

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-318**

**CLINICAL PHARMACOLOGY AND**  
**BIOPHARMACEUTICS REVIEW(S)**

## OFFICE OF CLINICAL PHARMACOLOGY REVIEW

---

NDA: 22-318	Submission Dates: March 31, 2008, January 6, 2009
Brand Name (proposed)	Renvela®
Generic Name	Sevelamer Carbonate
Reviewer	Islam R. Younis
Team Leader (Acting)	Robert O. Kumi
DCP	1
OND	Cardiovascular and Renal Drug Products
Applicant	Genzyme
Formulation, Strength	Powder, 2.4 g
Class/Indication	Phosphate Binder

---

**Background**

This review is an addendum to the clinical pharmacology review for NDA 21-318 by Genzyme; it evaluates a sevelamer carbonate-digoxin drug-drug interaction study. Genzyme listed this study as part of the NDA 22-318 submission without submitting the final study report. The office of clinical pharmacology review for NDA 22-318 was finalized on December 10<sup>th</sup>, 2008. Genzyme submitted the clinical pharmacology report for the sevelamer carbonate-digoxin drug-drug interaction study on January 6<sup>th</sup>, 2009.

**Recommendation**

The Office of Clinical Pharmacology finds the information included in the sevelamer carbonate-digoxin drug-drug interaction study acceptable. The following sentence should be added to the sevelamer carbonate powder for suspension label: **“In 18 healthy subjects receiving 9.6 grams of sevelamer carbonate once daily, sevelamer did not alter the pharmacokinetics of a single dose of digoxin”**.

Islam R. Younis, Ph.D.  
Reviewer, Clinical Pharmacology  
Division of Clinical Pharmacology I

Concurrence:

Robert O. Kumi, Ph.D.  
Team Leader (Acting), Clinical Pharmacology  
Cardio-Renal Drug Products  
Division of Clinical Pharmacology

---

	SVCARB01307
Investigator	Dennis Ruff, MD
Study Site	Healthcare Discoveries, Inc. San Antonio, TX 78209
Study Period	09/04/2007 - 11/30/2007

---

**Title**

An open label study to assess the potential pharmacokinetic interaction of a single dose of sevelamer carbonate powder with a single dose of oral digoxin and to investigate the pharmacodynamic effects of sevelamer carbonate on phosphorus absorption and excretion in healthy volunteers

**Objectives (Per Applicant):**

*Primary objective:* To investigate the effects of sevelamer carbonate powder for oral suspension on the pharmacokinetics of oral digoxin.

*Secondary Objectives:*

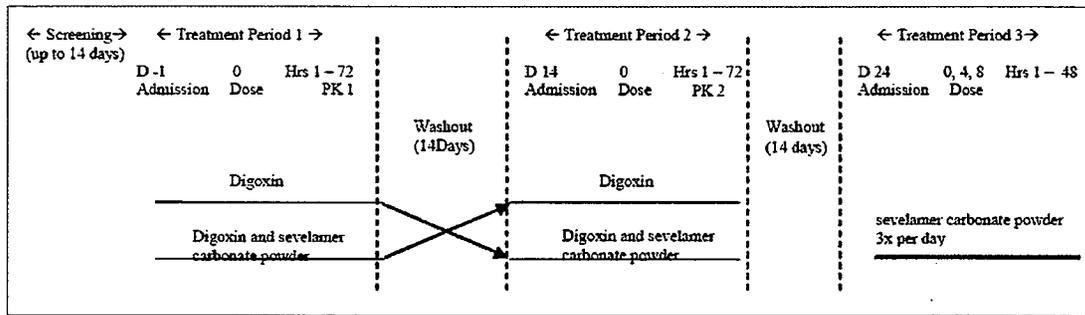
1. To assess the safety/tolerability of a single dose concomitant administration of sevelamer carbonate powder and oral digoxin.
2. To investigate the pharmacodynamic effects of sevelamer carbonate in healthy subjects on phosphorus absorption and excretion over time.

**Study Rationale**

Of relevance, the polymer drugs cholestyramine and colestipol (bile acid sequestering agents) interact with digoxin in humans. Digoxin has a narrow therapeutic window and it is commonly used in chronic kidney disease patients because of the significant incidence of cardiac disease in this population

**Study Design**

This was a single center, randomized, open-label, cross-over drug-drug interaction study in healthy volunteers. Digoxin dose was 1 mg (4 tablets x 0.25 mg qd) and sevelamer carbonate dose was 9.6 g (3 packets x 3.2 g mixed with 240 mL qd). The study schema is provided below:



### Test drugs

Digoxin/sevelamer were administered orally:

1. Digoxin: 0.25 mg tablets, (lot #. 007006 and 012106)
2. Sevelamer carbonate powder for suspension: (lot #. 45917)

b(4)

### Pharmacokinetic Sampling

Plasma samples for digoxin assay were collected pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 8, 12, 24, 36, 48, 60 and 72 hours post-dose during Periods 1 and 2.

### Statistical Method (Per applicant)

Digoxin pharmacokinetic parameters ( $AUC_{0-72}$  and  $C_{max}$ ) were computed by standard non-compartmental methods of analysis

Analyses of variance (ANOVA) was performed on the natural log transformed  $AUC_{0-72}$ ,  $AUC_{0-\infty}$ , and  $C_{max}$  parameters. The ANOVA model included sequence, regimen, and period as fixed effects, and subject nested within sequence as a random effect. Each ANOVA was used to calculate least squares means (LSM), the difference between regimen LSM, and the standard error associated with this difference. Exponentiation of the difference and associated 90% confidence interval yielded estimates of the (digoxin+sevelamer) / (digoxin alone) ratio and its 90% confidence interval. Equivalence between treatments was to be declared if the entire 90% confidence interval for the ratio of means both  $AUC_{0-72}$  and  $C_{max}$  were entirely contained within the interval {80 to 125%}. Otherwise, non-equivalence was to be declared.  $T_{max}$  was analyzed using Wilcoxon signed-ranks test. Statistical significance was declared if the p-value for the test was less than 0.05.

### Analytical Method

The quantification of digoxin in plasma was performed using an LC-MS/MS method. The method had a linear range of 0.05 to 8.0 ng/mL. The accuracy and precision of quality control samples were  $\leq 4.2\%$  and 0.3 - 4.4%, respectively. The long-term stability of digoxin in human plasma stored at  $-20^{\circ}\text{C}$  was 117 days.

According to the sponsor all samples were analyzed within the long term stability window.

**Reviewer Note:** A Validation report for the analytical methods was not provided by the sponsor.

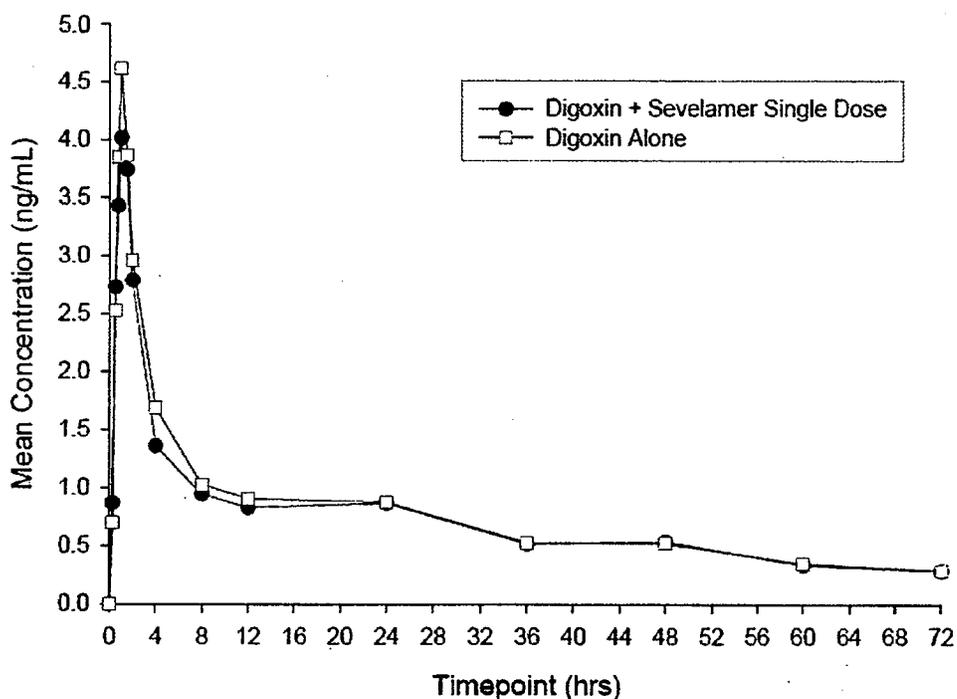
## Results

### Study Population

Eighteen healthy subjects, 10 males and 8 females, participated in the study with mean age of  $31.8 \pm 8.0$  (range 18.0 - 50 years).

### Pharmacokinetics

The co-administration of sevelamer carbonate did not alter the systemic exposure ( $C_{max}$  and  $AUC_{0-72}$ ) of digoxin as shown in the table below and Figure 1.



**Figure 1.** Mean digoxin plasma concentration-time profiles following oral administration of digoxin alone, and the co-administration digoxin and sevelamer carbonate.

Dependent Variable	Geometric Means		Ratio (T/R)	90% CI	
	Digoxin & Sevelamer Carbonate (T)	Digoxin Alone (R)		Lower	Upper
$AUC_{0-72}$ (ng h/mL)	4.22	4.35	96.9	81.5	115.2
$C_{max}$ (ng/mL)	50.69	52.03	97.4	91.1	104.23

The analysis excludes data from one subject who had digoxin  $C_{\max}$  of 10.1 ng/mL, following the administration of digoxin alone. The sponsor considered this value to be an outlier, using the T Procedure, compared to the  $C_{\max}$  values for the other subjects that ranged from 2.48 ng/mL to 6.29 ng/mL. The inclusion of this patient data in the analysis changes the lower bound of the 90% CI to 79.3.

**Reviewer Note:** The reviewer agrees with the sponsor analysis, given that the high digoxin  $C_{\max}$  value was observed following the administration of digoxin alone. As a result, this relatively high digoxin  $C_{\max}$  value can be attributed to instantaneous unexplained period effect in that subject and not due to the co-administration of sevelamer carbonate.

### **Safety Results (Per Applicant)**

No death or serious adverse events occurred during this study. All treatment adverse events were mild or moderate in intensity.

### **Conclusions**

Based on  $AUC_{0-72}$  and  $C_{\max}$  the exposure to digoxin was not impacted by the co-administration of sevelamer carbonate.

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Islam R Younis  
2/13/2009 02:10:08 PM  
PHARMACIST

Robert Kumi  
2/17/2009 11:50:52 AM  
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

---

NDA: 22-318	Submission Date: March 31, 2008
Brand Name (proposed)	Renvela®
Generic Name	Sevelamer Carbonate
Reviewer	Islam R. Younis
Team Leader	Robert O. Kumi (Acting)
DCP	1
OND	Cardiovascular and Renal Drug Products
Applicant	Genzyme
Formulation, Strength	Powder, 2.4 g
Class/Indication	Phosphate Binder

---

## Table of Content

1.0 Executive Summary.....	3
1.1 Recommendations.....	3
1.2 Phase 4 Study Commitments:.....	4
1.3 Summary of Clinical Pharmacology/ Biopharmaceutics Findings.....	4
2.0 Question Based Review.....	5
2.1 General attribute of sevelamer products.....	5
2.2 General clinical pharmacology.....	6
2.3 Intrinsic Factors.....	7
2.4 Extrinsic Factors.....	7
2.5 General Biopharmaceutics.....	8
2.6 Analytical Section.....	10
3. Labeling Recommendations.....	11
4. Appendices.....	12
4.1 Package Insert (proposed).....	12
4.2 Clinical Pharmacology and biopharmaceutics individual study review.....	28

## 1.0 Executive Summary

Genzyme submitted NDA 22-318, Renvela<sup>®</sup> powder for oral suspension (sevelamer carbonate) on March 31, 2008. The applicant has developed sevelamer carbonate powder for oral suspension as a phosphate binder for use in controlling serum phosphorus in patients with chronic kidney disease. The applicant proposed using the powder as an alternative formulation to sevelamer carbonate tablets (NDA 22-127) approved on October 19, 2007.

The sevelamer carbonate clinical development plan consisted of *in vitro* bioequivalence studies, three clinical studies, and two clinical pharmacology (drug-drug interaction) studies

### 1.1 Recommendations

The Office of Clinical Pharmacology I finds the information submitted to NDA 22-318 acceptable. The information establishes the *in vitro* bioequivalence between sevelamer hydrochloride tablets, sevelamer carbonate tablets, and sevelamer carbonate powder. The following comments are to be conveyed to the sponsor:

1. Comments on the *in vitro* bioequivalence studies:
  - I. In future submissions, please provide an explanation for the difference in phosphate binding affinity constant between sevelamer carbonate tablet and sevelamer carbonate powders
  - II. The sponsor should have provided disintegration time data for the sevelamer carbonate tablet formulation
  - III. There is a discrepancy in the SAS transformed data set and data sets provided in biopharmaceutics legacy study report (TR 2119-06-SC: Drug Discovery & Development Technical MEMO). This discrepancy should be avoided in future submissions.
2. Comments on sevelamer carbonate warfarin drug-drug interaction study:
  1. The study design and analysis have the following deficiencies:
    - I. Plasma sampling up to 72 hours is insufficient to characterize the pharmacokinetics of warfarin based on its long half-life of ~2.5 days. In future studies, plasma sampling as long as 168 hours is recommended.
    - II. The sponsor did not provide a thorough analysis of the effect of simultaneous administration of sevelamer carbonate and warfarin on the International Normalization Ratio (INR). In future studies, such analysis should be performed by the sponsor.
  2. The sponsor should have provided a full validation report for warfarin bioanalytical method.
3. The sponsor should provide the full report for sevelamer carbonate powder-digoxin drug-drug interaction study. The findings of this study will be added to sevelamer carbonate powder label,

once submitted and reviewed. The current labeling language of no interaction between sevelamer hydrochloride tablet and digoxin is acceptable.

### 1.2 Phase 4 Study Commitments: None

### 1.3 Summary of Clinical Pharmacology/ Biopharmaceutics Findings

1. Sevelamer carbonate powder and tablet formulations have similar binding capacity to phosphate as sevelamer hydrochloride tablet formulation following acid pretreatment. The binding affinity of sevelamer carbonate powder and tablet formulations to phosphate is less than that of the sevelamer hydrochloride tablet formulation without acid pretreatment. Phosphate binding affinity and capacity is similar between sevelamer carbonate powder and tablet formulations. In the following table  $k_1$  represents phosphate affinity constant, while  $k_2$  represents phosphate binding constant.

Formulation	Without Acid Pretreatment		With Acid Pretreatment	
	$k_1$ (mmol <sup>-1</sup> )	$k_2$ (mmol/g)	$k_1$ (mmol <sup>-1</sup> )	$k_2$ (mmol/g)
Sevelamer hydrochloride tablets (800 mg, lot #. 20769)	0.85	6.15	0.63	6.66
Sevelamer carbonate tablets (800 mg, lot #. 21069)	0.26	6.76	0.74	6.52
Sevelamer carbonate sachets (800 mg, lot #. 31136)	0.33	6.39	0.50	7.33
Sevelamer carbonate sachets (2.4 g, lot #. 30265)	0.33	6.39	0.85	6.70

2. The kinetics of phosphate binding of sevelamer carbonate powder and tablet formulations is comparable to that of the sevelamer hydrochloride tablet formulation.

3. There is no pharmacokinetic drug-drug interaction between sevelamer carbonate powder and warfarin.

12/01/2008

Islam R. Younis, Ph.D.  
Division of Clinical Pharmacology 1  
Office of Clinical Pharmacology

Date

FT signed by Robert Kumi, Ph.D. (Acting Team Leader)

Cc: NDA 22-241, HFD 110, HFD-860 (Younis, Mehta, Uppoor)

## 2.0 Question Based Review

A shortened version of the QBR will be adapted for this clinical pharmacology review since key QBR elements have been addressed previously in NDA 21-179 and NDA 22-127. The current NDA is a formulation change of sevelamer carbonate from tablets to powder.

### 2.1 General attributes of sevelamer products

Sevelamer hydrochloride capsule was approved in the US on October 30, 1998 (NDA 20-962), while sevelamer hydrochloride tablet was approved on July 12, 2000 (NDA 21-179). Sevelamer carbonate tablet was approved on October 19, 2007 (NDA 22-127).

#### *What is the main basis for developing sevelamer carbonate powder?*

Sevelamer carbonate powder was developed to overcome difficulty in swallowing tablets and capsules. The powder will benefit patients who require multiple tablets with each meal, or those who dislike or have difficulty using solid dosage forms of medications.

#### *2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation?*

Sevelamer carbonate [poly(allyaamine-co-N,N'-diallyl-1,3-diamino-2-hydroxypropane carbonate salt)] is a non-absorbed cross-linked polymer that is formulated in a powder form. Sevelamer carbonate powder for oral suspension is provided in a presentation containing 2.4 g of anhydrous sevelamer carbonate. Each 2.4 g sachet contains approximately \_\_\_\_\_ of the drug substance. \_\_\_\_\_ the remaining \_\_\_\_\_ is made up of excipients (Table 1).

b(4)

**Table 1.** Composition of sevelamer carbonate powder.

Component	Function	Composition per Unit Dose (%)	Composition per Unit Dose (mg)
Anhydrous Sevelamer Carbonate	Drug Substance		2400
Natural & Artificial Citrus Cream			
Propylene glycol alginate			
Sodium Chloride			
Sucralose			
Ferric Oxide (yellow)			

b(4)

**2.1.2. What are the proposed mechanism of action and therapeutic indication of sevelamer carbonate powder?**

Mechanism of Action: Sevelamer is a phosphate sequestering agent that binds phosphate in the small intestine. The bound phosphate will not be absorbed into the blood and will be excreted in the feces.

Proposed indication: Hyperphosphatemia (serum phosphorus level > 5.5 mg/dL) in patients with chronic kidney disease.

**2.1.3. What is the proposed dosage and route of administration?**

The pharmaceutical dosage form for sevelamer carbonate is 2.4 g powder for oral suspension. The dosing frequency will be 800 mg three times a day with meals. The label does not explain how to accurately dose 800 mg sevelamer carbonate powder out of the 2.4 g sevelamer carbonate powder sachets.

**2.2 General clinical pharmacology**

**2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?**

Three clinical studies and two clinical pharmacology study were conducted during the development of sevelamer carbonate powder for oral suspension (Table 2). The full report for study SVCARB01307 was not submitted, the sponsor is planning to submit the final report in December of 2008.

**Table 2.** Summary of sevelamer carbonate clinical studies.

Study #.	Objectives	General Design	Test Products	Duration	Number of subjects
SVCARB00205	Safety and efficacy	- Multicenter - Randomized - Open-label - Crossover	- Sevelamer carbonate powder: 800 mg mixed with water TID with meals. - Sevelamer HCl tablets: 800 mg TID with meals.	15 weeks	76 screened, 31 randomized
GD3-199-301	Safety and efficacy	- Multicenter - Randomized - Open-label - Parallel	- Sevelamer carbonate powder: 2.4g sachets mixed with water taken orally QD - Sevelamer HCl tablets: 800 mg taken orally TID	26 weeks	217 randomized
SVCRB01107	Drug-drug interaction	- One center - Open label - Crossover	- Sevelamer carbonate powder 4 x 2.4 g mixed with 8 oz water - Warfarin: 2 x 10 mg tablets	3 weeks	18 randomized
SVCARB01307	Drug-drug interaction	- One center - Open label - Crossover	- Sevelamer carbonate powder 3 x 3.2 g mixed with water - Digoxin: 4 x 0.25 mg tablets	NA	18 randomized

**2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies?**

Change in serum phosphorus level was the primary response endpoint. This is a well established marker for hyperphosphatemia and was accepted by the division of Cardiovascular and Renal Products.

**2.2.3 Exposure-response**

Exposure-response was not evaluated in this NDA.

**2.3 Intrinsic Factors**

Intrinsic factors were not evaluated in this NDA.

**2.4 Extrinsic Factors**

**2.4.1 What is the basis for conducting sevelamer-warfarin interaction study?**

The major potential mechanism by which sevelamer carbonate can interact with other drugs is by affecting their absorption. Of relevance, cholestyramine (non-absorbable bile acid sequestering-resin) interacts with warfarin in humans. Potential drug interactions with warfarin are of particular interest because it has a narrow therapeutic index and is commonly used in chronic kidney disease patients, because of the significant incidence of cardiac disease in this population.

**2.4.2 Is there is a drug-drug interaction between sevelamer carbonate powder and warfarin?**

No. The rate and extent of absorption (bioavailability) of warfarin was not impacted by the simultaneous administration of sevelamer carbonate powder, based on  $C_{max}$ ,  $AUC_{0-72}$ , and  $AUC_{0-\infty}$  (Table 3).

**Table 3.** R-warfarin and S-warfarin pharmacokinetics following warfarin administration (Reference), and sevelamer carbonate plus warfarin administration (Test).

	Dependent Variable	Geometric Means		Ratio (T/R)	90% CI	
		Test	Reference		Lower	Upper
<b>R-warfarin</b>	$C_{max}$	1168.0	1203.9	97.0	90.4	104.1
	$AUC_{0-72}$	42990.4	41565.7	103.4	98.7	108.4
	$AUC_{0-\infty}$	69122.0	63311.9	109.2	100.0	119.2
<b>S-Warfarin</b>	$C_{max}$	1124.6	1168.4	96.3	89.3	103.8
	$AUC_{0-72}$	31830.6	30878.8	103.1	98.0	108.5
	$AUC_{0-\infty}$	44359.5	42125.0	105.3	99.8	111.2

The sponsor did not analyze the effect of co-administration of sevelamer carbonate powder with warfarin on the international normalization ratio (INR), relative to the administration of warfarin alone. In the case of warfarin, even though a pharmacokinetic (PK) drug-drug interaction may not be present, a pharmacodynamic (PD) drug-drug interaction may be present and should be explored. The reviewer analysis of  $AUC_{INR0-1}$  did not show any PD interaction. In future submissions, both PK and PD analysis should be performed by the sponsor.

## 2.5 General Biopharmaceutics

### 2.5.1 What is the basis for conducting the *in vitro* bioequivalence studies?

Sevelamer salts are not absorbed into the systemic circulation, and so standard pharmacokinetic, dissolution or bioavailability studies are not appropriate to demonstrate the equivalency of sevelamer salts and/or formulations.

In order to show equivalency of sevelamer carbonate powder to sevelamer hydrochloride tablets, the sponsor conducted equilibrium binding and kinetic binding studies. This approach is consistent with FDA's 1993 Interim Guidance entitled, "Cholestyramine Powder *In Vitro* Bioequivalence". These *in vitro* studies were conducted to potentially demonstrate equivalency of the tested products in terms of affinity and binding constants derived from the equilibrium binding studies, and in terms of the ability to bind phosphate at the same rate in a zero ordered manner, derived from the kinetic studies.

The applicant also postulated the clinical efficacy of sevelamer carbonate powder is dependent on the phosphate binding capabilities of sevelamer.

### 2.5.4 How do the *in vitro* phosphate binding conditions and specifications ensure *in vivo* performance and quality of the product?

The *in vitro* bioequivalence studies help to demonstrate the equivalency in quality among the tested products. The value of these studies in demonstrating the *in vivo* performance is not established.

Sevelamer carbonate powder was compared to sevelamer hydrochloride tablets (reference product). Binding affinity ( $k_1$ ) and binding capacity ( $k_2$ ) were evaluated with and without acid pretreatment. Binding kinetics were evaluated at low and high phosphate concentration. The results showed similarity in the binding capacity of the two products. The binding affinity of sevelamer hydrochloride tablets was higher than sevelamer carbonate powder, without acid pretreatment. Tables 4 and 5 summarize the affinity and binding constants.

**Table 4.** Affinity and binding constants for sevelamer without acid pretreatment

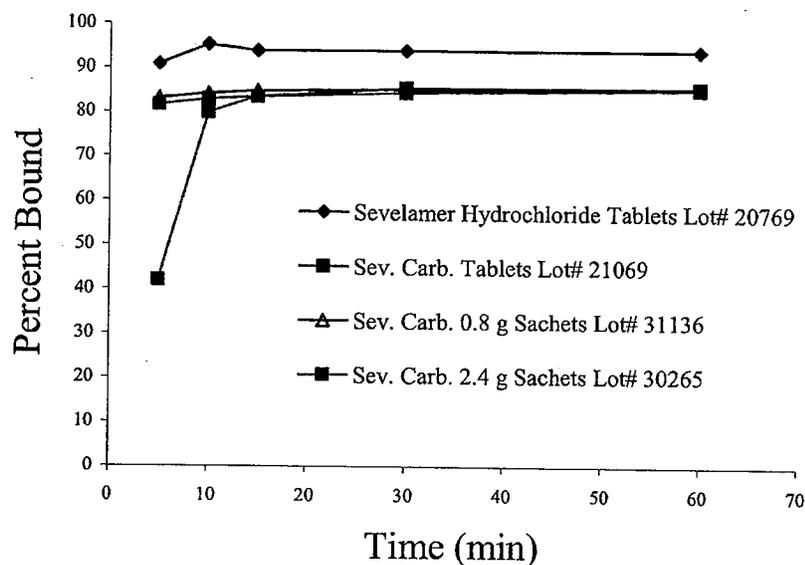
Formulation	$k_1$ ( $\text{mmol}^{-1}$ )	$k_2$ ( $\text{mmol/g}$ )
Sevelamer hydrochloride tablets (800 mg, lot #. 20769)	0.85	6.15
Sevelamer carbonate tablets (800 mg, lot #. 21069)	0.26	6.76
Sevelamer carbonate sachets (800 mg, lot #. 31136)	0.33	6.39
Sevelamer carbonate sachets (2.4 g, lot #. 30265)	0.33	6.39

**Table 5.** Affinity and binding constants for sevelamer with acid pretreatment

Formulation	$k_1$ ( $\text{mmol}^{-1}$ )	$k_2$ ( $\text{mmol/g}$ )
Sevelamer hydrochloride tablets (800 mg, lot #. 20769)	0.63	6.66
Sevelamer carbonate tablets (800 mg, lot #. 21069)	0.74	6.52
Sevelamer carbonate sachets (800 mg, lot #. 31136)	0.50	7.33
Sevelamer carbonate sachets (2.4 g, lot #. 30265)	0.85	6.70

Graphically, the kinetics of binding were comparable across sevelamer formulations (Figures 1 and 2). However, a similarity factor ( $f_2$ ) approach comparison indicated that:

- Sevelamer carbonate tablets exhibited a different kinetic profile at low phosphate concentrations compared to sevelamer hydrochloride tablets.
- Sevelamer carbonate powder had similar binding kinetics profiles to sevelamer hydrochloride tablets at low phosphate concentration.
- Both Sevelamer carbonate powder and tablet had similar binding kinetics profiles to sevelamer hydrochloride tablets at high phosphate concentration.

**Figure 1.** Phosphate binding profile at 2.5 mM

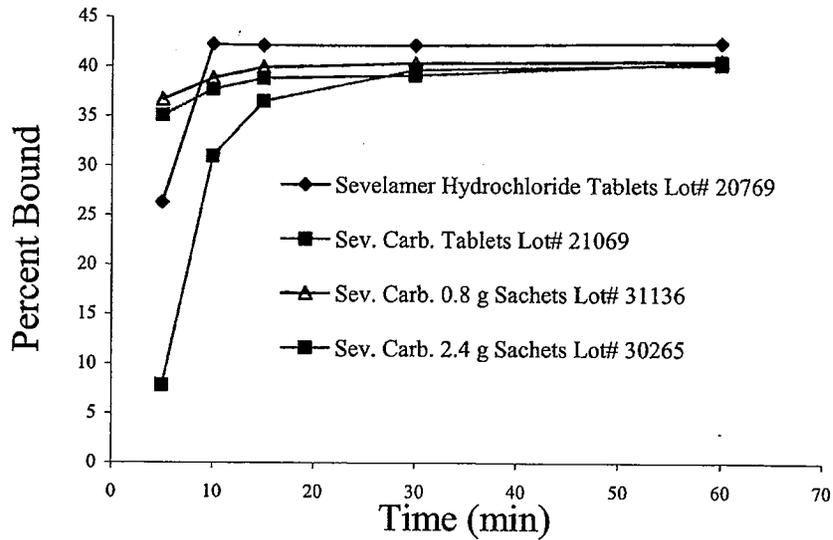


Figure 2. Phosphate binding profile at 38.7 mM

## 2.6 Analytical Section

### 2.6.1. How are the active moieties identified and measured in the plasma in the clinical and biopharmaceutics studies?

This NDA did not contain analytical information for the measurement of the active moieties. However, similar analytical methods as those for NDA 21-179 were employed for assessment of phosphate binding. Please refer to NDA-179 for details.

In the warfarin-sevelamer carbonate powder drug-drug interaction study, the sponsor did not provide a full validation report for warfarin bioanalytical method. Since the warfarin assay is well established, the bioanalytical method information provided in the study report were considered sufficient for the purpose of this review.

### **3. Labeling Recommendations**

The applicant's proposed labeling is not acceptable. The following sentences are to be added to drug-drug interactions section of clinical pharmacology, warfarin section (section 7.3):

In 14 healthy subjects receiving 9.6 grams of sevelamer carbonate powder once daily, sevelamer carbonate did not alter the pharmacokinetics of a single dose of 20 mg warfarin.

## **4. Appendices**

### **4.1 Package Insert (proposed)**

15 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

\_\_\_\_\_ § 552(b)(5) Deliberative Process

## 4.2 Clinical Pharmacology and biopharmaceutics individual study review

### 4.2.1 Equilibrium Binding Studies (Study #. TR-211906-SC)

#### Method

##### Reviewer note on Method

The equilibrium binding studies conducted are in general agreement with the Cholestyramine Guidance with some modifications. The amount of sevelamer and volume of the media used were 800 mg and 300 mL, respectively, compared to 10 mg of cholestyramine and 10 mL media in the Guidance. Also, the concentration range of the adsorbate ( $\text{KH}_2\text{PO}_4$ ) used was 1- 38.7 mM compared to 0.1- 30 mM recommended in the guidance. These modifications accommodate a sample size equivalent to one tablet of sevelamer hydrochloride or sevelamer carbonate or one sachet of sevelamer carbonate sachets (800 mg), and adheres with the recommendations by the Analytical Method Validation Conference for Bio/Rx Industry (October 1997) of not using less than 60 mg for all analytical work.

Per applicant, the concentration of phosphate used varies for different parts of the gastrointestinal tract with a range of approximately 5- 30 mM.

##### Equilibrium Binding Studies without Acid Pretreatment

The studies compared sevelamer hydrochloride tablets (800 mg), sevelamer carbonate tablets (800 mg), sevelamer carbonate powder (800 mg), and sevelamer carbonate powder (2.4 g). For the 2.4 powder sachets, an amount equal to 800 mg sevelamer was used to keep the experimental conditions the same. Samples ( $n = 6$ ) containing 800 mg of sevelamer, the adsorbate ( $\text{KH}_2\text{PO}_4$ ), and media (total volume = 300 mL), were incubated in an orbital shaker at 37 °C for 4 hours. Eight different concentrations of  $\text{KH}_2\text{PO}_4$  were used: 1, 2.5, 5, 7.5, 10, 14.5, 30, 38.7 mM.

##### Equilibrium Binding Studies with Acid Pretreatment

Sevelamer tablets or powder (800 mg) were acid pre-treated using 20 mL of 1N HCl. Samples were incubated for 1 hour at ambient temperature, followed by removal of the media and resuspension of sevelamer pellets in 0.1 N HCl for 24 hours (pH was less than 1). Excess HCl was removed and samples were treated the same way described above for “without acid pretreatment”.

##### Reviewer Note on Acid Pretreatment

*The approach followed by the applicant differs from the method outlined in the Cholestyramine Guidance. Unlike the Guidance recommendations, sevelamer was further incubated in 0.1 N HCl for 24 hours prior to the binding study and following the initial incubation in 1.0 N HCl for 1*

hour. The applicant did not explain the rationale behind the modifications, these modifications did not appear to bear any physiological relevance.

### Parameter Estimation

An eight point binding isotherm was used to estimate the following parameters

1.  $k_1$ : Binding affinity constant
2.  $k_2$ : Binding capacity constant
3. Bound and unbound phosphate concentrations
4. Percent phosphate bound
5. Amount of phosphate bound per gram of sevelamer at each phosphate concentration

$k_1$  and  $k_2$  were calculated using a Langmuir-type equation according to the Cholestyramine Guidance

$$\frac{x}{m} = \frac{k_1 k_2 C_{eq}}{1 + k_1 C_{eq}}$$

Upon rearrangement

$$\frac{C_{eq}}{x/m} = \frac{1}{k_1 k_2} + \frac{C_{eq}}{k_2}$$

$C_{eq}$  = Concentration of  $\text{KH}_2\text{PO}_4$  remaining in solution after equilibrium (mM)

$x$  = Amount of  $\text{KH}_2\text{PO}_4$  bound to sevelamer (mmol/g)

$m$  = Amount of sevelamer used (g)

### Reviewer Note on Parameter Estimation

The parameter estimation method is consistent with cholestyramine guidance and is acceptable. The estimation of parameters provided by the applicant was confirmed using an excel spread sheet and linear fit.

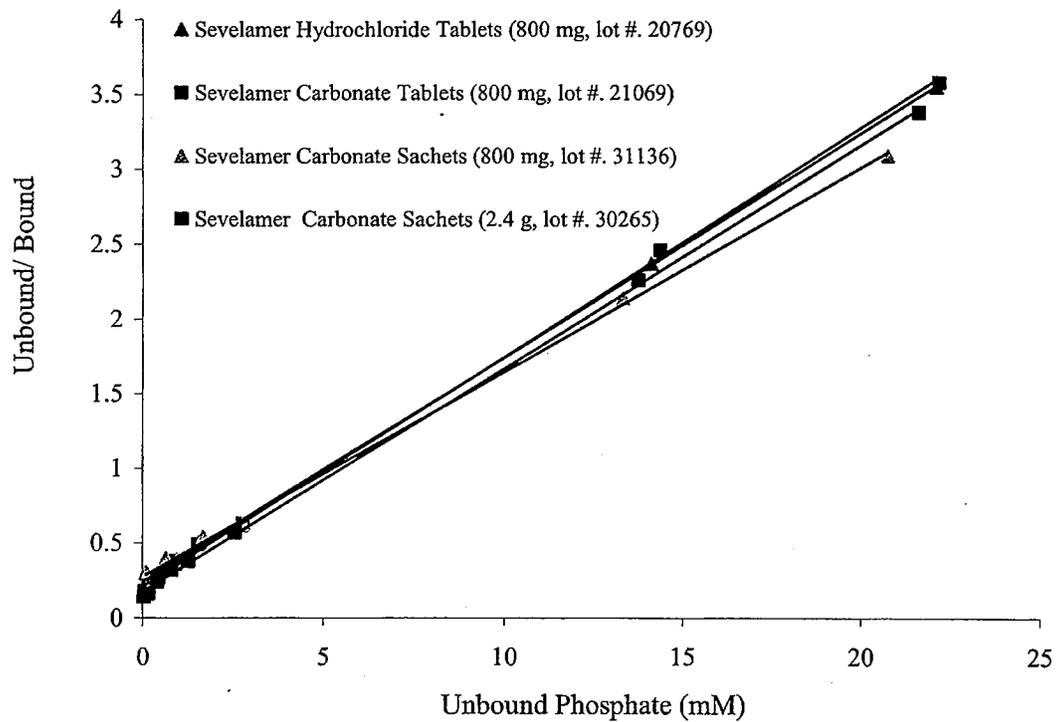
### Formulations:

1. Sevelamer hydrochloride tablets (800 mg, lot #. 20769)
2. Sevelamer carbonate tablets (800 mg, lot #. 21069)
3. Sevelamer carbonate sachets (800 mg, lot #. 31136)
4. Sevelamer carbonate sachets (2.4 g, lot #. 30265)

## Results

### Equilibrium Binding Studies without Acid Pretreatment

Figure 1 shows the Langmuir isotherms for the four formulations without acid pretreatment. Each point represents the average of six determinations. Table 1 shows the slope, intercept,  $k_1$ , and  $k_2$  values obtained for each formulation.



**Figure 1.** Sevelamer binding isotherm, with acid pretreatment.

**Table 1.** Langmuir plots parameters for sevelamer without acid pretreatment, per applicant.

Sample ID	Sevelamer Hydrochloride 800 mg Tablets, lot # 20769	Sevelamer Carbonate 800 mg Tablets, lot # 21069	Sevelamer Carbonate 0.8 g Sachet lot # 31136	Sevelamer Carbonate 2.4 g Sachet lot # 30265
Slope	0.163	0.148	0.157	0.161
Intercept	0.192	0.565	0.471	0.483
Affinity Constant, $k_1$	0.849	0.262	0.333	0.333
Binding Constant, $k_2$	6.15	6.75	6.39	6.22
RSQ	0.9996	0.9977	0.9982	0.9985

In general, the slopes and RSQ values obtained from the Langmuir plots of the four sevelamer formulations were comparable. The intercept of sevelamer hydrochloride is approximately 2.5 fold less than sevelamer carbonate. Since the affinity constant is inversely proportional to the intercept,  $k_1$  is 2.5 fold higher for sevelamer hydrochloride compared to sevelamer carbonate, suggesting a higher sevelamer hydrochloride affinity toward phosphate at pH 6.5.

There is a difference in the affinity constant between sevelamer carbonate and sevelamer hydrochloride. According to the applicant the large difference is due to the variation in carbonate concentration between samples as well as the possible competition between carbonate and phosphate in this system. In a previous communication<sup>1</sup> the applicant has shown variability of  $k_1$  as a function of carbonate concentration.

#### Reviewer comment on Difference

*Even though the affinity constant is dependent on carbonate concentration, there should not be a difference in  $k_1$  estimate between sevelamer carbonate tablets and sevelamer carbonate powder. In the experimental setup, the same amount of sevelamer carbonate was used (800 mg) and it will be anticipated that similar  $k_1$  values will be obtained. The sponsor will be asked to explain the difference in affinity constant between sevelamer carbonate tablet and powder formulations.*

<sup>1</sup> Genzyme Technical Memorandum, to Eugene Zhorov from Yvenet Montauban "Impact of carbonate on phosphate binding isotherms of Renagel 800 mg tablets by IC at pH 7 with BES"

Equilibrium Binding Studies with Acid Pretreatment

Figure 2 shows the Langmuir binding isotherms of the four sevelamer formulations following acid pretreatment. Each point represents the average of six determinations. Table 1 displays the binding the equilibrium binding parameters.

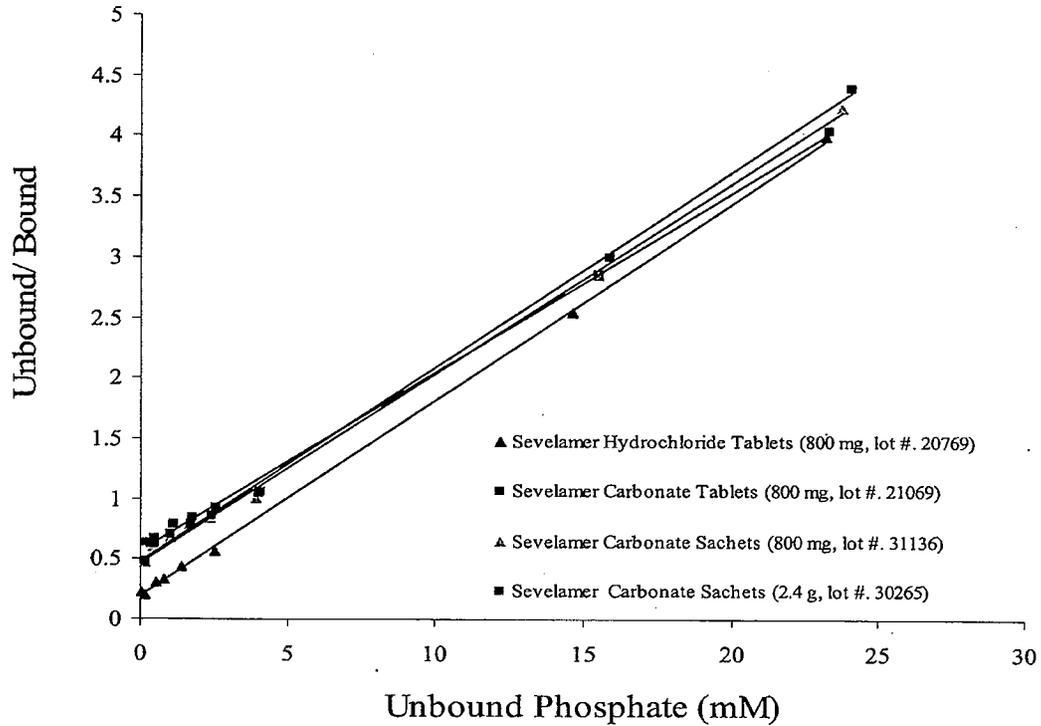


Figure 2. Sevelamer binding isotherms, with acid pretreatment.

Table 2. Langmuir plots parameters of sevelamer with acid pretreatment, per applicant.

Sample ID	Sevelamer Hydrochloride 800 mg Tablets, lot # 20769	Sevelamer Carbonate 800 mg Tablets, lot # 21069	Sevelamer Carbonate 0.8 g Sachet, lot # 31136	Sevelamer Carbonate 2.4 g Sachet, lot # 30265
Slope	0.150	0.153	0.137	0.149
Intercept	0.239	0.208	0.277	0.175
Affinity Constant, $k_1$	0.628	0.738	0.494	0.854
Binding Constant, $k_2$	6.66	6.52	7.32	6.71
RSQ	0.9993	0.9992	0.9986	0.9994

In general, the slopes and RSQ values obtained from the Langmuir plots of the four sevelamer formulations were comparable. Acid pretreatment reduced the variation in the affinity constant by over 60%, compared to the affinity constant obtained without acid pretreatment. The applicant explained the reduction of variability by the similarity in the degree of protonation between the two salts.

**Reviewer Notes:**

*The reviewer generated affinity and binding constants using linear regression. The obtained parameters were in excellent agreement with the applicant reported values*

**Conclusions**

The results demonstrate *in vitro* bioequivalence, in terms of binding equilibrium, among the four sevelamer formulations. The four formulations produced comparable phosphate binding capacity. There is a difference in the affinity constant between the hydrochloride and the carbonate salts under neutral conditions, this difference is diminished under acidic conditions and can be attributed to the degree of protonation of the two salts under different pH.

**4.2.2. Kinetic Binding Studies (Study #. TR-211906-SC)**

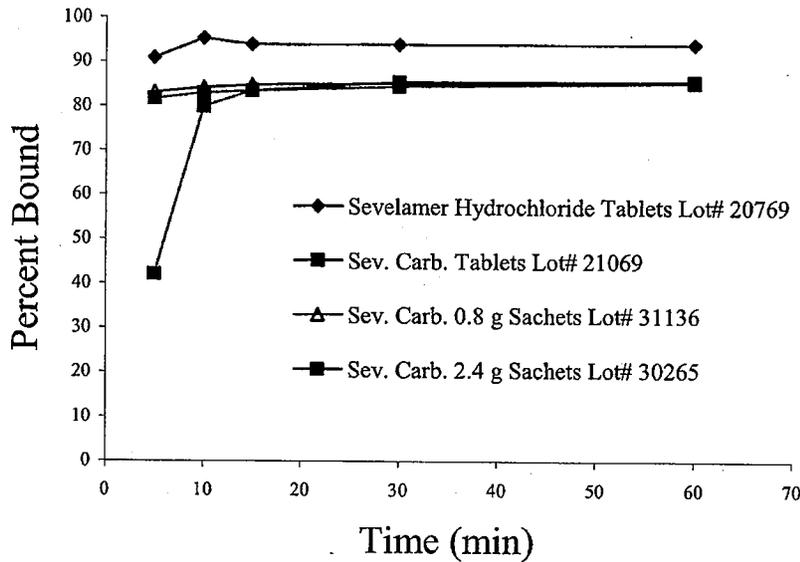
*Note: There is a discrepancy in the SAS transformed data set and data sets provided in biopharmaceutics legacy study report (TR 2119-06-SC: Drug Discovery & Development Technical MEMO). Data in the study legacy report were adopted in this review. This issue will be addressed in comments that will be sent to the sponsor.*

**Methodology**

Two kinetic experiments were conducted using either 2.5 mM or 38.7 mM of  $\text{KH}_2\text{PO}_4$  in 10 mM of BES (N,N-bis(hydroxyethyl)-2-aminoethanesulfonic acid) buffer and 80 mM NaCl. All experiments were carried out in an orbital shaker at 37 °C; samples (1.0 mL) were taken and immediately filtered at 5, 10, 15, 30, and 60 minutes for analysis of  $\text{KH}_2\text{PO}_4$  by ion chromatography. One test tube (n=6) was used to conduct the experiments for each phosphate concentration, since the removal of 1.0 mL did not affect the conditions and the concentrations in the flask.

**Results**

The percent of phosphate bound vs. times profiles for the four sevelamer formulations at 2.5 mM and 38.7 mM  $\text{KH}_2\text{PO}_4$  are depicted in figures 1 and 2, respectively.



**Figure 1.** Phosphate binding profile at 2.5 mM.

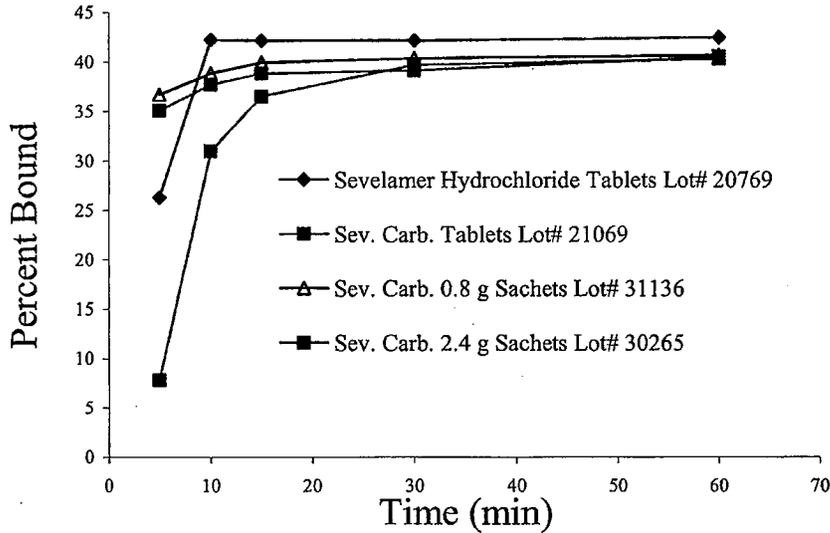


Figure 2. Phosphate binding profile at 38.7 mM.

Phosphate binding to sevelamer was fast in all four formulations and saturation was attained within fifteen minutes. Sevelamer has a maximum binding capacity of approximately 19.4 mM/g, estimated from the maximum percent binding obtained using 38.7 mM phosphate. In general the hydrochloride salt showed a higher binding capacity than the carbonate salt. Maximum binding capacity was reached almost instantly with the sachet formulation, and in 15 minutes with the tablet formulation.

**Reviewer Comment on the Kinetic Studies**

In order to compare the binding profiles of sevelamer carbonate formulations to sevelamer hydrochloride tablets, a similarity factor ( $f_2$ ) approach was adopted from the Dissolution Guidance. The following  $f_2$  values were obtained.

	$f_2$ value		
	Sev. Carb. Tablets Lot# 21069	Sev. Carb. 0.8 g Sachets Lot# 31136	Sev. Carb. 2.4 g Sachets Lot# 30265
2.5 mM $K_2HPO_4$	31	52	50
38.7 mM $K_2HPO_4$	50	64	65

The obtained  $f_2$  values indicate that sevelamer carbonate tablets exhibited a different kinetic profile at low phosphate concentrations. The clinical value of  $f_2$  values is unclear. The % RSD

was high for both tablet formulations samples withdrawn at 5 minutes. The applicant attributed this to the variation in the disintegration time of the tablets. The justification is reasonable, however, the data were not presented to support this hypothesis. The sponsor should provide disintegration time data of sevelamer tablet formulations, and correlate it with the initial variability in phosphate binding.

### **Conclusions**

The results demonstrate that sevelamer hydrochloride tablets, sevelamer carbonate tablets, and sevelamer carbonate powder bind phosphate in a similar manner.

#### 4.4.3. Sevelamer carbonate powder and warfarin drug-drug interaction study

---

Protocol #	SVCRB01107
Investigator	Dennis A. Ruff, MD
Study Site	Health Care Discoveries, Inc. 8307 Gault Lane. San Antonio, Texas 78209
Study Period	5/29/2007-07/02/2007

---

#### Title:

An open label study to assess the potential pharmacokinetic interaction of a single dose of sevelamer carbonate powder with a single dose of warfarin sodium in healthy volunteers

#### Objectives (Per Applicant):

*Primary objective:* To investigate the effects of sevelamer carbonate powder for oral suspension on the pharmacokinetics of warfarin sodium.

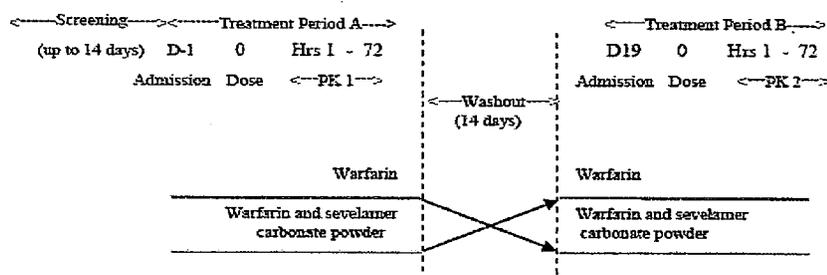
*Secondary objective:* To assess the safety/tolerability of a single dose concomitant administration of sevelamer carbonate powder and warfarin sodium.

#### Study Rationale

The major potential mechanism by which sevelamer carbonate can interact with other drugs is by affecting their absorption. Of relevance, cholestyramine, interacts in humans with warfarin. Potential drug interactions with warfarin are of particular interest because it has a narrow therapeutic index and is commonly used in chronic kidney disease patients because of the significant incidence of cardiac disease in this population.

#### Study Design:

Key features of the study design are illustrated in the scheme below and the following table.



General Study Design:	Open label, cross over, phase I drug-drug interaction study
Subjects:	18 Normal healthy male volunteers (age 18-50 years old)
Test products and dosing:	Warfarin/sevelamer carbonate powder: both drugs were administered orally: 1. sevelamer carbonate powder 4 x 2.4 g packets mixed with 8 oz water (9.6 g) 2. warfarin 2 x 10 mg tablet
Reference product:	Warfarin alone: 2 x 10 mg warfarin sodium tablet administered orally
Treatment Duration:	Four weeks including two dosing sessions separated by two weeks
Pharmacokinetic sampling:	Predose, 0.25, 0.5, 0.75, 1.0, 1.5, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours post dose.
Pharmacokinetic Analysis:	Values were generated for the following measures: $C_{max}$ , $T_{max}$ , AUC, $T_{1/2el}$ , and $AUC_{(0-\infty)}$
Pharmacodynamic Analysis:	Prothrombin Time (PT) and the International Normalization Ratio (INR) were measured pre dose and 1, 4, 12, 24, 36, 48, 60, and 72 hours post dose.

### Analytical Method:

Plasma samples were analyzed for R-warfarin and S-warfarin using a validated LC-MS-MS procedure. The method was validated for a range of 10.0 to 2000 ng/mL for both analytes (R-warfarin and S-warfarin), based on the analysis of 0.200 mL of K<sub>2</sub>-EDTA human plasma.

### Results

- Eighteen male subjects participated in the study with mean age of 33.6 years, standard deviation of 8.3 years, median of 33.5 years, and range of 21-49 years.
- Data from 15 subjects were used in the pharmacokinetic analysis.
- The mean percent area extrapolated for warfarin was 39.5% for warfarin tablets with sevelamer carbonate oral suspension (test treatment) and 36.2% for warfarin tablets alone (reference treatment).
- $T_{max}$  values for R-warfarin and S-warfarin, were longer when warfarin was co-administered with sevelamer carbonate powder compared to when warfarin was administered alone. This difference was statistically significant for R-warfarin, but not for S-warfarin as shown in the table below.

	Warfarin & Sevelamer	Warfarin	$T_{max}$ (h)	p-value (Wilcoxon signed rank)
R-warfarin	2.6	1.4		0.0449
S-warfarin	2.4	1.3		0.0549

- The pharmacokinetics of R-warfarin are tabulated below.

Dependent Variable	Geometric Means		Ratio(T/R)	90% CI	
	Test (T)	Reference (R)		Lower	Upper
C <sub>max</sub>	1168.0	1203.9	97.0	90.4	104.1
AUC <sub>0-72</sub>	42990.4	41565.7	103.4	98.7	108.4
AUC <sub>0-∞</sub>	69122.0	63311.9	109.2	100.0	119.2

Figure 1 displays the R-warfarin plasma concentration vs. time profiles.

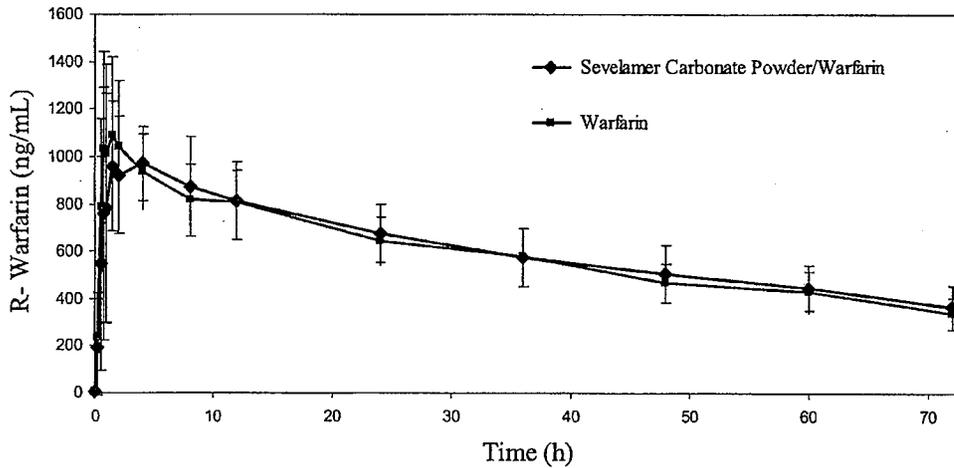
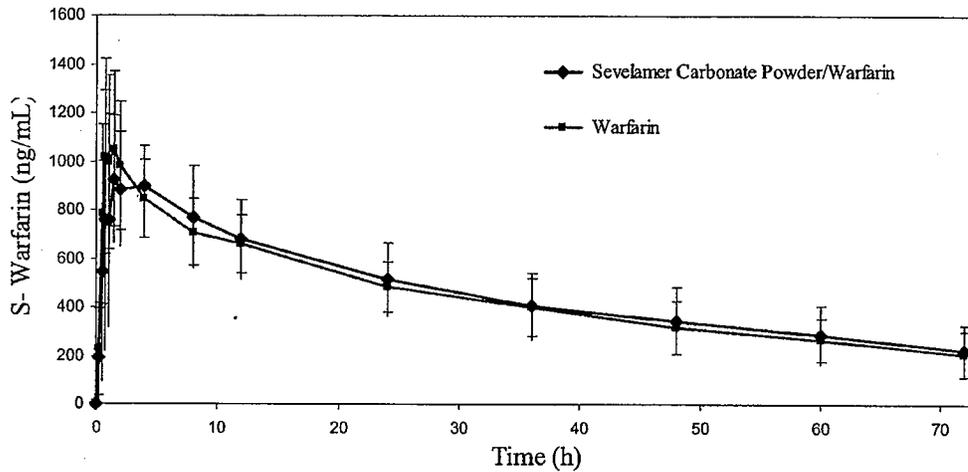


Figure 1. R-warfarin plasma concentration-time profiles. Each point represents the average (n=15), and error bars represent standard deviation, (reviewer generated).

- The pharmacokinetics of S-warfarin are tabulated below

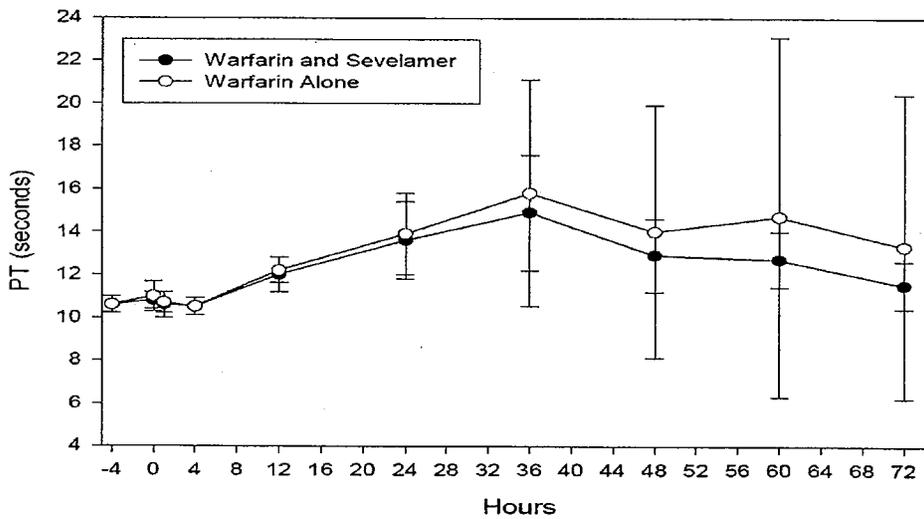
Dependent Variable	Geometric Means		Ratio(T/R)	90% CI	
	Test (T)	Reference (R)		Lower	Upper
C <sub>max</sub>	1124.6	1168.4	96.3	89.3	103.8
AUC <sub>0-72</sub>	31830.6	30878.8	103.1	98.0	108.5
AUC <sub>0-∞</sub>	44359.5	42125.0	105.3	99.8	111.2

Figure 2 displays the S-warfarin plasma concentration vs. time profiles.

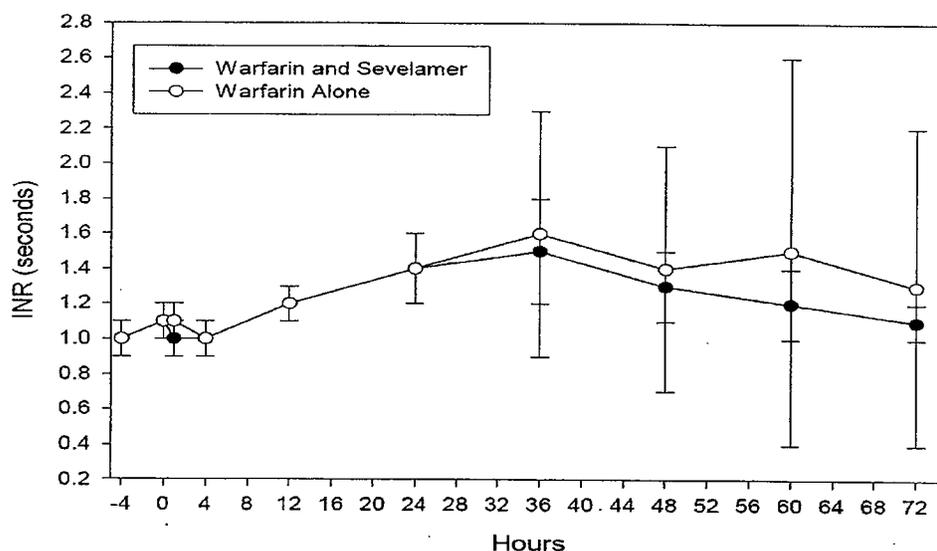


**Figure 2.** S-warfarin plasma concentration-time profiles. Each point represents the average (n=15), and error bars represent standard deviation, (reviewer generated).

- Pharmacodynamic analysis: Prothrombin Time (PT) and the International Normalization Ratio (INR) were measured up to 72 hours post dose. Mean PT did not differ between treatments until 24 hours post dose, where an increase in the warfarin only group is observed (Figure 3). The elevated PT of one subject (0112) resulted in higher mean values for the warfarin treatment. There were no clinically significant differences in mean INR between treatments at any time point in this study (Figure 4).



**Figure 3.** Prothrombin Time (PT) in seconds vs. time profile. Each point represents the mean (n = 15) and error bars represent the standard deviation.



**Figure 4.** International Normalization Ratio (INR) vs. time profile. Each point represents the mean ( $n = 15$ ) and error bars represent the standard deviation.

#### Conclusion

1. The rate and extent of absorption (bioavailability) of warfarin was not impacted by the simultaneous administration of sevelamer carbonate, based on  $C_{max}$ ,  $AUC_{0-72}$ , and  $AUC_{0-inf}$ .
2.  $T_{max}$  of R-warfarin, but not S-warfarin, is significantly longer upon the concomitant administration of sevelamer carbonate and warfarin, relative to the administration of warfarin alone.

#### Reviewer Comments/ Recommendations:

1. This study shows that sevelamer carbonate after single dose does not affect the bioavailability of warfarin (rate and extent of absorption).
2. The studied sevelamer carbonate dose of 9.6 g single dose is 4 times higher than the maximum single of 2.4 g, and 1.5 fold higher than the maximum recommended daily dose of 7.2 g (3 x 2.4)
3. The study design and analysis have the following deficiencies:
  - I. Plasma sampling up to 72 hours is insufficient to characterize the pharmacokinetics of warfarin based on its long half-life of ~2.5 days. This shortage of plasma sampling lead to extrapolating approximately 40% of AUC when  $AUC_{0-inf}$  was calculated. While this extrapolation is generally not acceptable, the reviewer did not find it significant in drawing the above stated conclusion. The rationale behind this decision is based on the fact that the interaction between sevelamer carbonate and warfarin, if present, will occur in the intestine and not in the blood stream, since sevelamer carbonate is not

absorbed. As a result, warfarin disposition can be predicted and extrapolated with confidence after the absorption phase. In future studies, plasma sampling as long as 168 hours is recommended.

- II. The sponsor did not provide a thorough analysis of the effect of simultaneous administration of sevelamer carbonate and warfarin on the International Normalization Ratio (INR). Visual inspection of INR vs. time profile shows no difference in average INR between the test and reference product. To show that sevelamer carbonate has no significant effect on INR when co-administered with warfarin, the reviewer calculated the  $AUC_{0-72}$  and  $INR_{max}$  of INR vs. time profile for the treatment and reference in all patients and checked to see if there is a significant difference. The results showed no significant difference in  $AUC_{0-72}$  and  $INR_{max}$  between the reference and treatment; results are displayed in appendix II. In future studies, this analysis should be performed by the sponsor.

3. Analytical Method: The sponsor did not provide a full validation report for the warfarin bioanalytical method. Since the warfarin assay is well established, the reviewer assumed that the sponsor performed analytical method validation according to the Bioanalytical Method Validation Guidance for Industry, and an appropriate validation report was generated. In future submissions, a full validation report for the analytical methods used should be provided.

**Appendix I.** INR AUC<sub>0-72</sub> and INR<sub>max</sub> following the administration of warfarin and sevelamer carbonate (test), and warfarin alone (reference). AUC0-72 was calculated using the trapezoidal rule, reviewer generated data. WinNonlin input spreadsheet.

Subject #	Treatment	Period	Sequence	INR AUC <sub>0-72</sub>	INR <sub>max</sub>
101	1	1	1		
101	2	2	1		
102	1	2	2		
102	2	1	2		b(4)
103	1	1	1		
103	2	2	1		
106	1	1	1		
106	2	2	1		
107	1	2	2		
107	2	1	2		b(4)
108	1	2	2		
108	2	1	2		
109	1	1	1		
109	2	2	1		
110	1	2	2		
110	2	1	2		b(4)
111	1	1	1		
111	2	2	1		
113	1	1	1		
113	2	2	1		
114	1	1	1		
114	2	2	1		b(4)
115	1	2	2		
115	2	1	2		
116	1	2	2		
116	2	1	2		
117	1	2	2		
117	2	1	2		b(4)
118	1	1	1		
118	2	2	1		

Treatment, 1 = sevelamer carbonate and warfarin, 2 = warfarin alone; sequence, 1 = sevelamer carbonate + warfarin period 1, and warfarin alone in period 2, 2 = warfarin alone in period one, and sevelamer carbonate + warfarin in period 2.



Iteration	function	Var(seq*sub)	Var(Residual)
0	-55.7945	0.0139295	0.000881125

Newton's algorithm converged.

Final variance parameter estimates:

Var(seq*sub)	0.0139295
Var(Residual)	0.000881125
Intersubject CV	0.118436
Intrasubject CV	0.0296903

REML log(likelihood)	31.9021
-2* REML log(likelihood)	-63.8042
Akaike Information Crit.	-51.8042
Schwarz Bayesian Crit.	-44.2556

Ordered Final Hessian Eigenvalues:

8.38007e+006  
31447.4

Solution

Effect:Level	Estimate	StdError	Denom_DF	T_stat	P_value	Conf	T_crit	Lower_CI	Upper_CI
int	4.36198	0.0459123	13.7	95.0067	0.0000	95	2.149	4.263	4.461
seq:1	0.148489	0.0620414	13	2.39338	0.0325	95	2.16	0.01446	0.2825
seq:2	Not estimable								
trt:1	0.0252859	0.0108631	13	2.32768	0.0367	95	2.16	0.001818	0.04875
trt:2	Not estimable								
per:1	0.0718256	0.0108631	13	6.61186	0.0000	95	2.16	0.04836	0.09529
per:2	Not estimable								

Sequential Tests of Model Effects

Hypothesis	Numer_DF	Denom_DF	F_stat	P_value
int	1	13	21041.2	0.0000
seq	1	13	5.72827	0.0325
trt	1	13	7.69864	0.0158
per	1	13	43.7167	0.0000

Sequential Sum of Squares

Hypothesis	DF	SS	MS	F_stat	P_value
seq	1	0.164631	0.164631	5.72827	0.0325
seq*sub	13	0.373622	0.0287402	32.6176	0.0000
trt	1	0.00678347	0.00678347	7.69864	0.0158
per	1	0.0385199	0.0385199	43.7167	0.0000
Error	13	0.0114546	0.000881125		

Partial Tests of Model Effects

Hypothesis	Numer_DF	Denom_DF	F_stat	P_value
int	1	13	20901.6	0.0000
seq	1	13	5.72827	0.0325
trt	1	13	5.41809	0.0367
per	1	13	43.7167	0.0000

Partial Sum of Squares

Hypothesis	DF	SS	MS	F_stat	P_value
------------	----	----	----	--------	---------

```

-----
          seq          1    0.164631    0.164631    5.72827    0.0325
      seq*sub        13    0.373622    0.0287402    32.6176    0.0000
          trt          1    0.00477402    0.00477402    5.41809    0.0367
          per          1    0.0385199    0.0385199    43.7167    0.0000
          Error        13    0.0114546    0.000881125
    
```

Least squares means

```

          trt  Estimate  StdError  Denom_DF  T_stat    P_value  Conf  T_crit  Lower_CI
Upper_CI
-----
          1    4.49742  0.0314926  13.8    142.809    0.0000   90   1.763   4.442
4.553
          2    4.47213  0.0314926  13.8    142.006    0.0000   90   1.763   4.417
4.528
    
```

Differences between means

```

          trt  Estimate  StdError  Denom_DF  T_stat    P_value  Conf  T_crit  Lower_CI
Upper_CI
-----
          1 - 2  0.0252859  0.0108631   13    2.32768    0.0367   90   1.771  0.006048
0.04452
    
```

Bioequivalence Statistics

User-Specified Confidence Level for CI's and Power = 90.0000  
 Percent of Reference to Detect for 2-1 Tests and Power = 20.0%  
 A.H.Lower = 0.800 A.H.Upper = 1.250

Formulation variable: trt

Reference: 2 LSMeans= 4.472133 SE= 0.031493 GeoLSM= 87.543283

Test: 1 LSMeans= 4.497419 SE= 0.031493 GeoLSM= 89.785118

Difference = 0.0253, Diff\_SE= 0.0109, df= 13.0  
 Ratio(%Ref) = 102.5608

```

          Classical          Westlake
CI 80% = ( 101.0673, 104.0764) ( 96.4649, 103.5351)
CI 90% = ( 100.6062, 104.5535) ( 95.9237, 104.0763)
CI 95% = ( 100.1813, 104.9969) ( 95.4469, 104.5531)
Average bioequivalence shown for confidence=90.00 and percent=20.0.
    
```

Two One-Sided T-tests

Prob(< 80%)=0.0000 Prob(> 125%)=0.0000 Max=0.0000 Total=0.0000

Anderson-Hauck Procedure

A.H. p-value = 0.000000

Power of ANOVA for Confidence Level 90.00

Power at 20% = 1.000000

Input File: Workbook - [Untitled1]

Date: 10/16/2008  
 Time: 14:15:37

WINNONLIN LINEAR MIXED EFFECTS MODELING / BIOEQUIVALENCE  
 Version 5.2 Build 200701231637  
 Core Version 17Oct2006

Sevelamer and Warfarin DDI study

Model Specification and User Settings

Dependent variable : INRmax  
 Transform : LN  
 Fixed terms : int+seq+trt+per  
 Random/repeated terms : seq\*sub  
 Maximum iterations : 50  
 Convergence Criterion : 1e-010  
 Singularity tolerance : 1e-010  
 Denominator df option : satterthwaite

Class variables and their levels

				sub :	101	102	103	106	107	108	109	110	111
113	114	115	116	117	118								
				trt :	1	2							
				per :	1	2							
				seq :	1	2							

Using method of moments for starting values

Starting estimates of variance parameters:

Var(seq\*sub) 0.0128241  
 Var(Residual) 0.00205065

Diagnostics

Total Observations : 30  
 Observations Used : 30  
 Obs. Missing Model Terms : 0  
 Residual SS : 0.0266584  
 Residual df : 13  
 Residual Variance : 0.00205065

Breakout of variance structure

-----  
 Variance Index : 1  
 Source : Random  
 Type : Variance Components  
 Columns : seq\*sub  
 Parameters : Var(seq\*sub)  
 -----

Variance Index : 2  
 Source : Assumed  
 Type : Identity  
 Columns : None  
 Parameters : Var(Residual)  
 -----

Variance parameter estimation at each iteration:

Iteration	Objective function	Var(seq*sub)	Var(Residual)
0	-50.5438	0.0128241	0.00205065

Newton's algorithm converged.

Final variance parameter estimates:

Var(seq\*sub) 0.0128241  
 Var(Residual) 0.00205065  
 Intersubject CV 0.113608

Intrasubject CV 0.0453073

REML log(likelihood) 26.6513  
 -2\* REML log(likelihood) -53.3027  
 Akaike Information Crit. -41.3027  
 Schwarz Bayesian Crit. -33.7541

Ordered Final Hessian Eigenvalues:  
 1.55438e+006  
 33699.3

Solution

Effect:Level	Estimate	StdError	Denom_DF	T_stat	P_value	Conf	T_crit	Lower_CI	Upper_CI
int	0.238552	0.0458984	14.7	5.19739	0.0001	95	2.136	0.1405	0.3366
seq:1	0.161687	0.0609071	13	2.65465	0.0198	95	2.16	0.03011	0.2933
seq:2	Not estimable								
trt:1	0.0301298	0.0165723	13	1.81809	0.0922	95	2.16-0.005672		0.06593
trt:2	Not estimable								
per:1	0.124543	0.0165723	13	7.51517	0.0000	95	2.16	0.08874	0.1603
per:2	Not estimable								

Sequential Tests of Model Effects

Hypothesis	Numer_DF	Denom_DF	F_stat	P_value
int	1	13	175.135	0.0000
seq	1	13	7.04719	0.0198
trt	1	13	5.40223	0.0370
per	1	13	56.4777	0.0000

Sequential Sum of Squares

Hypothesis	DF	SS	MS	F_stat	P_value
seq	1	0.195199	0.195199	7.04719	0.0198
seq*sub	13	0.360086	0.0276989	13.5074	0.0000
trt	1	0.0110781	0.0110781	5.40223	0.0370
per	1	0.115816	0.115816	56.4777	0.0000
Error	13	0.0266584	0.00205065		

Partial Tests of Model Effects

Hypothesis	Numer_DF	Denom_DF	F_stat	P_value
int	1	13	169.714	0.0000
seq	1	13	7.04719	0.0198
trt	1	13	3.30544	0.0922
per	1	13	56.4777	0.0000

Partial Sum of Squares

Hypothesis	DF	SS	MS	F_stat	P_value
seq	1	0.195199	0.195199	7.04719	0.0198
seq*sub	13	0.360086	0.0276989	13.5074	0.0000
trt	1	0.00677829	0.00677829	3.30544	0.0922
per	1	0.115816	0.115816	56.4777	0.0000
Error	13	0.0266584	0.00205065		

Least squares means

Upper_CI	trt	Estimate	StdError	Denom_DF	T_stat	P_value	Conf	T_crit	Lower_CI
0.4671	1	0.411797	0.0315607	14.9	13.0478	0.0000	90	1.754	0.3564
0.437	2	0.381667	0.0315607	14.9	12.0931	0.0000	90	1.754	0.3263

Differences between means

Upper_CI	trt	Estimate	StdError	Denom_DF	T_stat	P_value	Conf	T_crit	Lower_CI
0.05948	1 - 2	0.0301298	0.0165723	13	1.81809	0.0922	90	1.7710	0.0007814

Bioequivalence Statistics

User-Specified Confidence Level for CI's and Power = 90.0000  
 Percent of Reference to Detect for 2-1 Tests and Power = 20.0%  
 A.H.Lower = 0.800 A.H.Upper = 1.250

Formulation variable: trt

Reference: 2 LSmean= 0.381667 SE= 0.031561 GeoLSM= 1.464724

Test: 1 LSmean= 0.411797 SE= 0.031561 GeoLSM= 1.509528

Difference = 0.0301, Diff\_SE= 0.0166, df= 13.0  
 Ratio(%Ref) = 103.0588

	Classical	Westlake
CI 80% = (	100.7781, 105.3912)	( 95.4427, 104.5573)
CI 90% = (	100.0775, 106.1290)	( 94.6082, 105.3918)
CI 95% = (	99.4335, 106.8164)	( 93.8709, 106.1291)

Average bioequivalence shown for confidence=90.00 and percent=20.0.

Two One-Sided T-tests

Prob(< 80%)=0.0000 Prob(> 125%)=0.0000 Max=0.0000 Total=0.0000

Anderson-Hauck Procedure

A.H. p-value = 0.000000

Power of ANOVA for Confidence Level 90.00

Power at 20% = 1.000000

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Islam R Younis  
12/10/2008 07:34:50 AM  
PHARMACIST

Robert Kumi  
12/10/2008 03:50:22 PM  
BIOPHARMACEUTICS  
Islam, in the next meeting(s) you should let Anna/Norman  
know that you would like the comments conveyed  
to the applicant.