

Incidence of hypercalcemic episodes ($\text{Ca} \geq 11.0 \text{ mg/da}$) in the 201 study

	CALCIUM TREATMENT PERIOD N (%)	PHOSPHATE BINDER FREE PERIOD N (%)	RENAGEL OR PLACEBO TREATMENT PERIOD N (%)	P-VALUE* CALCIUM TREATMENT VS. RENAGEL OR PLACEBO
RenaGel (n=24)	6 (25)	3 (12.5)	0 (0)	0.0312
Placebo (n=12)	3 (25)	2 (17)	0 (0)	0.2500

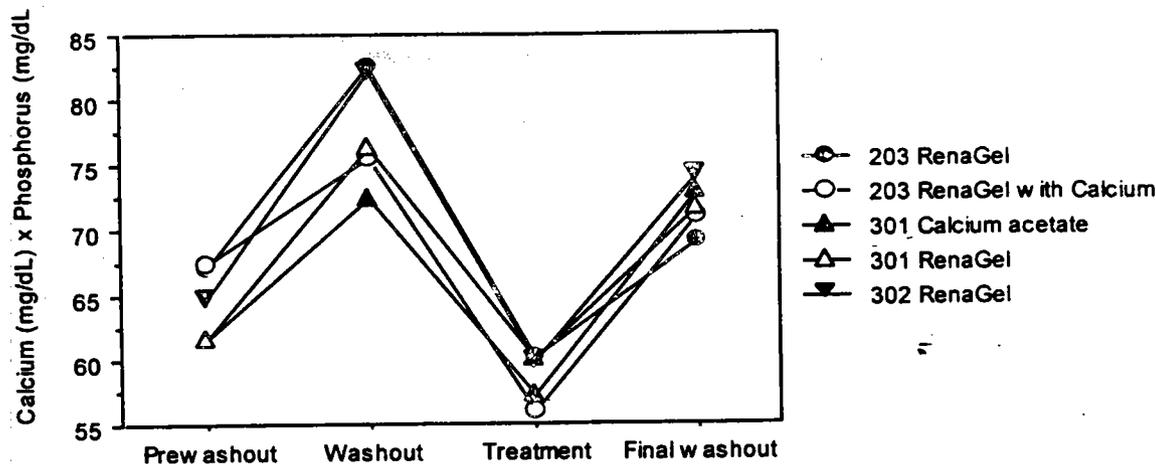
* Chi square test.

In the uncontrolled studies, the mean serum calcium remained stable throughout the trial—e.g., the results from the 302 trial, which are tabulated in that section above.

Thus both controlled and uncontrolled studies show that the mean serum calcium concentrations generally remain stable with RenaGel treatment. The incidence of hypercalcemic events is lower with RenaGel treatment than with calcium acetate treatment and appears to be the same as with placebo treatment.

Reduction in serum phosphorus is an important clinical goal, in part because of the potential to lower PTH levels and in part because of the consequent reduction in the calciumXphosphorus ion product. It is currently believed that reduction in the CaXP ion product decreases the risk of ectopic calcification, at least at some tissue sites. During clinical trials, reductions in mean serum phosphorus concentrations (with either RenaGel or calcium therapy) were associated with reductions in ion product, as shown graphically below for the three studies in which such calculations were made:

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In general, the reductions in serum phosphorus during treatment periods were associated with reductions in mean ion product of about 16-20. The results of the long-term extension (901) study, recently concluded, demonstrate a similar reduction of ion product of 18. In the crossover comparison study (301) the reductions in ion product associated with RenaGel were no different from those observed with calcium acetate, despite the higher serum calcium levels achieved with the latter. Further analysis of the changes in CaXP ion product across trials is given in the table below:

	PRE-WASHOUT TO WASHOUT	P	WASHOUT TO TREATMENT	P	TREATMENT TO FINAL WASHOUT	P
GTC-36-203						
RenaGel	+ 16.4	<0.0001	- 22.4	<0.0001	+ 8.5	0.0017
RenaGel with calcium	+ 9.8	0.0009	- 19.7	<0.0001	+ 15.0	0.0001
GTC-36-301*						
RenaGel	ND	ND	- 16.5	<0.0001	+ 11.7	<0.0001
Calcium acetate	ND	ND	- 15.8	<0.0001	+ 15.5	<0.0001
GTC-36-302						
RenaGel	ND	ND	- 21.0	<0.0001	+ 14	<0.0001

* Cross-over data presented combined. ND = not done. NA = not applicable.

Intact PTH: One reason to reduce the serum phosphorus level in ESRD patients is to lower the PTH. Throughout the NDA, within-group statistical comparisons are used to demonstrate highly significant reductions in circulating PTH levels in association with RenaGel treatment, in most of the studies. It is debatable, however, that these reductions carry any clinical significance for most of the patients in the studies. The mean and median PTH levels across four phase 2 and phase 3 studies (in the 201 study, the treatment duration was only 2 weeks) are shown in the table below:

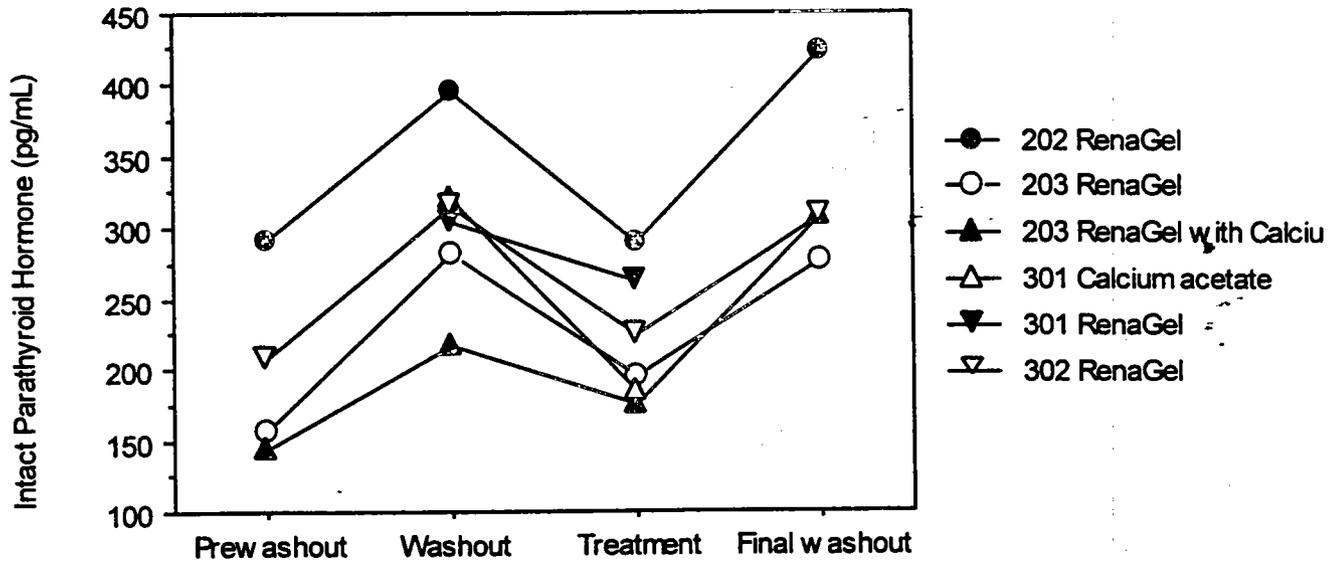
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Median (and mean) PTH levels, pg/ml

	PREWASHOUT MEDIAN (MEAN)	WASHOUT MEDIAN (MEAN)	TREATMENT MEDIAN (MEAN)	WASHOUT MEDIAN (MEAN)
GTC-10-202				
RenaGel	292 (461)	395 (546)	290 (542)	423 (600)
GTC-36-203				
RenaGel	156 (248)	282 (296)	194 (287)	276 (345)
RenaGel with calcium	143 (319)	217 (377)	175 (307)	307 (445)
GTC-36-301*				
RenaGel	ND	305 (430)	262 (382)	ND
Calcium acetate	ND	321 (430)	184 (330)	ND
GTC-36-302				
RenaGel	208 (332)	316 (450)	224 (355)	307 (417)

*Cross-over data presented combined. ND = not done.

For these studies, the median iPTH (pg/ml) concentrations are presented graphically in the following figure:



In these studies the mean and median PTH levels increased during the washout period (due to increases in phosphorus and decreases in calcium levels). With phosphate binder treatment, iPTH levels declined. The upper limit of normal for iPTH assays is generally 65 pg/ml.

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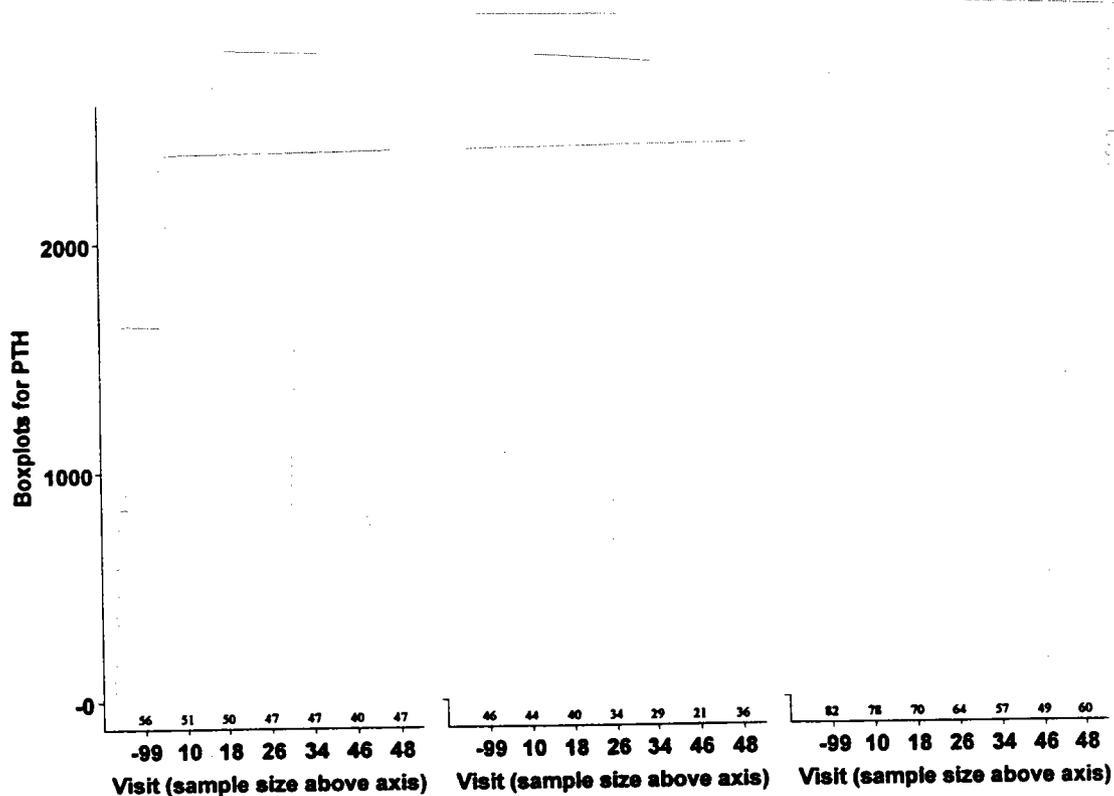
The median (and mean) changes in PTH during these studies are presented in the table below:

PROTOCOL TREATMENT	APPEARS THIS WAY ON ORIGINAL					
	PREWASHOUT TO WASHOUT MEAN (MEDIAN)	P	WASHOUT TO TREATMENT MEAN (MEDIAN)	P	TREATMENT TO WASHOUT MEAN (MEDIAN)	P
GTC-10-202						
RenaGel (n=48)	ND	ND	- 21 (ND)	NS	ND	ND
GTC-36-203						
RenaGel (n=34)	64 (110)	< 0.0001	-22 (-15)	NS	42 (68)	0.0113
RenaGel with calcium (n=36)	68 (119)	0.0001	- 67 (- 90)	0.0084	104 (126)	< 0.0001
GTC-36-301*						
RenaGel (n=75)	ND	ND	- 48 (-32)	0.0068	ND	ND
Calcium acetate (n=75)	ND	ND	- 101 (-79)	< 0.0001	ND	ND
GTC-36-302						
RenaGel (n=168)	ND	ND	- 62 (-90)	< 0.0001	77 (83)	< 0.0001

As shown in the more detailed analysis of protocol 301 (presented in the analyses of individual trials, above), calcium acetate treatment appeared superior to RenaGel in ability to reduce PTH concentrations.

In the long-term extension study, GTC-36-901 the PTH levels were essentially unchanged after 44 weeks of RenaGel therapy. The sponsor's proposed explanation for this, that the PTH levels would have increased over time if not for

RenaGel therapy, is unconvincing, for reasons discussed above. It is worth presenting again the box plot of median and inter-quartile PTH levels over time in this study. The data show that there was essentially no clinically meaningful change in PTH levels over time, even in the early periods of the study (D level= RenaGel dose level).



In summary, RenaGel treatment is capable of reducing the mean serum phosphorus in ESRD patients by about 2.0 mg/dl. Across trials, about 50% of patients achieved a reduction in serum phosphorus of 2.0 mg/dl or greater. Approximately 20% of patients had no response to RenaGel (or increased the serum phosphorus during treatment).

RenaGel treatment was not associated with increases in mean serum calcium levels. The incidence of hypercalcemic episodes (defined either as calcium levels ≥ 10.4 mg/dl or ≥ 11.0 mg/dl) was less on RenaGel treatment than during treatment with calcium acetate. In a placebo-controlled study lasting two weeks,

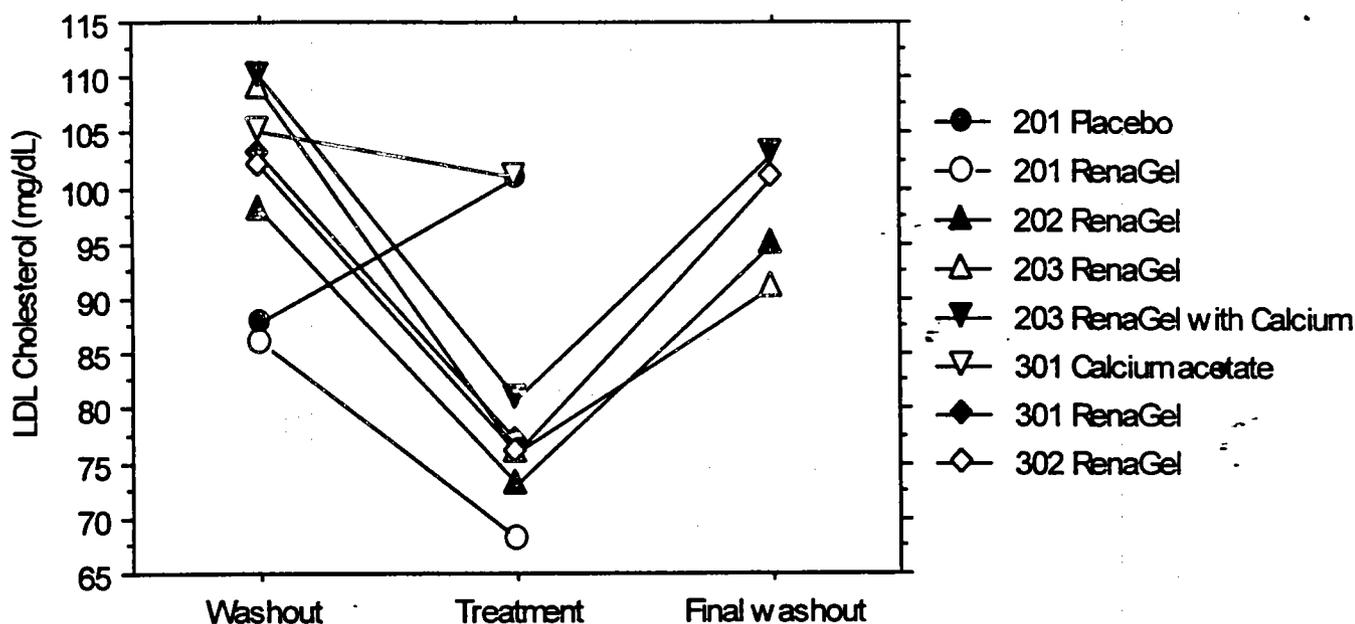
the incidence of significant hypercalcemia with RenaGel treatment did not differ from that observed with placebo treatment.

The calciumXphosphorus ion product declined with RenaGel treatment by 16-20. This decline was slightly less than that seen with calcium acetate treatment. Reductions in CaXP ion product of this magnitude are currently believed to be clinically beneficial.

The serum PTH levels changed in the expected directions during pre-washout, washout, treatment, and post-treatment washout periods in most, but not all, of the studies. Using within-group statistical comparisons, in most of the studies the reduction in PTH levels during RenaGel treatment was highly significant. However, the magnitude of the reductions was generally small (approximately 10-15% decline from baseline) and most likely clinically insignificant. Calcium acetate treatment appeared to produce greater reductions in serum PTH levels, although the clinical meaning of even these declines is not clear. In the long-term extension study, 44 weeks of RenaGel treatment was associated with no significant reduction in PTH levels throughout the course of the study.

Changes in lipids: Following the initial observation of a reduction in total and LDL cholesterol during phase 1 studies, changes in lipids became an efficacy endpoint in all subsequent clinical trials. In all the clinical trials, RenaGel treatment was associated with statistically and clinically significant reductions in LDL (and total) cholesterol levels. The percent change in LDL cholesterol from baseline ranged from -15% to -31%. Neither HDL cholesterol or triglyceride levels changed during these studies. During treatment periods, LDL cholesterol levels did not change in patients who were receiving calcium acetate (301 study) or placebo (201 study). A diagram of the changes in LDL cholesterol across trials is shown below:

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These reductions in LDL cholesterol persisted throughout the 44 weeks of RenaGel treatment in the 901-extension study.

Thus the changes in serum lipids were highly reproducible, as well as clinically and statistically significant. It should be noted that the average total and LDL cholesterol levels in the treatment population were within the normal range. Patients with baseline LDL cholesterol levels > 100 mg/dl had a far greater response to RenaGel treatment than did patients with LDL cholesterol levels that were < 100 mg/dl.

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10 Overview of Safety

Throughout the eight trials submitted to the NDA (including the 2 normal volunteer studies and the 6 clinical studies in ESRD patients on hemodialysis), RenaGel appeared to be well tolerated and associated with few evident treatment-emergent adverse events that could be ascribed to the use of the drug. However, because of medical and ethical considerations described above, there were unfortunately no placebo-controlled studies of greater than 2-weeks' duration; nor were there any active comparison studies which were greater than 8 weeks in duration. Further confounding the safety analysis is the fact that patients with ESRD are generally ill and vulnerable to numerous adverse clinical events. Thus the majority of analyses of adverse clinical and laboratory events

derived from uncontrolled observations against a high background level of illness.

In assessing the safety of RenaGel, data from preclinical and phase 1 clinical studies help to focus the analysis. In preclinical studies using radiolabeled drug, RenaGel was found not to be systemically absorbed. Clinical studies in normal volunteers yielded the same results. Absorption studies were not carried out in ESRD patients; however, it is unlikely that the drug is absorbed in humans with an intact, healthy gut. In preclinical pharm/tox studies, RenaGel, at doses greater than 6X maximum human dose, interfered with the absorption of some vitamins and nutrients. Because RenaGel may bind to bile acids, the absorption of fat-soluble vitamins may be particularly at risk. As noted above, no clinical drug interaction studies have been done. Furthermore, in reviewing all the clinical trials, it is impossible to determine when, in relation to RenaGel dosing, the patients received concomitant medications and vitamin supplements. In further discussions with the sponsor, it is clear that patients in the trials were (not unexpectedly) taking multiple medications and that the dosing of medications and vitamin supplements, in relation to the dosing of RenaGel, was largely left to the discretion of the individual investigators and physicians. Furthermore, an exclusionary criterion was use of anti-arrhythmic or seizure medications. Thus we have no data on blood levels of these drugs during RenaGel treatment.

It should also be appreciated that, across studies, exclusionary criteria also included a variety of gastrointestinal disorders, including: history of swallowing disorders, intestinal motility disorder, history of major GI tract surgery, and irregular bowel function. Thus, in patients with these disorders, the safety and efficacy of RenaGel have not been established in these studies.

Because of these considerations, any toxicity of RenaGel is likely to involve local effects on the GI tract and interference with the absorption of concomitantly administered drugs, vitamins, and other nutrients. Short-term toxic effects on the GI tract would most likely have been detected during the clinical trials. Since the longest period of drug exposure was 44 weeks, one cannot draw conclusions regarding GI adverse events with even longer use of the drug. As for drug interaction data, although there was no evidence for reduction in levels of digoxin, vitamins, and other nutrients, these data do not prove that any drug that is given concomitantly with RenaGel will be adequately absorbed systemically.

With these considerations in mind, an overview of the safety data yields the following conclusions:

In the two clinical studies that contained either a placebo arm (2 weeks' exposure to RenaGel in the 201 study) or an active comparison arm (8 weeks of RenaGel treatment in the 301 study), there was no difference between groups in the incidence of clinically manifest adverse events. Nor were there any

statistically significant differences in relevant laboratory parameters between treatment and control groups (with the exception of the changes in mineral-related parameters). However, as observed above, if the experiments were not designed to detect drug interactions, this subset of the laboratory safety data are of limited value.

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Safety data from the two controlled clinical trials are presented in the tables below:

For the placebo-controlled study (201):

VARIABLE	PLACEBO	RENAGEL	APPEARS THIS WAY ON ORIGINAL
Patients with no adverse experiences	6 (50.0%)	12 (50.0%)	
Patients with at least one adverse experience	6 (50.0%)	12 (50.0%)	

For all treatment-emergent events by body system:

ADVERSE EVENTS BY BODY SYSTEM	PLACEBO (N = 12)	RENAGEL (N = 24)	P-VALUE
Body as a whole			
Ascites	0 (0.0%)	1 (4.2%)	1.000
Chills	0 (0.0%)	1 (4.2%)	1.000
Flu	0 (0.0%)	1 (4.2%)	1.000
Headache	2 (16.7%)	0 (0.0%)	1.000
Pain	1 (8.3%)	0 (0.0%)	1.000
Abdominal pain	1 (8.3%)	0 (0.0%)	1.000
Chest pain	0 (0.0%)	1 (4.2%)	1.000
Pain neck	0 (0.0%)	1 (4.2%)	1.000
Cardiovascular system			
Hypotension	1 (8.3%)	2 (8.3%)	1.000

Syncope	0 (0.0%)	1 (4.2%)	1.000
Thrombosis	0 (0.0%)	1 (4.2%)	1.000
Thrombosis, arterial	2 (16.7%)	4 (16.7%)	1.000
Digestive system			
Diarrhea	2 (16.7%)	0 (0.0%)	1.000
Dyspepsia	0 (0.0%)	2 (8.3%)	1.000
Nausea	1 (8.3%)	0 (0.0%)	1.000
Vomiting	0 (0.0%)	1 (4.2%)	1.000
Metabolic and nutrition			
Edema	0 (0.0%)	1 (4.2%)	1.000
Edema, peripheral	1 (8.3%)	1 (4.2%)	1.000
Musculoskeletal system			
Myasthenia	1 (8.3%)	0 (0.0%)	1.000
Respiratory system			
Dyspnea	1 (8.3%)	2 (8.3%)	1.000
Edema, lung	0 (0.0%)	1 (4.2%)	1.000
Respiratory disorder	1 (8.3%)	1 (4.2%)	1.000
Rhinitis	0 (0.0%)	1 (4.2%)	1.000
Dermatological system			
Pruritus	1 (8.3%)	0 (0.0%)	1.000
Sweat	1 (8.3%)	0 (0.0%)	1.000
Special senses			

Amblyopia	0 (0.0%)	1 (4.2%)	1.000
Cataract	0 (0.0%)	1 (4.2%)	1.000
Urogenital system			
Dysmenorrhea	1 (8.3%)	0 (0.0%)	1.000

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The following table summarizes treatment-emergent events judged possibly or probably related to treatment.

ADVERSE EVENTS BY BODY SYSTEM	PLACEBO (N = 12)	RENAGEL (N = 24)	P-VALUE
Body as a whole			
Abdominal pain	1 (8.3%)	0 (0.0%)	1.000
Digestive system			
Diarrhea	1 (8.3%)	0 (0.0%)	1.000
Dyspepsia	0 (0.0%)	2 (8.3%)	1.000
Nausea	1 (8.3%)	0 (0.0%)	1.000
Vomiting	0 (0.0%)	1 (4.2%)	1.000
Special senses			
Amblyopia	0 (0.0%)	1 (4.2%)	1.000

There was no statistically significant difference in adverse events judged possibly or probably related to treatment between placebo and RenaGel ($p = 1.000$).

The crossover (301) study, in which RenaGel was compared to calcium acetate, was the only other controlled study conducted in ESRD patients in the NDA. In this study, the incidence of treatment-emergent and treatment-related adverse events did not differ between RenaGel and calcium acetate treatment groups, over 8 weeks of therapy with either drug.

For the four uncontrolled clinical trials (as for the controlled trials), the sponsor has provided extensive analyses of adverse events, both for each study and pooled across all studies. Data are analyzed by dose, by pre-defined population characteristics (safety population, intent-to-treat population, per-protocol, and treatment-emergent). Safety data are also analyzed by age, sex, race, and cause of ESRD. The aggregate data set is derived from exposure of 408 ESRD hemodialysis patients to RenaGel. The demographic and clinical characteristics of the population allow for an adequate assessment of the safety of RenaGel, within the design limitations discussed above.

The methodology for assessment of data, as well as the nature of the data collected, were essentially the same across all clinical studies. Patients were followed closely and laboratory determinations were extensive (serum chemistries, hematology, vitamin and other nutrient levels, PT, PTT), appropriate, and focused on anticipated side effects of the drug. Because control groups were absent from most of the clinical studies, possible dose relationships were reviewed by dividing the patients into low, medium or high RenaGel dose level categories. To determine dose category, the mean prescribed daily RenaGel dose over the course of treatment was determined for each patient. The patients were then ranked by mean dose and then divided into tertiles.

For the integrated safety analysis the safety population consisted of 384 patients derived from four clinical studies plus the experience during the extension study. Of these patients, 47 dropped out due to an adverse event, 14 withdrew consent, 8 terminated due to death, 2 were terminated for non-compliance, one patient was lost to follow-up, and 11 were discontinued for "other" reasons. Therefore, 301 patients completed the RenaGel treatment period.

For the entire pooled safety population of 384 patients, there were 2447 treatment-emergent adverse events among 336 patients. Eighty-eight percent of patients across the studies had treatment emergent adverse events. Overall, the proportion of patients with treatment emergent adverse events was similar across all three dose groups: 87%, 90% and 86% for the low, medium and high dose groups, respectively. There was also no dose trend within each body system. This relatively large overall rate of treatment emergent adverse events (88%) is common among ESRD patients. Within each dose group, the proportion of patients with mild, moderate or severe adverse events did not differ—that is, there was no association between severity of the adverse events and the dose of RenaGel.

25-hydroxyvitamin D changed from 33.6 ng/mL to 25.8 ng/mL ($p < 0.001$)

1,25-dihydroxyvitamin D changed from 12.1 pg/mL to 15.3 pg/mL ($p < 0.001$)

Vitamin E changed from 15.0 mcg/mL to 14.1 mcg/mL ($p < 0.001$).

Vitamin A levels did not change.

The decreases in 25-hydroxy vitamin D are the only changes of significant magnitude. The sponsor attributes these declines to seasonal changes, with diminished sunlight. This explanation is not terribly convincing. The increases in 1,25-dihydroxy vitamin D, the active form of the vitamin, may be due either to decreases in phosphorus levels, with consequent dis-inhibition of the renal 1α -hydroxylase, or to treatment with calcitriol itself. The small decreases in vitamin E levels are likely due to reduction of LDL cholesterol and the vitamin E within β -lipoprotein particles.

These findings do not suggest that RenaGel significantly interferes with the absorption of fat-soluble vitamins in this study population, if patients receive the drug and the vitamin supplements in the manner that they were administered in the studies. However, the findings lend little support to the idea that RenaGel does not interfere with vitamin absorption irrespective of the timing of administration of the two agents. Without clinical drug interaction studies, this issue remains an unresolved safety issue.

In summary, throughout the course of these studies, RenaGel treatment appeared to be well-tolerated. Most of the treatment-emergent adverse events that could be attributed to RenaGel were mild and involved the GI tract. There were essentially no dose-related increases in treatment emergent adverse events or treatment emergent adverse events considered possibly or probably related to RenaGel treatment. There were no clinically significant changes in safety laboratory tests associated with RenaGel treatment, overall or by dose. There was no evidence for prolongation of the prothrombin time or decreases in serum concentrations of the fat soluble vitamins A, E, or 1,25-dihydroxyvitamin D. There was a decrease in 25-hydroxy vitamin D noted in the extension study, but the 1,25-dihydroxy vitamin D level increased in that same study. For patients taking cardiac glycosides, there was no evidence that levels of digoxin were decreased during RenaGel therapy. Patients on warfarin did not show an increase or decrease in prothrombin times. However, for reasons noted above, these data cannot be taken as proof of lack of interference with systemic absorption of other drugs and nutrients.

Unresolved safety issues which also relate to labeling: 1)

have not been done in ESRD patients. Therefore, the claim cannot be made that this drug is not absorbed in ESRD patients. 2) Drug interaction studies have not been done in humans. Therefore, drugs, and vitamins may have to be given at least 1-2 hours before, or 3-4 hours after,

RenaGel administration. It should also be emphasized that patients on anti-seizure or anti-arrhythmia medications were excluded from the studies. Special precautions should be taken in administering RenaGel to these patients. These precautions should be placed in the label. 3) The safety and efficacy of RenaGel in patients with a variety of GI disorders have not been established, because these GI disorders were exclusionary criteria in the clinical trials.

10.1 Significant/Potentially Significant Events

10.1.1 Deaths

During the course of these studies, in the safety population there was a total of 11 deaths among 384 patients. This represents 0.09 deaths per patient year of exposure, compared to the national death rate of 0.25 deaths per patient year (USRDS, 1996). None of the deaths was judged by the investigators or the sponsor to be related to RenaGel. I have reviewed these deaths, and I agree with this assessment. The proportion of deaths reported in this study (2.9%) is less than what would be expected in this population. Ten of the 11 deaths were due to cardiovascular causes. This is the most common cause of death in ESRD. The eleventh death was due to a homicide (stabbing).

10.1.2 Other Significant/Potentially Significant Events

There were no events in this category. There were no serious adverse events that could reasonably be attributed to treatment with RenaGel.

10.1.3 Overdose Experience

There has not been a single incident of drug overdose with RenaGel.

10.2 Other Safety Findings

10.2.1 ADR Incidence Tables

An adverse event table is included above for the one placebo-controlled study. The sponsor has been asked to provide a table for the 301 crossover study. The table will most likely be included in the label. There was no pattern of adverse events in patients who dropped out of the trials.

10.2.2 Laboratory Findings

The sponsor has not provided ADR laboratory tables for the controlled studies, comparing the incidences of normal and abnormal laboratory values statistically between treatment groups. The sponsor has been asked to provide these in tabular form.

10.2.3 Special Studies

No special studies have been done to address specific questions

We have requested drug interaction studies in humans, and apparently these will be done post-marketing. Until these are done, appropriate cautionary labeling is indicated.

10.2.4 Drug-Demographic Interactions

Efficacy studies of drug-demographic and drug-disease interactions were done in the largest clinical trial, GTC-36-302. There were 170 patients in this study, affording a sufficiently large database for analysis. Using a linear regression model for efficacy in reducing the serum phosphorus level, the following demographic and disease factors were significant predictors for change in serum phosphorus:

Non-African-Americans show a greater serum phosphorus lowering effect, $p=0.0081$) and number of years on dialysis (a greater number of years on dialysis was associated with a greater serum phosphorus lowering effect, $p=0.0131$). The effects of race on phosphorus reduction were further analyzed and showed that 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 in serum phosphorus (from 8.6 mg/dL).

As for safety, certain demographic subgroups reported more adverse events in several body systems and for multiple individual adverse events. The sponsor offers no physiologic explanation for the increase of adverse events in these subgroups. These differences may be related to inherent differences in the subgroups or in propensity to report adverse events.

Gender: overall, there was no difference in proportion of male and female patients with adverse experiences. There were, however, differences in 4 body systems: body as a whole, cardiovascular, musculoskeletal, and special senses. More females than males reported body as a whole events (66% versus 53 %, $p=0.014$), cardiovascular events (46% versus 34%, $p=0.018$), musculoskeletal events (21% versus 11%, $p=0.005$), and special senses (10% versus 4 %, $p=0.016$). None of these differences could be attributed to RenaGel.

Age: there was no difference in overall adverse event incidence in patients greater than 55 years of age vs patients less than 55. By body system category, the following age-related differences were significant for the cardiovascular, metabolic/nutritional, and nervous systems. At age > 55 more patients compared to patients less than 55 years of age (44% versus 33%, $p=0.036$).

More patients at least 55 years of age reported metabolic/nutritional events compared to patients less than 55 years of age (31% versus 19%, $p=0.009$). More patients at least 55 years of age reported nervous events (23% versus 14%, $p=0.048$). There was a statistically significant difference between age categories for the following five individual adverse events with patients at least 55 years of age reporting more events than those less than 55 years of age: pain (26% and 18%, $p=0.048$), vascular anomaly (3% and 0%, $p=0.014$), rhinitis (6% and 1%, $p=0.006$), pneumonia (4% and 1%, $p=0.036$) and skin discoloration (3% and 0%, $p=0.014$). None of these differences in the incidence of adverse experiences was considered clinically significant.

Race: There was no difference in the overall percentage of African-American and Non-African-American patients with adverse experiences (86% versus 89%). The proportion of African-American experiencing a few individual adverse events was greater than for Non-African-Americans; bleeding time increased (3% and 0%, $p=0.028$), as did peripheral edema (12% and 4%, $p=0.007$) and hypocalcemia (6% and 2%, $p=0.042$). None of these differences in the incidence of adverse experiences was clinically significant.

Disease: Across disease categories, there was no difference in the overall percentage of patients with adverse events. The rates were 89%, 88% and 86% in patients whose primary etiology of ESRD was hypertension, diabetes and "other", respectively. Differences in incidence across primary etiology of ESRD categories were significant for the cardiovascular, metabolic/nutritional, and respiratory systems. More cardiovascular events were reported by patients with diabetes over those with hypertension or "other" (49%, 35% and 33%, $p=0.022$). More metabolic/nutritional events were reported by patients with diabetes over those with hypertension or "other" (32%, 25% and 19%, $p=0.048$). Similarly, more respiratory events were reported by patients with diabetes over those with hypertension or "other" (36%, 20% and 30%, $p=0.023$). Across primary causes of ESRD, differences were significant for several individual events. Infection was more prevalent in patients with hypertension and diabetes than in "other" (24%, 22% and 13%, $p=0.046$). Dyspepsia was most prevalent in patients with "other" as a cause of ESRF over hypertension or diabetes (17%, 13%, 7%, $p=0.050$). Hypochromic anemia was more common in patients with hypertension over diabetes and "other" (6%, 1%, 1%, $p=0.032$). These data are in keeping with the multiple organ effects of diabetes and are probably not due to a disease-related alteration in responses to RenaGel.

10.2.5 Drug-Disease Interactions

These are discussed above, in 10.2.4.

10.2.6 Drug-Drug Interactions

As described above, no drug interaction studies have been done in humans. Consequently, one cannot rule out the possibility that RenaGel has the potential to interfere with the absorption of other orally administered drugs and vitamins.

10.2.7 Withdrawal Phenomena /Abuse Potential:

Since RenaGel is not systemically absorbed, withdrawal of therapy should not have any direct effects on the central nervous system, nor should drug withdrawal exert any effects on cardiovascular or pulmonary function. In preclinical pharmacology studies, RenaGel had no activity on the central nervous system, respiratory system, or isolated smooth muscle of laboratory animals. In clinical trials, the discontinuation of RenaGel was associated with a return of serum phosphorus concentrations to pretreatment, generally elevated, levels. If a physician chooses to take a patient off RenaGel, another phosphate binder should be prescribed, as needed.

10.2.7 Human Reproduction Data

There are no human reproduction data available. Appropriate warnings regarding the increased need for vitamins and other nutrients during pregnancy have been introduced into labeling proposed by the agency. Similar precautions are introduced for labor, delivery and nursing.

11 Labeling Review

Proposed labeling changes are appended.

12 Conclusions

The sponsor has demonstrated that RenaGel is effective in lowering the serum phosphorus in hyperphosphatemic ESRD patients on hemodialysis. The effect was consistent across all clinical trials. In general the mean serum phosphorus level was reduced by about 2.0 mg/dl. In our analysis of the data, approximately 50% of patients treated with RenaGel had a reduction in serum phosphorus of 2.0 mg/dl by the end of the treatment period. Approximately 20% of patients had no hypophosphatemic response to RenaGel. These data were essentially the same as for calcium acetate treatment.

RenaGel treatment was associated with attainment of a lower mean calcium concentration than with calcium acetate. Furthermore, the number of hypercalcemic episodes was lower during RenaGel treatment than with calcium acetate treatment. In addition, the number of such episodes on RenaGel was lower than observed during the patients' previous treatment with calcium-based phosphate binders. The CaXP ion product was reduced with RenaGel treatment, by about 20, but the magnitude of reduction was no different from that observed

with calcium acetate therapy. Thus the clinical significance and/or advantage of the lower calcium values found with RenaGel, compared with calcium acetate, is not obvious.

In this regard, the mean PTH levels achieved during RenaGel treatment were somewhat higher than those achieved with calcium acetate. It is likely that this is due to the effects of the added calcium supplementation. The declines in PTH seen during RenaGel treatment were very modest (about 15%) and of unknown clinical significance. In the long-term extension study (901), there was essentially no reduction in serum PTH levels.

Based on these data, RenaGel appears to be about as effective as calcium acetate in reducing serum phosphorus levels, but the apparent benefits of lowering the phosphorus are less than (with respect to reduced PTH) or equal to (regarding decreased ion product) those achieved using calcium acetate. However, RenaGel may be particularly useful, and is probably superior to calcium acetate, in the subset of patients who are overtly hypercalcemic or who tend to become hypercalcemic with use of calcium-based phosphate binders. It is also possible that RenaGel plus a small evening dose of calcium acetate may be beneficial in some patients.

RenaGel was also consistently effective in reducing LDL cholesterol. The reductions were prompt and were clinically significant. Neither HDL cholesterol nor triglyceride levels changed with RenaGel therapy. This should provide an added advantage to RenaGel therapy, particularly in this patient population.

Tolerance to RenaGel, in terms of phosphate reduction or effects on lipids, did not occur with 44 weeks of treatment.

Within the limits imposed by the dearth of long-term controlled studies, RenaGel appears to be safe when administered to this patient population. The two issues of remaining concern derive from the anatomic site of action of the drug and the lack of clinical drug interaction studies. Therefore, the possibility that RenaGel can inhibit the systemic absorption of any number of drugs, vitamins, and other nutrients remains. Furthermore, the clinical trials excluded patients who were taking anti-seizure and anti-arrhythmia medications. These safety issues will remain until appropriate studies are done.

In addition, RenaGel has the potential to cause GI adverse events. Indeed, these were the most commonly noted treatment-related adverse events during the clinical trials. Nearly all of these were mild, however. Of note is that patients with a variety of GI disorders (including swallowing disorders, GI motility disorders, bowel irregularities, and major GI surgery) were consistently excluded from the trials. Therefore, the safety and efficacy of RenaGel have not been established in patients with these disorders.

Finally, RenaGel has not been studied in ESRD patients who are not on hemodialysis. This includes patients receiving peritoneal dialysis, as well as renal transplant patients. Therefore, the safety and efficacy of RenaGel therapy in this population have not been established.

In conclusion, RenaGel should be beneficial to hyperphosphatemic ESRD patients, particularly those who are prone to developing hypercalcemia. If used in the appropriate ESRD populations, with precautions regarding possible drug interactions, the risk/benefit ratio appears to be acceptable.

13 Recommendations

I recommend that RenaGel be approved for marketing, as long as the following are fulfilled:

1) The proposed label is changed to reflect the following:

- a) that absorption studies have not been carried out in ESRD patients; consequently, the term "non-absorbed" should be deleted;
- b) no direct or implied benefit of RenaGel on PTH levels should be included in the label;
- c) no studies have been carried out in ESRD patients who are not on hemodialysis; consequently the safety and efficacy of RenaGel have not been established in this sub-population of ESRD patients;
- d) no studies have been carried out in patients with dysphagia, swallowing disorders, GI motility disorders, or major GI tract surgery; consequently, the safety and efficacy of RenaGel have not been established in such patients;
- e) RenaGel does not provide calcium or alkali supplementation; serum calcium, bicarbonate, and chloride levels should be monitored;
- f) no drug interaction studies have been done in humans; consequently, when giving any concomitant drug for which alterations in systemic absorption could have significant clinical effects, that drug should be given at least one hour before, or three hours after, administration of RenaGel; in addition, patients were excluded from clinical trials if they were taking antiarrhythmic medications such as quinidine, procainamide, tocainide, or amiodarone or a medication for the control of a seizure disorder such as phenytoin, phenobarbital, valproate, or carbamazepine. Therefore, it would be prudent to add to the label the precaution that patients taking anti-arrhythmia and anti-seizure medications were excluded from clinical trials. Special precautions should be taken when administering RenaGel to such patients.
- g) the proportion of patients who respond to RenaGel should be provided in the label; this is best done using a cumulative distribution plot of the percent of patients who achieve a given reduction, or greater, in serum phosphorus.

2) The sponsor provides a commitment to carry out phase 4

/S/

/S/ Bruce S. Schneider, MD

Medical Officer, DMEDP, HFD-510

~~Bruce~~ /S/
10-16-98

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Juan Carlos Pelayo, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
Rockville, MD 20857

5600 Fishers Lane
Tel (301) 594-5378 FAX: (301) 594-5494

Memorandum

MAY 1 2 1998

FROM: Juan Carlos Pelayo, M.D., Medical Officer, HFD-110

/S/ 4/27/98

THROUGH: Shaw T. Chen, M.D., Ph.D., Medical Officer Group Leader, HFD-110
Raymond J. Lipicky, M.D., Director, Division of Cardio-Renal Drug Products

/S/ 4/30/98
/S/ 5/10/98

TO: Bruce S. Schneider, M.D., Medical Officer, HFD-510
Solomon Sobel, M.D., Director, Division of Metabolism and Endocrine Drug Products

SUBJECT: RenaGel[®], NDA 20-926

DATE RECEIVED: March 23, 1998

DATE COMPLETED: April 27, 1998

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INTRODUCTION

GelTex pharmaceuticals Inc. has submitted to the Division of Metabolism and Ehdocrine Drug Products a New Drug Application (NDA 20-926) for RenaGel[®], a phosphate binder capsules indicated for the control of hyperphosphatemia in patients with end-stage renal disease undergoing hemodialysis.

The Division of Metabolism and Endocrine Drug Products is requesting that we: 1) assess the design of a clinical trial¹ proposed by the sponsor to evaluate the efficacy of RenaGel[®] therapy in patients with end-stage renal disease prior to hemodialysis, and 2) provide commentary on the NDA itself.

The following is a list of the documents provided to the Division of Cardio-Renal Drug Products for review by Division of Metabolism and Endocrine Drug Products:

- i. Desk Copy NDA 20-926, Vol. 1: Index, Labeling, Summary.
- ii. Desk Copy NDA 20-926, Vol. 31: Integrated Summary of Efficacy and Safety.

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¹ This proposal is for a supplemental NDA which will be filed following approval of RenaGel[®] for hemodialysis patients.

BACKGROUND

Patients with chronic renal failure or end-stage renal disease (ESRD) undergoing hemodialysis develop hypocalcemia, hyperphosphatemia, secondary hyperparathyroidism and loss of bone mineral. These complex metabolic alterations invariably lead over time to a distinct bone disease known as renal osteodystrophy.

In most patients with reduced number of filtering nephrons, resulting in a glomerular filtration rate $\leq 25\%$, the urinary phosphate excretion is diminished and thus phosphorus accumulation occurs leading to hyperphosphatemia. Clinical data indicate that early treatment of hyperphosphatemia, with phosphate binders, is critical to the prevention of bone disease and associated morbidity in patients with chronic renal failure or end-stage renal disease undergoing hemodialysis. Orally administered phosphate binders, i.e., aluminum and calcium salts², produce insoluble phosphates which are not absorbed through the gastrointestinal tract. However, current available phosphate binders to correct hyperphosphatemia are not devoided of important side-effects such as encephalopathy, osteomalacia, hypercalcemia and metastatic calcifications, etc. Thus, there is a need for a phosphate binder with a better safety profile than current therapies in this patient populations.

RenaGel[®] (sevelamer hydrochloride) is a cross-linked poly(allylamine), non-absorbable phosphate-binding polymer free of aluminum and calcium. The sponsor has initially developed RenaGel[®] for the treatment of hyperphosphatemia in patients with end stage renal disease undergoing hemodialysis.

RESULTS-NDA 20-926

What follows is a rather succinct review³ of the significant results of clinical studies in NDA 20-926 submitted to the Division of Metabolism and Endocrine Drug Products.

The clinical development program for RenaGel[®] consisted of two normal healthy volunteer protocols and six trials all conducted in patients with ESRD on hemodialysis (Table 1). In all the last mentioned clinical trials, serum phosphorus concentration was used as the primary efficacy endpoint⁴.

Table 1. RenaGel[®] Clinical Studies

Protocol #	Title	RenaGel [®] Dose ¹ g/Day	Duration
GTC-02-101	Double-blind, placebo-controlled, parallel design study of RenaGel [®] in normal subjects.	3-15	8 Days
GTC-10-801	Absorption of ¹⁴ C-RenaGel in healthy young and old male and female volunteers.	7	-
GTC-10-201*	Double-blind, placebo-controlled, parallel design study of RenaGel [®] in hemodialysis patients.	1-8.5	2 Weeks
GTC-10-202	Open-label, dose titration study of RenaGel [®] in hemodialysis patients.	1-9	8 Weeks
GTC-36-203	Randomized, open-label, dose titration study of RenaGel [®] vs. RenaGel [®] with calcium acetate in hemodialysis patients.	2.8-9.8	12 Weeks
GTC-36-301	Open-label, cross over study of RenaGel [®] and calcium acetate in hemodialysis patients.	2.8-9.8	8 Weeks

² PhosLo[®], calcium acetate, is the only FDA approved phosphate binder labeled for that indication.

³ Of note, the medical reviewer did not perform independent analyses of the data.

⁴ Secondary efficacy variables included: incidence of hypercalcemic episodes, secondary hyperparathyroidism, and serum cholesterol and LDL levels.

Table 1. (continued)

GTC-36-302	Open-label, dose titration study of RenaGel® in hemodialysis patients.	2.8-9.8	8 Weeks
GTC-36-901**	An extended use study of RenaGel® in hemodialysis patients.	2.8-9.8	Up to 26 Weeks

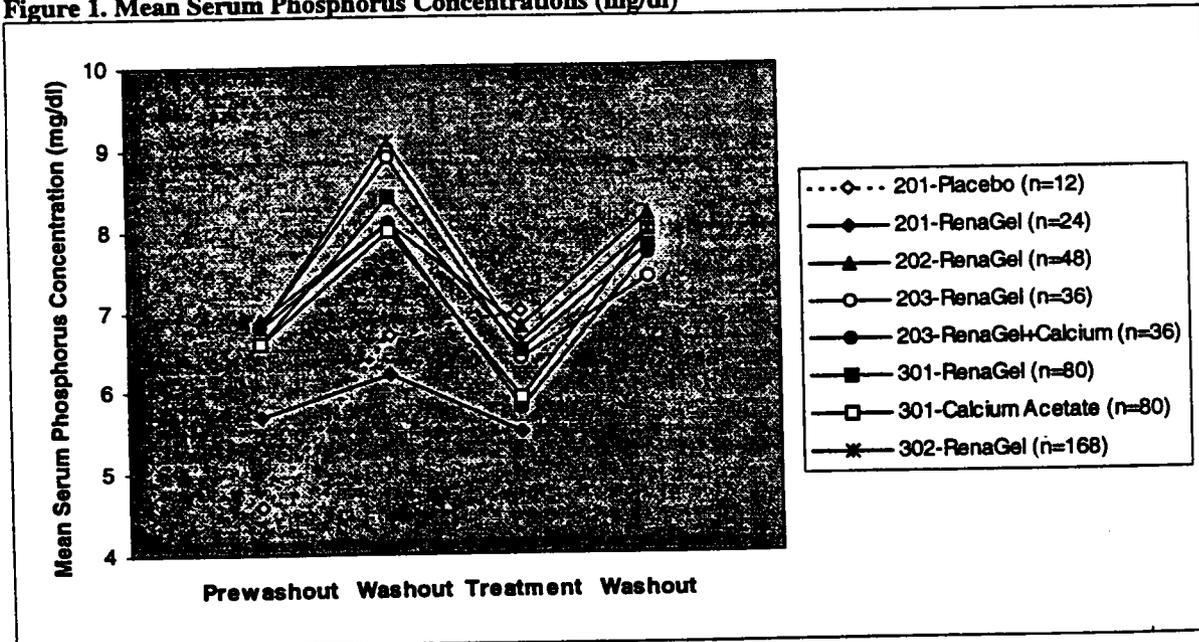
[Adapted from NDA 20-926, Vol. 1, page 133, Table 3.21. *Anhydrous. *This study was not included in the integrated summary of safety. **Interim report.]

Overall, the demographic characteristics of the patients randomized to the RenaGel® studies were representative of the ESRD population of the United States⁵.

Treatment with a phosphate binder was one of the entry criterion. Calcium carbonate or acetate were the most common (>80%) phosphate binders prescribed prior to study entry.

Efficacy: The primary endpoint, in all the clinical trials, was the change in serum phosphorus concentration from the end of a phosphate binder free washout period to the end of an active treatment period (Figure 1). In each clinical trial, the mean serum phosphorus increased upon withdrawal of the patients' own phosphate binders, and it was significantly decreased by the administration of RenaGel® alone or in combination with calcium acetate (Study GTC-36-203) or calcium acetate alone (Study GTC-36-301). Conversely, placebo treatment (Study GTC-10-201) was associated with a progressive rise in mean serum phosphorus over time. The range for these mean values was 5.5 mg/dl to 6.8 mg/dl in the RenaGel® groups. Withdrawal of treatment was followed by an increase in serum phosphorus.

Figure 1. Mean Serum Phosphorus Concentrations (mg/dl)



[Adapted from NDA 20-926, Vol. 1, page 112, Table 3.14.]

Of note, the observed responses in mean serum phosphorus concentrations to RenaGel® treatment occurred in a

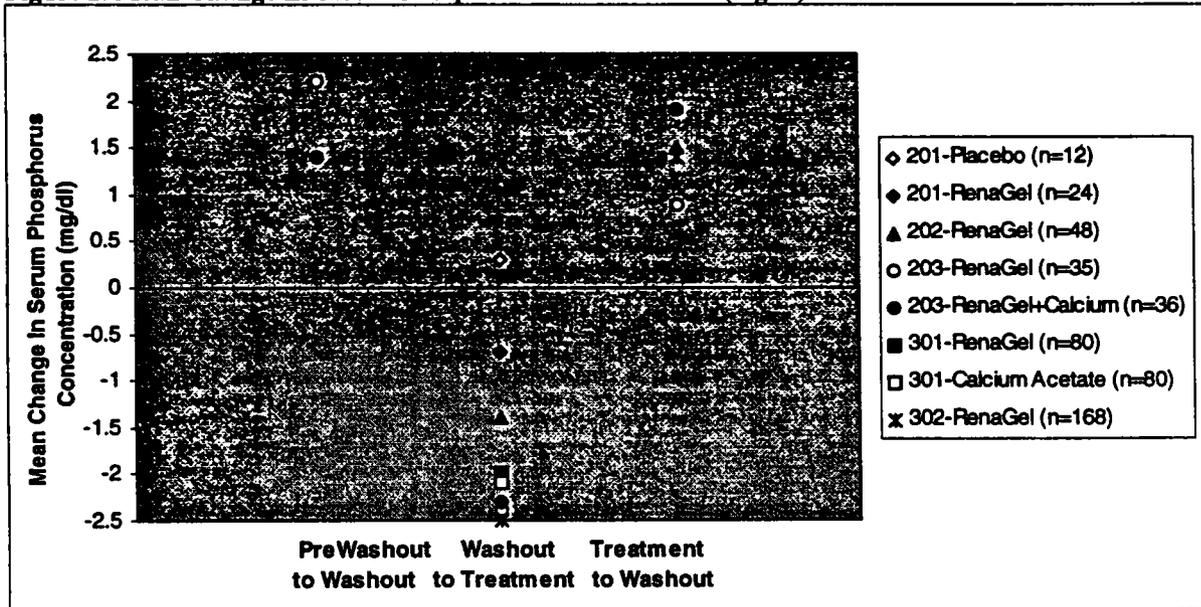
⁵ NDA 20-926, Vol. 31, page 120, Table 8.31.

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background of constant and similar mean dietary phosphorus intake across study periods⁶.

The mean change in serum phosphorus concentration, in all clinical trials, is depicted in Figure 2. The mean serum phosphorus changes ranged from -0.7 mg/dl to -2.5 mg/dl in the RenaGel® groups.

Figure 2. Mean Change In Serum Phosphorus Concentrations (mg/dl)



[Adapted from NDA 20-926, Vol. 1, Table 3.15, pages 113-114.]

The results of the statistical analyses (i.e., p-values) for the aforementioned mean changes in serum phosphorus concentrations, and the percentage of patients responding to treatment are given in Table 2. The declines documented in serum phosphorus concentrations with RenaGel® treatment were statistically significant. Of the three-hundred and sixty-eight patients treated with RenaGel® alone or in combination with calcium acetate, 303 patients were identified as responders (82%).

Table 2. P-Values For Mean Changes In Serum Phosphorus Concentrations

Protocol # Rx	Pre Washout to Washout	Washout to Treatment	Treatment to Washout	Percentage Responding* n(%)
GTC-10-201				
Placebo (n=12)	N/A	0.43	N/A	ND
RenaGel (n=24)	N/A	0.05	N/A	ND
GTC-10-202				
RenaGel (n=48)	N/A	0.0001	0.0001	29(60%)
GTC-36-203				
RenaGel (n=48)	<0.0001	0.0001	0.0029	33(94%)
RenaGel+Ca (n=48)	<0.0001	<0.0001	<0.0001	34(94%)

⁶ NDA 20-926, Vol. 31, page 129, Table 8.37.

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Table 2. (continued)

GTC-36-301				
RenaGel (n=80)	ND	<0.0001	ND	71(88%)
Calcium Acetate (n=80)	ND	<0.0001	ND	77(94%)
GTC-36-302				
RenaGel (n=168)	ND	<0.0001	<0.0001	136(81%)

[Sponsor's analyses (intent-to-treat). Adapted from NDA 20-926, Vol. 1, Table 3.15, pages 113-114. N/A= Not Applicable. ND= Not Done. *Adapted from NDA 20-926, Vol. 31, Table 8.36, page 128. Response=decline in serum phosphorus to prewashout level or 5.5 mg/dl (6.0 mg/dl for GTC-10-202).]

According to the sponsor, greater doses of RenaGel[®] were associated with greater serum phosphorus lowering effect and lead to a greater percentage of patients who responded, studies GTC-36-301 and GTC-36-302, respectively. Table 3 summarizes the doses of phosphate binder at the end of the treatment period.

Table 3. Doses Of Phosphate Binder At The End Of Treatment

Protocol #	Final Dose g/Day (Anhydrous)
GTC-10-202	
RenaGel [®] (n=48)	6.7 (6.4)
GTC-36-203	
RenaGel [®] (n=35)	5.1 (4.8)
RenaGel [®] +Ca (n=36)	4.4 (4.2)
GTC-36-301	
RenaGel [®] (n=81)	5.2 (4.9)
Calcium Acetate (n=82)	(5.0)
GTC-36-302	
Renagel [®] (n=168)	5.7 (5.4)

[Adapted from NDA 20-926, Vol. 31, Table 8.56, page 166.]

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In the aggregate, the results of RenaGel[®] therapy on serum calcium levels are equivocal⁷. The rate of occurrence of hypercalcemic episodes was diminished by RenaGel[®] therapy as compared with calcium-based regimens⁸. Calcium-phosphorus product followed the same pattern observed for the mean serum phosphorus concentrations, i.e., RenaGel[®] treatment had a lowering effect on the calcium-phosphorus product⁹.

Mean serum iPTH concentrations declined significantly with phosphate binder treatment¹⁰. This reduction in serum iPTH levels appears to be of a greater magnitude with the administration of RenaGel[®] plus calcium acetate or calcium acetate than with RenaGel[®] alone. Observation that is in keeping with what it is known about signals triggering PTH synthesis/secretion, i.e., hyperphosphatemia and hypocalcemia.

Unlike placebo or calcium acetate administration, RenaGel[®] treatment was associated with a reduction in LDL cholesterol, the percentage change ranged .

Finally, the results from the extension study (GTC-36-901) suggest that tolerance to RenaGel[®] therapy does not develop over time.

⁷ NDA 20-926, Vol. 31, Table 8.38, page 133.

⁸ NDA 20-296, Vol. 31, Tables 8.40 & 8.41, page 138.

⁹ NDA 20-926, Vol. 31, Figure 8.20, page 143.

¹⁰ NDA 20-926, Vol. 31, Figure 8.45, page 149.

¹¹ NDA 20-926, Vol. 31, Figure 8.23, page 156, & Table 8.48, page 155.

Safety: Assessment of adverse events is hindered because the appendices with the individual full report of the studies and accompanying tables were not provided to the Division of Cardio-Renal Drug Products for review.

PROPOSED CLINICAL TRIAL

The formal document of the proposed study was not supplied to the Division of Cardio-Renal Drug Products for review. According to the consult from the Division of Metabolism and Endocrine Drug Products, "the sponsor proposes a multicenter, open-label, dose escalation efficacy and safety study involving 80-100 patients. The primary endpoint is reduction in serum phosphorus concentration." The patient population to be studied is defined by those patients with chronic renal failure with glomerular filtration rate in the 10-20 ml/min range. The sponsor plans to make comparisons between serum phosphorus values obtained at the end of the treatment period and those found at baseline.

COMMENTS

With the caveat that the review of this NDA did not entail an independent analysis of the raw data, the following commentary is being offered.

- I. Data on serum phosphorus concentrations, from the controlled studies, are persuasive that administration of RenaGel[®] is associated with a statistically significant lowering-effect on serum phosphorus. And this effect most likely is the result of the ability of RenaGel[®] to bind dietary phosphate, thus preventing its absorption through the gastrointestinal tract. Greater doses of RenaGel[®] were associated with greater serum phosphorus lowering effect and lead to a greater percentage of patients who responded. Calcium-phosphorus product followed the same pattern observed for the mean serum phosphorus concentrations, RenaGel[®] treatment had a lowering effect on the calcium-phosphorus product. In another words, the results indicate that RenaGel[®] is an effective phosphate binder in hyperphosphatemic patients with ESRD receiving hemodialysis.
- II. Although, the safety profile of this new molecular entity was not fully assessed in this review, some concerns need to be raised. The sponsor agrees that RenaGel[®] has the ability to bind bile acids and thereby to lower serum cholesterol and LDL, effect which is interpreted as beneficial. Furthermore, it is argued that RenaGel[®] does not interfere with fat soluble vitamin absorption. Perusal of the data on serum levels of these vitamins and prothrombin time, to the contrary suggests that RenaGel[®] may significantly affect the absorption of fat soluble vitamins, that is Vitamins A, D, E, and K.
- III. Because there is, over time, a decline in serum calcium in those patients receiving RenaGel[®] alone, it might be useful to include in the package insert a statement about that observation and thus the need for calcium supplementation. This finding is not surprising since some of the studies prohibited the intake of calcium salts. It is also well known that in order to maintain this patients normocalcemic they required both 1,25-OH₂ vitamin D₃ and calcium supplementation. Similarly, serum carbon dioxide decreases significantly over time, most likely due to the lack/reduction of alkali supplementation because the administration of calcium salts, calcium acetate or carbonate, was absent or significantly curtailed in most of the studies. In this regard, commentary in the package insert appears to be justified. The message that needs to be conveyed to the prescribing physician is that although RenaGel[®] is an effective therapy for hyperphosphatemia, unlike the calcium salts, does not provide calcium or alkali supplementation, which are a requirement in the studied patient population.

With regards to the proposed protocol: a double-blind, placebo-controlled, dose-ranging, parallel group study is, perhaps, the most adequate experimental design to assess the efficacy and safety of RenaGel[®] in patients with chronic renal failure with glomerular filtration rate in the 10-20 ml/min range. Notwithstanding, the commentaries that follow are provided in an attempt to answer some of the concerns and questions raised by the Division of Metabolism and Endocrine Drug Products about the proposed clinical trial.

- I. The chosen primary endpoint, i.e., change in serum phosphorus from baseline to end of treatment period, is a

surrogate of clinical benefit. However, it is an acceptable variable to assess efficacy in this disease, because of the recognized morbidity accompanying chronic hyperphosphatemia, i.e., metastatic calcifications, high serum PTH levels and the associated bone disease, in addition to the inherent difficulty of defining a feasible endpoint of clinical benefit in this particular metabolic alteration.

- II. **Open-label versus double-blind design.** To preserve the integrity/goodness of the study, the proposed clinical trial should ideally be conducted in a blinded manner. Of the reasons¹² given by the sponsor to justify the use of an open-label design the only tenable one, if PhosLo[®] would be used as an active control, is the distinct form that the drugs are currently supplied, i.e., tablets vs. capsules. No problem one can discern if the sponsor designs a placebo-controlled trial, since placebo could be manufactured and thus administered as capsules. Nevertheless, the concern of performing an open-label study is somewhat lessened by the fact that the selected primary endpoint could be measured in a blinded fashion.
- III. **Uncontrolled versus controlled design (placebo and/or active control).** In this regard, the argument presented by the sponsor is that "it would be difficult and possibly unethical to have a placebo-controlled design in this 12-week study of hyperphosphatemic patients who are not receiving dialysis." Thus, the question being asks by the reviewing Division is whether "in this population of ESRD patients, with GFR's in the 10-20 ml/min range, would addition of a control group pose medical or other problems?"

As part of the clinical development program the sponsor designed a placebo-controlled study in ESRD patients receiving hemodialysis, i.e., patient population with GFR markedly less than 10 ml/min. This study consists of three phases: a one to three week single-blind placebo run-in, followed by randomization of eligible patients into six week, double-blind randomized treatment phase and finally a two week, single-blind placebo run-out. Thus, in total some patients might receive as much as 11 weeks of placebo. This exposure was not anticipated by the sponsor or our Division to pose undue risk to those patients who may received placebo for the maximum duration. It should be noticed that this length of exposure to placebo is not that much different from the 12-week proposed in the study using RenaGel[®]. Furthermore, unlike the patients in the later trial, the patient population in the proposed RenaGel[®] study will be comprised of patients with higher GFR who do not require supportive dialysis, and thus they should be capable of excreting a higher percentage of the daily dietary intake of phosphorus. In spite of the aforementioned assertion, a difficult to quantify, albeit finite number of patients receiving placebo might develop high serum phosphorus levels (>10 mg/dl) leading to a potentially dangerously elevated phosphate-calcium product (>80 mg²/dl²) and withdrawal of trial medication because of the risk of metastatic calcifications. This risk could be abrogated by periodic surveillance, i.e., weekly measurements of serum phosphorus, and the inclusion of an "escape clause" in the protocol. The next best alternative will be to perform an active-controlled trial using PhosLo[®] as the active control. The justifications offered by the sponsor for the need to conduct an uncontrolled clinical trial in this patient population are not defensible on medical grounds.

- IV. **Number (80-100) of patients proposed to be studied.** The lack of a power analysis at hand prevents one, as far as efficacy is concerned, from offering any commentary on the selected sample size. With respect to the assessment of safety in the defined population, the proposed number of patients, albeit small by itself, is adequate as part of the whole clinical database.

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CC: Orig. to NDA 20-926

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HFD-510 / B.S. Schneider / J. Weber

HFD-110

HFD-110 / J.C. Pelayo / D. Throckmorton / S.T. Chen

¹² That is: 1) RenaGel[®] comes in as an elongated capsule while the active control PhosLo[®] comes in as a tablet form, and 2) PhosLo[®] is associated with cases of hypercalcemia, event that in and out of itself would lead the investigator to deduce the treatment.