CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020926

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA #: 20-926

OCT 9 1998

Drug: Renagel (sevelamer hydrochloride)

Sponsor: Gel Tex Pharmaceuticals, Inc.

Indication: Control of hyperphosphatemia in patients with end stage renal disease (ESRD)

Date of Submission: November 3, 1997

Statistical Reviewer: Joy Mele, M.S. (HFD-715)

Volume Numbers in Statistical Section: Volumes 64 to 95

Medical Input: Bruce Schneider, M.D. (HFD-510)

Introduction

The sponsor has provided the results from 3 Phase 2 studies (Table 1) and 2 Phase 3 studies (Table 2) to establish the safety and efficacy of Renagel for the control of hyperphosphatemia in patients with end stage renal disease (ESRD). Also, the sponsor has conducted a long-term extension study (GTC-36-901) where completers of the Phase 2/3 studies could continue Renagel treatment at their own discretion for an additional 44 weeks. The primary focus of this review is the sponsor's Phase 3 program; these studies are described in the sponsor's proposed labeling. The efficacy results observed in the Phase 2 studies were consistent with those observed for the Phase 3 studies.

Table 1. Phase 2 Trials

Study	Design	Treatment Arm (N)	Trt. Duration
GTC-10-201	Rand., DB, parallel, controlled	Placebo (12) Renagel (24)	2 weeks
GTC-10-202	Open label dose titration	Renagel (48)	8 weeks
GTC-36-203	Rand., open label dose titration	Renagel (75) Renagel+Ca (19)	12 weeks

Table 2. Phase 3 Trials

Study	Design	Treatment Arm (N)	Trt. Duration
GTC-36-301*	Open label cross-over, rand.	Renagel/PhosLo +Ca (42) PhosLo/Renagel +Ca (42)	8 weeks for each trt. period
GTC-36-302*	Open label dose titration	Renagel (172)	8 weeks

*Study summarized in the labeling.

Study 301 (conducted 7/96 to 2/97)

Study 301 is an open label, cross-over study designed to show the efficacy of Renagel in lowering of serum phosphorus in hemodialysis patients. Following a washout period of 2 weeks, patients with a serum phosphorus > 6 mg/dl were randomized to a sequence; Renagel/calcium acetate (Sequence 1; RG/CA) or calcium acetate/Renagel (Sequence 2; CA/RG). Starting doses (TID dosing) were based on level of serum phosphorus as shown below.

SERUM PHOSPHORUS	RENAGEL (capsule=.465g)	CALCIUM ACETATE (tablet=.667g)
> 6.0 to < 7.5 mg/dL	6 capsules per day	3 tablets per day
≥7.5 to < 9.0 mg/dL	9 capsules per day	6 tablets per day
≥ 9.0 mg/dL	12 capsules per day	9 tablets per day

Following 2 weeks of treatment and every 2 weeks thereafter on treatment, doses were titrated according to the scheme below to attain a phosphorus serum level of 2.5 to 5.5 mg/dL.

Serum Phosphorus	**Titration**
>5.5	Add 3 capsules/tablets per day
2.5 to 5.5	No change
<2.5	Decrease dose by ≤3 capsules/tablets per day at discretion of investigator

The treatment periods were as follows:

Washout 1	Weeks 1-2
Treatment 1	**Weeks 3-10**
Washout 2	Weeks 11-12
Treatment 2	**Weeks 13-20**
Washout 3	Weeks 21-22

Patient Disposition and Demographics

A total of 109 patients were screened at 8 sites for this study; 84 patients (42 to each sequence) were randomized to sequence after the initial washout period. The primary reason for discontinuation after the first washout was failure to meet the hyperphosphatemia criterion.

During the trial, four Sequence 1 patients and five Sequence 2 patients discontinued treatment (Table 3).

Table 3. Patient Disposition by Sequence

	Sequence 1 RG/CA	Sequence 2 CA/RG
Randomized	42	42
Completed 1st Trt. Period	40	40
Completed 2nd Trt. Period	38	37
ITT Population	41	42
Per-Protocol Population[1]	19	16

1 The primary reasons for exclusion from the per-protocol population was less then 70% compliant and/or less than 8 weeks of treatment.

The primary reason for discontinuation from Renagel was an adverse event (Table 4).

Table 4. Reasons for Discontinuation by Treatment and Sequence

	Renagel		Calcium Acetate	
	Seq 1	Seq 2	Seq 1	Seq 2
Adverse Event	1	3	0	0
Death	0	0	2	0
Non-compliance	1	0	0	2

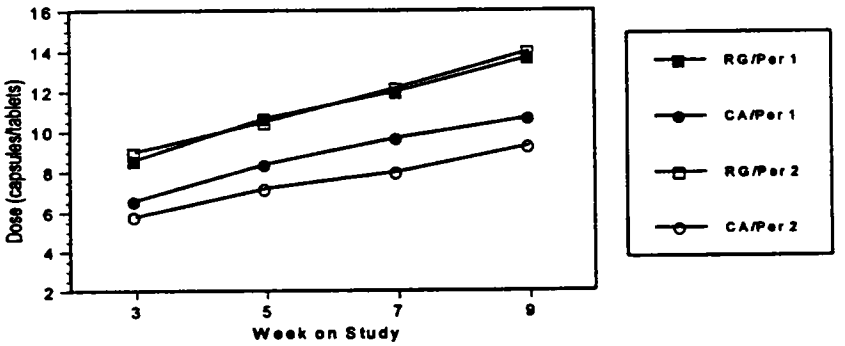
The randomized groups were balanced with regard to demographics and medical history at baseline. Patients ranged in age from 19 to 86 years with mean of 55 years. 54% of the patients were male. A majority of the patients were black (56%); about one third were Caucasian. The primary causes of ESRD were hypertension (Seq1:29%, Seq2:43%), nephritis (Seq1:12%, Seq2:17%) and diabetes (Seq1:19%, Seq2:29%). More Sequence 1 patients (8/42) had a kidney transplant than Sequence 2 patients (2/42). The average duration of dialysis was about 4 years (range of <1 to 21 years). About half of the patients were administered vitamin D during the trial; analyses by vitamin D use showed no significant modification of the treatment effect due to vitamin D use for any efficacy measure.

Dosing

In the NDA, the sponsor reports the actual dose taken so their data reflects compliance. This reviewer has summarized the data for the prescribed dose; the latter is larger than the actual dose taken since compliance was about 78% for both treatments.

The dosing for Renagel was comparable in both periods (Figure 1) with a mean starting dose of about 4 grams and a mean ending dose of about 6.5 grams. For calcium acetate, prescribed dosing (and actual dosing) was higher in the first period than the second period by about 0.7 gram (1 tablet). The mean starting dose for calcium acetate was 4.4/3.9 grams (Per 1/Per 2) and the mean ending dose was 7.1/6.2 grams.

Figure 1 Mean Dose for Each Treatment by Week Within Period



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For about ⅓ of the patients on either treatment for both periods, the starting dose was the maximum dose allowed (12 capsules for Renagel and 9 for calcium acetate). Patients could be titrated by a maximum of 9 additional capsules/tablets; 23% of Renagel-treated patients and 15% of calcium acetate patients were titrated to their maximum dose.

Since this study is unblinded, it is possible for the titration to be biased in favor of Renagel. This reviewer compared dose levels and phosphorus levels and did not find that the calcium acetate patients were underdosed so the data does not suggest that the dosing was biased.

Efficacy Results

Serum Phosphorus (Primary Efficacy Results)

The statistical methods section of the protocol for Study 301 simply states that "efficacy will be evaluated on the basis of changes in serum phosphorus from the end of the wash-out periods to the end of the treatment periods"; the primary objective of the trial is stated likewise. The comparison of Renagel to the calcium acetate arm is named as a secondary objective. No sample size calculations were provided in the protocol; therefore, it is not clear whether the trial is adequately powered to show superiority or non-inferiority for the treatment comparison. The medical reviewer believes that it is sufficient to show by within-group comparisons that Renagel significantly reduces serum phosphorus. No comparative efficacy claims are made in the sponsor's proposed label.

Sponsor's Results

The sponsor presented the results for 4 comparisons:

1. change from baseline (serum phosphorus at the end of treatment (LOCF) minus the baseline serum phosphorus at the end of the washout period) comparisons within treatment group and within sequence (Wilcoxon signed rank test)
2. between treatment comparisons of change from baseline within sequence (Wilcoxon signed rank test)
3. overall between treatment comparison (ANOVA with terms for treatment, sequence and sequence by treatment).
4. between treatment comparisons of responder rates within sequence (McNemar's test)

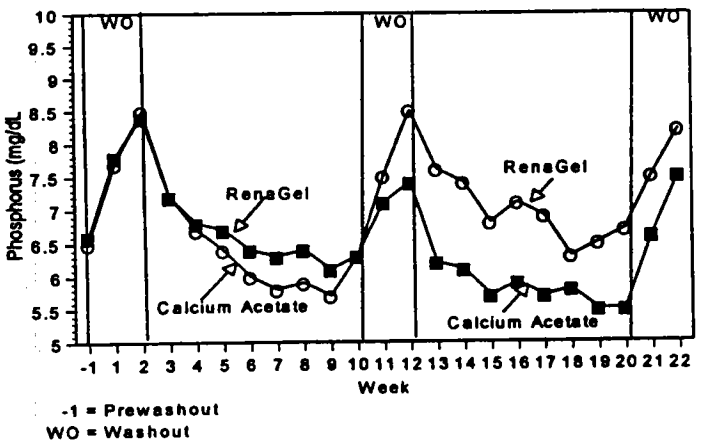
Change from baseline comparisons for each treatment (Table 5 below) were all statistically significant ($p<.0001$) while no differences were evident between the treatment groups ($p>.4$); the mean changes from baseline were all about 2. The ANOVA yielded no significant effects for treatment, sequence or sequence by treatment.

Table 5. Study 301
Serum Phosphorus at Baseline and Change at End of Treatment
Mean (SD)

	Period 1		Period 2	
	Renagel (Seq1) n=40	Ca Acetate (Seq2) n=40	Renagel (Seq2) n=40	Ca Acetate (Seq1) n=40
Baseline	8.3 (1.7)	8.6 (1.9)	8.6 (2.7)	7.4 (1.9)
Change	-2.0 (2.0)	-2.2 (1.9)	-1.9 (2.5)	-2.0 (1.9)

Mean serum phosphorus levels plotted over time in Figure 1 (reviewer's graph) show that serum phosphorus clearly increases during washout and decreases during treatment with larger effects seen for calcium acetate over Renagel; these differences are not significantly different.

Figure 2 Study 301 Mean Serum Phosphorus Levels For the Duration of the Trial



A responder analysis performed by the sponsor (where responder was defined as a patient whose phosphorus level returned to prewashout levels (i.e. levels on pre-randomization treatment) or 5.5 mg/dL at any timepoint during the treatment period) showed no significant differences between the treatment groups (Table 6; p>.13); however, the response rates were slightly higher in the calcium acetate group.

Table 6. Study 301
% Responders

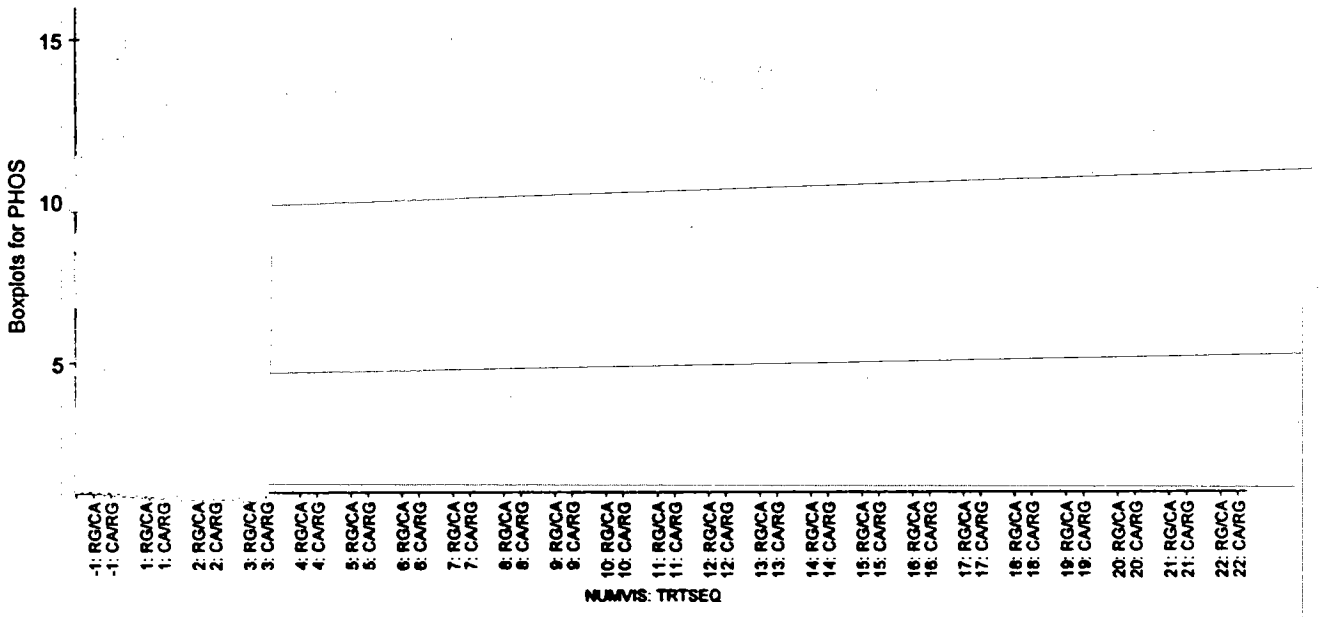
	Period 1		Period 2	
	Renagel (Seq1) n=40	Ca Acetate (Seq2) n=40	Renagel (Seq2) n=40	Ca Acetate (Seq1) n=40
Phosphorus≤5.5 or Prewashout Level at Any Timepoint	85.4%	92.9%	90.0%	95.0%

Reviewer's Results for Serum Phosphorus

To further evaluate the phosphorus changes over time for both treatment sequences, this reviewer produced boxplots (Figure 3) to examine the distribution of the data. For each pair of boxes, the first box represents the data for Sequence 1 (Renagel/Calcium acetate) and the second box; Sequence 2 (calcium acetate/Renagel). It is clear that the phosphorus levels go up during the washout periods (weeks 1, 2 , 11, 12, 21 and 22) and gradually fall during treatment. As was seen for the mean plots, the downward shift appears to be greater for calcium acetate than Renagel.

Of particular note in Figure 3 is the magnitude of the effect during pre-washout (-1) and also the low percentage of patients reaching a responder level of 5.5 (about 25%). It appears that most patients were considered responders due to returning to pre-washout levels and that those prewashout levels may not be good indicators of response.

Figure 3 Boxplots by Visit and Sequence



To illustrate the latter point further this reviewer looked at the phosphorus responses by patient and found that some patients appeared to be misclassified suggesting that the responder definition was not reliable. A few selected patients are shown in the graphs on the following page.

Figure 4 Phosphorus Levels for Patient 204

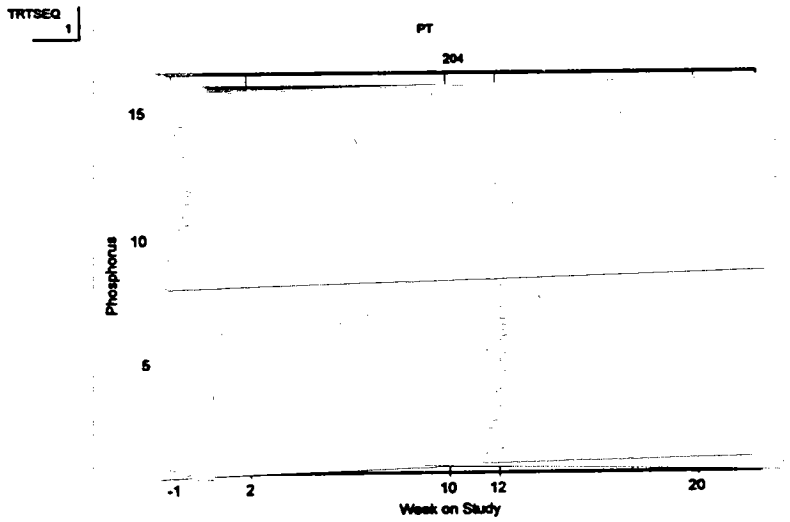


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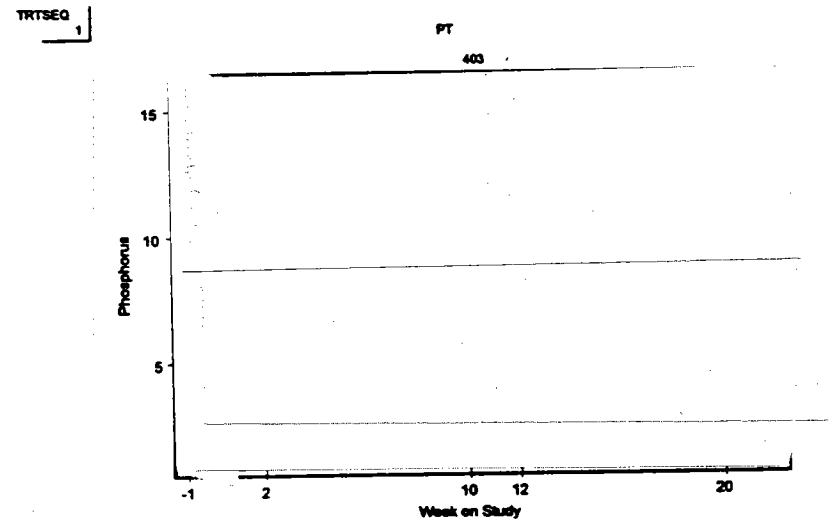
Figure 5 Phosphorus Levels for Patient 403



Both patients shown above received Renagel during the first period and calcium acetate during the second period. Patient 204 (Figure 4) is counted as a responder on Renagel; however, the data does not indicate that the patient is responding after Week 3 so Patient 204 appears to be a nonresponder. Patient 403 (Figure 5) was classified as a nonresponder on Renagel, however the data shows that phosphorus steadily decreased during the first treatment period. These inconsistencies suggest that the responses should be summarized in an alternative manner. The medical reviewer suggested that we look at 2 alternative definitions of responder; phosphorus ≤6 and % decrease from baseline ≥20%. The results based on these responder definitions are summarized in Table 7 on the next page.

Table 7. Study 301
% Responders
Reviewer's Analysis

	Period 1		Period 2	
	Renagel (Seq1) n=40	Ca Acetate (Seq2) n=40	Renagel (Seq2) n=40	Ca Acetate (Seq1) n=40
Phosphorus Response at 1 or more timepoints				
≤6	80%	81%	78%	85%
% decrease ≥20%	95%	93%	80%	79%
Phosphorus Response at 2 or more timepoints				
≤6	63%	74%	63%	80%
% decrease ≥20%	78%	83%	68%	77%

These responder rates (Table 7) are consistently lower than the rates obtained using the sponsor's responder definition (Table 6); again, the rates are higher on calcium acetate than on Renagel. It is a clinical judgment as to which definition best characterizes a responder.

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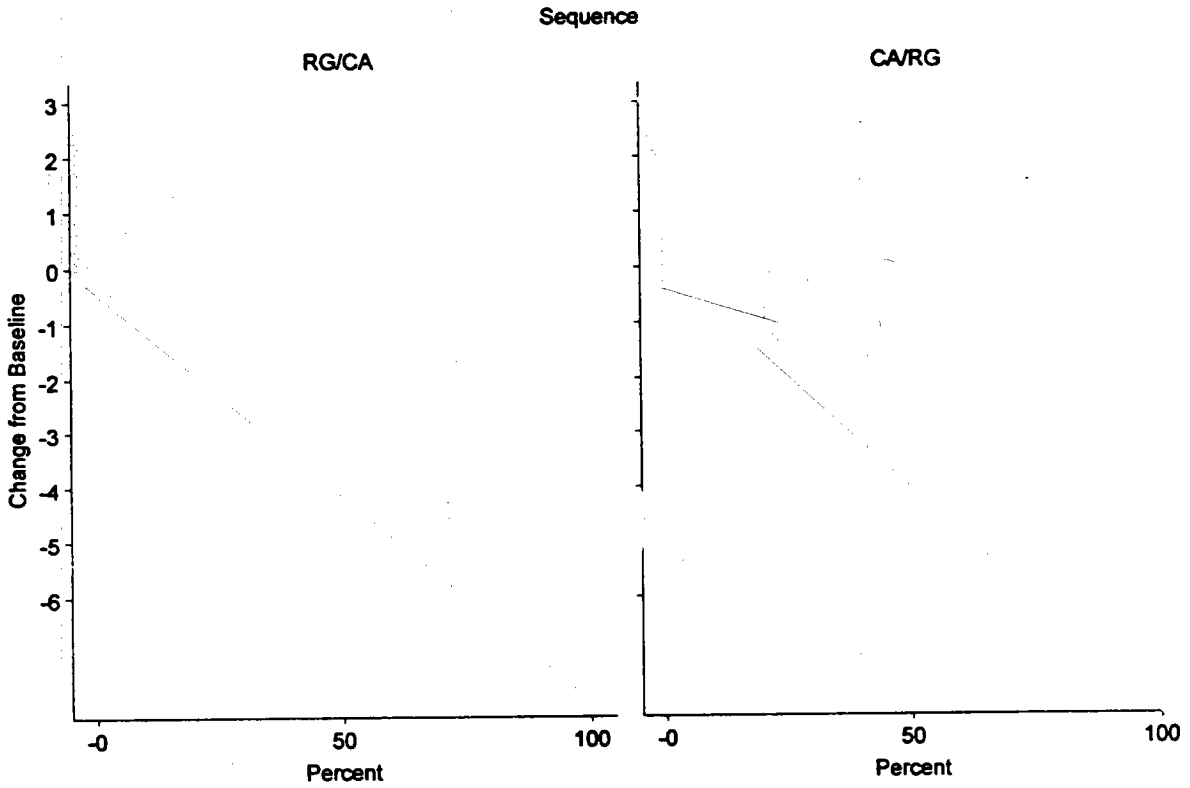
Since the primary efficacy measure was change from baseline at the end of the treatment period, this reviewer looked at the distribution of responses at endpoint for each period. The graphs are shown by sequence in order to compare responses within sequence

.Figure 6 Phosphorus Change from Baseline at Endpoint



Open Circles = 1st period results
Gray Circles = 2nd period results

In Figure 6, the change from baseline data for each patient is ordered by magnitude and each point represents a single patient. The data is similar for both treatment groups within sequence and between sequences. During the first period, the median response was about -2.4 in both groups and during the second period the median response was about -1.8 in both groups.

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Figure 7 Renagel Response versus Calcium Acetate Response for Each Patient in Study 301

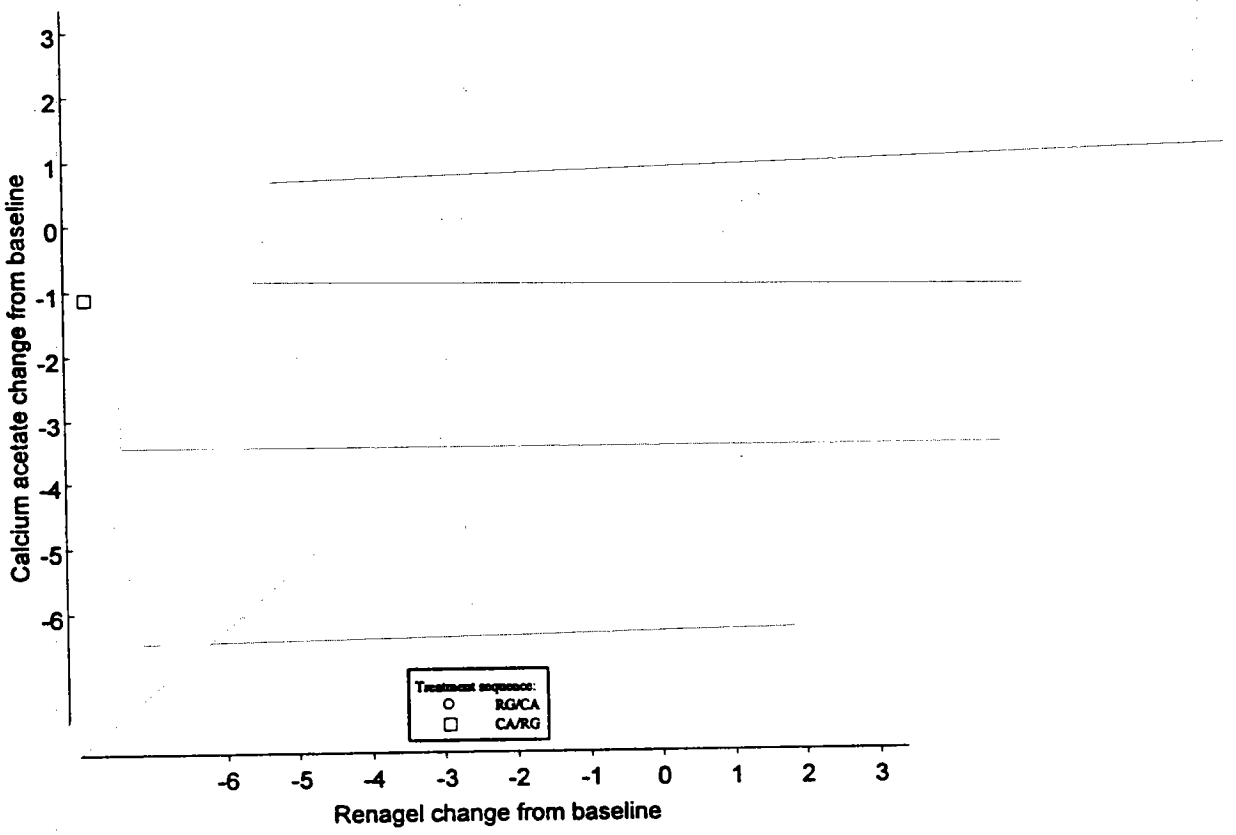

Figure 7 shows the change from baseline data for all patients at endpoint with the x-axis representing the Renagel response and the y-axis the calcium acetate response. Points close to the identity line indicate that the responses for those patients were similar on both treatments. For about 70% of the patients, phosphorus decreased on both treatments. Only 2% of the patients did not improve at all on either treatment; 17% of the patients improved on calcium acetate but not on Renagel and 11% of the patients improved on Renagel but not on calcium acetate. About 63% of the patients had a better response on calcium acetate than Renagel (points below the identity line in Figure 7).

Secondary Efficacy Variables

Serum Calcium

The sponsor performed analyses on serum calcium analogous to those performed for serum phosphorus. The ANOVA revealed a significant treatment effect ($p<.0001$) with greater increases observed for calcium acetate than Renagel (Table 8).

Table 8. Study 301
Serum Calcium at Baseline and Change at End of Treatment
Mean (SD)

	Period 1		Period 2	
	Renagel (Seq1) n=40	Ca Acetate (Seq2) n=40	Renagel (Seq2) n=40	Ca Acetate (Seq1) n=40
Baseline	9.0 (0.7)	9.1 (0.8)	9.1 (0.8)	9.1 (0.9)
Change	+0.1 (0.5)	+0.6 (0.8)	+0.2 (0.6)	+0.7 (0.7)

A graph of mean serum calcium by week, presented in Appendix 1 of this review, shows that treatment differences are evident at each week (except Week 13).

The product of calcium and phosphorus (Ca times P) is of clinical importance and therefore was examined by this reviewer; the product was not presented by the sponsor. A graph of the mean of the product by week, presented in Appendix 1 of this review, suggests no differences between the groups, so the differences in calcium observed for Renagel compared to calcium acetate do not translate into a benefit in the calcium phosphorus product.

In the sponsor's proposed labeling, it is suggested that a product greater than 66 can lead to adverse effects for the patient. This reviewer looked at the percentage of patients with values above 66; those numbers are summarized in Table 9 below. A higher percentage of the patients exposed to Renagel had a product of greater than 66 than calcium acetate patients; a difference of about 10% was observed whether one counted ≥ 1 or ≥ 2 events.

Table 9. Study 301
Phosphorus Calcium Product > 66
Reviewer's Analysis

	Renagel n=84	Ca Acetate n=84
Greater than 66 at 1 or more timepoints	74%	64%
Greater than 66 at 2 or more timepoints	50%	39%

The rate of hypercalcemic episodes (Ca≥10.4 mg/dL) was significantly higher for calcium acetate compared to Renagel (Table 10). Rates by week on treatment ranged from 11% to 24% for calcium acetate and from 1% to 7% for Renagel.

Table 10. Study 301
% of Patients with Hypercalcemic Episodes

	Period 1		Period 2	
	Renagel (Seq1) n=40	Ca Acetate (Seq2) n=40	Renagel (Seq2) n=40	Ca Acetate (Seq1) n=40
Any Timepoint	14.6%	50.0%	22.5%	40.0%

To look at the paired observations, this reviewer created Table 11 below which shows the concordant and discordant pairs. The majority of the patients (55%) had no hypercalcemic episodes on treatment; no patients had an episode on Renagel but not on calcium acetate.

Table 11. Hypercalcemic Episode at Any Timepoint

	On Calcium Acetate	
	Episode	No Episode
On Renagel		
Episode	14 (18%)	0 (0%)
No Episode	22 (28%)	44 (55%)

Serum Intact Parathyroid Hormone (iPTH)

Serum iPTH decreased on both treatments with larger decreases seen for calcium acetate (Table 12). ANOVA results showed no significant effects for treatment, sequence or treatment by sequence. The within treatment group effects were not significant for Renagel in the first period (p=.11) and were significant in the second period (p=.03); the calcium acetate changes were significant in both periods (p<.0003).

Table 12. Study 301
Serum iPTH and Change at End of Treatment

	Period 1		Period 2	
	Renagel (Seq1) n=36	Ca Acetate (Seq2) n=39	Renagel (Seq2) n=39	Ca Acetate (Seq1) n=36
Baseline				
Mean (SD)	409 (370)	458 (598)	449 (497)	401 (388)
Median	299	321	305	332
Change				
Mean (SD)	-54 (196)	-146 (283)	-43 (139)	-51 (293)
Median	-12	-59	-58	-100

Serum Lipid Levels

Serum lipid levels of total cholesterol (TC), LDL cholesterol, HDL cholesterol and triglycerides (TG) were measured at the end of each washout period and after 4 and 8 weeks of treatment in each period. Significant differences for changes in TC and LDL were observed between treatments with larger decreases observed for Renagel compared to calcium acetate ($p<.0001$, ANOVA) and within the Renagel treatment group ($p<.0001$, Wilcoxon Signed Rank test) (Table 13). No significant changes in HDL or TG were observed.

Table 13. Study 301
Serum Lipid Levels at Baseline and Change at End of Treatment
Mean (SD)

	Period 1		Period 2	
	Renagel (Seq1) n=37	Ca Acetate (Seq2) n=39	Renagel (Seq2) n=39	Ca Acetate (Seq1) n=37
TC (mg/dL)				
Baseline	177 (43)	169 (56)	170 (51)	165 (40)
Change	-32 (24)	+0.2 (18)	-22 (25)	+5.3 (21)
LDL (mg/dL)				
Baseline	107 (34)	107 (55)	98 (32)	104 (35)
Change	-28 (25)	-8 (43)	-23 (25)	+0.2 (20)
HDL (mg/dL)				
Baseline	38 (12)	38 (14)	39 (15)	36 (11)
Change	+1 (5)	-1 (6)	-1 (9)	+4 (7)
TG (mg/dL)				
Baseline	161 (116)	140 (111)	178 (175)	130 (62)
Change	-24 (70)	+38 (177)	+10 (78)	+6 (58)

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Reviewer's Comments on Study 301

The data from Study 301 shows that Renagel significantly decreases phosphorus levels after 8 weeks of therapy; this was the primary objective of the study. The secondary objective of the trial was to show that the effects on phosphorus were comparable for Renagel and calcium acetate. Comparability was not defined in the protocol or the study report and the sponsor makes no direct comments regarding comparability in the labeling. Several analyses performed by the sponsor and by this reviewer showed no significant differences in phosphorus lowering with both groups showing an average decrease of about 2 mg/dL (Table 14). The treatment difference and the confidence interval for the treatment difference slightly favor calcium acetate over Renagel. The confidence interval suggests that a difference as large as .75 in favor of calcium acetate over Renagel and a difference as large as .48 in favor of Renagel over calcium acetate are consistent with the data observed in this trial. If .75 is a difference that is clinically acceptable, then the sponsor has shown that Renagel is comparable to calcium acetate.

Table 14. Study 301 Phosphorus Change from Baseline at Endpoint

	Renagel	Ca Acetate	Mean Trt. Difference for Paired Differences1	95% Confidence Interval
Change from Baseline at Endpoint	-1.98	-2.13	-0.14	-0.75, 0.48

These paired differences are not statistically significant p=.65.

With regard to secondary endpoints, Renagel did not cause a significant increase in calcium compared to calcium acetate and produced significantly fewer hypercalcemic episodes (about 20% fewer). The phosphorus calcium product was not shown to be beneficially impacted by Renagel compared to calcium acetate. The effect on iPTH was similar for the 2 treatments. Renagel significantly decreased total cholesterol and LDL and did not affect TG and HDL..

1 The unpaired results are similar with a mean difference of -0.15 and 95% confidence interval of -0.80 to 0.49.

Study 302 (conducted 6/96 to 12/96)

Study 302 is an open label dose titration trial designed to study the effect of Renagel on serum phosphorus in hemodialysis patients. All patients with serum phosphorus>6mg/dL after a washout period of 2 weeks were treated with Renagel for a total of 8 weeks. The primary efficacy measure was change from baseline of serum phosphorus at the end of treatment. The treatment period was preceded by a 2 week washout period and followed by a 2 week washout period.

Starting doses (TID dosing with meals) were based on level of serum phosphorus after a 2-week washout period as shown below.

SERUM PHOSPHORUS	RENAGEL (capsule=.465g)
> 6.0 to < 7.5 mg/dL	6 capsules per day
≥7.5 to < 9.0 mg/dL	9 capsules per day
≥ 9.0 mg/dL	12 capsules per day

The dose could be titrated every 2 weeks to achieve a serum phosphorus level between 2.5 and 5.5 mg/dL. The maximum dose allowed was 21 capsules per day.

The treatment periods were as follows:

Washout 1	Weeks 1-2
Treatment	**Weeks 3-10**
Washout 2	Weeks 11-12

Patient Disposition and Demographics

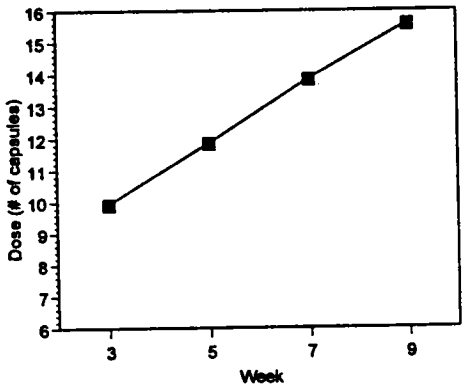
A total of 217 patients were screened at 16 sites; 168 of those patients received Renagel treatment, had valid post-baseline phosphorus data and comprised the ITT population. The primary reason for not receiving treatment was failure to meet the entry criterion for hyperphosphatemia (serum phosphorus>6 mg/dL). 144 patients completed eight weeks of treatment; the primary reason for noncompletion was an adverse event (17 patients).

Patients in the ITT population ranged in age from 18 to 86 years with mean of 53 years. 66% of the patients were male. A little more than half of the patients were black (52%); about one third were Caucasian. The primary causes of ESRD were hypertension (31%), nephritis (14%) and diabetes (23%). The average duration of dialysis was about 4 years (range of <1 to 20 years).

Dosing

Figure 8 depicts the mean prescribed dose at Weeks 3, 5, 7 and 9 (those are the weeks at which the dose could be titrated to the next level). The mean starting dose was 9.9 capsules (4.6 grams) and the mean ending dose was 15.5 capsules (7.2 grams). The final prescribed doses ranged from 6 to 24 capsules per day. About half of the patients began dosing at 12 capsules (the highest starting dose allowed). About one quarter of the patients attained the maximum dose of 21 capsules at the end of treatment.

Figure 8 Mean Prescribed Renagel Dose(capsules per day) by Week on Study



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Efficacy Results

Serum Phosphorus (Primary Efficacy Results)

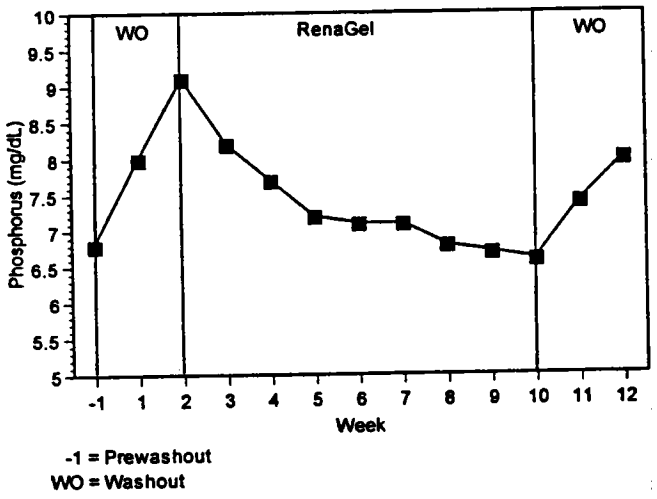
The change from baseline (last week of first washout period) from the last week on treatment was considered the primary endpoint according to the protocol. The average change from Week 2 to Week 10 was a decrease of about 2.5 mg/dL (Table 15, p<.0001, Wilcoxon signed rank test).

Table 15. Study 302
Serum Phosphorus at the End of Washout and Change at End of Treatment

	Renagel (N=168) Mean (SD)
End of Washout 1	9.1 (2.4)
End of Treatment Change	-2.5 (2.3)
End of Washout 2	8.0 (2.2)

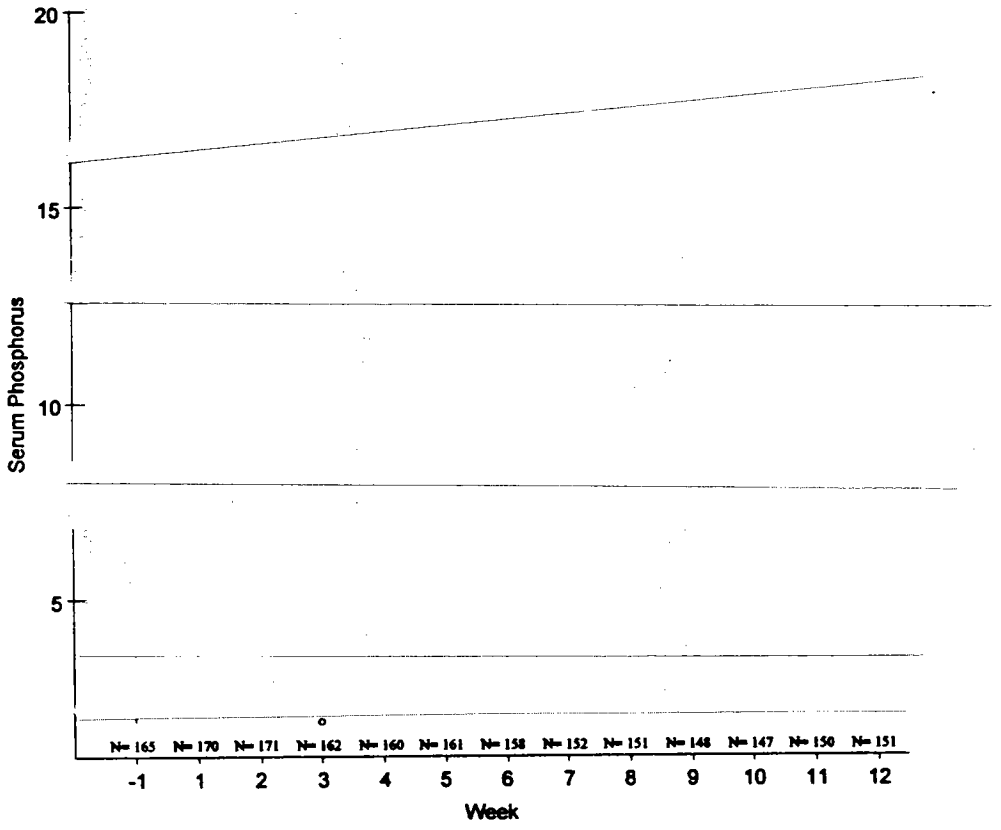
The mean serum phosphorus levels by visit (Figure 9) clearly show that over 8 weeks of treatment the phosphorus levels steadily decrease to the level at prewashout (Visit -1). Upon removel of Renagel, the phosphorus levels increase.

Figure 9 Mean Serum Phosphorus Levels Over the Duration of Study 302



The boxplots in Figure 10 below illustrate the distribution of the phosphorus data at each week on study. The downward shift is very evident during the treatment period of Weeks 3 to 10 and the Week 10 distribution indicates an improvement over the prewashout levels.

Figure 10 Boxplots by Visit for Study 302



According to the sponsor's definition of a responder (phosphorus at pre-washout level or ≤5.5 mg/dL), 81% of the patients were responders at some week during the treatment period; about 55% of the patients responded within the first 3 weeks of treatment. Using the alternate definitions for a responder presented in earlier for Study 301, this reviewer computed the percentage of responders (Table 16). A cutoff of 6 is clearly a more stringent definition producing responder rates of 65% when counting 1 or more timepoints and only 54% when counting only 2 or more timepoints; these values are not consistent with Study 301 where the rates were higher (80% and 63%, respectively).

Table 16. Study 302
% Responders
Reviewer's Analysis

	% of Responders
Phosphorus Response <u>at 1 or more timepoints</u>	
≤6	65%
% decrease ≥20%	85%
Phosphorus Response <u>at 2 or more timepoints</u>	
≤6	54%
% decrease ≥20%	76%

Secondary Efficacy Variables

Serum Calcium

The serum calcium levels increase an insignificant amount during Renagel treatment (mean of 0.3, Table 13). Plots created by this reviewer (see Appendix 2, page 24) showed essentially no shift in the calcium distribution after washout.

The incidence of hypercalcemic episodes (Ca>10.4) at the prewashout visit (Table 17) and during Renagel treatment are the same (22%). About half of the Renagel patients had only one episode during the whole treatment period (i.e. 12% had an episode at 2 or more timepoints).

Table 17. Study 302
Serum Calcium

	Mean (SD) At End of Period	Hypercalcemic Episodes at Anytime
Prewashout	9.6 (1.0)	22%
Washout 1	9.1 (0.8)	10%
Treatment Effect	+0.3 (0.6)	22%
Washout 2	9.2 (0.9)	14%

Serum iPTH

Serum iPTH is a highly variable measure with values at baseline (end of Washout 1) ranging from 36 to 2005; the mean and median changes were -90 and -63 respectively in the Renagel group (Table 18). These within group changes were statistically significant. The Renagel levels at endpoint are comparable to the prewashout levels.

Table 18. Study 302
Serum iPTH

	Median At End of Period	Mean (SD) At End of Period
Prewashout	208	333 (381)
Washout 1	316	450 (420)
Treatment Change	-63	-90 (222)
Washout 2	307	417 (390)

Serum Lipid Levels

The results for the serum lipid levels are consistent with what was observed in Study 301; TC and LDL significantly decrease while no changes in HDL and TG are evident (Table 19)

Table 19. Study 302
Serum Lipid Levels

	TC	LDL	HDL	TG
Washout 1	171	102	35	170
Treatment Change (% change)	-26 (-14%)	-26 (-18%)	0 (+2%)	+3 (+13%)
Washout 2	168	101	35	165

Study 901 (Extension Study)

Study 901 was a long-term extension study designed to follow patients, who had been previously treated in a Renagel dose titration study, for 44 weeks (Study Weeks 3 to 46) on open-label Renagel treatment. Baseline for this study was the patient's value after washout and before Renagel treatment in their previous study.

The investigator determined a Renagel starting dose based on the patient's previous Renagel experience, the patients dietary phosphate intake, and the investigator's clinical judgment. At weeks 3, 4, and 6 and then every four weeks, the investigator could titrate the Renagel dose in an attempt to achieve a serum phosphorus level between 2.5 and 5.5 mg/dL, inclusive. The sponsor defined 3 dose levels to examine dose-response relationships; Low (<4.5 g or <9.7 capsules), Medium (4.5-6 g or 9.7 to 12.9 capsules) and High (>6 g or >12.9 capsules). The percentage of patients at each dose level at the onset of therapy and the average over the duration of therapy is shown below.

Dose Level	Starting Dose	Average Dose on Study
Low	42%	30%
Medium	23%	25%
High	35%	45%

A total of 192 patients were enrolled in this study; the number of patients by previous study are shown in the table below. Most of the patients in 901 came from the Phase 3 studies (301 and 302); about half of the patients enrolled in all the studies continued into the long-term extension.

Table 20. Patient enrollment in Study 901

Previous Study	# (%) in 901	% of Previous Study
202	8 (4%)	17%
203	29 (15%)	31%
301	63 (33%)	75%
302	92 (48%)	53%
All	192 (100%)	48%

Of the 192 patients enrolled, 111 (58%) patients completed the full 44 weeks of Renagel treatment.

The demographic profile of the 901 patients was similar to the profile in each study.

The results for several parameters suggested by the medical reviewer are presented as boxplots in Appendix 3 (pages 25 to 35).

The results for serum phosphorus show that the effect is sustained for the duration of the 44 weeks and, when Renagel treatment is withdrawn, phosphorus levels return to baseline levels (see boxplot on page 26). About 55% of patients who completed the 44 weeks of treatment showed a decrease of 2 or greater at endpoint; about 25% of these completers had attained a phosphorus level of about 5.

Serum calcium and iPTH show no changes overtime; this was also true if results were examined by dose level.

No significant changes in chloride, CO2, ferritin, hemoglobin, iron binding capacity, iron saturation, RBC, total iron, PT and Vitamins A , E and D1,25-hydroxy were observed. The data does suggest that Vitamin D 25-hydroxy decreases over time (page 34). This was evident at each dose with more variability seen at the medium and high doses.

Reviewer's Overall Comments

The sponsor has presented results from 2 Phase 3 8-week trials. Both of these trials were open-label studies; Study 301 was a crossover trial with calcium acetate as the comparator and Study 302 was uncontrolled.

The results from Studies 301 and 302 show that Renagel significantly and consistently decreases the serum phosphorus level from baseline (Table 21). About 50% of the patients in each study showed endpoint decreases of 2 or greater. Only about ¼ of the patients had their phosphorus level reduced to a value under 5.5.

LDL and TC were significantly reduced by more than 20% with Renagel treatment. HDL and TG did not change.

In Study 301, the sponsor showed that hypercalcemic episodes were significantly reduced for Renagel over calcium acetate (see Tables 10 and 11).

Table 21. Renagel Efficacy Results at Endpoint (Week 8 LOCF) for ITT Sample
Studies 301 and 302

	Study 301 (N=84)	Study 302 (N=168)
Phosphorus (mg/dL)		
Baseline	8.4	9.1
Mean at endpoint	6.4	6.6
Mean change	-2.0	-2.5
Calcium (mg/dL)		
Baseline	9.1	9.1
Mean at endpoint	9.3	9.4
Mean change	+0.2	+0.3
Hypercalcemic episodes at anytime during treatment (% of patients)		
≥10.4	18.5%	21.9%
≥11	4.9%	10.5%
iPTH (mg/dL)		
Baseline	305	316
Median at endpoint	262	224
Median change	-32	-63
TC (mg/dL)		
Baseline	173	172
Mean at endpoint	147	144
Mean change	-27	-26
LDL (mg/dL)		
Baseline	103	158
Mean at endpoint	77	149
Mean change	-25	-27
HDL (mg/dL)		
Baseline	38	36
Mean at endpoint	38	35
Mean change	0	+0.5
TG (mg/dL)		
Baseline	170	174
Mean at endpoint	163	176
Mean change	-7	+3

The results for Study 901, a long-term extension study, show that the effects seen in the 8-week Phase 3 studies are sustained for up to 44 weeks.

There may be some concern that both Phase 3 studies are open-label studies and that a lack of blinding may bias results. Due to the consistency of the results across studies (including the Phase 2 studies not presented in this review), the objectivity of the primary endpoint (serum phosphorus) and the clear changes seen when Renagel was withdrawn, this reviewer believes the results are robust to the lack of blinding. Overall the results from Studies 301 and 302 support the sponsor's claim that Renagel lowers serum phosphorus and reduces hypercalcemic episodes. Also labeling statements regarding lipid lowering (LDL and TC) are supported by the data.

/S/

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Joy D. Mele, M.S.
Mathematical Statistician

Concur:

Ed Nevius, Ph.D.
Director of DOB2

/S/ 10/9/98

Todd Sahlroot, Ph.D.
Team Leader DOB2

/S/ 10/8/98

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ON ORIGINAL

cc:
Archival NDA#20-926
HFD-510
HFD-510/BSchneider, GTroendle, SSobel
HFD-715/Division 2 File, Chron, JMele, TSahlroot

Mele/x76376/DOB2/Word-Renagel.rev/10/6/98

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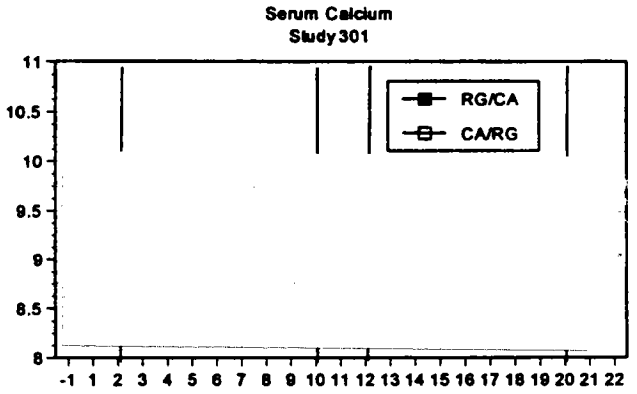
Appendix 1.



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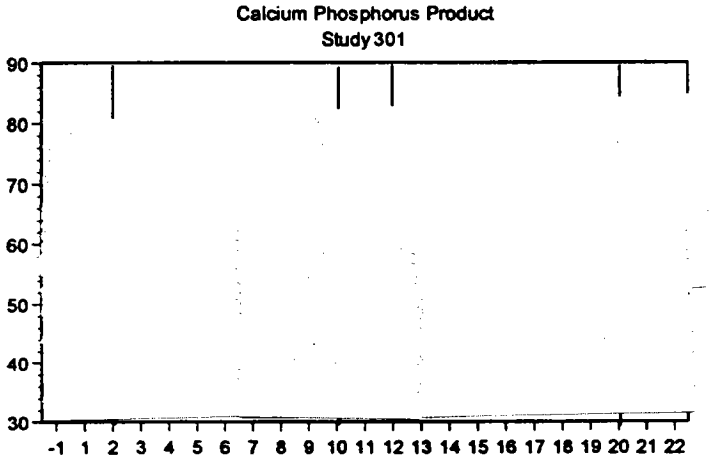

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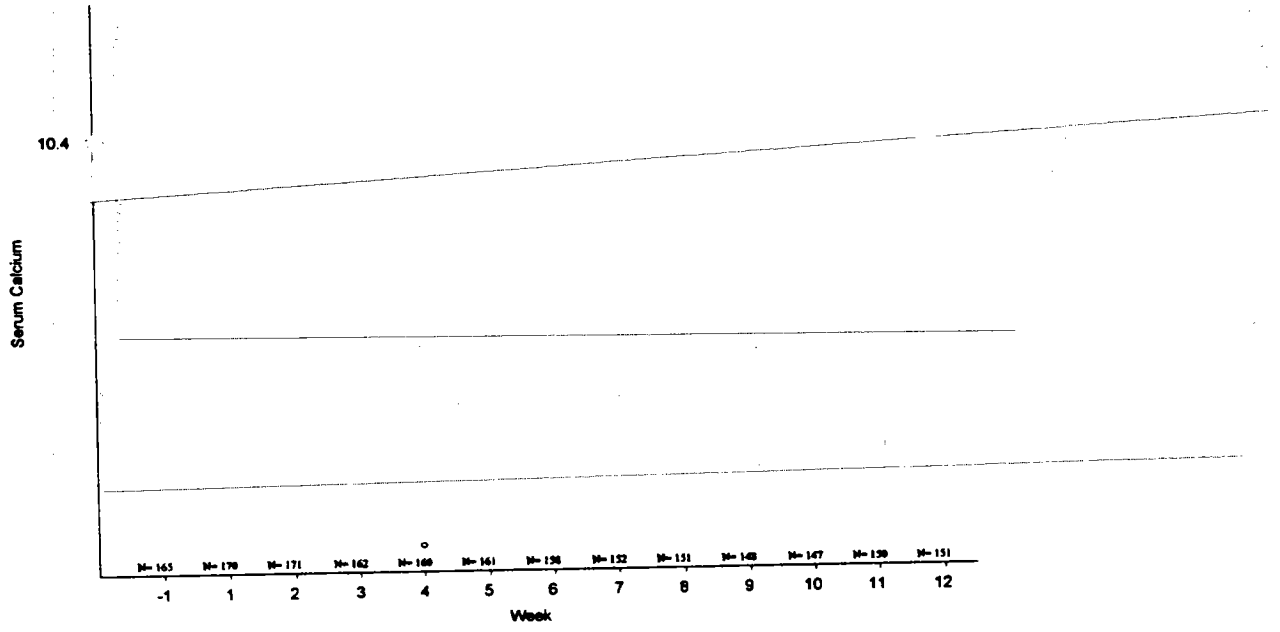
Appendix 2. Serum Calcium Boxplots for Study 302



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Appendix 3. Boxplots for Study 901

Details about the boxplots for Study 901:

1. Visit -99 represents the end of washout before Renagel treatment from the previous study in which the patient participated.
2. The Renagel treatment period runs from Visit 3 to Visit 46.
3. Visits 47 and 48 are during washout.
4. The oval in the middle of the box represents the median.
5. The box shows the range from the 25th to the 75th percentile.
6. Outliers are shown as symbols beyond the whiskers.

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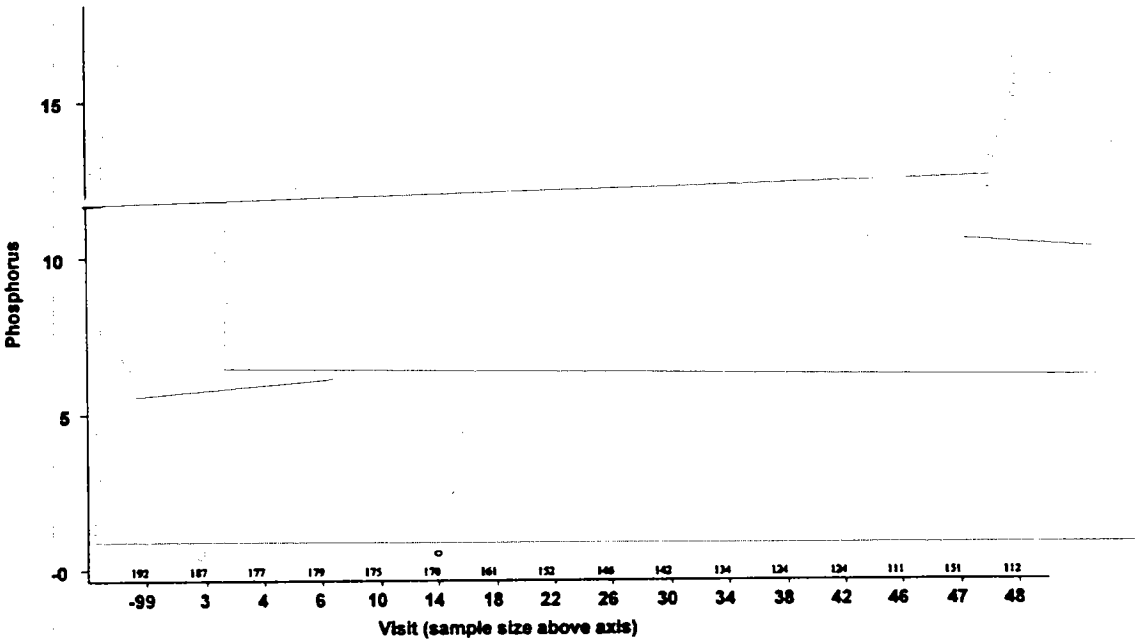
Phosphorus
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10
5
-0
192 187 177 179 175 170 161 152 146 142 134 124 124 111 151 112
-99 3 4 6 10 14 18 22 26 30 34 38 42 46 47 48
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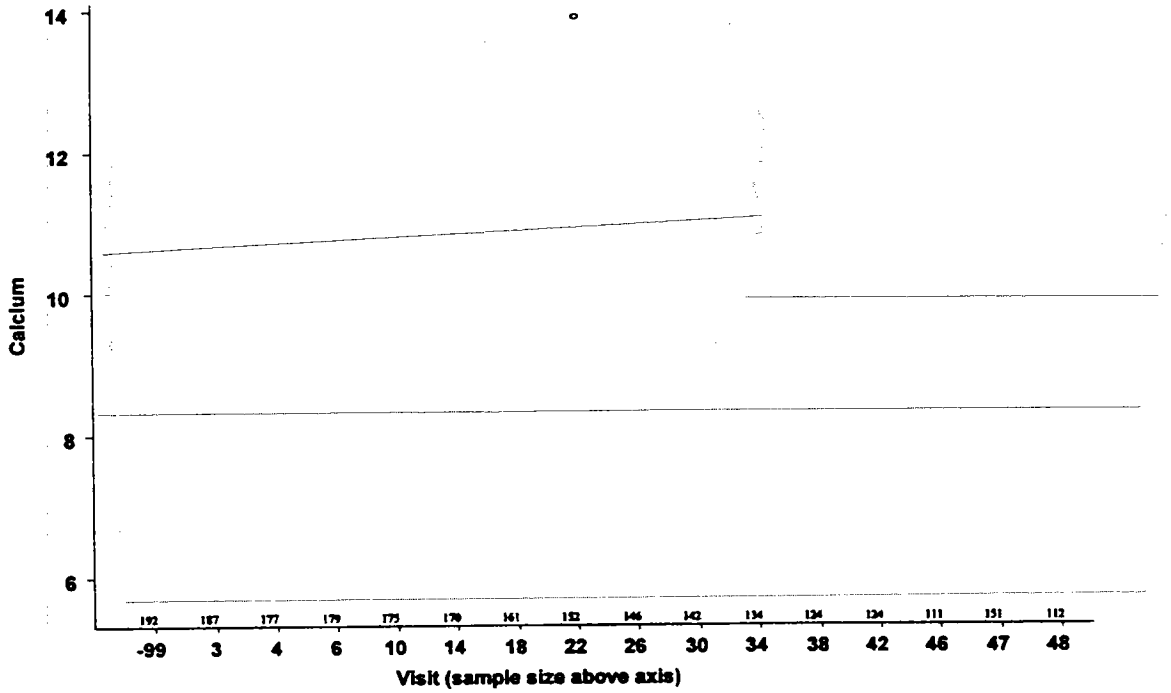
Calcium
14
12
10
8
6
192 187 177 179 175 170 161 152 146 142 134 124 124 111 151 112
-99 3 4 6 10 14 18 22 26 30 34 38 42 46 47 48
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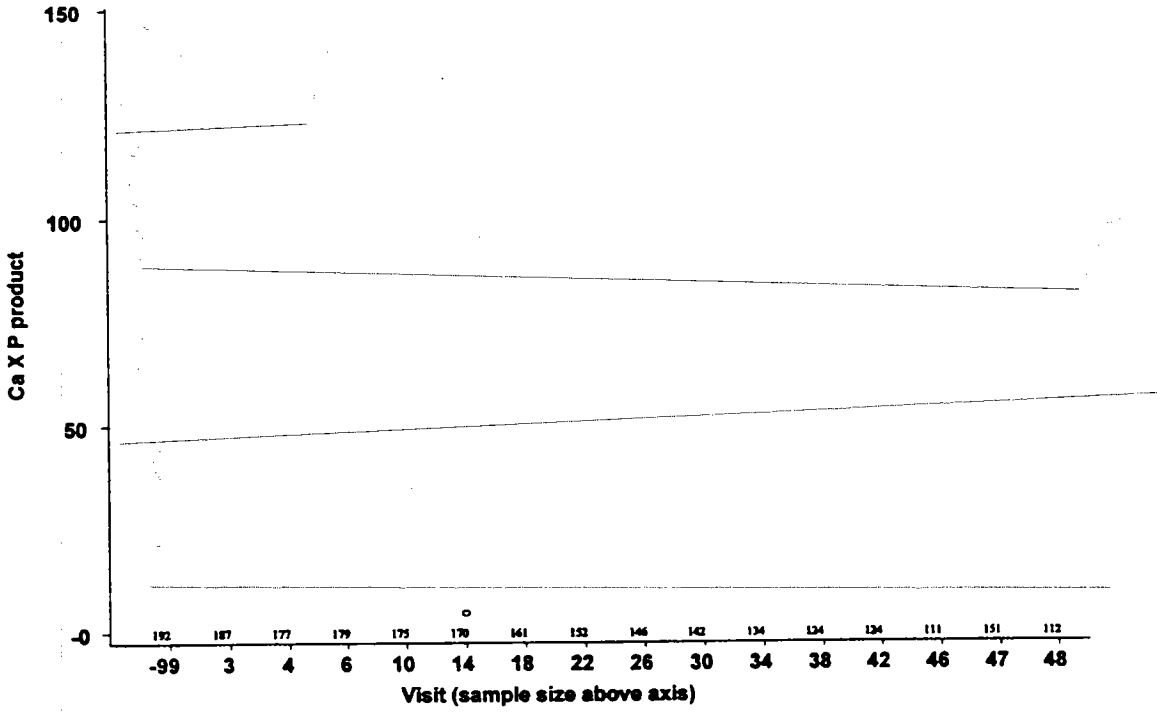
150
100
50
-0
Ca X P product
192 187 177 179 175 170 161 152 146 142 134 134 134 111 151 112
-99 3 4 6 10 14 18 22 26 30 34 38 42 46 47 48
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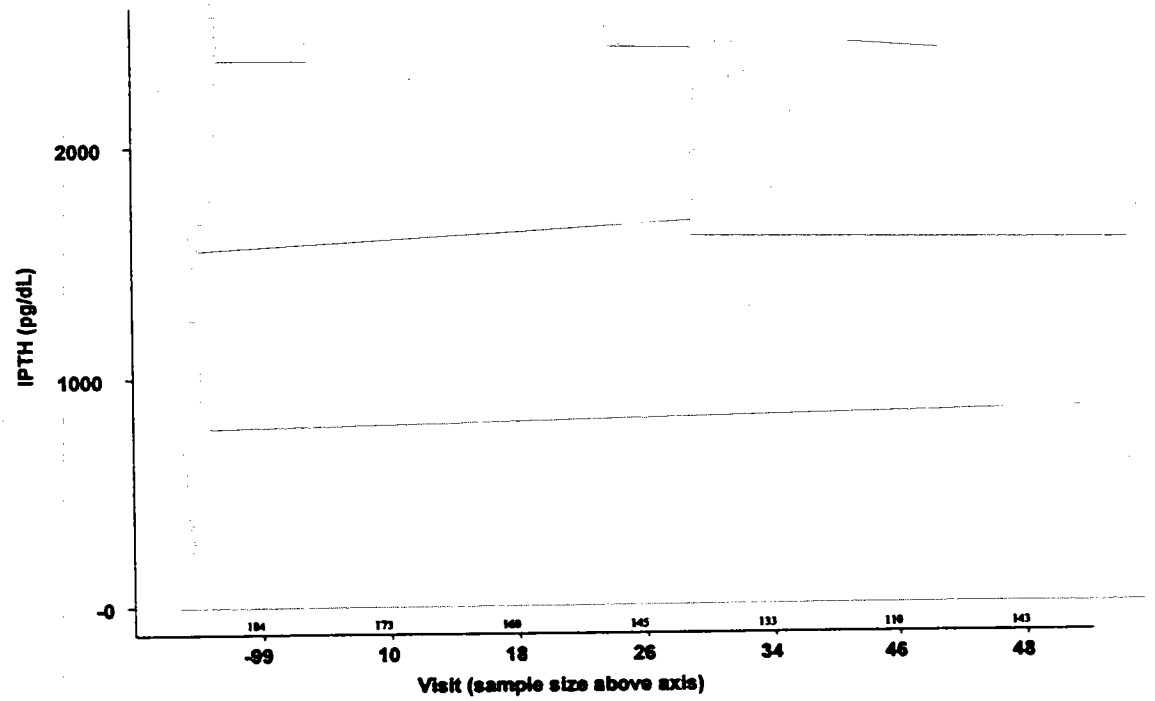
2000
1000
-0
IPTH (pg/dL)
184 173 160 145 133 110 143
-99 10 18 26 34 46 48
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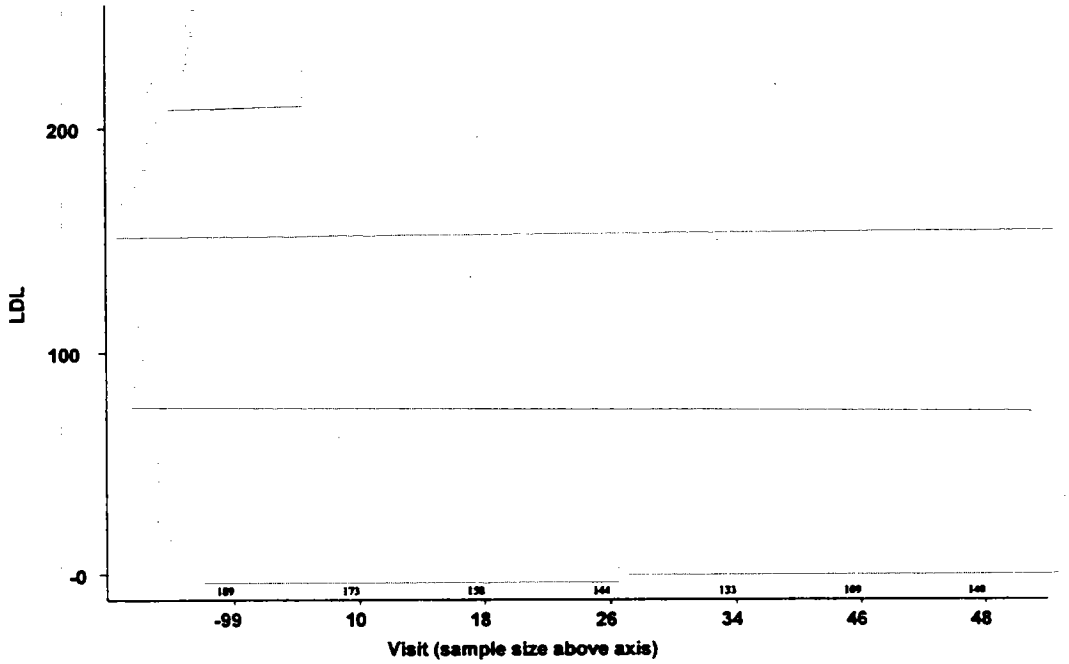

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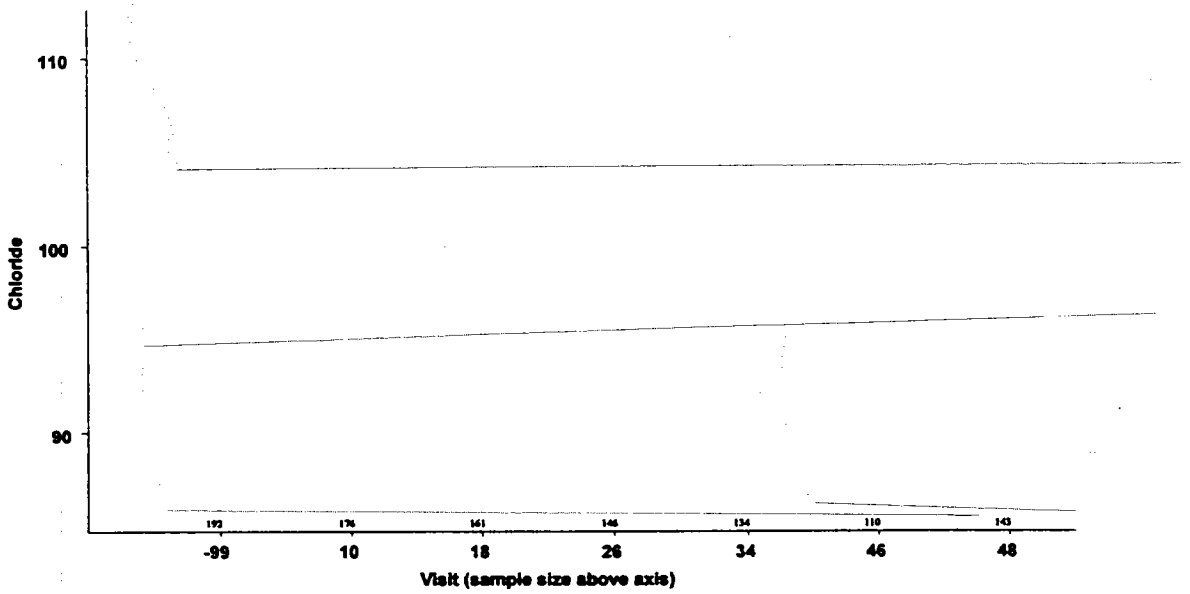
Chloride
110
100
90
192
176
161
146
134
110
143
-99
10
18
26
34
46
48
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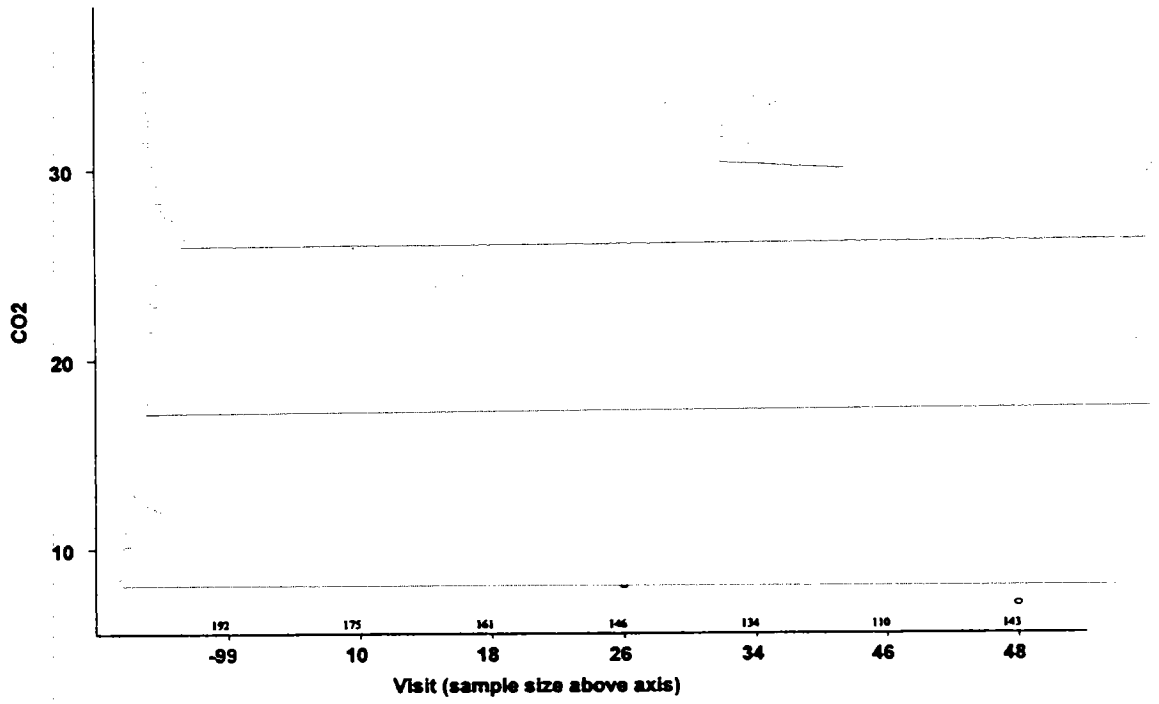
CO2
30
20
10
192
175
161
146
134
110
143
-99
10
18
26
34
46
48
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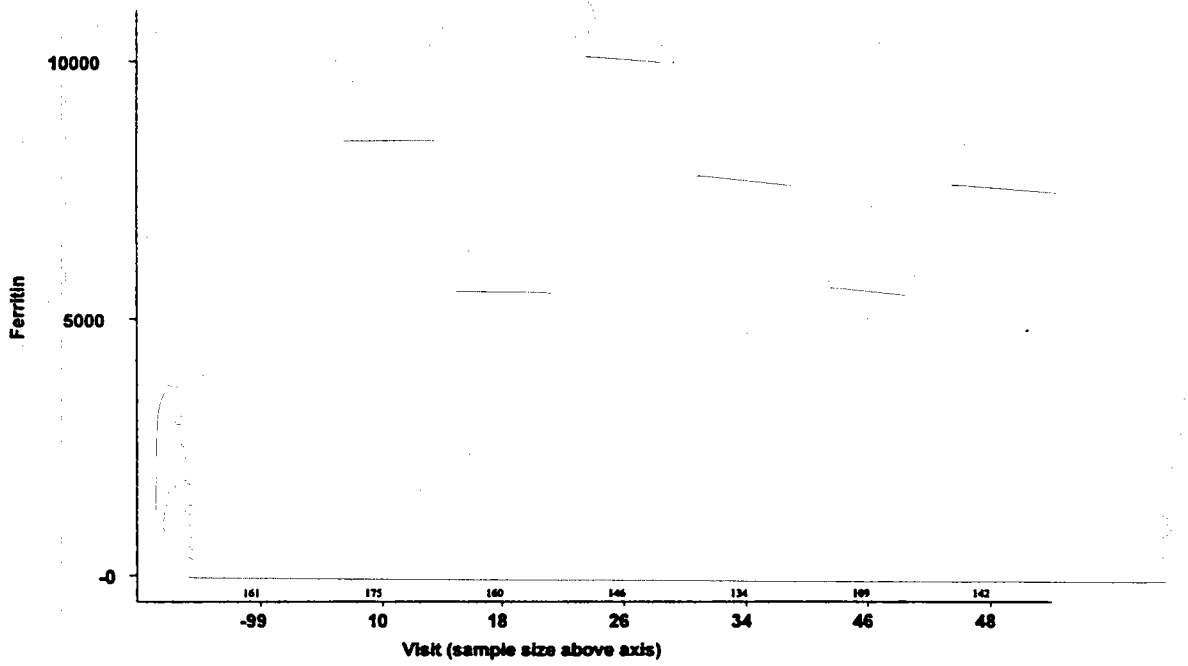
10000
5000
-0
Ferritin
161
175
160
146
134
109
142
-99
10
18
26
34
46
48
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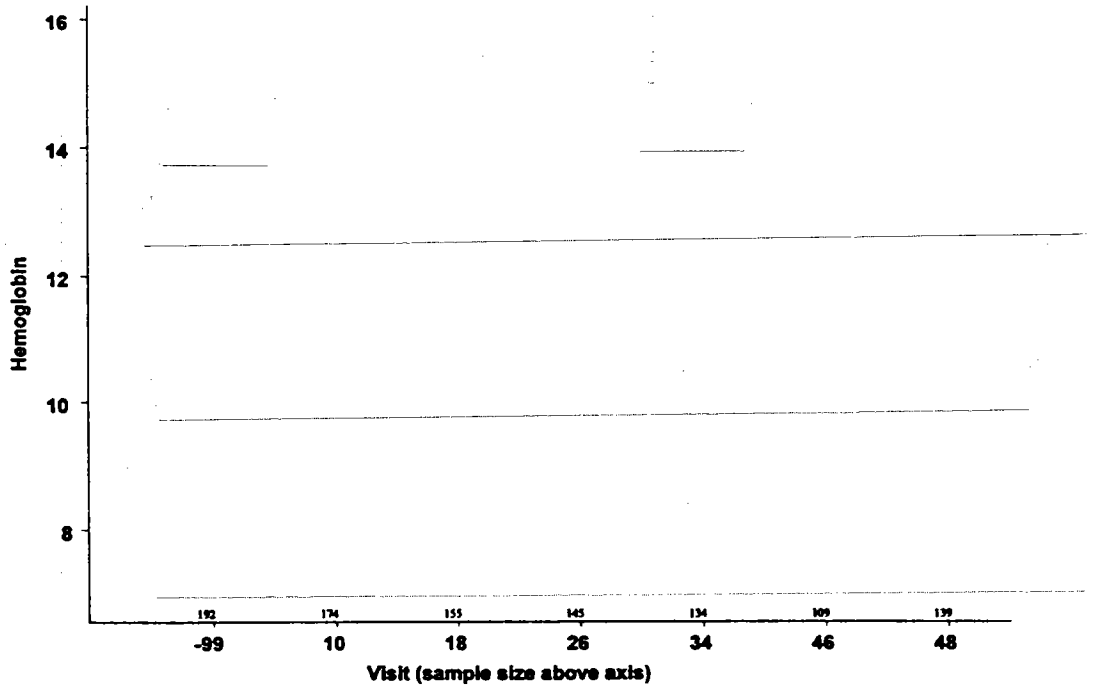
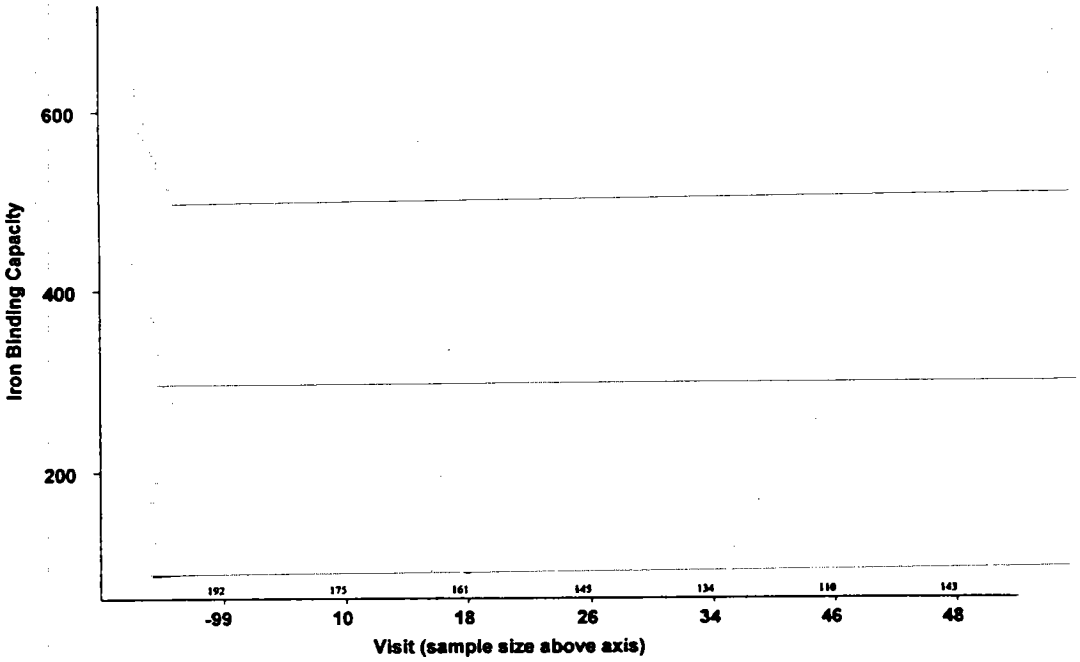

16
14
12
10
8
Hemoglobin
192
174
155
145
134
109
139
-99
10
18
26
34
46
48
Visit (sample size above axis)


Iron Binding Capacity
600
400
200
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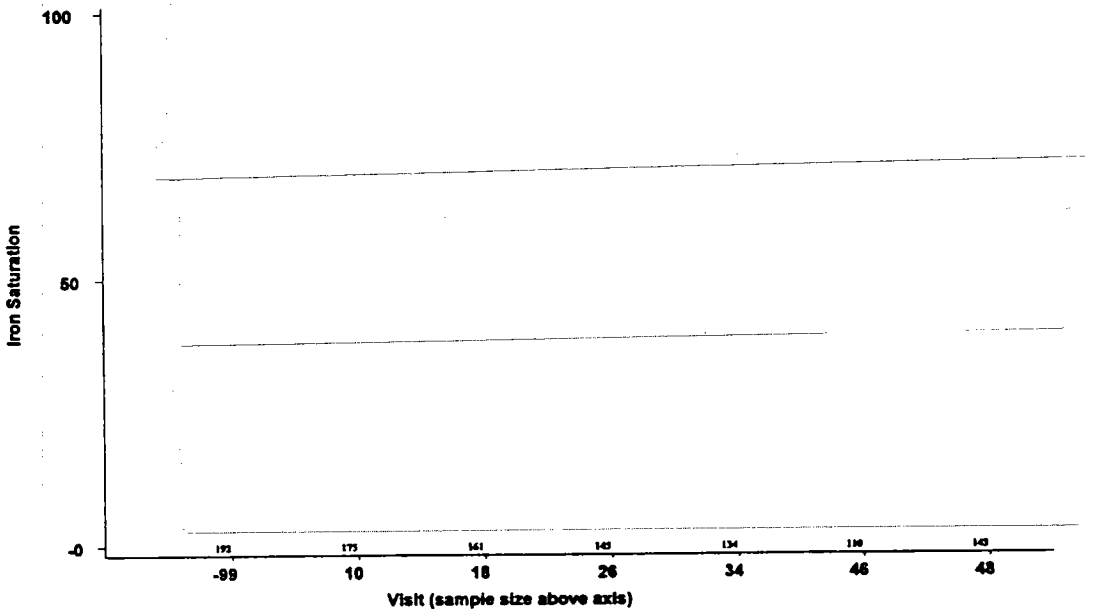
175
161
145
134
110
143
-99
10
18
26
34
46
48
Visit (sample size above axis)


Iron Saturation
100
50
-0
193
175
161
145
134
110
143
-99
10
18
26
34
46
48
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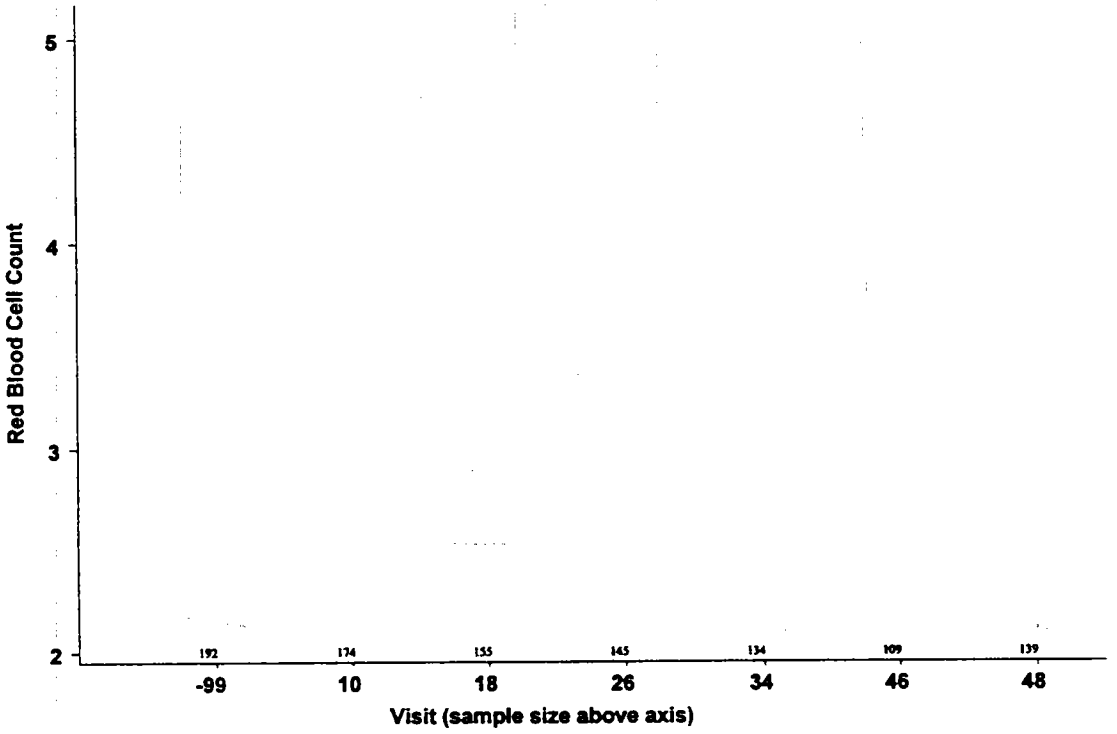
Red Blood Cell Count
5
4
3
2
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174
155
145
134
109
139
-99
10
18
26
34
46
48
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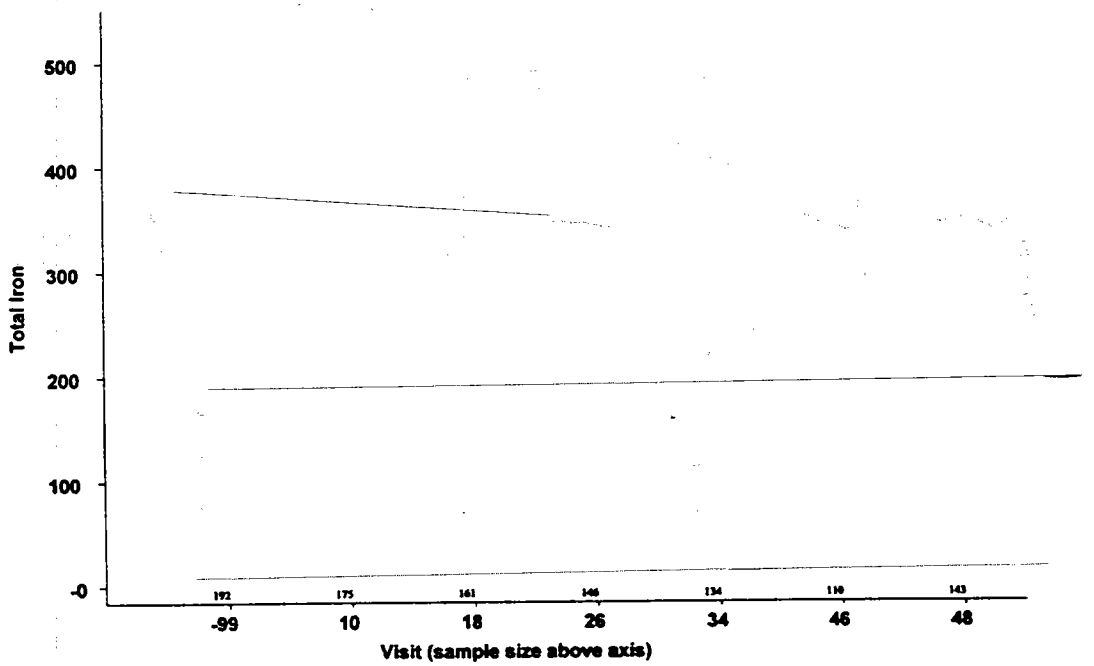
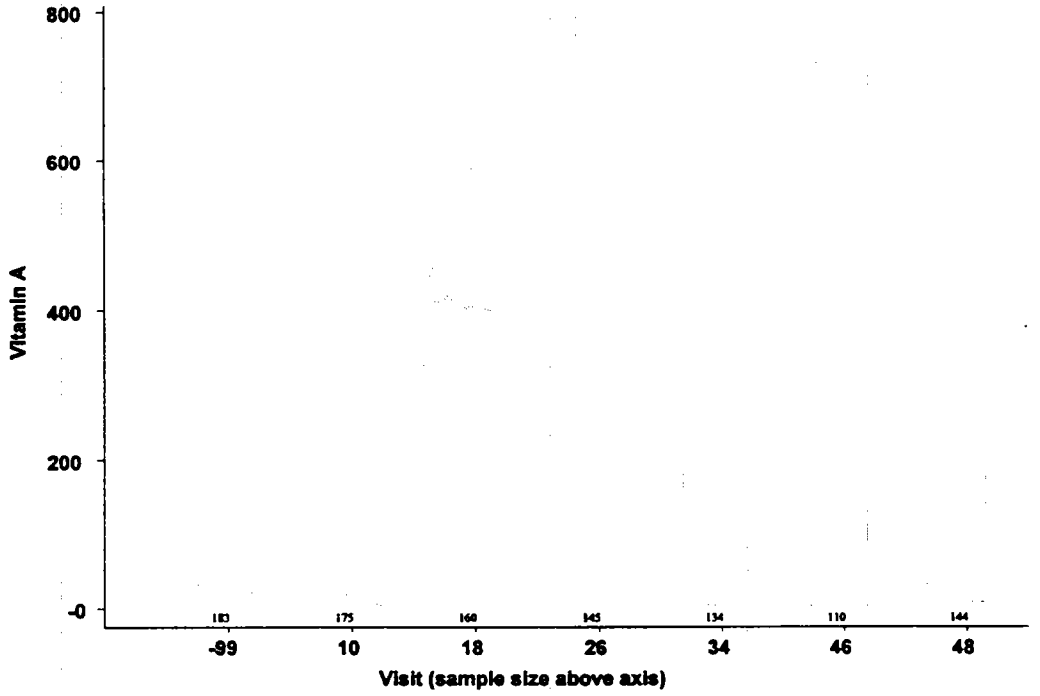
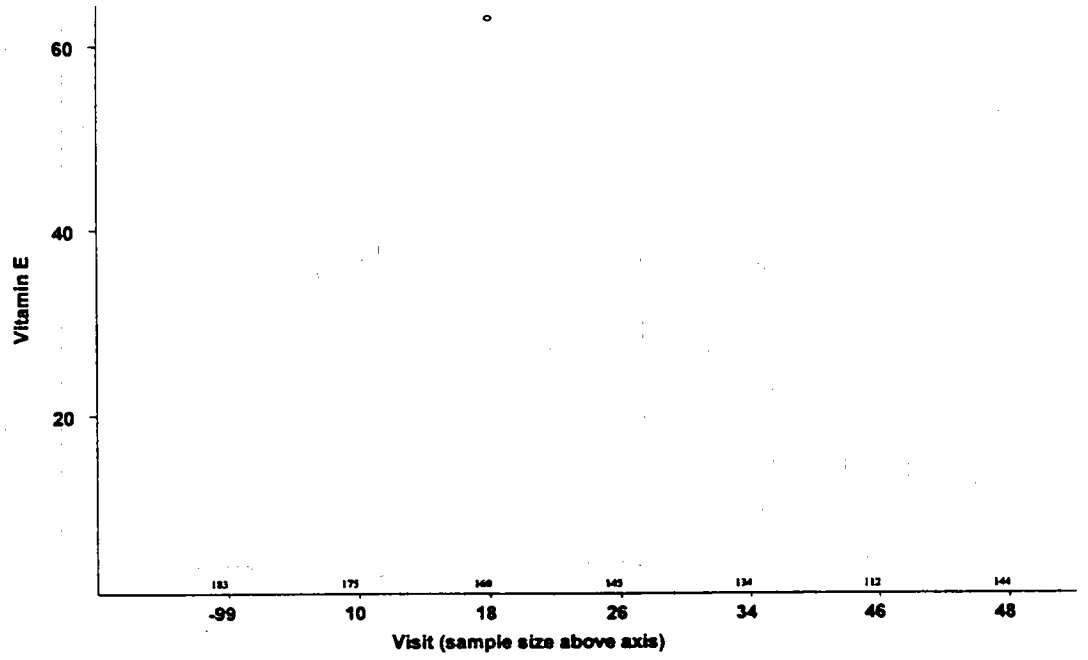

Total Iron
500
400
300
200
100
-0
192
175
161
146
134
110
143
-99
10
18
26
34
46
48
Visit (sample size above axis)


800
600
400
200
-0
Vitamin A
183
175
160
145
134
110
144
-99
10
18
26
34
46
48
Visit (sample size above axis)


60
40
20
Vitamin E
183
175
160
145
134
112
144
-99
10
18
26
34
46
48
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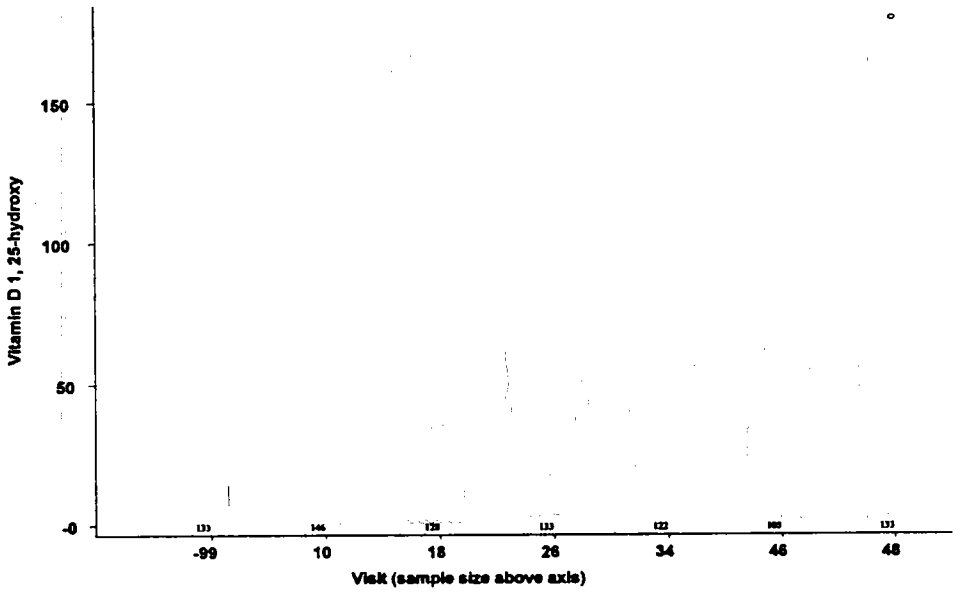
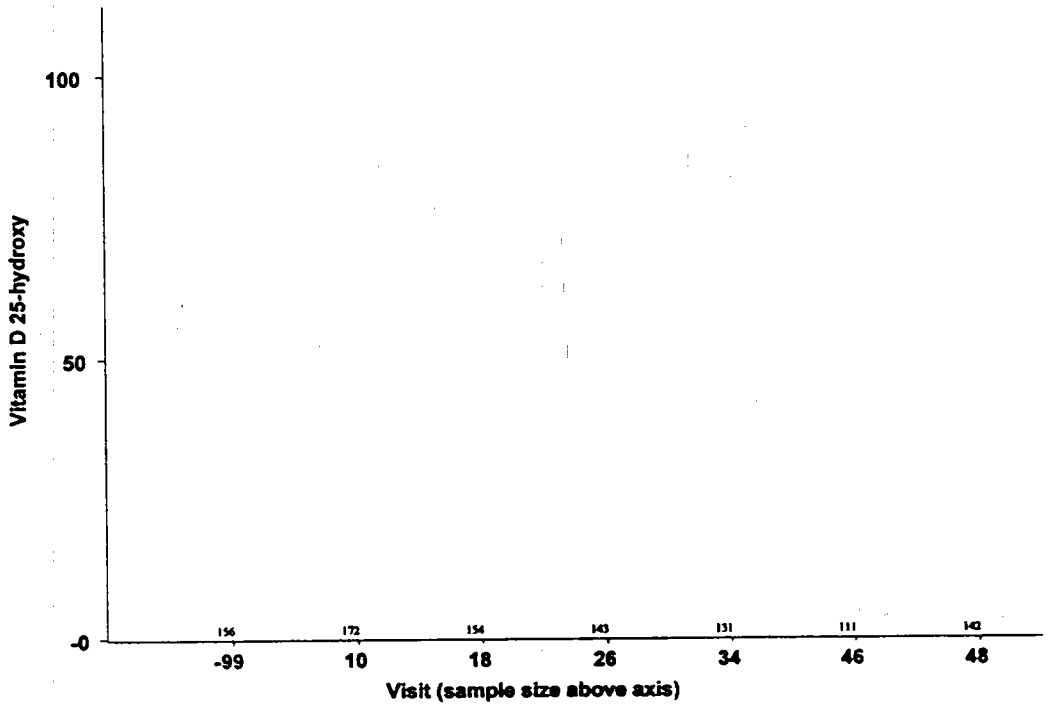
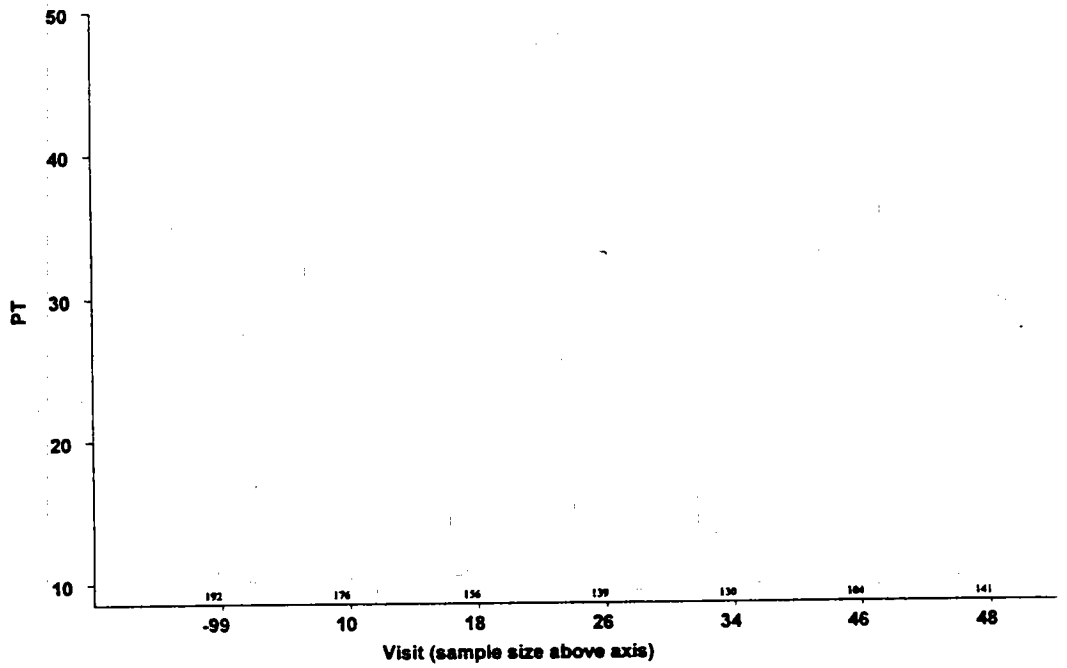

Vitamin D 1, 25-hydroxy
150
100
50
-0
-99
10
18
26
34
46
48
Visit (sample size above axis)


Vitamin D 25-hydroxy
100
50
-0
156
172
154
143
131
111
142
-99
10
18
26
34
46
48
Visit (sample size above axis)



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