

CHANGES IN SERUM PHOSPHORUS OVER TIME, SEQUENCE 1 GROUP

Week#	treatment	serum Phosphate		
		mean (SD)	Δ Phosphate	p value
-1	Pre-washout	6.6 (2.0)		
2	Washout	8.4 (1.8)		
4	RenaGel	6.8 (1.5)		
6	"	6.4 (1.8)		
8	"			
10	End RenaGel	6.3 (1.6)	-2.0 (2.0) week 10-week 2	0.0001
12	Washout	7.4 (1.9)	+1.2 (2.0) week 12-week 10	0.0002
14	Calcium acetate	6.1 (1.7)		
16	"			
18	"			
20	End calcium acetate	5.5 (1.5)	-2.0 (1.9) week 20-week 12	0.0001
22	washout	7.5 (2.1)	+2.0 (2.1) week 22-week 20	0.0001

Similar results were observed with patients in the sequence 2 group

RenaGel and calcium acetate were equally effective in lowering the serum phosphorus, when expressed as mg phosphorus reduction from baseline (post-

A graph of the serum phosphorus levels over time is presented below:



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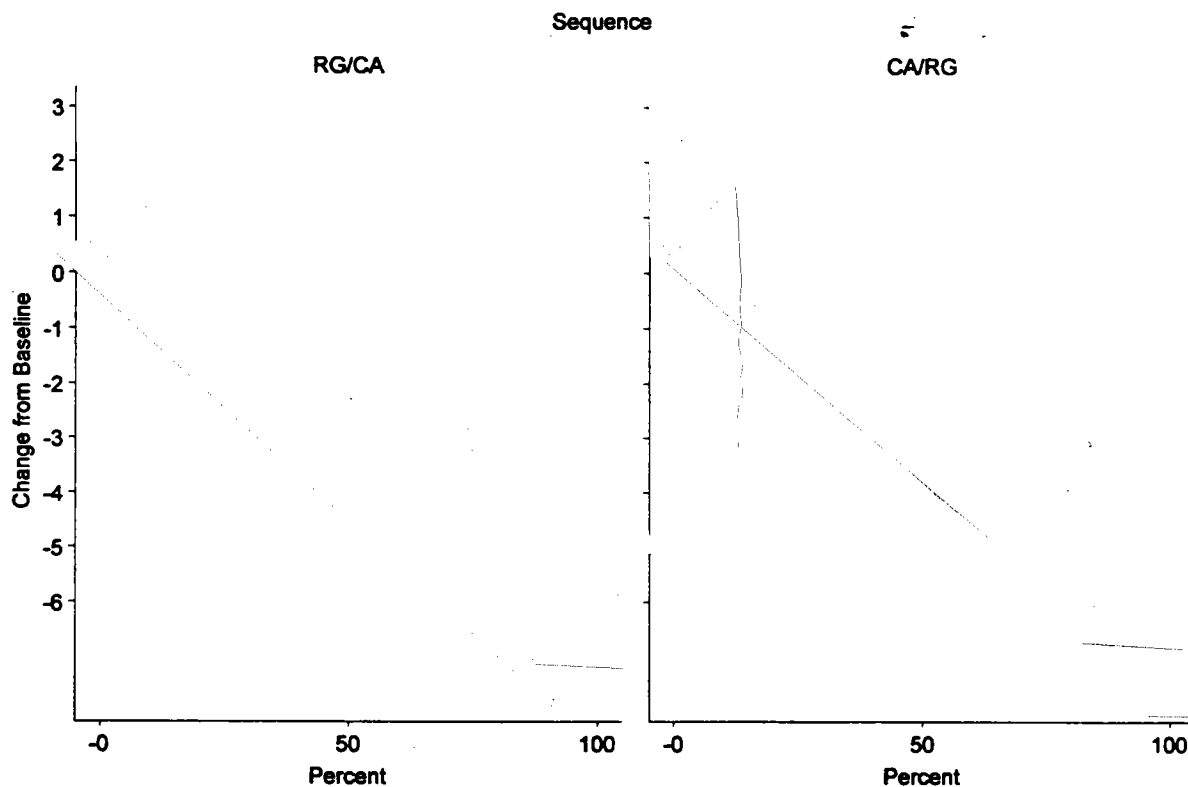
apparent effect of the phosphate changes observed in either sequence group. Furthermore, there was no difference in this regard between RenaGel and calcium acetate.

Responder rate: An important parameter is the responder rate, and the sponsor has analyzed the number (and %) of responders in most of the clinical trials. Response to treatment was pre-defined as serum phosphorus levels reaching either the patient's prewashout level or 5.5 mg/dL, whichever occurred first. Analysis of the intent-to-treat population showed that 87.7% of the patients responded to RenaGel treatment: 44% achieved first response within the first week of RenaGel treatment and 14.8% achieved first response within the second week. During calcium acetate treatment, 77 patients 93.9% of patients achieved response during the study: 46.3% achieved first response within the first week of calcium acetate treatment and 17.1% achieved first response within the second week of calcium acetate treatment.

There was no statistically significant difference between RenaGel and calcium acetate treatment in the percentage of patients achieving response in either of the two sequence groups. In the sequence 1 group, 35 patients (85.4%; CI 74.6%-96.2%) achieved response with RenaGel treatment, while 38 patients (95.0%; CI 88.2%-101.8%) achieved response with calcium acetate treatment ($p=0.125$). In the sequence 2 group, 36 patients (90.0%; CI 80.7%-99.3%) achieved response with RenaGel treatment, while 39 patients (92.9%; CI 85.1%-100.7%) achieved response with calcium acetate treatment ($p=1.00$).

Comments: Taken at face value, this is an impressive response rate. However, a responder analysis that is based strictly on these definitions can be misleading. The implication of the sponsor's definition is that an "ideal" responder would have had a reasonable pre-washout phosphate level of, say, 5.5-6.5 mg/dl, or less. Such a patient's phosphate level would have risen somewhat during the washout period and then dropped to the pre-washout level, or to ≤ 5.5 , during the treatment. On the other hand, a patient could have had a phosphate level of 7.5mg/dl during pre-washout, 7.5 after washout, and 7.5 during treatment. Such a patient would also have been grouped as a responder, since he/she achieved a pre-washout level during treatment. Although this example may seem exaggerated, there are no data that would rule out such a scenario. Indeed, analysis of individual patient data shows that there were hyperphosphatemic patients in the pre-washout period as well as during treatment. Without a patient-by-patient analysis, or a better definition of responder (e.g., a patient whose phosphate goes from some clinically acceptable value, x , to at least $x+2$ during washout, and then back to x or to 5.5 during treatment), it is difficult to draw conclusions regarding clinically significant response rates.

To give a different view of responder rate, without any pre-defined definition of responder, we have graphed all the individual patient data points in a cumulative distribution plot, shown below.

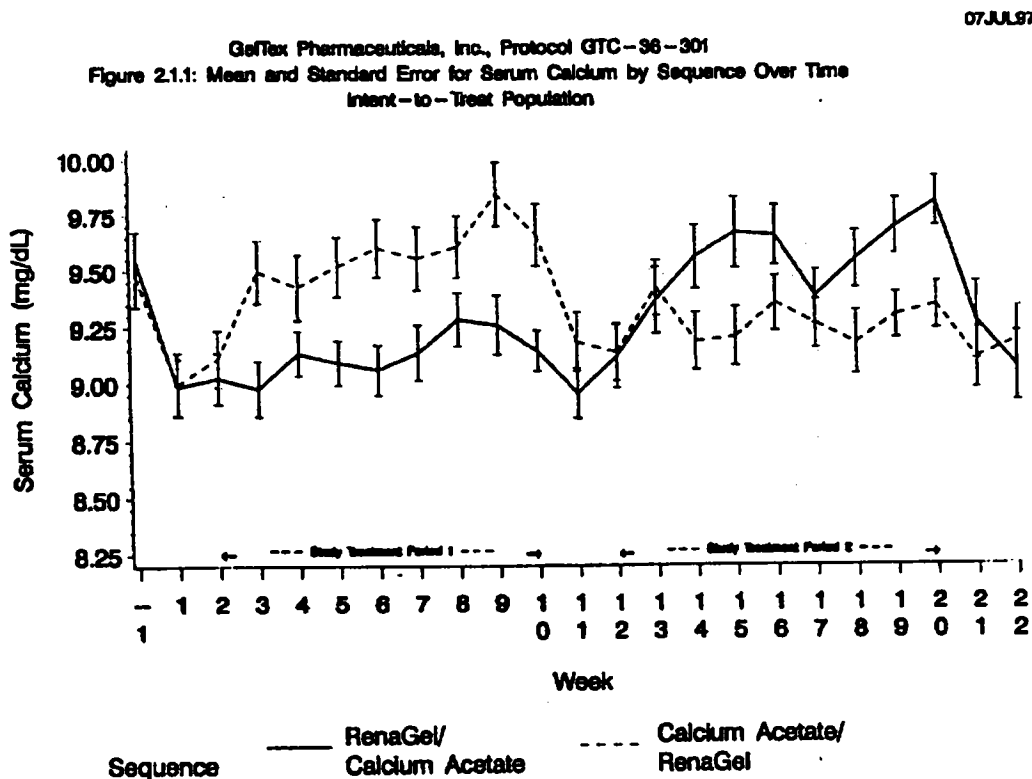


In this figure, each panel represents data for each of the two treatment series. Within panels, each data point represents the change (washout-final) in serum phosphorus level for each patient in both of the treatment phases (open circles = RenaGel; closed circles = calcium acetate). Thus for each 40-patient group, the response rate to RenaGel can be compared to the response rate of the same patients to calcium acetate. The x-axis represents the cumulative percent of patients achieving a drop in serum phosphorus at least as great as the corresponding point on the y-axis. The data show that the response rate to RenaGel was about the same as the response rate to calcium acetate. About 50% of patients had a fall in serum phosphorus of 2 mg/dl or more in response to either drug in either sequence arm. Approximately 20-25% of patients had no response, or a rise, in serum phosphorus during treatment with either drug.

Serum calcium: Changes in the serum calcium level were included as a secondary efficacy objective. Analyses of serum calcium concentrations during the study showed small but statistically significant rises in mean serum calcium over baseline in both treatment groups. There were no differences, between RenaGel and calcium acetate groups, in baseline calcium concentrations. However, by the end of the eight-week treatment period, there was a statistically significant difference between treatments in serum calcium levels (for both sequence 1 and sequence 2 groups). In the sequence group 1, the mean final serum calcium level was 9.2 mg/dL (std=0.6) for RenaGel treatment and 9.8 mg/dL (std=0.7) for calcium acetate treatment ($p<0.0001$). In sequence group 2, the mean final serum calcium level was 9.3 mg/dL (std=0.7) for RenaGel treatment and 9.6 mg/dL (std=0.9) for calcium acetate treatment ($p=0.0066$).

Changes in serum calcium concentrations over time are represented in the figure below:

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In agreement with these data, there was also a statistically significant difference between treatments for the magnitude of the change in serum calcium from baseline to final for both sequences. In sequence 1, the mean change in serum calcium over the eight week treatment was 0.1 mg/dL (std=0.5 mg/dL) for RenaGel treatment and 0.7 mg/dL (std=0.7 mg/dL) for calcium acetate treatment ($p<0.0001$). In sequence 2, the mean change in serum calcium over the eight week treatment was 0.2 mg/dL (std=0.6 mg/dL) for RenaGel treatment and 0.6 mg/dL (std=0.8 mg/dL) for calcium acetate treatment ($p=0.0116$).

An ANOVA model for serum calcium change from baseline to end of the treatment period (provided for both the intent-to-treat and per-protocol populations in Tables 7.2.1 and 7.2.2 of Appendix) showed a statistically significant treatment difference ($p<0.0001$) that was associated with greater elevations in serum calcium during calcium acetate treatment compared to RenaGel treatment. There was no sequence effect ($p=0.8228$) and no sequence by treatment interaction ($p=0.2875$). The ANOVA model for the per-protocol population was comparable to the model in the intent-to-treat population.

Individual patient listings of serum calcium levels are provided in Listing 7.1 of the NDA Appendix.

In this study, the serum calcium rose more during calcium acetate treatment than with RenaGel. From Week 2 to Week 10, the mean increase in calcium in the RenaGel group in sequence 1 was 0.1 mg/dL, compared with the rise of 0.5 mg/dL in the calcium acetate treatment group in sequence 2 ($p=0.0022$). In addition, during the second treatment period (Week 12 to Week 20), there was a statistically significant difference between the calcium acetate treatment in sequence 1 (mean change of 0.7 mg/dL) and the RenaGel treatment in sequence 2 (mean change of 0.2 mg/dL) ($p=0.0022$).

Vitamin D use (defined as *any* use of the vitamin during the study period) had no statistically significant effect on the changes in serum calcium found in any of the treatment arms of the study and no effect on the differential changes in calcium levels observed between RenaGel and calcium acetate therapies.

Hypercalcemic events: A hypercalcemic event was defined as a single serum calcium determination that was ≥ 10.4 mg/dL, with or without associated symptoms. Overall, 15 patients (18.5%, CI 10.0%-27.0%) had hypercalcemic events during RenaGel treatment and 37 patients (45.1%, CI 34.3%-55.9%) had hypercalcemic events during calcium acetate treatment. These differences were statistically significant. When analyzed by number and frequency of hypercalcemic events, there were also statistically significant differences between the treatment groups: during the 8-week treatment period, the incidence of hypercalcemic events ranged from 1% to 7% per week during RenaGel treatment and 11% to 24% per week during calcium acetate treatment. The

difference in the number of hypercalcemic events between the two treatments was also statistically significant within each sequence group.

The number of patients having a hypercalcemic event differed significantly between the two treatment groups (RenaGel vs. calcium acetate) within each treatment sequence as well. Within sequence 1, 6 patients (14.6%; CI 3.8%-25.4%) had hypercalcemic events during RenaGel treatment and 16 patients (40.0%; CI 24.8%-55.2%) had hypercalcemic events during calcium acetate treatment ($p=0.0020$). In sequence 2, 9 patients (22.5%; CI 9.6%-35.4%) had hypercalcemic events during RenaGel treatment and 21 patients (50.0%; CI 34.9%-65.1%) had hypercalcemic events during calcium acetate treatment ($p=0.0020$). The data are summarized in the table below:

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HYPERCALCEMIC PATIENTS (# AND %)

SEQUENCE #	RENAGEL	CALCIUM ACETATE	P VALUE
SEQUENCE 1	6 (14%, CI 3.8%-25.4%)	16 (40.0%, CI 24.8%-55.2%)	$P=0.0020$
SEQUENCE 2	9 (22.5%, CI 9.6%-35.4%)	21 (50.0%, CI 34.9%-65.1%)	$P=0.0020$

Effects of vitamin D use on the incidence of hypercalcemic events: As noted above, vitamin D use had no statistically significant effect on changes in the mean calcium concentrations in either treatment group. However, vitamin D replacement status affected the incidence of hypercalcemic events as follows: Within each sequence, there was no difference between RenaGel and calcium acetate treatment in the frequency of hypercalcemic events among vitamin D users. However, in non-vitamin D-users (approximately 40 % of the study population), there was a treatment-related difference.

In sequence 1 patients on vitamin D, two patients (15.4%; CI -4.2%-35.0%) had hypercalcemic events during RenaGel treatment and five patients (38.5%; CI 12.0%-65.0%) had hypercalcemic events during calcium acetate treatment ($p=0.25$). In the sequence 2 group, three patients (20.0%; CI -0.2%-40.2%) had hypercalcemic events during RenaGel treatment and six patients (40.0%; CI 15.2%-64.8%) had hypercalcemic events during calcium acetate treatment ($p=0.25$). Among non-vitamin D users, there was a statistically significant difference between treatments in the frequency of hypercalcemic events within each sequence. In the sequence 1 group, four patients (14.3%; CI 1.3%-27.3%) had hypercalcemic events during RenaGel treatment and 11 patients (40.7%; CI

22.2%-59.2%) had hypercalcemic events during calcium acetate treatment ($p=0.0156$). In the sequence 2 group, six patients (24.0%; CI 7.3%-40.7%) had hypercalcemic events during RenaGel treatment and 15 patients (55.6%; CI 36.9%-74.3%) had hypercalcemic events during calcium acetate treatment ($p=0.0156$).

Comment: As noted above, vitamin D use had no effect on the mean changes in serum calcium levels or on the differences in serum calcium levels that were observed between the two treatment groups. Analysis of the effects of vitamin D use on the incidence of hypercalcemic events showed a trend, among users, in the direction of more hypercalcemic events during calcium acetate treatment than during RenaGel treatment; however, the differences were not statistically significant. In non-users, the difference between the two treatment groups was statistically significant, with a clear increase in hypercalcemic events in the calcium acetate treatment group, over that found in the RenaGel group. The reason for the greater number of hypercalcemic events among non-vitamin D users is not clear. Overall, the data demonstrate that calcium acetate treatment carries a greater risk of calcium elevation than does RenaGel therapy. This result is not unexpected.

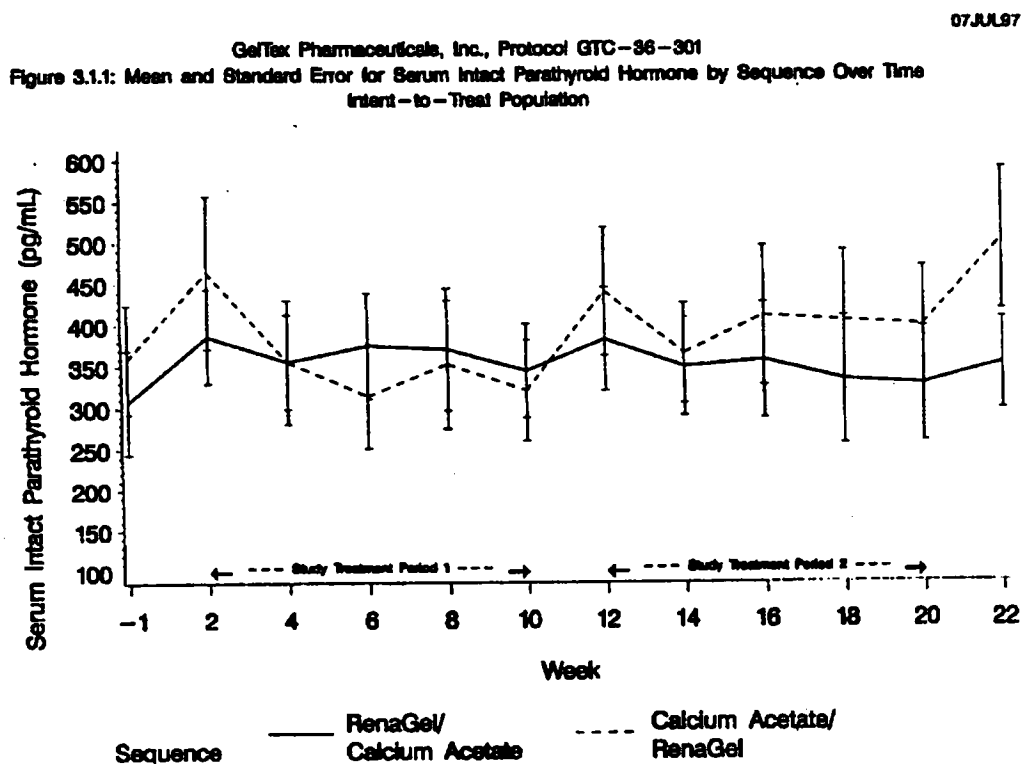
Serum PTH: Reductions in intact PTH (iPTH) levels were a primary efficacy objective. During the study, serum iPTH levels significantly changed in both the RenaGel and calcium acetate treated patients. Overall, for the intent-to-treat population, mean baseline serum iPTH level was 430.1 pg/mL (std=438.2 pg/mL) for RenaGel treatment and 430.3 pg/mL (std=505.7 pg/mL) for calcium acetate treatment. After 8 weeks of treatment, the mean iPTH level was 381.9 pg/mL (std=417.0 pg/mL) in the RenaGel group and 329.7 pg/mL (std=408.3 pg/mL) in the calcium acetate group. The mean change in iPTH over the 8-week treatment was -48.2 pg/mL (std=167.6 pg/mL, $p=0.0068$) for RenaGel and -100.6 pg/mL (std=289.7 pg/mL, $p<0.0001$) for calcium acetate treatment.

When analyzed within each sequence, there was no statistically significant difference between treatment groups in iPTH levels at baseline. No statistically significant difference was found in either final PTH levels or in the magnitude of PTH reduction between treatment groups in sequence 1. In contrast, in the sequence 2 group, there was a statistically significant difference between treatment groups in final iPTH levels as well as in the magnitude of reduction in PTH: the mean final serum iPTH level was 406.8 pg/mL (std=458.7 pg/mL) for RenaGel treatment and 311.5 pg/mL (std=377.8 pg/mL) for calcium acetate treatment ($p<0.0001$). The mean change in iPTH levels over 8 weeks of treatment was -42.6 pg/mL (std=139.1 pg/mL) for RenaGel treatment and -146.3 pg/mL (std=283.0 pg/mL) for calcium acetate treatment ($p<0.0156$). Results for the per-protocol population were similar, with statistically significant reductions in

PTH levels in both treatment groups, but with lower final PTH levels and greater absolute reductions in PTH in the calcium acetate group than in the RenaGel group.

Changes in PTH levels over time and by sequence are represented in the figure below:

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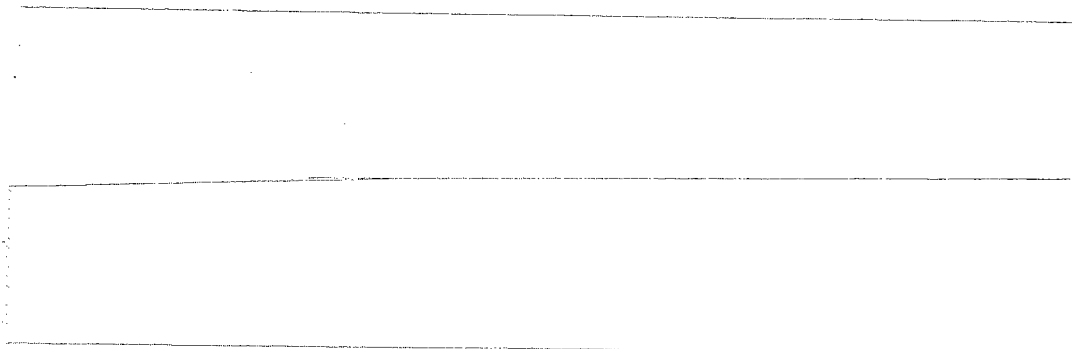


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Comments: The mean baseline levels of intact PTH, as measured by 2-site assays, were in the range, 330 to 430 pg/ml, which is often found in this patient population. The reductions in PTH levels observed after 8 weeks of therapy with either RenaGel or calcium acetate were statistically significant. However, the reductions in PTH associated with RenaGel were fairly small (approximately 10-15% of baseline), while those associated with calcium acetate were approximately 25-35% of baseline. It is possible that long-term 35% reductions in PTH concentrations can have beneficial effects on bone, although the effects of reducing PTH to levels that are still substantially elevated are largely unproven. However it is unlikely that 12% reductions in PTH levels would have any beneficial effects.

It would be important to know how many patients achieved normal (<65 pg/ml in most assays) or near-normal (approximately 120 pg/ml) levels. To convey a clearer picture of the ranges in PTH over time, we have presented the data as boxplots of median and inter-quartile ranges of PTH levels throughout the study:



The boxplots represent the interquartile ranges of PTH concentrations. Throughout the trial, the PTH levels while on calcium acetate were consistently lower than those achieved while on RenaGel. For example, at weeks 4,6,8, and 10, the PTH levels appear higher in the RG/CA group

(patients on RenaGel at those time points) than in the CA/RG group (patients on calcium acetate at that time). During weeks 14, 16, 18, and 20, the patients on RenaGel (CA/RG) had higher PTH levels than those on calcium acetate (RG/CA). The data also depict a great spread in PTH levels, with many patients' levels remaining elevated throughout the course of the study and little overall reponse to RenaGel.

Changes in serum lipids: The final efficacy objective was a change in serum lipids. Valid data were available in both treatment groups for 76 patients: 37 patients in the sequence 1 group and 39 patients in the sequence 2 group. Changes in total cholesterol were observed with RenaGel treatment but not with calcium acetate treatment. In the intent-to-treat analysis, the mean baseline total cholesterol level (Week 2) was 173.3 mg/dL (std=47.1 mg/dL) for RenaGel treatment and 167.2 mg/dL (std=48.6 mg/dL) for calcium acetate treatment. By the end of the 8-week treatment period, the mean total cholesterol level was 146.8 mg/dL (std=42.8 mg/dL) for RenaGel and 169.9 mg/dL (std=51.4 mg/dL) for calcium acetate. The mean change in total cholesterol was -26.5 mg/dL (std=24.5 mg/dL, $p<0.0001$) for RenaGel treatment and 2.7 mg/dL (std=19.5 mg/dL, $p=0.2599$) for calcium acetate treatment. Results for the per-protocol population were similar.

(Further analysis showed that the results were independent of treatment sequence: mean total cholesterol levels and absolute reductions in cholesterol at final were observed during RenaGel treatment but not during calcium acetate treatment ($p<0.0001$ for all comparisons). An ANOVA model for total cholesterol change from baseline to end of treatment for both the intent-to-treat and per-protocol populations also demonstrated a difference between RenaGel and calcium acetate treatments in total cholesterol levels ($p<0.0001$).

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(**LDL Cholesterol:** Reductions in LDL cholesterol were observed with RenaGel treatment but not with calcium acetate treatment. In the intent-to-treat analysis, the mean baseline LDL cholesterol level (Week 2) was 102.5 mg/dL (std=33.0 mg/dL) for RenaGel treatment and 105.0 mg/dL (std=46.0 mg/dL) for calcium acetate treatment. By the end of the 8 week treatment period, the mean LDL cholesterol level was 77.2 mg/dL (std=28.0 mg/dL) for RenaGel treatment and 100.9 mg/dL (std=34.4 mg/dL) for calcium acetate treatment. The mean change in LDL cholesterol over the eight week treatment was -25.3 mg/dL (std=24.6 mg/dL, $p<0.0001$) for RenaGel treatment and -4.1 mg/dL (std=33.3 mg/dL, $p=0.8394$) for calcium acetate treatment. Results were similar for the per-protocol population. The results are summarized in the table below:

REDUCTIONS IN LDL CHOLESTEROL FOLLOWING 8 WEEKS OF RENAGEL OR CALCIUM ACETATE: INTENT-TO-TREAT POPULATION

LDL CHOLESTEROL

TREATMENT	BASELINE	POST 8-WEEKS	Δ LDL	p VALUE
RenaGel	102.5 (33.0)	77.2 (28.0)	-25.3 (24.6)	p<0.0001
Calcium acetate	105.0 (46.0)	100.9 (34.4)	-4.1 (33.3)	p= 0.8394

HDL Cholesterol: There were no significant changes in HDL cholesterol levels in either treatment group.

Triglycerides: Similarly, there were no statistically significant changes in serum triglyceride levels in either treatment group.

8.2.2.4.2 Safety outcomes

Detailed listings of all adverse events and treatment-emergent adverse events are provided in the Appendix of the NDA. In general, there were no differences between treatment groups in the number of adverse events, irrespective of the grouping of these events.

A total of 334 treatment-emergent adverse events occurred among 64 patients (78.0%) during RenaGel treatment, and 290 adverse events occurred among 65 patients (79.3%) during calcium acetate treatment (p=1.00). The "body as a whole" category was the body system with the greatest number of adverse events, accounting for 68 adverse events among 36 patients (43.9%) during RenaGel treatment and 65 adverse events among 38 patients (46.3%) during calcium acetate treatment (p=1.00). Pain, infection, and headache were included in the "body as a whole" category, and no differences were found, between RenaGel and calcium acetate treatment, in the frequency of adverse events assigned to any of these categories.

The cardiovascular, digestive, and respiratory systems accounted for the preponderance of adverse events. The following summary is taken from the NDA: *There were 56 cardiovascular events among 24 patients (29.3%) during RenaGel treatment and 53 events among 29 patients (35.4%) during calcium acetate treatment (p=0.5716). Hypotension occurred among nine patients (11.0%) during RenaGel treatment and among ten patients (12.2%) during calcium acetate treatment (p=1.00). There were 68 digestive system events*

among 28 patients (34.1%) during RenaGel treatment and 36 events among 23 patients (28.0%) during calcium acetate treatment ($p=0.2649$). The most frequent digestive disorders included: diarrhea with 18 events among 13 patients (15.9%) during RenaGel treatment and 10 events among 8 patients (9.8%) during calcium acetate treatment ($p=0.1185$); dyspepsia with 9 events among 9 patients (11.0%) during RenaGel treatment and 3 events among 3 patients (3.7%) during calcium acetate treatment ($p=0.1460$); and vomiting with 14 events among 10 patients (12.2%) during RenaGel treatment and 4 events among 4 patients (4.9%) during calcium acetate treatment ($p=0.146$).

There were 23 respiratory system events among 8 patients (9.80%) during RenaGel treatment and 33 events among 18 patients (22.0%) during calcium acetate treatment ($p=0.0963$). The most frequent respiratory system events included: increased cough with 4 events among 3 patients (3.7%) during RenaGel treatment and 9 events among 9 patients (11.0%) during calcium acetate treatment ($p=0.1094$) and dyspnea with 5 events among 3 patients (3.7%) during RenaGel treatment and 11 events among 7 patients (8.5%) during calcium acetate treatment ($p=0.4531$).

The only statistically significant treatment difference in adverse events occurred with the urogenital body system category. There were 14 urogenital body system events among 11 patients (13.4%) during RenaGel treatment versus one event among one patient (1.2%) during calcium acetate treatment ($p=0.0063$). The only urogenital adverse event judged by the investigator to be possibly or probably related to RenaGel was oliguria which occurred in one patient.

There was no difference between treatment groups in intensity of treatment-emergent adverse events. The digestive system had the greatest number of treatment-emergent events related to treatment: 35 events among 14 patients (17.1%) during RenaGel treatment and 10 events among 8 patients (9.8%) during calcium acetate treatment ($p=0.2101$). There was a treatment difference in dyspepsia: 7 events among 7 RenaGel patients (8.5%) vs 1 event among one patient (1.2%) during calcium acetate treatment ($p=0.0703$).

The incidence of treatment-related hypercalcemic adverse events which were assessed by the investigators was 3 events among 3 patients (3.7%) during calcium acetate treatment and no events during RenaGel treatment ($p=0.2500$).

Twelve serious adverse events occurred among 9 patients (11.0%) during RenaGel treatment, and 9 occurred among 7 patients (8.5%) during calcium acetate treatment. None of these events was judged to be related to treatment.

Two patients died during the study, both in the sequence 2 treatment group and both after calcium acetate treatment. One patient's death (patient #04-008) was listed as "secondary to natural causes," and the other patient (patient 04-009)

died from cardiovascular dysfunction. The deaths were judged not to be related to calcium acetate treatment.

Comment: A review of these deaths disclosed that the first patient, a 68-year-old male, had a history of arteriosclerotic heart disease, with coronary bypass graft, CHF, chronic atrial fibrillation, angina, and hypertension. He was found dead one day after completing 8 weeks of calcium acetate treatment. The second patient, a 77 y.o. male, had a history of diabetes, chronic atrial fibrillation, hypertension, CHF, and peripheral vascular disease. He was found unresponsive 12 days after completing calcium acetate therapy. The investigator judged that his death was unrelated to calcium acetate.

The sponsor has supplied an adverse event table for this study. This is appended to the review.

Blood chemistry:

Sodium: small changes in serum sodium concentrations were observed for both treatment groups: mean sodium levels decreased by approximately 1 meq/l in both groups, but remained in the normal range for both groups (means for both groups were approximately 139 meq/l).

Potassium: no changes in either treatment group.

Chloride: Small, statistically significant increases in mean serum chloride concentrations were seen in association with RenaGel treatment. For patients in sequence 1, mean chloride increased 1.7 mEq/L (from 101.3 mEq/L, $p=0.0115$) during RenaGel treatment. With cessation of RenaGel treatment at Week 10, there was a statistically significant decrease in chloride of 1.5 mEq/L (from 102.9 mEq/L, $p=0.0069$) at the end of the second washout period.

During calcium acetate treatment, mean chloride decreased 1.2 mEq/L (from 101.5 mEq/L, $p=0.0194$). Cessation of calcium acetate treatment at Week 20 was followed by an increase in chloride of 0.1 mEq/L (from 100.4 mEq/L, $p=0.9296$) at the end of the third washout period.

For the sequence 2 group, mean chloride increased 1.2 mEq/L (from 101.7 mEq/L, $p=0.0460$) during RenaGel treatment. Cessation of RenaGel treatment at Week 20 was followed by a statistically significant decrease in chloride of 2.3 mEq/L (from 102.8 mEq/L, $p=0.0001$) at the end of the third washout period. Mean chloride did not change in the calcium acetate group in sequence 2.

Since the changes in chloride during the treatment periods were within the normal range they were not considered clinically significant.

CO₂ content: In sequence 1 patients, this parameter changed significantly during RenaGel treatment and calcium acetate treatment. For sequence 2, the CO₂ content changed only during calcium acetate. The mean CO₂ content decreased 1.5 mEq/L (from 16.2 mEq/L, p=0.0039) during RenaGel treatment in sequence 1. Cessation of RenaGel treatment was followed by an increase in CO₂ content of 0.9 mEq/L (from 14.6 mEq/L, p=0.2945) at the end of the second washout period. Mean CO₂ content increased 2.2 mEq/L (from 15.4 mEq/L, p=0.0037) during calcium acetate treatment. Cessation of calcium acetate at Week 20 was followed by a statistically significant decrease in CO₂ content of 1.2 mEq/L (from 17.9 mEq/L, p=0.0157) at the end of the third washout period.

For the sequence 2 group, mean CO₂ content increased 1.9 mEq/L (from 14.5 mEq/L, p=0.0017) during calcium acetate treatment. Cessation of calcium acetate treatment at Week 20 was followed by a statistically significant decrease in CO₂ content of 1.3 mEq/L (from 16.3 mEq/L, p=0.0149) at the end of the second washout period. In sequence 2, the mean CO₂ content did not significantly change during RenaGel treatment.

Comments: The changes in serum chloride and CO₂ content are possibly related. Although they are small and although both parameters remained within the normal range, these changes may signify a small loss of alkali caused by binding of bicarbonate in the GI tract. Close monitoring of these parameters is warranted during long-term safety studies (see below). It should be noted that these values are routinely monitored as part of serum chemistry panels that are obtained frequently in hemodialysis patients..

Serum glucose: did not significantly change during either RenaGel or calcium acetate treatment for both sequences.

Uric acid and magnesium: Small, clinically insignificant decreases in serum uric acid levels were seen in both treatment groups. The serum magnesium levels did not change during RenaGel therapy.

Total iron, iron binding capacity, and ferritin levels: did not change with either therapy in either treatment sequence.

Hepatic function tests: No clinically significant changes were seen in levels of ALT (SGPT), AST (SGOT), bilirubin, LDH, protein, globulin, albumin, or alkaline phosphatase (bone, intestine, and liver isoenzymes of alkaline phosphatase were assessed separately).

Renal function: No clinically significant changes were seen in BUN or creatinine in association with RenaGel treatment.

Hematology: No clinically significant changes were seen in hemoglobin, hematocrit, red cell count, indices, platelets, or leukocytes, in either treatment group.

PT, PTT, INR, vitamins A, vitamins D, vitamins E, and digoxin:

PT and PTT did not change significantly during treatment with either RenaGel or calcium acetate.

Small reductions in INR were seen (reductions of 0.2, from 1.3 during calcium acetate and 0.2 from 1.4 during RenaGel). These reductions were reversible, statistically significant, but clinically insignificant.

Vitamin A levels did not change in either treatment group.

Vitamin D: Small, statistically significant decreases in 25-hydroxy D levels were seen in patients not using a vitamin D supplement (decreases of approximately 9 ng/ml in both RenaGel and calcium acetate treatment groups). For 1,25-dihydroxy D, there were no changes in the sequence 2 group for either treatment and no changes in sequence 1 for the RenaGel group. Levels of the vitamin increased by 2.6 pg/ml in the calcium acetate group in sequence 1. There was no significant change in 1, 25-dihydroxy D by vitamin D usage.

Vitamin E: did not significantly change during either RenaGel or calcium acetate treatment for both sequences.

Digoxin: There were no changes in serum digoxin levels seen in any of the seven patients taking this medication, either during the RenaGel phase of treatment or during treatment with calcium acetate.

Comments: The safety data show that there are no clinically significant laboratory changes associated with the use of RenaGel for 8 weeks. Anticipated changes in blood levels of fat-soluble vitamins did not occur during this study. The use of clotting parameters as surrogates for vitamin K levels in humans is widely accepted.

8.2.2.5 Conclusions regarding efficacy and safety data

This pivotal phase 3 study clearly demonstrated that RenaGel was effective in reducing the serum phosphorus level in hemodialysis patients. Furthermore, RenaGel was as effective as calcium acetate in this regard:

both agents reduced the serum phosphorus levels by approximately 2 mg/dl. Although the sponsor has used a responder analysis to claim that 87.7% of RenaGel patients and 93.9% of calcium acetate-treated patients responded to treatment, these numbers are misleading, as discussed above. Our analysis of the same data showed that only 50% of patients had a reduction in serum phosphorus levels of 2 mg/dl or more.

It is worth noting that, in ESRD patients, reductions in serum phosphorus of 2 mg/dl or more are clinically significant. The relationship between RenaGel responders and calcium acetate responders is not clear from the data as presented and analyzed by the sponsor.

The incidence of hypercalcemic events (defined as serum calcium levels $\geq$ 10.4 mg/dL), and the number of patients with hypercalcemia, were significantly greater in the calcium acetate-treated group than in patients treated with RenaGel: 18.5% of patients during 8 weeks of RenaGel vs. 45.1% during 8 weeks of calcium acetate treatment. In addition, by the end of the eight weeks of treatment, mean serum calcium levels increased 0.2 mg/dL during RenaGel treatment and by 0.6 mg/dL during calcium acetate treatment. These differences between treatment groups were all highly statistically significant.

Intact parathyroid hormone levels decreased during both RenaGel and calcium acetate treatment, but the decreases were significantly greater during calcium acetate treatment: PTH levels decreased 48.2 pg/mL from 430.1 pg/mL during RenaGel treatment and 100.6 pg/mL from 430.3 pg/mL during calcium acetate treatment. It should be noted that the mean reductions in PTH levels during RenaGel treatment were statistically significant, but quite small in magnitude.

Total and LDL cholesterol levels were significantly reduced during RenaGel treatment, while HDL cholesterol and triglyceride levels were unchanged. Calcium acetate treatment had no effect on any measured lipid moiety.

RenaGel was well tolerated during the 8 weeks of exposure. The incidence of treatment-related adverse events, as well as that of serious adverse events, was similar between RenaGel and calcium acetate treatment. There were no clinically significant changes in laboratory parameters with either RenaGel or calcium acetate treatment. This analysis included serum chemistry, liver function tests, renal function tests, hematology, coagulation tests, and serum vitamin levels. However, as discussed above it was not clear when, in relation to RenaGel administration, concomitant medications and vitamins were given.

During the study, there were no clinically significant changes in vital signs or in physical examinations administered after treatment.

8.2.3 Reviewer's Trial #5 Sponsor's protocol # GTC-36-302

8.2.3.1 Objectives: The primary objectives of this study were:

- 1) to determine the efficacy of RenaGel treatment in lowering serum phosphorus in hemodialysis patients, and
- 2) to determine the safety of RenaGel in hemodialysis patients.

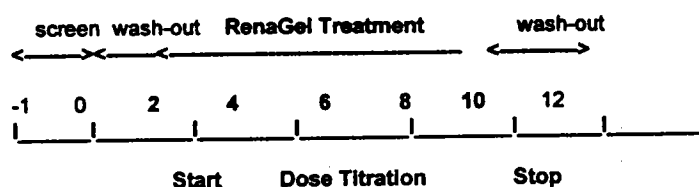
The secondary objectives were:

- 1) to determine the effect of RenaGel treatment on lipid profiles in hemodialysis patients, and
- 2) to determine the effect of RenaGel on intact PTH levels in hemodialysis patients.

8.2.3.2 Design

This was a phase 3, uncontrolled, open label, multi-center study involving approximately 170 hemodialysis patients. The study lasted 13 weeks, during which the patients received RenaGel for 8 weeks. Adult hemodialysis patients on stable doses of calcium and/or aluminum based phosphate binders were eligible. During the entire study period, patients maintained their normal dialysis schedules and normal dietary habits, but were taken off their usual phosphate binders.

Following screening, patients underwent a 2-week phosphate binder washout period. Those patients whose serum phosphate levels exceeded 6.0 mg/dl during washout were eligible for treatment with RenaGel for the next 8 weeks. The starting dose of RenaGel (2, 3, or 4 capsules of 465 mg each, depending on serum phosphate, given tid with meals). At the end of each of the three subsequent two-week periods, the investigator could adjust the RenaGel dose in an attempt to achieve a serum phosphorus level between 3.0 and 4.0 mg/dl. Following the treatment phase, patients underwent a second washout period, at the end of which serum phosphate levels were measured, to confirm that reductions in phosphate were due to RenaGel therapy. A diagram of the protocol is shown below:



Comments: This was the largest phase 3 trial submitted to the NDA, with the exception of the open label extension study. The trial exposes 174 patients to RenaGel for 8 weeks. For reasons discussed above, inclusion of a placebo control group was considered to be unethical in an 8-week trial. This trial design will afford within-group comparisons among treatment, pre-washout, and two washout periods. This "off-on-off" design is similar to that in trial #4 (above), but without an active drug comparison arm. The weakness of the design is that there is no comparison or placebo group, and therefore the value of the safety and efficacy data are limited. This trial and trial #4 (above) are the two pivotal studies which the sponsor uses as the basis of the proposed labeling claims.

8.2.3.3 Protocol

8.2.3.3.1 Population and Procedures: The population consisted of adult men and women with ESRF on hemodialysis three times per week, for 3 months or longer. Patients must have been on a stable dose of a phosphate binder (calcium or aluminum) for at least one month prior to screening. If patients were receiving vitamin D replacement therapy, the dose must have been stable for at least one month prior to screening.

Other inclusion/exclusion criteria were the same as in trial #4. Patients with significant GI disorders were excluded.

Following screening and the two-week washout period, patients were placed on starting dose of RenaGel, based on degree of hyperphosphatemia, as described above. RenaGel capsules (465 mg) were given during meals, tid. At two-weekly intervals, the dose of RenaGel was titrated, depending on the serum phosphate level. During the study, blood samples were collected weekly, prior to dialysis. Dietary intake data were collected, as described above in trial #4, at each of the washout and treatment periods.

Patients were prohibited from taking aluminum or magnesium-based antacids during the study. Calcium salts were also prohibited, except for bedtime calcium supplement as prescribed by the investigator. Investigators were asked not to prescribe new medications during the study, if possible. Vitamin D replacement therapy was maintained at initial dose, unless reduction or cessation were indicated for safety reasons. Digoxin levels were measured at the end of week 2 and every two weeks during the RenaGel treatment and second wash-out periods in all patients taking cardiac glycosides.

Comments: As in other clinical trials, it is not clear from the protocol when concomitant medications and vitamins were administered, relative to the dosing of RenaGel. The sponsor again includes this 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 RenaGel treatment." The meaning of this is unclear.

Compliance was assessed by counting capsules which remained in the patients' bottles at the conclusion of treatment periods.

A schedule of data collection is provided below:

Week	Tests	Notes:
1	Phosphorus and calcium	
2	Chemistry profile PTH Hematology profile PTPTT Vitamins A, D, and E	Phosphate binder washout period
3	Phosphorus and calcium	RenaGel
4	Phosphorus and calcium PTH	Treatment
5	Phosphorus and calcium	Period
6	Chemistry profile PTH Hematology profile PTPTT	
7	Phosphorus and calcium	
8	Phosphorus and calcium PTH	
9	Phosphorus and calcium	
10	Chemistry profile PTH Hematology profile PTPTT Vitamins A, D, and E	

11	Tests	Second
12	Phosphorus and calcium	washout
	Chemistry	
	profile	period
	PTH	
	Hematology	
	profile	
	PTPTT	
	Vitamins A, D, and E	

Comments: The drug dose regimen is appropriate and based on prior experience with RenaGel in earlier studies. The scheduling of laboratory evaluations is appropriately timed to capture the required data. The laboratory assessments meet requirements for achievement of safety and efficacy evaluation goals. The temporal relationship of any vitamin supplementation to meals is not clear. This may have implications for proper labeling of the drug, in terms of unpredictability of absorption of concomitant vitamins and drugs.

8.2.3.3.2 Endpoints

As in all the clinical studies, the primary efficacy analysis is based on the change in serum phosphorus. In this study the analysis is based on the change in phosphorus from the last week of the first wash-out period (Week 2) to the end of the RenaGel treatment period (Week 10). Secondary efficacy parameters include changes in intact PTH and serum lipid levels (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) during the RenaGel treatment period.

In this, and in all the clinical studies, safety was evaluated on the basis of adverse experiences (reported and/or observed), changes in laboratory values (chemistry profile; hematology profile; PT, PTT; and vitamins A, D, and E), and changes in physical examination.

Comments: The outcome variables are clearly stated, objective, and easily measured using standard laboratory procedures. The endpoints are appropriate and consistently applied within this study (and across other clinical studies in the NDA). There are no significant changes in planned analyses. The outcome variables were not changed after the study. Although more than one outcome variable has been selected, all outcome parameters are appropriate, and the results of one analysis do not affect the results of any other.

8.2.3.4 Results

8.2.3.4.1 Populations enrolled/analyzed

A total of 217 patients entered the study, and 172 patients entered the RenaGel treatment period. Most of the 217 enrolled patients who failed to enter the treatment phase did so because of failure to meet washout hyperphosphatemia (6.0 mg/dl) criteria.

Of the 172 patients who received study medication, 144 patients completed the 8-week RenaGel treatment period. Seventeen patients discontinued RenaGel because of an adverse event. Two patients died of cardiac complications, one patient was discontinued due to non-compliance, three withdrew consent, one patient was lost to follow-up, and five patients were excluded for "other" reasons.

Major demographic characteristics of the safety (those who took at least one dose of RenaGel) population (172 patients):

Mean age	53 years
Sex	64.5% male/35.5% female
Mean weight	79.8 kg (range 25-175 kg)
Caucasian	33.7%
African-American	52 %
Hispanic	13.4 %
Asian	0.6 %
Other	0.6 %

The primary causes of ESRD were: hypertension (30.2%), nephritis (13.4%), diabetes (22.7%), polycystic disease (5.2%) and other (28.5%). Twelve percent of the safety population had a history of kidney transplant, 7.6% had a parathyroidectomy, and 51.7% reported Vitamin D analogue use (49.4% intravenous and 2.3% oral). The mean duration of dialysis was 3.6 years, ranging from less than 1 year to 20 years. Renal history and overall demographics for the intent-to-treat and per-protocol populations were comparable to those of the safety population.

Comments: Asians are again under-represented in this study population. Otherwise, the demographics and medical histories are representative of

the intended treatment population. The number and causes of dropouts were within reasonable expectations for this patient population. The majority of patients who met criteria ultimately completed the study. The sponsor provides separate analyses for the intent-to-treat, the per-protocol, and the safety populations. The results did not differ among these separately-analyzed populations (see below).

8.2.3.4.2 Efficacy endpoint outcomes

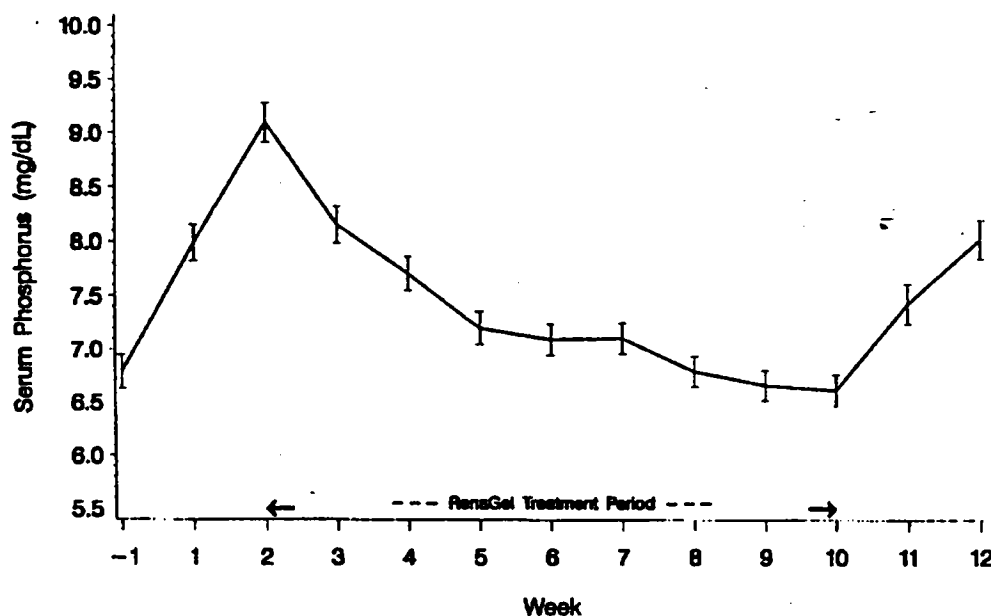
Serum phosphorus:

Mean serum phosphorus while on the original phosphate binder (Week -1) was 6.8 mg/dL (std=2.0). Following the 2-week phosphate binder washout period, the mean serum phosphorus rose to 9.1 mg/dL (std=2.4). After two weeks of RenaGel, (Week 4), the mean serum phosphorus was 7.7 mg/dL (std=2.1). Titration of the dose at Week 4 and Week 6 lowered serum phosphorus levels to prewashout levels by Week 8 (mean=6.8 mg/dL, std=1.9 mg/dL). At the conclusion of the RenaGel treatment period (Week 10), the mean serum phosphorus was 6.6 mg/dL (std=1.9). The mean change in serum phosphorus from Week 2 to Week 10 was -2.5 mg/dL (std=2.3 mg/dL, $p<0.0001$). After the second 2-week phosphate binder washout period, mean serum phosphorus rose again to 8.0 mg/dL (std=2.2).

A graph of the mean serum phosphorus concentrations over time appears below:

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Figure 1.1.1: Mean and Standard Error for Serum Phosphorus Over Time
Intent-to-Treat Population



Vitamin D use (approximately 50% of the patients) was associated with slightly lower phosphate levels than in non-users, but did not affect the magnitude of reduction overall: (Week 10 – Week 2) = -2.6 mg/dl (SD 2.5) for vitamin D users and - 2.4 (SD 2.0) for the non-users.

A linear regression model showed that the following were significant predictors of the change in serum phosphorus: RenaGel dose (higher dose was associated with a greater phosphorus lowering effect, $p=0.0021$), race (non-African-Americans had a greater serum phosphorus lowering effect, $p=0.0081$), number of years on dialysis (greater number of years on dialysis was associated with a greater serum phosphorus lowering effect, $p=0.0131$), and baseline iPTH (lower baseline iPTH was associated with a greater serum phosphorus lowering effect, $p=0.0085$). When reduction in serum phosphorus was analyzed by race, reductions in serum phosphorus were greater among non-African Americans than African Americans throughout the RenaGel treatment period (Week 2 to Week 10). By the end of RenaGel treatment (Week 10), non-African-Americans had a 2.9 mg/dL reduction in serum phosphorus (from 9.7 mg/dL) while African-Americans had 2.1 mg/dL reduction (from 8.6 mg/dL).

Responder rate: Using the same definition of response as in trial #4 (and throughout the study)— serum phosphorus levels falling either to pre-washout levels or to 5.5 mg/dl— 81% of the intent-to-treat population responded to RenaGel by the end of the 8-week treatment period. Sixty-seven % of these patients responded within the first 3 weeks of treatment. Vitamin D usage did not

affect response rates (Appendix, tables 6.5.1 and 6.6.1). Results in the per-protocol population were comparable.

Comments: The same reservations (raised earlier in trial #4) regarding the meaning of responder rate as defined by the sponsor apply here. We have not re-calculated the cumulative frequency of response for this study.

Serum calcium: The mean serum calcium went from 9.6 mg/dl (SD 1.0) pre-washout (Week -1) to 9.1 mg/dl (SD 0.8) after washout, to 9.4 mg/dl (SD 0.9) at the end of the 8-week treatment period. The mean change from washout to the end of the 8-week treatment period was 0.3 mg/dl (SD 0.6), $p < 0.0001$.

Patients using vitamin D supplementation had higher serum calcium levels throughout the study. For these patients, mean serum calcium was 9.7 mg/dL at pre-washout, 9.1 mg/dL at baseline, 9.5 mg/dL at the end of RenaGel treatment, and 9.4 mg/dL at the end of the second washout. For patients not using vitamin D supplementation, mean serum calcium was 9.5 mg/dL at pre-washout, 9.0 mg/dL at baseline, 9.2 mg/dL at the end of RenaGel treatment, and 9.1 mg/dL at the end of the second washout. From baseline (Week 2) to the end of RenaGel treatment (Week 10), mean serum calcium increased 0.3 mg/dL for patients using vitamin D supplementation and 0.2 mg/dL for patients not using vitamin D supplementation. These results were comparable for the per-protocol population.

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The weekly changes in serum calcium over the entire study period, by vitamin D replacement status, are shown in the table below. The data are taken from calcium levels provided in the Appendix.

S E R U M C A L C I U M , M G / D L		
WEEK	NO VIT. D SUPPL.	+VIT. D SUPPL.
-1 (pre-washout)	9.5	9.7
1	8.9	9.2
2 (baseline, post-washout)	9.0	9.1
3 begin RenaGel	9.1	9.3
4	9.2	9.2
5	9.1	9.3
6	9.2	9.4
7	9.1	9.5
8	9.2	9.4
9	9.2	9.4
10 (final, end RenaGel)	9.2	9.5
11	9.1	9.3
12 post-washout	9.1	9.4

Comments: The mean calcium levels at each determination were slightly higher in the vitamin D group. Of note, however, is the stability in mean calcium levels during 8 weeks of RenaGel therapy, irrespective of vitamin D use.

Serum PTH: Statistically significant changes in intact PTH levels were observed in this study. At pre-washout (Week -1) the mean PTH was 332.5 pg/mL (std=381.). Following two weeks of washout (Week 2Baseline), mean serum iPTH was 449.9 pg/mL (std=419.6). After two weeks of RenaGel, mean iPTH fell to 366.5 pg/mL (std=385.1). After 6 weeks of RenaGel, the iPTH was 347.2 pg/mL (std=361.5 pg/mL). By the end of the RenaGel treatment period (Week

10), the mean iPTH was 354.6 pg/mL (std=385.0). The mean change in serum iPTH from Week 2 to Week 10 was -90.0 pg/mL (std=221.5 pg/mL, $p<0.0001$). Following the second 2-week washout period, the mean PTH was 417.4 pg/mL (std=390.4). This represented a statistically significant increase of 82.8 pg/mL (std=192.1 pg/mL, $p<0.0001$).

Comment: The sponsor has presented the Calcium x Phosphorus ion product changes in the safety section, but I am including these data in the efficacy section because this is believed to represent a clinical benefit of phosphorus reduction.

The CaXP product changed significantly from Week 2 to Week 10, overall. Mean calcium x phosphorus decreased 21.0 (from 82.1, $p<0.0001$). There was a significant dose effect, with greater calcium x phosphorus reductions seen at higher RenaGel doses ($p=0.0154$). The low dose group decreased by 14.5, the moderate dose group decreased by 21.3, and the high dose group decreased by 23.8. Cessation of RenaGel at Week 10 was followed by a statistically significant increase in ion product of 14.1 ($p<0.0001$) at the end of the second washout period.

Comment: the magnitude of these reductions in ion product are clinically significant.

The sponsor analyzed the effects of vitamin D supplementation on PTH levels over time throughout the study period (data in Appendix). Vitamin D administration (defined, as above, as any vitamin D supplementation given during the study period) resulted in consistently lower PTH levels and a greater PTH response to RenaGel. The serum PTH levels in non-vitamin D users declined by 67.5 pg/ml from baseline to the end of RenaGel therapy, whereas in vitamin D users, the PTH decline was 111.5 pg/ml.

The changes in PTH levels over time, and according to vitamin D supplementation status, are displayed in the table below. Data were taken from the intent-to-treat population (original data appear in the Appendix of the NDA). The results in the per-protocol population are similar.

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WEEK #	SERUM PTH LEVEL, PG / ML	
	NO VITAMIN D SUPPL.	+ VITAMIN D SUPPL.
-1	328.4	335.9
2 baseline	454.0	446.0
6 (week 4 of RenaGel)	401.1	339.8
8	380.9	315.1
10 (final)	386.4	324.6
12 (after 2 nd washout)	467.2	375.4
Change from week 2		
Week 4	-65.6	-88.6
Week 8	-73.1	-120.1
Week 10 (final)	-67.5	-111.5
Week 12 (after 2 nd washout)	+53.2	-48.8

Correlations among serum phosphorus, calcium, and PTH are presented in the NDA, using Spearman correlation analyses. Using the changes from baseline to the end of treatment [-2.5 mg/dL (std=2.3 mg/dL, $p<0.0001$) for phosphorus, + 0.3 mg/dL (std=0.6 mg/dL, $p<0.0001$) for calcium, and -90.0 pg/mL (std=221.5 pg/mL, $p<0.0001$) for PTH]:

- 1) the changes in serum phosphorus and serum calcium displayed a statistically significant, negative correlation ($r=-0.2389$, $p=0.0018$);
- 2) the changes in serum phosphorus and serum iPTH were positively correlated with borderline significance ($r=0.1306$, $p=0.0936$); and
- 3) the changes in serum calcium and serum iPTH displayed a statistically significant, negative correlation ($r=-0.2252$, $p=0.0035$).

In addition, the changes from pre-washout (Week -1) to baseline and from end of treatment (Week 10) to the end of the second washout (Week 12) were statistically significant for:

- (1) serum phosphorus versus serum calcium,
- (2) serum phosphorus versus serum iPTH, and
- (3) serum calcium versus serum iPTH. Results were comparable for the per-protocol population.

Comments: Clearly, vitamin D supplementation augmented the ability of RenaGel to lower the serum PTH levels. This is in keeping with the known actions of vitamin D, on calcium absorption and also on the parathyroid cell itself. The correlations among PTH, phosphorus, and calcium noted above are also consistent with known mineral physiology. It is worth noting again that the magnitude of mean reductions in PTH were small in patients who were not supplemented with vitamin D (approximately 15% reduction from baseline). The mean reductions in PTH levels among vitamin D users was -111 pg/ml, or a 25 % reduction from baseline. At final (Week 10) the mean PTH level in non-vitamin D users was somewhat higher than that at pre-washout (i.e., while on usual phosphate binders), whereas the corresponding Week 10 PTH level in vitamin D users appeared to be lower than that found during pre-washout. Although a comparison of the PTH levels at these two time points was not planned, and although statistical analysis of these comparisons is not provided, the efficacy of RenaGel in lowering PTH in the absence of vitamin D (and perhaps calcium) supplementation appears to be very modest in this study.

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