 days and then dosed with \_\_\_\_\_ RenaGel p.o. During the day of administration of the radioactivity and for several days thereafter, blood, urine, and feces were collected \_\_\_\_\_. Blood and fecal \_\_\_\_\_ were \_\_\_\_\_. Although there was no standard curve provided to validate the recovery efficiency of \_\_\_\_\_ from blood samples, the data showed that virtually all of the administered \_\_\_\_\_ was excreted in the stool \_\_\_\_\_.

---

---

The conclusion of this study, that RenaGel is not systemically absorbed in normal humans, was justified by the data. No RenaGel absorption studies were performed in patients with ESRD.

There were no safety issues raised in either of the phase I studies.

In the six clinical trials, slightly over 400 patients were exposed to RenaGel, for periods ranging from 2 to 44 weeks. All patients were on hemodialysis for ESRD. The demographics, renal histories, general medical histories, and total size of the study population provide an adequate representation of the intended treatment population.

#### **Phase II-III studies:**

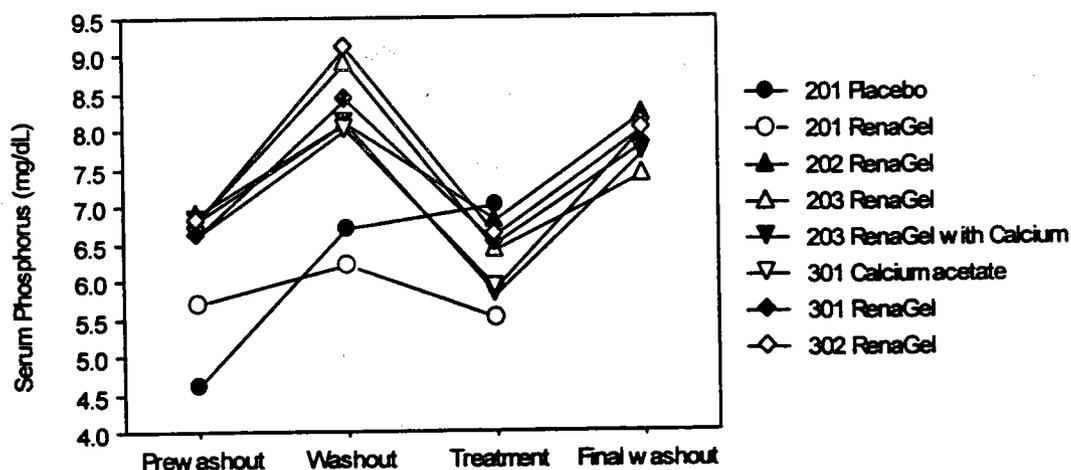
RenaGel was developed to bind dietary phosphate in the GI tract, thus reducing the serum phosphorus concentration in patients with ESRD. Therefore, a change in the serum phosphorus was the principal efficacy endpoint of all the clinical trials. Of the clinical trials, one (GTC-10-201) was double-blind and placebo-controlled. In this study, patients were exposed to RenaGel for 2 weeks. Another (GTC-36-301) was a larger, phase III clinical trial that compared RenaGel to calcium acetate, using an open-label crossover design. This study exposed patients to RenaGel for weight weeks. The four other studies were open-label uncontrolled clinical trials.

Throughout the studies, the primary efficacy outcome was a change in the serum phosphorus concentration from baseline to the end of the study. The experimental paradigm involved taking patients off their usual phosphate binder therapy for two weeks. Those patients who achieved serum phosphorus levels of 6.0 or greater were then eligible to enter the treatment phase of the study. Throughout the treatment phase, serum chemistries were repeatedly measured. Following the treatment phase, the patients were taken off RenaGel for two weeks, after which the battery of tests was repeated. This "off-on-off" protocol was necessary because extended placebo-controlled trials were medically

unsound. Dietary phosphate intake was closely monitored by recall interviews and diaries throughout the studies.

In all the studies, the overall intent-to-treat and per-protocol populations showed a statistically significant decline in the mean serum phosphorus level. The magnitude of the decline was about 2.0 mg/dl. Furthermore, the serum phosphorus rose again following the second two-week washout period. There was no evidence that the changes in serum phosphorus were due to alterations in dietary phosphate intake. Thus, although most of these studies were uncontrolled and open-labeled, the aggregate data demonstrate that RenaGel therapy can lower the mean serum phosphorus concentrations.

The following figure, taken from the NDA, shows the changes in mean phosphorus levels across the five clinical trials. In all the studies, the mean serum phosphorus levels rose during washout, declined significantly with RenaGel (or calcium acetate) therapy, and rose again upon withdrawal of RenaGel. The only exception to this was the placebo group in the 201 study, in which the phosphorus level increased during the treatment period.



In these studies the greater the washout serum phosphorus level, the greater the reduction in phosphorus with treatment. RenaGel treatment lowered the mean serum phosphorus to pre-washout levels or slightly below, in all the studies. The only exception was the placebo group in the 201 study, in which the phosphorus level increased over prewashout level during the treatment phase.

While the mean serum phosphorus concentrations changed in the expected directions in all the studies, it should be emphasized that not all patients responded to RenaGel. In most of the studies, the claim is made that the responder rate is as high as 80-90%. However, as discussed above, this is dependent on a definition of "responder" that includes an individual who, at any time during the course of RenaGel treatment, achieves a phosphorus level of 5.5 mg/dl or returns to a pre-washout serum phosphorus, even if the pre-washout phosphorus level is elevated.

While any definition of responder is arbitrary, such a definition should carry some clinical meaning. For example, the achievement of one normal serum phosphorus level during an eight-week trial may or may not be clinically meaningful, depending on the phosphorus levels achieved throughout the remainder of the trial. If a single phosphorus level is used to define the responder endpoint, and if that level is determined at the end of the study, as the sponsor has done, then a clearer impression of responder rate can be obtained from a cumulative distribution plot, which we have generated below. The data used in the generation of this plot were taken from results of the GTC-36-301 study, in which RenaGel was compared to calcium acetate, in a cross-over design. This was the pivotal phase III study in the NDA. This figure displays the proportion of patients (y-axis) achieving a reduction in serum phosphorus (from baseline to final) that was at least as large as the corresponding value on the x-axis.

**APPEARS THIS WAY  
ON ORIGINAL**

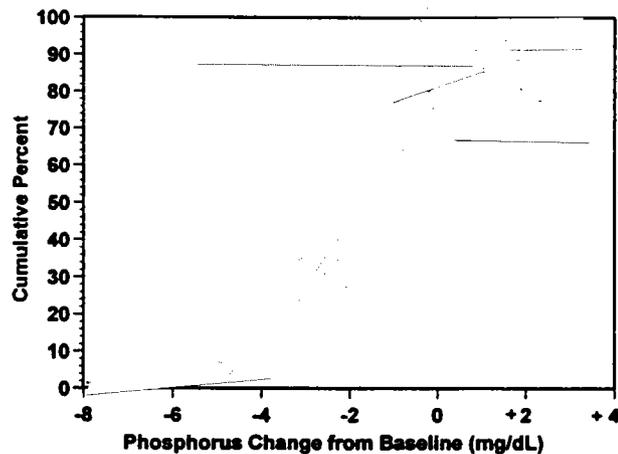


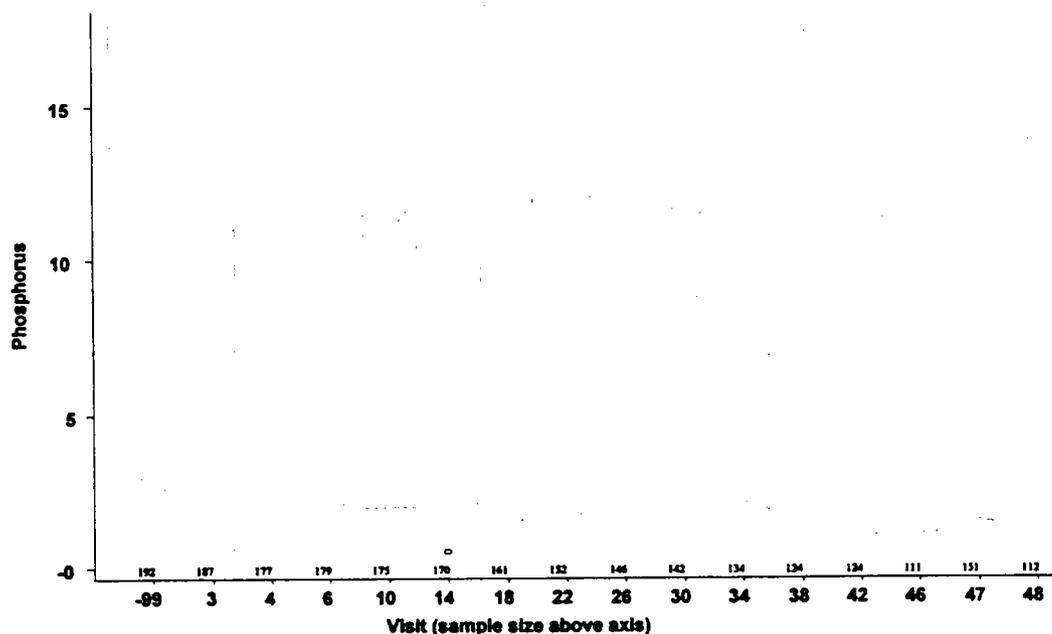
Figure 1. Cumulative percent of patients who attained a phosphorus change from baseline at least as large as the value on the X-axis. A shift to the left of a curve indicates a better response.

APPEARS THIS WAY  
ON ORIGINAL

As shown in this figure, RenaGel and calcium acetate were essentially equivalent in ability to lower the serum phosphorus. However, it should be noted that only 50% of the patients achieved a reduction in phosphorus of 2 mg/dl or more by the endpoint. Roughly 20% of the patients did not respond or increased the phosphorus level, and another 30% experienced a decrease between 0 and 2 mg/dl.

APPEARS THIS WAY  
ON ORIGINAL

Another way to assess efficacy is to examine the responses of the treatment population over time. The figure below is a box-plot of the serum phosphorus level over time during the long-term extension study (901). The boxes contain the median and inter-quartile range for serum phosphorus concentrations.



The value at time point -99 represents the baseline washout phosphorus level. The treatment endpoint is at Week 46. Week 48 is the end of the second washout period. The data demonstrate that while the median phosphorus levels changed in the expected direction, most of the patients remained hyperphosphatemic throughout the course of the study.

In summary, data from six clinical trials convincingly demonstrate that RenaGel treatment reduced the mean phosphorus concentration by about 2.0 mg/dl. The mean responses across all the trials ranged from -0.7 to -2.5 mg/dl. In general, only 50% of patients reduced their serum phosphorus concentrations by 2 mg/dl or more, and 20-25% of patients had no response to RenaGel. The responses to RenaGel were similar to those achieved with calcium acetate, as determined by direct comparison and by comparison to phosphate levels found during pre-washout periods.

**Serum calcium and the CaXP ion product:** Changes in these parameters were not explicitly-stated as efficacy outcome variables. However, the sponsor includes these responses as efficacy variables in the overview of efficacy section of the NDA and an overview of these outcomes is provided here. In the individual trials within the NDA, the calcium response is analyzed as a safety outcome.

Hypercalcemia is a potential complication of therapy with calcium-based phosphate binders, and the sponsor makes the claim that RenaGel therapy avoids this adverse effect. ESRD patients suffer from disorders of calcium, phosphorus, and vitamin D metabolism. The end result of this process is secondary hyperparathyroidism, renal osteodystrophy, hypocalcemia, hypercalcemia, and ectopic calcification. The goal of therapy is to reduce the

serum phosphorus, while maintaining adequate calcium (and vitamin D) supplementation. Parathyroid hormone levels should decline significantly with proper therapy. Appropriately, the sponsor has examined the effects of RenaGel on hypercalcemia, the CaXP ion product, and serum intact PTH levels.

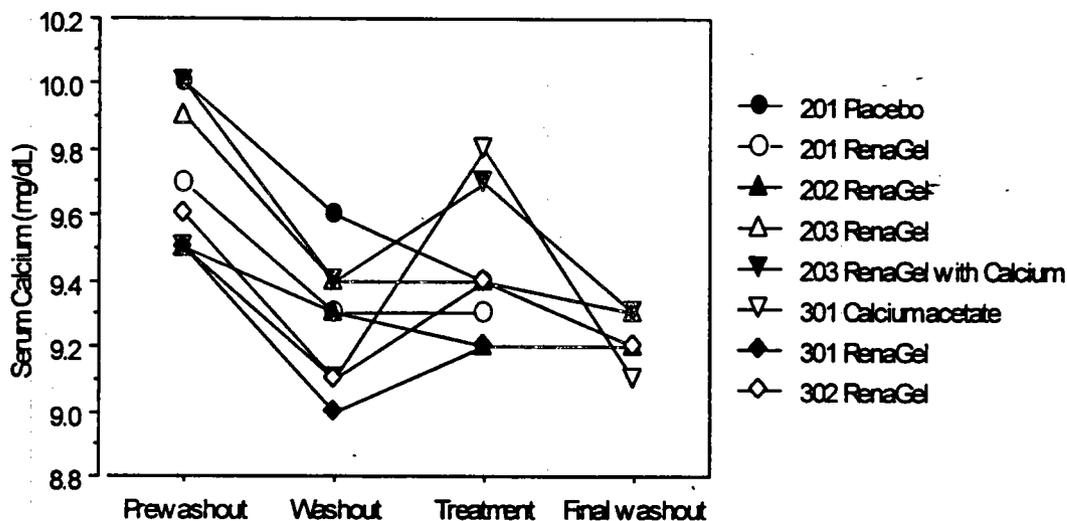
In all the clinical trials, the mean serum calcium concentrations declined during the washout periods. This was most likely due to the use of calcium-based phosphate binders prior to washout, combined with the elevation in serum phosphorus. With RenaGel treatment the mean serum calcium levels changed very little. In three of the studies, (GTC-10-201, GTC-10-202, and GTC-36-203), no change or a slight decrease was noted. In GTC-36-301 and GTC-36-302, there was a slight increase; however, the mean serum calcium concentration remained below the pre-washout level. Only with calcium acetate treatment did the serum calcium concentration in the treatment period exceed the calcium concentration seen at pre-washout. An overview of the calcium responses across the studies is presented in the table below:

**APPEARS THIS WAY  
ON ORIGINAL**

PROTOCOL TREATMENT	PREWASHOUT	WASHOUT	TREATMENT	WASHOUT
<b>GTC-10-201</b>				
Placebo (n=12)	10.0	9.6	9.4	NA
RenaGel (n=24)	9.7	9.3	9.3	NA
<b>GTC-10-202</b>				
RenaGel (n=48)	9.5	9.3	9.2	9.2
<b>GTC-36-203</b>				
RenaGel (n=35)	9.9	9.4	9.4	9.3
RenaGel plus calcium (n=36)	10.0	9.4	9.7	9.3
<b>GTC-36-301*</b>				
RenaGel (n=80)	9.5	9.0	9.2	9.2
Calcium acetate (n=80)	9.5	9.1	9.8	9.1
<b>GTC-36-302</b>				
RenaGel (n=168)	9.6	9.1	9.4	9.2

- Cross-over data presented combined.

A graphic representation of mean serum calcium levels over time during the five clinical trials is presented below:



Thus the results across all the clinical trials show that the reduction in mean serum phosphorus during RenaGel treatment was not associated with an elevation in mean serum calcium.

In addition, the sponsor has quantified the number of "hypercalcemic episodes" during RenaGel and calcium acetate treatment periods. A hypercalcemic episode is defined as a serum calcium  $\geq 10.4$  mg/dl. In this analysis, the results taken from the 301 crossover study are the most meaningful because the trial had a comparison arm. In this study, the overall frequency of having at least one hypercalcemic event during 8 weeks of RenaGel was 18%, compared with 45% for calcium acetate. Using a higher calcium concentration of 11.0 mg/dl as a cut-off level for clinically significant hypercalcemia, 20% of patients (in sequence 1 of the 301 trial) had at least one episode of hypercalcemia during the calcium acetate treatment period, while only 5% of the same patients experienced this level of hypercalcemia while taking RenaGel ( $p=0.03$ ). In the sequence 2 patients, the results were almost identical: 24% of patients had at least one episode of hypercalcemia while on calcium acetate, while only 5% of these patients had hypercalcemia while taking RenaGel ( $p=0.03$ ).

In the one placebo-controlled study, (GTC-10-201) the incidence of clinically significant hypercalcemia ( $Ca \geq 11.0$  mg/dl) during 2 weeks of RenaGel was zero, compared to 6, or 25% of the same patients during the prior calcium-based phosphate binder treatment period. The data for RenaGel patients plus placebo-treated patients are shown in the table below: