CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

Division of Pharmaceutical Evaluation I

NDA:	**21-468**	
SUBMISSIONS DATES:	Original NDA	April 30,2002
	Orig Amed N000(BB)	August 27, 2002
	Orig Amed N000(C)	August 27, 2002
	Orig Amed N000(BM)	November 1, 2002
	Orig Amed N000(BC)	November 4, 2002
	Orig Amed N000(BC, BL)	November 27, 2002
	Orig Amed N000(BC,BM)	December 20, 2002
BRAND NAME:	FOSRENOL™	
GENERIC NAME:	Lanthanum Carbonate Hydrate	
STRENGTHS	250 & 500 mg Chewable Tablets	
SPONSOR:	Shire Pharmaceutical Development, Inc.	
PK REVIEWER:	Angelica Dorantes, Ph.D.	
TEAM LEADER:	Patrick Marroum, Ph.D.	
OCPB DIVISION:	Pharmaceutical Evaluation I	
ORM DIVISION:	Cardio-Renal Drug Products	
SUBBMISSION TYPE:	New Molecular Entity (Type 1S)	
INDICATION:	[ ]	

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-468**	**Brand Name**	**Fosrenol**
OCPB Division (I, II, III)	**DPEI**	**Generic Name**	**Lanthanum Carbonate**
Medical Division	**DCRDP**	**Drug Class**	**-**
OCPB Reviewer	**Angelica Dorantes, Ph.D.**	**Indication(s)**	[redacted]
OCPB Team Leader	**Patrick Marroum, Ph.D.**	**Dosage Form**	**250 and 500 mg chewable tablets**
		Dosing Regimen	**3 times per day**
Date of Submission	**April 30, 2002**	**Route of Administration**	**Oral**
OCPB Estimated Due Date	**December, 2002**	**Sponsor**	**Shire pharmaceuticals Inc.**
PDUFA Due Date	**February 2, 2003**	**Priority Classification**	**Standard**
Division Due Date	**January 2003**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data,	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:	X	1	1	
Blood/plasma ratio:				
Plasma protein binding:	X	1	1	In vitro
Pharmacokinetics (e.g., Phase I) -				
HEALTHY VOLUNTEERS-				
single dose:	X	3	3	
multiple dose:	X	1	1	
Patients-				
single dose:	x	1	1	
multiple dose:	[redacted]	1	1	
Dose proportionality -				
fasting / non-fasting single dose:	x	1	1	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	1	1	citrate
In-vivo effects of primary drug:	x	3	3	warfarin, digoxin, & metoprolol
In-vitro:	x	1	1	Vitamins, nutrients, & others
Subpopulation studies -				
ethnicity:	x	2	2	
gender:				
pediatrics:				
geriatrics.				
renal impairment:	x	1	1	End stage renal disease (ESRD) patients
hepatic impairment:				

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	x	5	5	lanthanum trough levels
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
as reference:	X			
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	2	2	
Dissolution:	X	5	5	
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		20	20	

FILABILITY AND QBR COMMENTS

	"X" if yes	Comments
Application filable ?	X	
Comments to be sent to the firm ?	X	To facilitate the review of this NDA, an electronic submission including Volume 2.1 information and individual PK study reports, is needed.
QBR questions (key issues to be considered)		1. Is mass balance/ADME information in humans available for lanthanum carbonate? 2. Is in-vivo protein binding information available? 3. What is the % of lanthanum carbonate absorbed after oral administration? 4. Is the pharmacokinetic profile of lanthanum in healthy subjects and end of stage renal patients similar? 5. Does food have an effect on the bioavailability of lanthanum carbonate? 6. Are lanthanum plasma levels relevant to the safety of the product in ESRD patients? 7. Following chronic administration, what are the accumulation levels of lanthanum in organs/tissues/bones of ESRD patients? 8. Is the provided dissolution information acceptable? 9. Is the clinical pharmacology and biopharmaceutic information included in the proposed labeling acceptable to OCPB?
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC NDA 21-468, HFD-850(Lee), HFD-110(Hinton), HFD-860(Dorantes, Marroum, Mehta), DFS (Biopharm)

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IV. EXECUTIVE SUMMARY

NDA 21-468 for Lanthanum Carbonate Chewable Tablets

On April 30, 2002, Shire Pharmaceuticals submitted NDA 21-468 for FOSRENOL™ (Lanthanum Carbonate Hydrate) 250 and 500 mg Chewable Tablets. Lanthanum carbonate hydrate is an inorganic salt that acts in the lumen of the gut by binding to dietary phosphorus released from the food during digestion. Fosrenol is indicated for [redacted]

[redacted]. The recommended initial total daily dose of lanthanum in adults is 750 mg. In clinical studies, most patients required a total daily dose between 1500 and 3000 mg of lanthanum carbonate to reduce plasma phosphate levels to less than 6.0 mg/dl.

A total of 18 studies were provided to support the "Human Pharmacokinetic and Biopharmaceutics" section of the NDA. The pharmacokinetics of lanthanum from orally administered lanthanum carbonate as chewable tablets were investigated in studies LAM-IV-101, -105, -108, -109, -110, and -111. The in-vitro interaction in gastric fluid of lanthanum with several medications was investigated in study V00160-LAM-IIIG and the in-vivo interaction of lanthanum with citrates, warfarin, digoxin, and metoprolol was assessed in studies LAM-IV-112, -113, -114, and -115. The plasma lanthanum trough levels were monitored in the target population throughout the development program (Phase II/III studies LAM-IV-202, 204, 301, 302, and 307). In addition, in vitro studies V00117-LAM-IIIG and SRU 006/002701 were conducted to address lanthanum's protein binding and P450 inhibition issues, respectively. The dissolution information for the lanthanum chewable tablets was provided in several Amendments to the original NDA.

Based on the overall clinical pharmacology data, it can be concluded that an exposure-response relationship with respect to lanthanum plasma levels and its efficacy & safety does not exist. Plasma and urine are not the appropriate biological matrices to evaluate lanthanum's absorption/distribution/metabolism/elimination, and the pharmacokinetic results obtained from these biological fluids do not represent the total body exposure to lanthanum.

Summary information derived from the provided studies is presented next

- Neither the absolute nor the relative bioavailability of Fosrenol was not investigated in humans, but it may be assumed that lanthanum is poorly absorbed following single or multiple administration of Fosrenol. In healthy subjects mean values for lanthanum Cmax were $\leq$0.5 ng/ml and the mean range

of Tmax was between 4-6 hours following single and multiple administration of Fosrenol. The plasma elimination half-life was about 36 hours. The percentage of lanthanum excreted in feces was not determined. The percentage of lanthanum excreted in urine was <0.00005% of the dose.

- Lanthanum plasma levels increased with dose but not in a linearly proportional manner. A two, four, and eight fold increase in dose resulted in a 1.4, 1.8, and 2.4 fold increase in mean Cmax and in 1.5, 2.3, and 3.5 increase in mean $AUC_{0\text{-}12h}$.

- The effect of food on the bioavailability of Fosrenol was not evaluated, but the timing of food intake relative to lanthanum administration (during and 30 minutes after food intake) appears to have a small effect on the systemic levels of lanthanum.

- Lanthanum is highly bound (>99%) to human plasma proteins in vitro. Binding of lanthanum to human serum albumin, α1-acid glycoprotein, and transferrin was equally extensive. The binding of lanthanum to erythrocytes was not investigated.

- No information was provided regarding the mass balance of lanthanum in humans after IV and/or oral administration. However, animal data indicate that lanthanum carbonate is absorbed and deposited in most tissues, from which it is eliminated very slowly. Lanthanum concentrations in some tissues were several orders of magnitude higher than plasma concentrations. Particularly high lanthanum levels were observed in the gastrointestinal tract, liver, lung, and bone. For humans, the accumulation of lanthanum in tissues presents a concern for long term safety.

- Lanthanum is not metabolized and is not a substrate of CYP450. In vitro metabolic inhibition studies showed that lanthanum at concentrations of 10 and 40 mcg/ml did not have relevant inhibitory effects on any of the CYP450 isoenzymes tested (1A2, 2C9/10, 2C19, 2D6, & 3A4/5).

- The effect of lanthanum on p-glycoprotein was not evaluated in vitro, but the in vivo DDI-study with digoxin (p-glycoprotein probe) showed that lanthanum did not affect digoxin's PK, indicating that lanthanum is not a substrate nor an inhibitor of p-glycoprotein.

- The potential for a physico-chemical interaction (precipitation) between lanthanum and six commonly used medications (warfarin, digoxin, frusemide, phenytoin, metoprolol, & enalapril) in the stomach (simulated gastric fluid, SGF) was investigated. The overall results showed that the probability of having precipitation of insoluble complexes of X-drug-lanthanum in the stomach is low.

- Lanthanum carbonate is highly bound to plasma proteins (>99%) and is not a substrate or an inhibitor of CYP450 enzymes. Thus, the possibility that Fosrenol will precipitate any interaction by the perturbation of plasma protein binding or cytochrome P450 mediated metabolism is low. Studies in healthy subjects have shown that lanthanum does not affect the pharmacokinetics of warfarin, digoxin or metoprolol. The pharmacokinetics of lanthanum were unaffected by co-administration of citrate-containing compounds.

- A study evaluating the pharmacokinetic of lanthanum in dialysis patients showed that plasma levels of lanthanum in patients with compromised renal function were about 3 times higher than those in control subjects. The kidneys excreted negligible amounts of lanthanum with minimal lanthanum in

the diasylate. Thus, patients with compromised renal function may accumulate higher concentrations of lanthanum in tissues.

- Lanthanum trough levels were evaluated in ESRD (end-stage renal disease) patients receiving hemodialysis during the clinical studies. The overall results from these studies showed that during chronic administration for up to 1 year, lanthanum mean concentrations were about 0.6 ng/ml, there was minimal increase in plasma lanthanum concentration with dose, and there was no accumulation with time (up to 52 weeks).

A. RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPEI) has reviewed the information included in original NDA 21-468 and its amendments for FOSRENOL (Lanthanum Carbonate) Chewable Tablets. OCPB is of the opinion that at the present time the clinical pharmacology information provided in NDA is incomplete. The sponsor needs to provide additional data to address the following reviewer concerns.

Reviewer Comments:

1. **Dissolution:**

Method: Based on the review of the overall dissolution data and taking into account that; 1) the newly proposed method — and a specification of Q= —, at — minutes would not provide any useful dissolution information, 2) all the stability data were generated using crushed tablets, and 3) the NDA's action date is getting closer, OCPB is of the opinion that the originally proposed dissolution method for the crushed tablets (USP Apparatus 2, —rpm, and [ ] of [ ]) can be accepted on **an interim basis,** with the understanding that the sponsor will continue with the development of a more adequate dissolution methodology for the whole tablets.

Specification: The originally proposed dissolution specification of Q= — % at — minutes is not acceptable. The provided dissolution data for several clinical and stability lots using crushed tablets showed that a specification of — % at — minutes would be more appropriate for both, the 250 and 500 mg Fosrenol chewable tablets.

Commitment: Due to the fact that the originally proposed dissolution method would be acceptable only on an interim basis, the sponsor should continue pursuing the development of appropriate dissolution methodology for the whole tablets. The sponsor should make the commitment to submit to the Agency within the first year from the approval date, a final report including the development and validation of a revised more suitable dissolution method for the whole tablets. Also, the report should include complete dissolution data for at least 3 production lots of the 250 and 500 mg tablets (at least 12 units/lot) using the revised method.

2. **Bio-Waiver/Bio-Study:**

It should be noted that the sponsor is seeking the approval of both, the 250 and 500 mg strengths of lanthanum carbonate chewable tablets. However, only the 250 mg strength was used in the Phase 2 and Phase 3 clinical studies. Therefore, from the OCPB's viewpoint to get approval of the 500 mg chewable tablet, the sponsor should provide: **1)** appropriate information to support a bio-waiver, **or** **2)** data from a bio-study. Please note that if a bio-study is conducted, the sponsor should demonstrate that the 500 mg chewable tablets are clinically bioequivalent to the 250 mg chewable tablets.

The sponsor should be aware that to get approval of a bio-waiver for the 500 mg strength the following requirements need to be satisfied:

- Clinical safety/efficacy data covering the dosing range of the higher strength
- Linear elimination kinetics over the therapeutic range **or** data from a mass balance study showing that lanthanum is not absorbed systemically
- The formulations of the higher and lower strengths should be proportionally similar
- Comparative dissolution profile data for the whole tablets using the same dissolution procedures

3. **Mass Balance:**

No information was provided regarding the mass balance of lanthanum in humans after IV and/or oral administration. Animal data indicate that lanthanum carbonate is absorbed and deposited in most of the tissues from which it is eliminated very slowly. Therefore, for safety reasons, it is very important to know in humans the percentage of total dose that is absorbed and the time that lanthanum would take to be eliminated from the body.

4. **Labeling:**

The labeling revisions described in pages 29-31 of this review are recommended for the "**CLINICAL PHARMACOLOGY; Pharmacokinetics**", "**PRECAUTIONS; Drug Interactions**", and "**DOSAGE AND ADMINISTRATION**" sections of the proposed labeling.

Please convey the Recommendation and Reviewer comments as appropriate to the sponsor.

Angelica Dorantes, Ph.D.
Division of Pharmaceutical Evaluation I, OCPB
Office of Clinical Pharmacology and Biopharmaceutics

Briefing Day: 1/9/03 (Mehta, Sahajwalla, Marroum, Dorantes, Pelayo, Hunt, Huang, Heep, Koerner, Joshep)

FT Signed by Patrick Marroum, Ph.D. /S/

cc: NDA 21-468, HFD-110, HFD-860 (Dorantes, Sahajwalla, Mehta), and CDR (Biopharm).

V. Summary of Clinical Pharmacology & Biopharmaceutic Findings

The following clinical pharmacology studies were provided in the Original NDA

In Vitro Protein Binding Studies:

Study Report V00117-LAM-IIIG: In vitro protein binding of lanthanum to human plasma, human α1-acid glycoprotein, transferrin, and albumin.

In Vitro Metabolic Studies:

Study Report SRU 006/002701: Lanthanum carbonate potential inhibition of cytochromes P450 in human liver microsomes.

In Vitro Drug Interaction Studies:

Study Report V00160-LAM-IIIG: Lanthanum carbonate: In vitro drug interaction in gastric fluid.

Studies in Healthy Subjects:

Study LAM-IV-101: A double-blind rising study to evaluate the safety, tolerance, and pharmacokinetics of a rare earth salt vs. placebo in twelve healthy volunteers.

Study LAM-IV-105: A double-blind tolerance study to evaluate the safety, tolerance, pharmacokinetics, and pharmacodynamics of a rare earth salt vs. placebo when administered with food in healthy volunteers.

Study LAM-IV-108: A Phase I, single center, randomized, double-blind, placebo controlled, ascending dose study to assess the safety, tolerability, and pharmacokinetics of lanthanum carbonate chewable tablets in healthy male Japanese volunteers.

Study LAM-IV-109: A Phase I, single center, randomized, placebo controlled, multiple dose study to assess the pharmacokinetics and safety of lanthanum carbonate and to determine the reduction in urinary phosphate excretion in healthy male subjects.

Study LAM-IV-110: A Phase I, single center, randomized, open-label, three-way crossover study comparing the phosphate ion binding of lanthanum carbonate chewable tablets when administered before, during, or after food in healthy subjects.

Drug Interaction Studies:

Study LAM-IV-112: A Phase I, single center, randomized, open-label, three-way crossover study to assess the effects of co-administration of citrate on the systemic absorption of Lanthanum following a single oral dose.

Study LAM-IV-113: A Phase I, single center, open-label, randomized crossover study to assess the effects of lanthanum carbonate on the pharmacokinetic parameters of warfarin following a single oral dose.

Study LAM-IV-114: A Phase I, single center, open-label, randomized crossover study to assess the effects of lanthanum carbonate on the pharmacokinetic parameters of digoxin following a single oral dose.

Study LAM-IV-115: A Phase I, single center, open-label, randomized crossover study to assess the effects of lanthanum carbonate on the pharmacokinetic parameters of metoprolol following a single oral dose.

Drug-Interactions Report: An assessment of the potential of Fosrenol (lanthanum carbonate) to interact with co-prescribed medicines in a renal dialysis patient population.

Studies in the Target Population:

Study LAM-IV-111:	A pharmacokinetic study in healthy volunteers and dialysis patients following single and multiple doses of lanthanum.
Study LAM-IV-202:	A Phase II, dose ranging, placebo-controlled parallel group study to assess the efficacy and safety of "Lamba" for reduction of gastrointestinal phosphate absorption in patients receiving hemodialysis or continuous ambulatory peritoneal dialysis (CAPD).
Study LAM-IV-204:	A dose ranging, placebo-controlled study to assess the efficacy and safety of lanthanum carbonate for reduction of serum phosphate in chronic renal failure in patients receiving hemodialysis.
Study LAM-IV-301:	A Phase III, open label, comparator controlled parallel group study to assess the efficacy and safety of lanthanum carbonate for reduction of gastrointestinal phosphate absorption and maintenance of control of serum phosphate in chronic renal failure patients receiving hemodialysis.
Study LAM-IV-302:	A Phase III, dose titration, randomized, double blind placebo controlled parallel group study to assess the efficacy and safety of lanthanum carbonate for reduction and maintenance of serum phosphorous levels in chronic renal failure patients receiving hemodialysis.
Study LAM-IV-307:	An open label, randomized, multicenter, Phase III, comparator controlled parallel group study to assess the long-term efficacy and safety of lanthanum carbonate in chronic renal failure patients receiving hemodialysis.

The overall conclusions/Comments derived from the provided studies are as follows:

Concentration-Exposure Relationship:

- An exposure-response relationship with respect to lanthanum plasma levels and its efficacy & safety does not exist. The plasma data collected in several clinical pharmacology and clinical studies, do not provide adequate information regarding lanthanum's total body exposure. There are concerns with respect to lanthanum's accumulation in tissues and its long-term safety.

Pharmacokinetics:

- **Effect of Food:** The food effect on the bioavailability of lanthanum carbonate could not be evaluated in study LAM-IV-110, because poor tolerability was experienced by more than 20% of the subjects in the "fasted/before food" arm and it was dropped from the study. Please note that that the labeling recommends to take Fosrenol with food because food increases the tolerability of the drug with respect to gastrointestinal events and lanthanum binds to the phosphate in the meals.

- **Dose proportionality:** Data from study LAM-IV-108 showed that lanthanum plasma levels increased with dose but not in a linearly proportional manner. A two, four, and eight fold increase in dose resulted in a 1.4, 1.8, and 2.4 fold increase in mean Cmax and in 1.5, 2.3, and 3.5 increase in mean $AUC_{0\text{-}12h}$.

- **Healthy subjects;**
  The data from several studies conducted in healthy subjects indicate that oral administration of large doses of lanthanum carbonate (up to 3000 mg/day) resulted in the attainment of very low lanthanum plasma levels and extremely low percentage of the administered dose excreted in urine ($4\text{-}5x10^{-5}$ %). Thus, based on these results, it appears that lanthanum carbonate is minimally absorbed after oral administration. However, data from animal studies indicate that lanthanum carbonate is indeed absorbed (about 6% in dogs) and following chronic administration, it is deposited in several tissues from which it is eliminated very slowly. Thus, in view of the lack of human mass balance data, the assumption that lanthanum carbonate is practically not absorbed, is questionable.

Based on the overall PK data, it can be concluded that plasma and urine are not the appropriate biological matrices to determine lanthanum's absorption/distribution/elimination. and the results obtained from these biological fluids do not provide any relevant information with respect to lanthanum's total body exposure and its relationship with safety.

- **Target Population:** Study LAM-IV-111 evaluated the pharmacokinetics of lanthanum in dialysis patients. The results showed that the levels of lanthanum in dialysis patients were about 3 times higher than control subjects with minimum amount of lanthanum recovered in urine and in the diasylate. Thus, it can be assumed that patients with compromised renal function will have higher levels of accumulation of lanthanum in different tissues (i.e., bone, liver, kidney, lung, etc.).

  Also. lanthanum trough levels were determined in chronic renal failure patients receiving hemodialysis (target population) in clinical studies LAM-IV-202, -204, -301, 302, and --307. The overall results from these studies showed that in general, lanthanum mean concentrations were about 0.6 ng/ml, there was minimal increase in plasma lanthanum concentration with dose, and there was no accumulation with time (up to 52 weeks).

Protein Binding:

- Lanthanum was highly bound (>99%) to human plasma proteins in vitro over the concentration range 0.1-250 ng/ml. Binding of lanthanum to human serum albumin, human α1-acid glycoprotein, and human transferrin in vitro was equally extensive There was no evidence of a concentration-dependent reduction in binding over the range investigated.

Metabolism:

- **Mass Balance:** No information was provided regarding the mass balance of lanthanum in humans after IV and/or oral administration. However, mass balance data in animal showed that in rats, the mean total recovery of an IV dose of lanthanum over a 42 days period was 76.4% of the administered dose. In dogs, the mean recovery of lanthanum after an oral dose was about 94%. Thus, animal data indicate that lanthanum carbonate is indeed absorbed and deposited in most of the tissues from which it is eliminated very slowly. Animal data suggest that with the exception of the stomach, tissue lanthanum concentrations reach a steady-state by week 26. For humans, the accumulation of lanthanum in tissues (i.e., liver, kidney, bone, GI. etc.) presents a concern from the long-term safety point of view.

  In Vitro Drug Metabolism: In vitro metabolic inhibition studies showed that lanthanum carbonate at concentrations of 10 and 40 mcg/ml did not have relevant inhibitory effects on any of the CYP450 isoenzymes tested (1A2, 2C9/10, 2C19, 2D6, & 3A4/5).

In Vitro- Drug Interactions:

- **Gastric Fluid:** The potential for a physico-chemical interaction (precipitation) between lanthanum and six commonly used medications (warfarin, digoxin, furosemide, phenytoin, metoprolol, & enalapril) in the stomach (simulated gastric fluid, SGF) was investigated. The overall results showed that the probability of having precipitation of insoluble complexes of X-drug-lanthanum in the stomach, is low. Also, the results showed that lanthanum carbonate reacts with SGF forming lanthanum chloride, which is a more soluble salt than lanthanum carbonate. Thus, it may be assumed that the oral absorption of lanthanum, as lanthanum chloride is higher.

In Vivo- Drug Interactions:

- **Citrates:** The co-administration of citrate containing products (orange juice & Effercitrate tablets) did not have any effect on the pharmacokinetics of a single 1000 mg oral dose of lanthanum carbonate.

- **Digoxin:** The co-administration of multiple 1000-mg oral doses of lanthanum carbonate did not have any effect on the pharmacokinetics associated with a single 0.5-mg oral dose of digoxin.

- **Metoprolol:** The co-administration of multiple 1000-mg oral doses of lanthanum carbonate did not have any effect on the pharmacokinetics asscciated with a single 100-mg oral dose of metoprolol.

- **Warfarin:** The co-administration of multiple 1000-mg oral doses of lanthanum carbonate did not have any effect on R & S-warfarin's pharmacokinetics associated with a single 10-mg oral dose of warfarin. Please note that this study used a low dose of warfarin and did not evaluate the pharmacodynamic interaction between these drugs (bleeding time or prothrombin time).

Assessment of Potential Drug interactions in ESRD Patients:

- A conservative assessment of the potential of Fosrenol (lanthanum carbonate) to interact with concomitant medications prescribed in renal dialysis patients during Phase 2 and 3 clinical studies, was performed. It was concluded that, of the theoretically possible mechanisms, those affecting absorption are the most likely to occur. In these instances, the interaction will be physico-chemical, resulting from chelation and binding, rather than from anything related to drug transport mechanisms. It was considered very unlikely that Fosrenol will precipitate any interaction by the perturbation of plasma protein binding or cytochrome P450 mediated metabolism, two very common sources of adverse drug- drug interaction.

- Within the ESRD clinical setting, evaluating drugs prescribed during Phase 2 and 3 studies with Fosrenol, it is considered that, overall, the potential for any clinically significant drug-drug interactions is very low. However, there is a theoretical possibility that co-administration of Fosrenol with antibiotics, gabapentin, cardiac glycosides, anti-histamines and levothyroxin might result in changes in pharmacokinetic profiles. It would be prudent to exercise caution when considering such combinations.

Dissolution:

- There are concerns regarding the overall dissolution data for FOSRENOL chewable tablets. The provided data for the whole tablets showed incomplete dissolution (less than — at 2 hrs in [ ] rpm). This low dissolution profile may be related to the fact that the tablets have very high hardness and therefore, very slow disintegration. Thus, the limiting step appears to be disintegration and not dissolution, Please note that lanthanum carbonate's solubility in [ ] [ ] thus theoretically lanthanum whole tablets should be completely dissolved in a short time.

  Based on the review of the overall dissolution data, OCPB is of the opinion that the originally proposed dissolution method for the crushed tablets (USP Apparatus 2, — rpm, and [ ]) can be accepted on **an interim basis,** with the understanding that the sponsor will continue with the development of more adequate dissolution methodology for the whole tablets. However, the original proposed dissolution specification of Q= — at — minutes is not acceptable and a specification of — at — minutes is recommended.

Analytical Methodology:

- Overall, the information for the validation and quality control samples of the analytical methodologies used in the different studies, is satisfactory.

Formulation:

- The to–be-marketed 250 mg chewable tablet formulation was used in the Phase II/III studies, however, it should be noted the 500 mg chewable tablet was never used in any of the clinical trials.

VI. QUESTION BASED REVIEW

A. GENERAL ATTRIBUTES

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

Molecular Formula: Lanthanum is a trivalent rare earth metal (La^{3+}) Atomic weight of 138.91. The molecular formula of lanthanum (III) carbonate hydrate is $La_2(CO_3)_3 \bullet 3\text{-}5(H_2O)$ with a molecular weight of [redacted] (457.8 to the anhydrous basis).

PKa: Lanthanum carbonate is a salt of carbonic acid. The pKa values for carbonic acid have been determined to be 10.33 and 6.35

Solubility: Lanthanum (III) carbonate hydrate is practically insoluble in water. Lanthanum carbonate [redacted]. It is insoluble [redacted]
Solubility studies at varying pHs have shown that lanthanum carbonate hydrate has [redacted] solubility at [redacted] with increasing solubility in [redacted]

Polymorphism: Although there are different [redacted] phases for lanthanum carbonate associated with [redacted] there is no evidence for [redacted] of lanthanum carbonate.

- **What are the highlights of the formulation of the drug product?**

The NDAs final drug formulation is an unflavored chewable tablet formulation with the dosage strength expressed in elemental lanthanum. The final drug formulation currently has two strengths 250 mg and 500 mg. The sponsor indicated their plans to market both strengths.

- **What is the proposed mechanism of drug action and therapeutic indication?**

Lanthanum carbonate is a phosphate binder; the chemical basis for this being the ionic binding properties of La^{3+}, which has an overwhelming preference for oxygen donor atoms of which the most common ligands are carboxyl and phosphate (PO_4) groups. In the presence of HCl in the stomach, a proportion of administered lanthanum carbonate is converted to the more highly soluble chloride salt with the release of carbon dioxide, The relatively high solubility of the chloride salt implies a greater absorption potential of La^{3+}. The activity of lanthanum carbonate as a phosphate binder is dependent on the availability of soluble La^{3+} in the gastrointestinal (GI) tract and the high affinity of La^{3+} for PO_4^{2-}. This binding results in the formation of highly insoluble lanthanum phosphate salt, which is excreted, thus significantly reducing phosphate absorption.

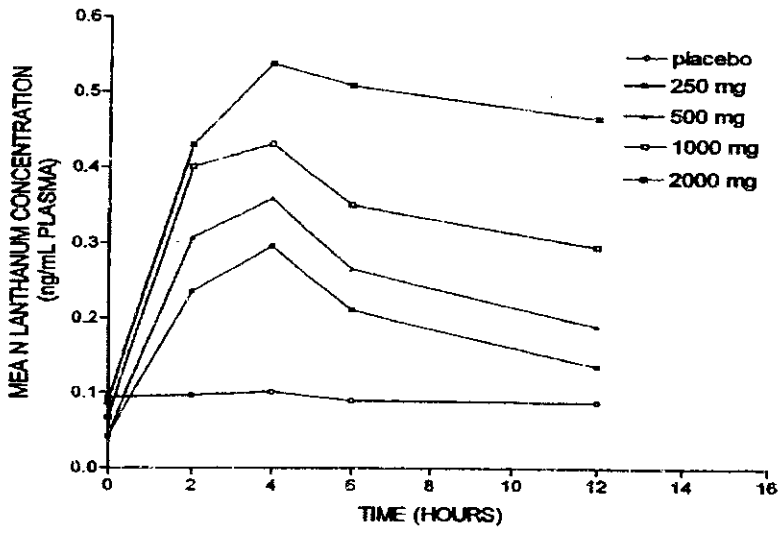
Fosrenol is indicated for [redacted]

- **What is the proposed dosage and route of administration?**
  The recommended initial total daily dose of lanthanum for adults is 750 mg by mouth (chewable tablets). In clinical studies, most patients required a total daily dose between 1500 mg and 3000 mg lanthanum to reduce plasma phosphate levels to less than 6.0 mg/dL. The dose should be divided and taken with each meal, for example 250 mg – 500 mg depending on the size of the meal. The dose should be titrated weekly to a level that achieves maintenance of acceptable serum phosphate levels. Serum phosphate levels should be monitored weekly until optimal serum phosphate level is reached, and then on a regular basis thereafter (monthly). Dosage can be increased in increments of 750 mg per day if tolerated.

B. GENERAL CLINICAL PHARMACOLOGY

- **Is the active moiety appropriately identified and measured to assess pharmacokinetic parameters?**
  Lanthanum carbonate was determined in plasma and its pharmacokinetics were estimated in several studies in healthy subjects and patients under single and multiple dose conditions.

- **Based on PK parameters, what is the dose-concentration relationship?**
  Data from study LAM-IV-108 showed that lanthanum plasma levels increased with dose but not in a linearly proportional manner. The next figure illustrates the mean plasma concentrations of lanthanum vs. time following administration of the treatments.



A two, four, and eight-fold increase in dose resulted in a 1.4, 1.8, and 2.4 fold increase in mean Cmax and in 1.5, 2.3, and 3.5 increase in mean $AUC_{0\text{-}12h}$.

- **Do plasma levels change with time following chronic dosing?**
  Lanthanum carbonate levels were determined in plasma during the Phase II/III clinical studies, however, no PK parameters were calculated. The next Table summarizes the ranges of mean concentrations of lanthanum in plasma obtained at specific time-points within each study in the randomized patients.

	RANGE OF PLASMA LANTHANUM LEVELS (MEAN (SD)) IN PHASE II/III STUDIES		
Study Number	**Dose Range of Lanthanum (mg/day)**	**Duration of Treatment (weeks)**	**Range of Plasma Lanthanum Levels (ng/ml)**
LAM-IV-202	375-2250 Dose Titration (Part 1)	4	0.16 (0.31)-0.69 (0.55)
	375-2250 Maintenance Fixed Dose (Part 2)	4	0.39 (0.37)-0.67 (0.98)
LAM-IV-204	225-2250 Fixed Dose Levels	6	0.21 (0.22)-0.86 (0.91)
LAM-IV-301	750-3000 Adjustable Dose Levels	49	0.38 (0 25)-0.67(0.65)
LAM-IV-302	375-3000 Dose Titration to Fixed Dose Levels	10	0.35 (0.44)-0.78 (1.05)
LAM-IV-307	375-3000 Dose Titration to Fixed Dose Levels	52	0.4 (0.76)-0.6 (1.15)

The ranges of the mean plasma lanthanum levels were relatively similar across the Phase II/III studies with the highest mean level at <1 ng/ml.

- **What is the inter-subject variability of PK parameters?**
  Inter-subject variability was very high. The variability in PK parameters Cmax and AUC was >50%.

- **What are the characteristics of the exposure-response relationship for efficacy and safety?**
  Fosrenol is a product designed to have a local therapeutical effect in the gut (phosphate binder). Fosrenol efficacy is based on the decrease and maintenance of appropriate serum phosphate levels. Thus, the concentrations of lanthanum in plasma are very low and do not represent the actual total body exposure to lanthanum, because under chronic conditions there is accumulation of lanthanum in several tissues. Overall, for Fosrenol an exposure-response relationship with respect to lanthanum plasma levels and its efficacy & safety does not exist.

- **What is the metabolism of the active moiety?**
  Other than lanthanum ability to react with HCl in the stomach, forming lanthanum chloride, lanthanum is not metabolized.

C. INTRINSIC FACTORS

- **What intrinsic factors influence exposure and/or response?**
  The sponsor did not specifically evaluate the influence of gender, weight, and height in lanthanum's pharmacokinetics. Since lanthanum is not metabolized, there are no reasons to expect clinically relevant differences in exposure between male and female patients. Plasma lanthanum levels in the Phase II/III studies support the absence of gender differences. With respect to age and race, plasma levels were comparable among the younger and elderly subjects/patients participating in the Phase I, II & III studies conducted in Japan, U.S., U.K., and Europe.

  However, disease conditions may influence exposure to lanthanum. For example dialysis patients presented about 3 times higher lanthanum plasma concentrations than control subjects and the

number of adverse events in the dialysis group was also higher. The following table compares plasma PK parameters and the extent of urinary excretion for healthy subjects and dialysis patients.

SUMMARY OF MEAN (%CV) PK PARAMETERS OF LANTHANUM FOR HEALTHY AND RENAL SUBJECTS						
	Single Dose Studies					
Study No.	Treatment Group	Dose of Lanthanum	Sampling Interval (hr)	AUC0-t ng.h/ml	Cmax (ng/ml)	% Urinary Excretion
LAM-IV-108	Healthy subjects	1000 mg	12	4.02 (31.5)	0.45 (31.4)	4.8×10^{-5} (34.00)
LAM-IV-111	Control Group	1000 mg	48	1.12 (135.8)	0.18 (94.9)	3.4×10^{-5} (111.4)
LAM-IV-111	Dialysis Group*	1000 mg	48	3.10 (93.2)	0.30 (59.9)	5.4×10^{-5} (243.6)
LAM-IV-111	Dialysis Group**	1000 mg	48	6.36 (104.1)	0.56 (90.3)	0.34×10^{-5} (194)
	Multiple Dose Studies					
LAM-IV-109	Healthy subjects	1000 mg tid x 5 days	24	9.99 (21.6)	0.53 (28.9)	3.1×10^{-5} (37.8)
LAM-IV-111	Control Group	1000 mg tid x 11 days	72	10.95 (37.5)	0.42 (40.4)	14.8×10^{-5} (46.3)
LAM-IV-111	Dialysis Group***	1000 mg tid x 11 days	72	31.1 (130.3)***	1.06 (98 3)	0.55×10^{-5} (72.7)

*No post-dose dialysis
** Dialysis occurred, 4 hrs post-dose
***Dialysis occurred routinely during the 11 day dosing period and at 4 hrs after the single dose of the last day.

- **What dosage regimen adjustments are recommended for the elderly, renal impaired, and hepatic impaired patients ?**

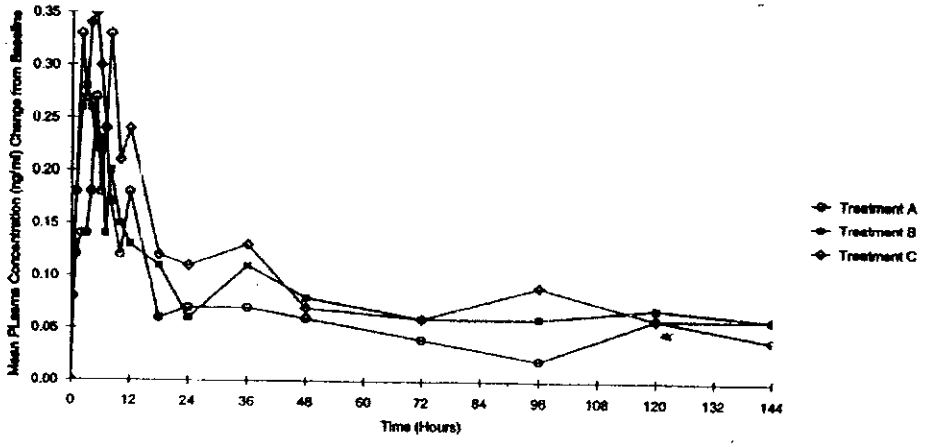
Due to the fact that the dose of lanthanum is individualized for each patient, no specific dose adjustments are necessary in elderly/renal/hepatic patients. Fosrenol should be titrated weekly to a level that achieves maintenance of acceptable serum phosphate levels (less than 6.0 mg/dL). Serum phosphate levels should be monitored weekly until an optimal serum phosphate level is reached, and then on a regular basis thereafter (monthly). In clinical studies, most patients required a total daily dose between 1500 mg and 3000 mg lanthanum to reduce plasma phosphate levels to <6.0 mg/dL.

D. EXTRINSIC FACTORS

- **Drug-Drug Interactions**

Physico-Chemical Interaction: The potential for drug-drug interactions between Fosrenol and co-administered medications was evaluated. It was concluded that, of the theoretically possible mechanisms, those affecting absorption are the most likely to occur. The potential for a physico-chemical interaction (precipitation) between lanthanum and six commonly used medications (warfarin, digoxin, furosemide, phenytoin, metoprolol, & enalapril) in the stomach (simulated gastric fluid, SGF) was investigated. The overall results showed that the probability of having precipitation of insoluble complexes of X-drug-lanthanum in the stomach, is low.

Also, the effect of citrates on the absorption of lanthanum into plasma was assessed in study LAM-IV-112. The results showed that he co-administration of citrate containing products (orange juice & Effercitrate tablets) did not have any effect on the pharmacokinetics of a single 1000 mg oral dose of lanthanum carbonate. The mean plasma lanthanum concentration-time profile and mean PK parameters using baseline corrected plasma lanthanum data are presented below.

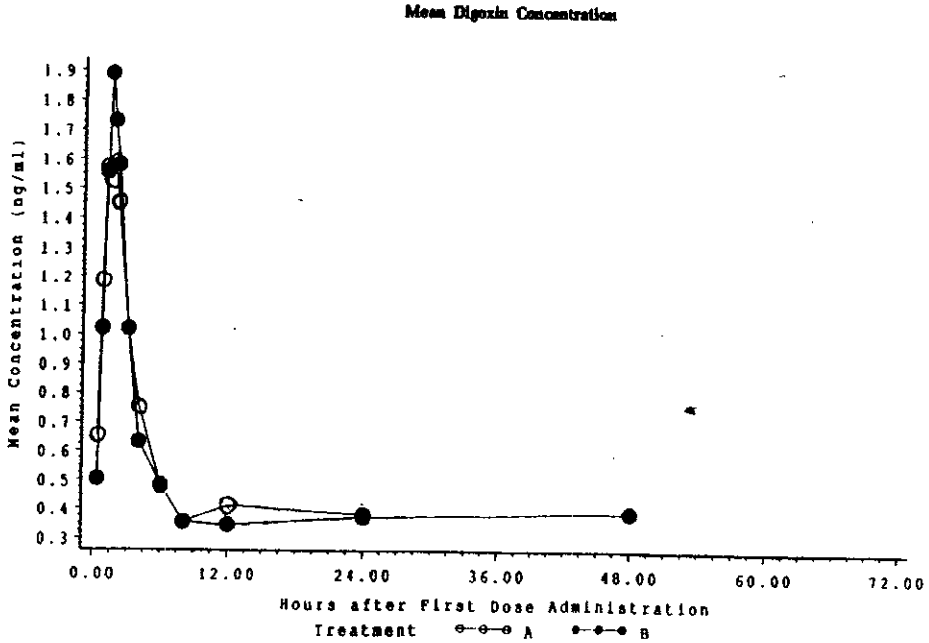


Note: Calculated from results with adjustment for lanthanum contamination.
Treatment A - 4 x 250mg lanthanum chewable tablets
Treatment B - 4 x 250mg lanthanum chewable tablets + 200ml room temperature orange juice
Treatment C - 4 x 250mg lanthanum chewable tablets + 2 x Effercitrate tablets in 200ml water

Protein & Metabolic Interaction: Lanthanum carbonate is highly bound to plasma proteins (>99%) and is not a substrate of CYP450 enzymes. In vitro metabolic inhibition studies showed that lanthanum carbonate at concentrations of 10 and 40 mcg/ml does not have relevant inhibitory effects on CYP1A2, 2C9/10, 2C19, 2D6, & 3A4/5. Thus, the possibility that Fosrenol will precipitate any interaction by the perturbation of plasma protein binding or cytochrome P450 mediated metabolism, two very common sources of adverse drug-drug interaction, is low. Within the ESRD clinical setting, although Fosrenol may have a low potential for clinical interactions, there is a theoretical possibility that co-administration of Fosrenol with antibiotics, gabapentin, cardiac glycosides, anti-histamines and levothyroxin might result in changes in pharmacokinetic profiles. It would be prudent to exercise caution when considering such combinations.

The sponsor decided to extend the in vitro findings to the clinical setting by evaluating the possible interaction of commonly co-administered drugs. Then, three in vivo metabolic studies were conducted in healthy subjects with the objectives of assessing the effects of 4000 mg total dose of lanthanum on the pharmacokinetics of warfarin, digoxin, and metoprolol.

- **Digoxin:** The co-administration of 4 daily 1000-mg oral doses of lanthanum carbonate did not have any effect on the pharmacokinetics associated with a single 0.5-mg oral dose of digoxin. The mean plasma concentration vs. time profiles for digoxin following treatment A and B are illustrated in the next Figure.



Treatment A = A single oral dose of digoxin 0.5 mg 30 minutes after the end of breakfast.

Treatment B = Four daily oral dose of lanthanum 1000 mg immediately after the end breakfast followed by a single oral dose of digoxin 0.5 mg, 30 minutes later.

- **Metoprolol:** The co-administration of 4 daily 1000-mg oral doses of lanthanum carbonate did not have any effect on the pharmacokinetics associated with a single 100-mg oral dose of metoprolol. A summary of PK and statistics for metoprolol is presented in the next table.

PARAMETER	MEAN (SD) PHARMACOKINETIC PARAMETERS & STATISTICS FOR METOPROLOL		
	Treatment A	Treatment B	90% CI
$AUC_{0\text{-last}}$ (ng.h/ml)	1459.23 (922.01)	1391.59 (953.8)	86.9-103.4
$AUC_{0\text{-last}}$ (ng.h/ml)*	1731.97 (1002.44)	1546.57 (1090.49)	88.8-107.9
Cmax (ng/ml)	269.93 (119.45)	234.76 (106.57)	73.3-112.6
Tmax (hours)	1.95 (-)	2.08 (0.843)	90.3-104.8
T1/2 (hours)	4.68 (-)	4.51 (1.488)	95.4-110.8

Treatment A = A single oral dose of metoprolol 100 mg, 30 minutes after the end of breakfast.

Treatment B = Four daily oral dose of lanthanum 1000 mg immediately after breakfast, followed by a single dose of metoprolol 100 mg 30 minutes later.

- **Warfarin:** The co-administration of 4 daily 1000-mg oral doses of lanthanum carbonate did not have any effect on R & S-warfarin's pharmacokinetics associated with a single 10-mg oral dose

of warfarin. As shown in the following table, the 90% confidence intervals for all PK parameters were within the 80-125% Agency's bioequivalence criteria for log-transformed data.

PARAMETER	MEAN (SD) PHARMACOKINETIC PARAMETERS & STATISTICS FOR WARFARIN					
	R-Warfarin Enantiomer			S-Warfarin Enantiomer		
	Treatment A	Treatment B	90% CI	Treatment A	Treatment B	90% CI
$AUC_{0\text{-last}}$ (ng.h/ml)	27222.8 (4404.5)	26400.4 (5172.6)	92.0-102.6	15900.8 (4904.4)	14962.5 (4150.1)	90.2-99.6
$AUC_{0\text{-inf}}$ (ng.h/ml)	31056.9 (4889.8)	30476.9 (5681.2)	91.8-100 4	18831.8 (5413.2)	17776.9 (4641.8)	90.2-100.0
Cmax (ng/ml)	558 0 (43.12)	556.9 (65.74)	95.4-103.6	537.64 (60.52)	541.6 69.66)	97.0-104.2
Tmax (hours)	3.00 (0.555)	3.29 (0.995)	-	2.71 (0.611)	2.86 (0.770)	-
T1/2 (hours)	45.33 (7.52)	44.82 (8.66)	-	32.32 (5.83)	30.81 (6.60)	-

Please note that this study used a low dose of warfarin and did not evaluate the pharmacodynamic interaction between these drugs (bleeding time or prothrombin time).

- **Are there any unresolved issues related to metabolism, transporters, & drug interactions?**

The following issue has not been resolved:

- **Mass Balance:** No information was provided regarding the mass balance of lanthanum in humans after IV and/or oral administration. Animal data indicate that lanthanum carbonate is absorbed and deposited in most of the tissues from which it is eliminated very slowly. For example, the next table presents the percentage of lanthanum remaining in tissues 6 months after termination of the treatment (dogs received 4 weeks oral administration of 2000 mg La/kg/day).

TISSUE		MEDIAN LANTHANUM CONCENTRATIONS (ng/g)	
		Lanthanum Concentration after 4 Weeks of Treatment	Lanthanum Concentration Following 6 Months of Washout
GI Tract	Esophagus	94	30
	Stomach	8837	4750
	Ileum	1012	165
	Jejunum	60	16
	Duodenum	4294	22
	Colon	390	8
	Rectum	12893	33
Bone & Teeth	Femur shaft	330	167
	Femur growth plate	767	664
	Sternum	40	396
	Teeth	8320	2430
Other Organs	Liver	1454	1196
	Lungs	366	126
	Heart	17	<8

Animal data indicate that the concentrations of lanthanum in tissues appear to reach steady-state at week 26 of dosing, with the exception of the GI system where continuous accumulation occurs.

The following table compares the concentrations of lanthanum in tissues of animals following chronic oral administration.

	RANGE OF MEDIAN CONCENTRATIONS (mcg/g wet tissue)		
Species	Mouse	Rat	Dog
Weeks Dosed	80 weeks	78 weeks	52 weeks
Maximum Dose	1500 mg (salt)/kg/day	1500 mg (salt)/kg/day	2000 mg (salt)/kg/day
	LOW CONCENTRATION TISSUES (<LLoQ to 1.0 mcg/g wet tissue)		
Aorta	0.481-0.482	1.09-1.48	ND
Adrenals	<0.642-<1.46	0.216-0.544	ND
Brain	0.031-0.059	<0.007-0.059	0.046-0.056
Epidermis	0.087	0.089	ND
Eyes	0.145-0.146	0.094-0.428	ND
Heart	0.115-0.139	0.052-0.077	0.130-0.455
Kidney	0.197-0.291	0.784-1.54	0.503-0.659
Lacrimal Glands	ND	0.099-0.140	ND
Mammary Gland	0.141-0.234	0.707-0.782	ND
Ovaries	0.312	0.578	ND
Pituitary	<3.35-<3.86	0.961-1.85	ND
Prostate	<0.175	0.177	0.086
Salivary Gland	0.185-0.193	0.079-0.144	0.171-0.227
Sciatic Nerve	<0.460-<0.532	0.038-0.267	ND
Seminal Vesicles	0.050	0.097	ND
Skeletal Muscle	0.057-0.071	0.023-0.076	0.787-0.905
Spinal Cord	3.05-6.90	2.88-3.10	0.243-0.313
Spleen	0.820-1.43	0.892-2.12	0.086-0.115
Submandibular LN	0.992-1.06	0.694-1.09	ND
Testes	0.113	0.201	0.789
Thymus	<0.320-0.226	0.034-0.230	0.197-0.814
Thyroids	<1.524-1.475	0.285-0.418	ND
Urinary Bladder	<0.197-0.292	0.087-0.135	0.374-1.95
Uterus	0.203	0.126	3.87
Vagina	0.313	0.102	ND
	INTERMEDIATE CONCENTRATION TISSUES (>1.0-10 mcg/g wet tissue)		
Bone Marrow	ND	ND	1.06-8.13
Femur-Plate	5.63-8.15	3.39-4.45	3.23-3.89
Femur-Shaft	3.60-5.08	2.23-4.24	1.84-2.51
Liver	2.34-3.59	1.26-1.90	7.25-11.1
Sternum	3.49-6.71	2.48-2.78	ND
	HIGH CONCENTRATION TISSUES (>10 mcg/g wet tissue)		
Cecum	716-2337	467-534	ND
Colon	222-506	128-158	24.8-122
Duodenum	79.8-190	96.4-123	11.4-13.1
Ileum	370-3696	989-1354	ND
Jejunum	38.4-87.2	537-583	ND
Mesenteric LN	24.0-53.8	86.1-767	1.37-1.54
Esophagus	22.4-23.6	174-214	ND
Rectum	23.3-90.9	6.06-19.5	35.1-60.6
Stomach	2024-2189	578-827	248-349

With respect to humans, analysis of bone biopsy material from study LAM-IV-103 provides evidence that there is accumulation of lanthanum in the bone. Therefore, it could be inferred that most probably lanthanum is widespread in the whole body and its concentration and retention in some tissues (i.e., kidney, liver, bone, GI) presents a concern for long term safety.

E. GENERAL BIOPHARMACEUTICS

- **Based on BCS principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?**

  Lanthanum carbonate appears to be a BCS Class IV (poorly soluble and poorly permeable drug). The provided solubility data indicate that lanthanum carbonate is poorly soluble in water and the percentage of total dose excreted in urine after oral administration is very low (about $4x10^{-5}$%). However, no mass balance or absolute bioavailability studies were conducted in humans, thus, the actual absorption of lanthanum carbonate following oral administration is unknown.

- **What is the relationship between the formulations used during the clinical development and the to-be-marketed formulations?**

  Three drug formulations were developed during the clinical program. The first drug formulation was a capsule formulation with strengths expressed in lanthanum carbonate. The second drug formulation was an unflavored tablet formulation with strength expressed in lanthanum carbonate. The final drug formulation is an unflavored chewable tablet formulation with the dosage strength expressed in elemental lanthanum. The final drug formulation is the to-be-marketed formulation and was used in the Phase II/III clinical trials. The quantitative formulations for the 250 and 500mg tablets are listed in the following table.

FORMULATION	250 mg Chewable Tablet	500 mg Chewable Tablet
Lanthanum Elemental	250mg	500mg
Lanthanum Carbonate Hydrate		
Dextrates		
Colloidal silicon dioxide		
Talc		
Magnesium Stearate		
Diameter	16 mm	22mm
Total Weight	**1800mg**	**3600mg**

Reviewer Comment:

1. *Please note that only the 250 mg chewable tablet was used in the Phase II/III clinical trials.*

proposed [

Formulation	Formulation Comparison of the Current [ ] Chewable Tablets	
	Current 250 mg Tablet	Current 500 mg Tablet
Lanthanum Elemental	250mg	500mg
Lanthanum Carbonate Hydrate		
Dextrates		
Colloidal silicon dioxide		
Talc		
Magnesium Stearate		
Diameter	16 mm	22mm
Total Weight	**1800mg**	**3600mg**

Reviewer Comments:

1. [

2. [

3. [

- **What is the effect of food on the bioavailability of lanthanum carbonate?**
  Fosrenol is indicated to be taken with food, however, the food effect on the bioavailability of lanthanum carbonate could not be evaluated in study LAM-IV-110, because poor tolerability was experienced by more than 20% of the subjects in the "fasted/before food" arm and it was dropped from the study.

  Please note that study –110 also evaluated the timing of food intake on the pharmacokinetics of lanthanum. Subjects were administered 1000 mg of lanthanum during and 30 minutes after food intake, three times per day (total daily dose, 3000 mg) on 3 consecutive days. The results showed

that the timing of food intake relative to lanthanum administration appeared to have a small effect on the systemic levels of lanthanum. The mean (SD) plasma lanthanum pharmacokinetic parameters and statistical comparisons are shown in the following table.

PHARMACOKINETIC PARAMETERS	MEAN (SD) LANTHANUM PK PARAMETERS & PLASMA CONCENTRATIONS			
	Treatment C (After food)	Treatment B (During food)	% Difference	P-Value
Cmax (ng/ml)	0.233 (0.074)	0.209 (0.078)	10.36	0.0738
Tmax (hr)	4.55 (1.31)	5.09 (0.867)	-8.35	0.0847
AUC_{0-t} (ng.hr/ml)	0.882 (0.325)	0.717 (0.325)	21.53	0.0001*
C24 (ng/ml)	0.392 (0.132	0.328 (0.146)	20.16	0.0124*
C72 (ng/ml)	0.445 (0.157)	0.391 (0.162)	13.83	0.0331*
* Difference is statistically significant, p<0.05				

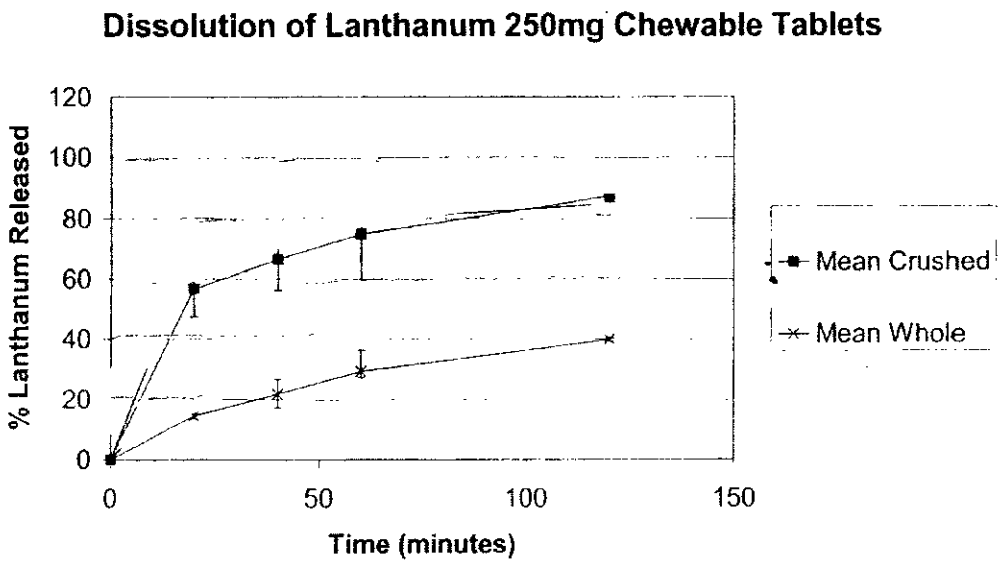
- **What are the proposed dissolution method and specification?**

During the development of the dissolution testing method for lanthanum carbonate chewable tablets 250 and 500 mg, various aqueous dissolution media and the crushing activity (used to mimic chewing) was evaluated. The results of Validation Report showed that for whole tablets there was very little or no detectable dissolution in [ ] buffers [ ] but that [ ] was a suitable medium.

To evaluate the crushing activity the lanthanum carbonate tablets were prepared as follows:

- WHOLE tablet
- [ ]
- CRUSHED tablet; single tap of a pestle to break each tablet into 4-6 pieces, then each large piece was broken again with a single tap of the pestle
- [ ]

The results are presented in the next Figure and Table.



	Dissolution Data for Lanthanum Carbonate 250 mg Tablets (Lot No. 0H2772)			
	Testing conditions: USP Apparatus II (paddle), — rpm, — of — Percent of Lanthanum Released			
Sampling Time	Whole tablet		Crushed tablet	
20 min	14.4 (3.7)		56.7 (10.8)	
40 min	21.8 (14.0)		66.6 (8.5)	
60 min	29.3 (11.9)		74.8 (6.4)	
120min	39.8 (1.2)		87.3 (3.9)	

Mean of 6 tablets(%RSD)

Based on these results, the sponsor decided that CRUSHED tablets provided optimum tablet preparation and release profile. The proposed dissolution methodology and specifications for the lanthanum carbonate 250 and 500 mg CRUSHED chewable tablets are as follow:

PROPOSED DISSOLUTION METHOD AND SPECIFICATIONS FOR LANTHANUM CARBONATE CRUSHED CHEWABLE TABLETS	
Variable	**Parameter**
Apparatus Type	USP Apparatus 2 (paddle)
Dissolution Medium	—
Speed of Rotation	— rpm
Sample Pull Times	20, 40, 60, and 120 minutes
Specification	Q= — at — minutes

On August 27, 2002, the sponsor provided additional dissolution data in the reports entitled, "Development of a Dissolution Test for Lanthanum Carbonate Tablets (Report No. 1, dated December 7, 1999)" and "Validation of the Lanthanum Carbonate Dissolution Method (Report No. 2, dated 29 February 2000)". The results from these reports using crushed tablets and the above dissolution method are summarized next.

	Summary of Dissolution Data for Crushed Lanthanum Carbonate 250 mg Tablets						
	DATA FROM REPORT 1: PERCENT OF LANTHANUM DISSOLVED Mean of 6 tablets (SD)						
Manufacture	**LOT NO.**	**20 min**	**40 min**	**60 min**	**120 min**	**180 min**	**240 min**
—	9C2735	14.6 (2.86)	23.3 (1.01)	29.8 (1.21)	39.1 (1.1)	50.1 (2.21)	62.5 (2.98)
	9C2736	20.1 (1.61)	33.3 (0.90)	41.5 (0.97)	73.5 (3.78)	96.1 (1.13)	96.3 (3.17)
	9C2737	18.8 (0.94)	30.3 (1.58)	39.9 (1.91)	63.8 (4.57)	92.3 (3.66)	97.0 (3.78)
—	96156	19.4 ((0 39)	33.0 (1.33)	41.3 (1.77)	65.5 (2.19)	89.8 (2.37)	96.3 (1.46)
	96157	31.5 (1.21)	54.9 (2.29)	71.4 (2.78)	ND	98.0 (1.59)	ND
	96173	31.0 (1.95)	54.5 (2.4)	72.2 (3.52)	96.6 (3.50)	99.9 (3.17)	99.1 (2.33)
	DATA FROM REPORT 2: PERCENT OF LANTHANUM DISSOLVED Mean of 6 tablets (SD)						
Manufacture	**LOT NO.**	**20 min**	**40 min**	**60 min**	**120 min**	**180 min**	**240 min**
—	9C2735	89.1 (3.02)	98.0 (2.75)	97.5 (1.41)	102.4 (2.48)	102.2 (3.04)	100.7 (4.26)
	9C2736	91.7 (1 99)	94.2 (1.36)	94.8 (2.25)	96 4 (1.13)	96.6 (1.66)	96.3 (0.967)
	9C2737	86.5 (5 55)	95.4 (4.30)	98.9 (1.80)	100 7 (2.13)	101.6 (2.64)	100.8 (0.952
—	96189	85.9 (2.92)	94.4 (3.89)	96.3 (2 46)	97.0 (3.65)	96.7 (3.25)	97.3 (2.96)
	96191	83 6 (3 70)	94.0 (1.58)	95 4 (1.22)	96.6 (2.76)	98.0 (2.19)	97.8 (1.44)

These results clearly show inconsistency in the dissolution data. For example, the same lots manufactured by [ ] have lower dissolution profiles and higher variability in Report 1 than in Report 2.

OCPB's concerns regarding the overall dissolution data were conveyed to the sponsor on September 5, 2002. It was noted that the dissolution guidance recommended the use of whole tablets in case the patient swallows the whole tablet or does not chew the tablet enough. OCPB encouraged the sponsor to develop a more appropriate dissolution methodology for the whole tablets (i.e., several dissolution media ( ) and rotation of speed, etc.). After that, the sponsor initiated a dissolution method redevelopment and on November 4 and 27, 2002, they submitted additional dissolution information and a proposal for the use of 250 & 500 mg — tablets and the following dissolution method and specification:

PROPOSED DISSOLUTION METHOD AND SPECIFICATIONS FOR LANTHANUM CARBONATE — CHEWABLE TABLETS	
Variable	**Parameter**
Apparatus Type	USP Apparatus
Dissolution Medium	—
Speed of Rotation	— rpm
Specification	Q= — % at — minutes

On December 12, 2002, OCPB informed the sponsor that the newly proposed dissolution method and specification were not acceptable for a chewable product. It was mentioned that perhaps, the problems they were having in getting appropriate dissolution data for their chewable tablets were related to the fact that their tablets have very high hardness and therefore, very slow disintegration. Thus, the limiting step appears to be disintegration and not dissolution (solubility of lanthanum in the dissolution medium, [ ] is [ ]

Reviewer Comments:

1. *It should be noted that the PK and clinical studies that were provided in the original NDA submission used many different lots of lanthanum carbonate chewable tablets. However, the sponsor provided dissolution data only for the 250 mg tablets: lots 96156, 96157, 96173, 96189, and 96191 used in clinical study LAM-IV-301 and lots 9C2735, 9C2736, and 9C2737 used in clinical study LAM-IV-307.*
2. *Please note that the author of Report 2, [ ] indicated that some practical modifications were made to the original method , [ ] Thus, as shown in the previous Table, it appears that these modifications help to improve the dissolution of lanthanum tablets.*
3. *Based on the review of the overall dissolution data and taking into account that; 1) the newly proposed method and specification — tablets and a Q= —, at — minutes) would not provide any useful dissolution information and 2) all the dissolution-stability data were generated using crushed tablets, OCPB is of the opinion that the originally proposed dissolution method for the crushed tablets (USP Apparatus 2, — rpm, and [ ]), can be accepted on an interim basis.*

However, the original proposed dissolution specification of Q= — ; at — minutes is not acceptable. The data from Report 2 show that a specification of — at — minutes would be more appropriate.

- **What other significant, unresolved issues related to in vitro dissolution or in vivo BA/BE need to be addressed?**
  - ***Bio-waiver:*** It should be noted that the sponsor is seeking the approval of both, the 250 and 500 mg strengths of lanthanum carbonate chewable tablets. However, as described in the next table only the 250 mg strength was used in the Phase 2 and Phase 3 clinical studies and a bio-waiver for the 500 mg chewable tablet was never requested.

LANTHANUM CARBONATE CHEWABLE TABLETS USED IN PK AND CLINICAL STUDIES

STUDY NO.	LOT NUMBER
LAM-IV-105	20662 (500 mg)
LAM-IV-108	22924 (250 mg)
LAM-IV-109	96156 (250 mg)
LAM-IV-110	96192 (250 mg)
LAM-IV-111	9L2748 (250 mg)
LAM-IV-112	96190 (250 mg)
LAM-IV-113	90378 (250 mg)
LAM-IV-114	90378 (250 mg)
LAM-IV-115	90378 (250 mg)
LAM-IV-202	22923 (125 mg) 22924 (250 mg)
LAM-IV-204	28496 (25 mg), 28497(75 mg), 28768(150 mg), 28540 (250 mg)
LAM-IV-301	96155, **96156**, **96157**, 96170, **96173**, 96174, 96185, **96189**, 96190, **96191**, 96192, 90378, 90379 (250 mg)
LAM-IV-302	9F2700 (250 mg)
LAM-IV-307	**9C2735, 9C2736, 9C2737**, 9F2700, 9F2799, 9G2712, 9L2745, 9L2744, 9L2746, 9L2748, 9L2749, 9L2750, 9L2751 (250 mg)

Reviewer Comment:

1. *From the OCPB's viewpoint, to get approval of the 500 mg chewable tablet, the sponsor should; 1) provide appropriate information (according to the guidance) to support the bio-waiver, **or** 2) provide data from a bio-study.*
2. *The sponsor should be informed that to get approval of a bio-waiver for the 500 mg strength the following requirements need to be satisfied:*
   - *Clinical safety/efficacy data covering the dosing range of the higher strength*
   - *Linear elimination kinetics over the therapeutic range or data showing that lanthanum is not systemically absorbed.*
   - *The formulations of the higher and lower strengths should be proportionally similar*
   - *Comparative dissolution profile data for the whole tablets using the same dissolution procedures*

Additional dissolution data: Due to the fact that the originally proposed dissolution method would be acceptable only on an interim basis, the sponsor should make the commitment to continue pursuing the development of an appropriate dissolution methodology for the whole tablets. Within the first year from approval date, the sponsor should submit to the Agency a final report including the development and validation of a revised dissolution method.

Also, the report should include complete dissolution data for at least 3 production lots of the 250 and 500 mg tablets (at least 12 units/lot) using the revised method.

Reviewer Comment:

1. *Please note that the Agency's recommendation for a final dissolution method and specification for the 250 & 500 mg Fosrenol (lanthanum carbonate) chewable tablets would be based on the information provided in this report.*

F. Analytical

- **Where the bioanalytical methods used to support CPB studies acceptable?**

Initial studies utilized analytical methods for lanthanum levels in biological fluids, offering sensitivity in the parts per billion range, and suggested that lanthanum was not systemically absorbed. Early clinical studies therefore focused on assessment of the safety and pharmacodynamic aspects of lanthanum carbonate.

A subsequent development of a more sensitive analytical method, with a lower limit of quantification in the parts per trillion range, provided the first evidence that lanthanum was detectable in plasma, albeit at extremely low levels. Consequently, a number of studies initially considered unnecessary, including human pharmacokinetic & biopharmaceutic studies, were implemented.

Lanthanum in biological fluids (plasma, urine, bile, and cerebrospinal fluid), feces, and a variety of tissues was measured using validated [ ] methods. The [ ] method was used for sample screening and for the quantitation of biological fluids and tissue lanthanum concentrations in excess of — g/ml. For some early ADME and toxicity studies, the limit of quantitation (LOQ) for serum and urine was — ng/ml. Subsequently, sensitivity was improved and for pivotal pharmacokinetic, tissue distribution, repeat-dose toxicity and carcinogenicity studies the LOQ for biological fluids was — ng/ml

In the pilot studies with the capsule formulation (LAM-IV-101 and LAM-IV-104), [ ] was used for analysis of lanthanum levels in plasma with a level of detection at — ng/g. All of the clinical studies subsequent to the above referenced pilot studies with the capsule formulation were performed with a tablet formulation. Among these studies the pharmacokinetic studies used validated [ ] methodology to assay lanthanum levels in plasma or serum and urine.

The [ ] method involves the [ ] The lanthanum concentration is determined by comparing the ratio of the analyte response to the internal standard response — with a standard curve defined by calibration standards. An initial validation was conducted for lanthanum plasma concentrations covering an anticipated clinical sample range of —. ng/ml lanthanum. A subsequent validation was conducted in the lower range of — ng/ml lanthanum. This method was found to be linear, accurate, and precise over this concentration range.

Reviewer Comment:

1. *Overall, the validation information provided in this submission for the analytical methods that were used to evaluate lanthanum carbonate in the several biological fluids is appropriate and acceptable.*

13 pages redacted from this section of the approval package consisted of draft labeling

B. ATTACHMENT 2

Includes:

- Summary of Pharmacokinetic Studies in Healthy subjects:
  Study No. LAM-IV-105
  Study No. LAM-IV-108
  Study No. LAM-IV-109
  Study No. LAM-IV-110

- Summary of a Pharmacokinetic Study in Dialysis Patients:
  Study No. LAM-IV-111

STUDY LAM-IV-105

Title: A Double-Blind Rising Dose Tolerance Study To Evaluate The Safety, Pharmacokinetics And Pharmacodynamics Of A Rare Earth Salt vs. Placebo When Administered With Food In Healthy Volunteers.

Investigator: [

]

Study Period/Site: [

]

Study Objectives:

- To evaluate the safety and tolerance of lanthanum carbonate when administered with food in a three times per day dosing regimen.
- To evaluate the rate and extent of absorption of lanthanum in the presence of food.
- To evaluate the effect of lanthanum carbonate on urinary phosphorus excretion following 3 days of treatment.

Study Population:

Fourteen subjects meeting inclusion/exclusion criteria were enrolled in Part I, two subjects received placebo on each dosing day; twelve subjects (10 active, 2 placebo) from part I were enrolled in Part II. A summary of the demographic information is presented below.

VARIABLE	CATEGORY	PART I	PART II
No. of Subjects		14	12
Gender	Male	14	12
Age (yrs)		30.8 (7.8)	32.0 (7.76)
Height (cms)		177.4 (5.14)	178.87 (3.8)
Weight (kgs)		77.83 (7.12)	79.48 (6.22)
Smoker	No Yes	6 8	5 7
Race	Caucasian	14	12

Study Design:

This was a randomized, double-blind, placebo-controlled, dose escalation study divided into two parts. In Part I, 14 subjects received increasing total daily doses of lanthanum carbonate or placebo on alternate days until reaching either 9.0 g per day or a maximum tolerated total daily dose. In Part II, 12 of the 14 were randomly assigned to receive either 9.0 g lanthanum carbonate or placebo for 3 consecutive days. Dosing frequency was three times per day throughout the study.

Treatments and Mode of Administration:

The test product was lanthanum 500 mg chewable tablets (Lot No. 20662), manufactured by [

]

The reference product was a placebo inert tablet, which was physically indistinguishable from lanthanum 500 mg chewable tablets.

In Part I, subjects were administered increasing total daily doses on alternating days, according to one of the following 7 sequences of treatments:

HABCDEHF AHBCDEFH ABHCDEFG ABCHDEFG ABCDHEFG ABCDEHFG ABCCDEFG

Where: A = 0.5 g Lanthanum Carbonate, B = 1.0 g Lanthanum Carbonate,
C = 1.5 g Lanthanum Carbonate, D = 2.5 g Lanthanum Carbonate,
E = 4.0 g Lanthanum Carbonate, F = 6.0 g Lanthanum Carbonate,
G = 9.0 g Lanthanum Carbonate, and H = Placebo.

In Part I, the study drug/placebo was administered with a phosphate controlled meal (phosphate level = 1200 mg per day at 8:00 am, 2:00 PM, and 8:00 PM). Administration of the active drug commenced at one dose per day, and gradually increased to three doses per day. To preserve the study blinding, each subject received three doses of a study drug on each dosing day. On Day 1, only the 8:00 am dose was active drug, the other two doses (2:00 PM and 8:00 PM) were placebo drug. On Day 3, the 8:00 am and 2:00 PM doses were active drug, the 8:00 PM dose was placebo drug. Starting on Day 5, all three doses were active drug or placebo drug (as specified in the randomization). The same number of chewable tablets (combination of active and placebo) was administered at each dosing time, as per the randomization for that dosing level/day. The subjects and staff were blinded as to the tablet combination (active and placebo) which was prepared by the clinic pharmacist.

In Part II, the study drug/placebo was administered with a phosphate controlled meal (phosphate level = 1200 mg per day at 8:00 am, 2:00 PM, and 8:00 PM). As with Part I, the same number of chewable tablets (combination of active and placebo) was administered at each dosing time, as per the randomization. Again, the subjects and staff were blinded as to the tablet combination.

Subjects in both parts were not permitted to lie down for the first two hours following each drug administration to assure sufficient stomach emptying. The duration of treatment was 20 days.

Assessments:

- ***Pharmacokinetics:*** Serum samples were obtained at -0.25, 2.00, 4.00, 5.75 and 11.75 hours after each dose in Part I. In Part II, samples were collected at -0.25, 4.00, 11.75, 23.75, 26.00, 28.00, 29.75, 35.75, 47.75, 50.00, 52.00, 53.75, and 59.75 hours after the initial dose.

- ***Safety:*** Vital signs, ECG, and clinical laboratory test were collected at specified intervals throughout the study. Physical examinations were done before and after the study.

Bioanalytical method:

Plasma and urine samples were analyzed for lanthanum content by a validated [ ] assay at [ ]

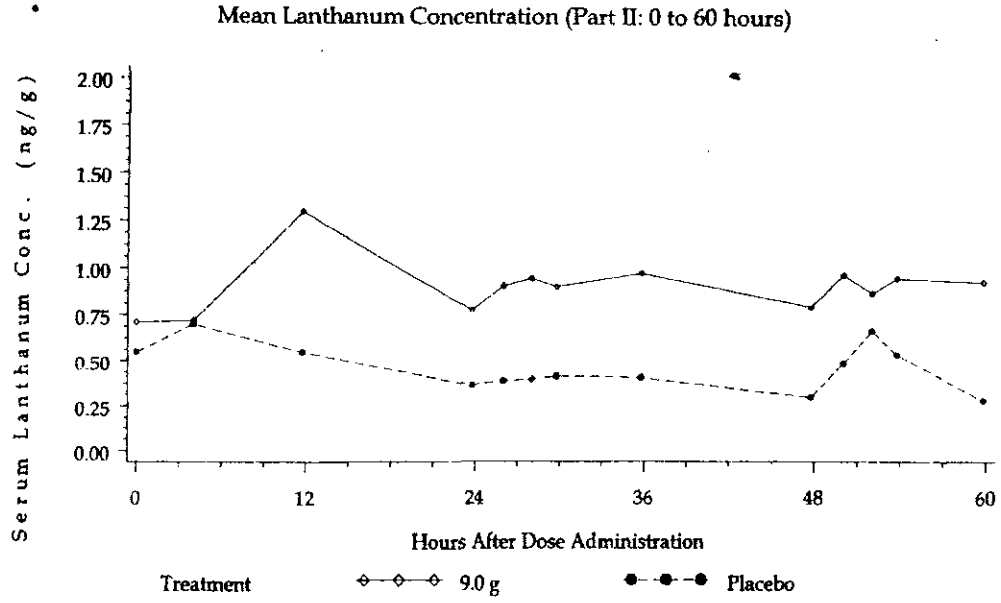
Statistical Methods:

Statistical methods consisted of displaying descriptive statistics, such as the mean and the standard deviation or percentages. Tests of hypothesis were carried out at the 5% level. For PK, two samples t-tests were applied to the lanthanum concentrations observed at each of the scheduled times in Part II.

Results:

Safety: There were a total of 125 treatment-emergent adverse events reported by 13 subjects. No serious adverse events were reported during the study. There were 12 episodes of nausea (in 6 subjects) and three episodes of vomiting reported by one subject during the 20 day of the study. Headache was the most adverse event reported with 21 episodes. Also, there were several clinical laboratory tests that exceeded the normal ranges during the study

Pharmacokinetics: Serum lanthanum levels in the study ranged from below the limit of detection to — ng/g with the average levels ranging from [ ] ng/g. In Part II, average serum lanthanum levels in the group receiving 9.0 g lanthanum carbonate were statistically significantly higher than the average levels in the placebo group (lanthanum group, [ ] ng/g; placebo group,[ ] ng/g). Next plot illustrates the mean lanthanum concentration vs. time profile for Part II of the study.



Sponsor's Conclusions:

1. Administering lanthanum carbonate three times a day with food increased the tolerability of the drug with respect to gastrointestinal (GI) adverse events.
2. The extent of absorption was insignificant for the oral administration of lanthanum at all tested dose levels. The rate of lanthanum absorption was relatively low with the maximum concentration of lanthanum being reached after the second dose and the lanthanum levels remaining constant through the rest of the three day treatment period.
3. Administration of lanthanum carbonate significantly reduced the amount of urine phosphorus excretion, suggesting that decreased GI uptake of phosphate was achieved by administering lanthanum.
4. No clinically significant trends in vital signs, physical examinations or routine clinical laboratory tests were observed regarding subject safety in respect to the different treatment regimens. Administration

of lanthanum carbonate did not significantly affect other pharmacodynamic markers such as serum levels of sodium, calcium, creatinine, creatinine clearance, phosphate, and parathormone; and urine levels of creatinine.

Reviewer Comments:

1. Please note that in this study the PK results are reported in ng/g instead of ng/ml. To convert to ng/ml, multiply plasma concentration by 1.054, density of plasma.
2. The sampling scheme was not optimal. The first sample was taken 2 hrs after drug administration, thus, there is no information for the absorption phase and Cmax might not be captured.
3. The types of meals given in this study were not included and the specific effect of food on the rate and extent of absorption of lanthanum carbonate was not evaluated.
4. This reviewer does not agree with the sponsor's statement that absorption of lanthanum is insignificant after oral administration. Animal data have show that lanthanum carbonate is absorbed and is deposited in tissues from which is eliminated very slowly. If it is assumed that about 6% of a 3000 mg/day dose is absorbed, then approximately 180 mg of lanthanum will be absorbed daily. Thus, following chronic administration, most probably lanthanum will accumulate in several tissues (bone, liver, kidney, GI, etc.).
5. With respect to safety, for a drug that according to the sponsor is practically not absorbed, there are many adverse events and changes in the clinical safety measurements. Therefore, the medical reviewer of DCRDP should determine the clinical relevance of these results on the overall safety of lanthanum carbonate.
6. The sponsor provided appropriate assay validation information and quality control samples data.

Study LAM-IV-108

Title:

A Phase I, Single Center, Randomized, Double-Blind, Placebo Controlled, Ascending Dose Study To Assess The Safety, Tolerability And Pharmacokinetics Of Lanthanum Carbonate Chewable Tablets In Healthy Male Japanese Volunteers.

Investigator: [ ]

Study Period/Site: August 1998-October 1998, [ ]

Study Objectives:

To determine the safety, tolerability and pharmacokinetic profile in 10 healthy male Japanese subjects following single ascending doses of placebo (0 mg), 250mg, 500mg, 1000mg and 2000mg of elemental lanthanum (477mg, 954mg, 1908mg and 3816mg of lanthanum carbonate).

Study Population:

Ten healthy male subjects meeting inclusion/exclusion criteria were enrolled in the study. Demographic values are summarized in the next Table.

ITEM	NO. OF SUBJECTS	MEAN (SD)
Age	10	23.7 (0.95)
Height (cm)	10	171.9 (3.5)
Body Weight (kg)	10	61.7 (8.1)
Body Mass (BMI)	10	20.8 (2.3)

Study Design:

This was a randomized, single-administration, double blind, ascending dose with randomized placebo design study in which subjects were randomized to receive one of five different treatment sequences (A-E). At each of the 5 dose periods the study drug (lanthanum carbonate or placebo) was administered once a day within 30 minutes of eating and there was a two-day washout between each dosing period.

Treatments and Mode of Administration:

- The test product was lanthanum 250 mg chewable tablet, Lot No. 22924 (containing lanthanum as 477 mg lanthanum carbonate).
- The reference product was a placebo inert tablet, which was physically indistinguishable from lanthanum 250 mg chewable tablets.

All subjects received the same meal to minimize variability in dietary phosphate available for binding with lanthanum carbonate. Subjects received a single dose of the study drug (lanthanum carbonate or placebo) on each of 5 days with a two-day washout between doses. The dosing schedule is presented below.

	SEQUENCE				
	A	B	C	D	E
Phase 1: Day 1	P	250	250	250	250
Phase 2: Day 1	250	P	500	500	500
Phase 3: Day 1	500	500	P	1000	1000
Phase 4: Day 1	1000	1000	1000	P	2000
Phase 5: Day 1	2000	2000	2000	2000	P
P = Placebo All doses are in units of 250 mg lanthanum chewable tablets (containing lanthanum as 477 mg of lanthanum carbonate)					

Assessments:

- ***Pharmacokinetics:***
  Blood samples were taken five times a day, pre-dose and 2, 4, 6, and, 12 hours post study drug administration. Urine was collected for the 24 hour period prior to dosing and for 24 hours post-dosing. Urine was pooled, volume was measured and about 60 ml were frozen for analysis.

  The following pharmacokinetic parameters were evaluated:
  - Area under the plasma concentration time curve between 0 and 12 hours (AUC0-12h).
  - The maximum concentration of drug in plasma between the first time point after dosing (2 hours) and the last time point (12 hours) Cmax.
  - The time to reach the maximum concentration (Tmax).
  - The amount of lanthanum (ng) in urine samples (urine lanthanum mass) collected during a 24-hour period post dosing was also determined.

- ***Safety:*** subjects were evaluated for vital signs, ECGs, physical examination, clinical laboratory parameters, and adverse events.

Bioanalytical Methods:

Plasma and urine samples were analyzed for lanthanum content by fully validated [ ] assays at [ ]

Plasma: A method was developed to determine concentrations of lanthanum (La) in plasma by [ ] using — as an internal standard. This assay involves [ ] The concentration of La was determined by comparing the ratio of the analyte response to the internal standard response with a standard curve defined by calibration standards.

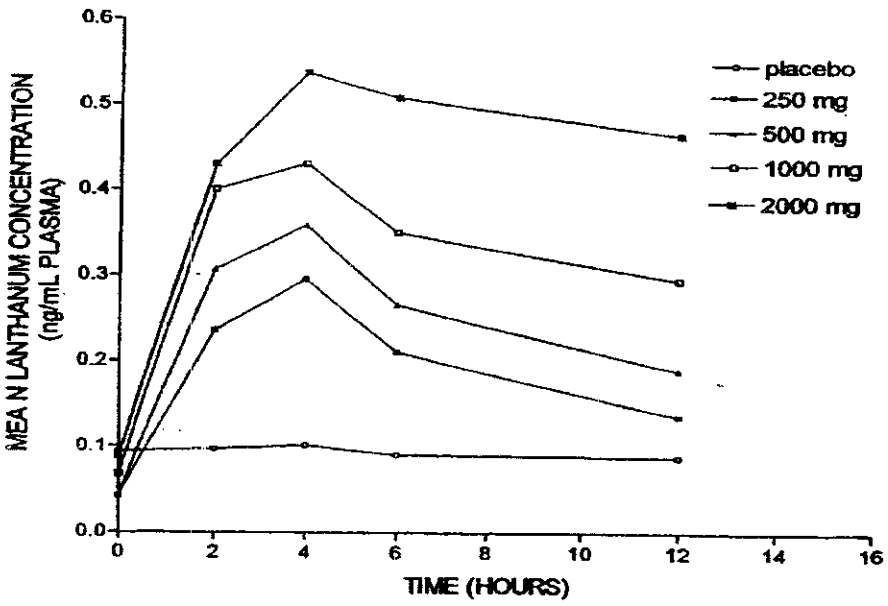
Urine: A method was developed to determine concentrations of La in human urine by [ ] using — as an internal standard. A ten-fold dilution of the sample with dilute nitric acid (1 %) was used for the sample preparation step. The La concentration was determined by comparing the ratio of the analyte response to the internal standard response with a standard curve defined by calibration standards.

The above analytical methods were validated for the concentration ranges [redacted] ng/ml of La in plasma and [redacted] ng/mL of La in urine. The methods were linear, accurate, and precise over this concentration ranges. The average within-day precision was <10% RSD for all concentrations. The average within-day accuracy was within 10% of the theoretical value for all concentrations in plasma and urine except the [redacted] ng/ml in plasma that was <20%. The absolute recovery comparing aqueous calibration standards to a full calibration curve prepared in plasma was within 15% and in urine was within 10%, for each point. The correlation coefficients of the calibration curves for all validation run days was >0.9999 for the matrix calibration curves.

Results:

Pharmacokinetics: Due to the limited blood sampling schedule for plasma pharmacokinetic analysis employed in this study the actual maximum concentration (Cmax) of lanthanum in plasma could not be determined. Therefore, references to Cmax in this report relate to the highest observed concentration of lanthanum in plasma and may not reflect the true Cmax values. Similarly the timings for Tmax are those at which the highest plasma lanthanum concentrations were observed and may not reflect the true Tmax values.

The next figure illustrates the mean plasma concentrations of lanthanum vs. time following administration of the treatments.



The mean pharmacokinetic parameters for lanthanum are presented in the next table. Administration of relatively large doses of lanthanum, ranging from 250mg to 2000mg (477mg to 3816mg of lanthanum carbonate), resulted in the attainment of extremely low plasma levels of lanthanum. A two, four and eight fold increase in lanthanum carbonate dose resulted in a 1.4, 1.8 and 2.4 fold increase in mean Cmax. Mean AUC(0-12h) increased 1.5, 2.3 and 3.5 fold over the same dose range.

MEAN (±STANDARD DEVIATION) PLASMA LANTHANUM PHARMACOKINETIC PARAMETERS			
DOSE OF LANTHANUM (MG)	AUC0-12H (NG.HR/ML)	CMAX (NG/ML)	TMAX (HR)
Placebo	1.12 (0.57)	0.11 (0.5)	5.20 (3.79)
250	2.36 (0.66)	0.30 (0.078)	3.60 (0.84)
500	3.01 (0.95)	0.38 (0.124)	3.40 (0.97)
1000	4.02 (1.27)	0.45 (0.141)	3.20 (1.03)
2000	5.45 (2.08)	0.56 (0.222)	6.00 (3.40)

There was a dose dependent increase in mean total amount of lanthanum excreted in urine but this was not directly proportional to dose. The percentage of the administered dose recovered in urine was inversely related to dose but not in a directly proportional manner. Urinary recovery of lanthanum over the 24-hour period post dosing was extremely low representing less than 0.0001 % of the administered dose. The mean 24 hour urinary excretion decreased from 8.58×10^{-5} % at the lowest dose (250mg) to 3.82×10^{-5} % at the highest dose administered (2000mg). Lanthanum's excretion data are presented below.

EXCRETION OF LANTHANUM IN URINE OVER A 24 HOUR POST-DOSE PERIOD		
DOSE OF LANTHANUM (MG)	MEAN AMOUNT OF LANTHANUM EXCRETED IN URINE (MG)	% EXCRETED
250	0.2144×10^{-3}	8.58×10^{-5}
500	0.3286×10^{-3}	6.57×10^{-5}
1000	0.4786×10^{-3}	4.79×10^{-5}
2000	0.7631×10^{-3}	3.82×10^{-5}

Safety: There were 11 treatment emergent AEs reported during the study. Diarrhea, sicchasia and heartburn were the most frequently reported events. A total of four AEs arose in the 2000mg dose group, two in the 1000mg dose group, one in the 250mg dose group and four in the placebo dose group. No events occurred at the 500mg dose level. No serious AEs were reported during the study.

Systolic and diastolic blood pressure values four hours after treatment were seen to be higher in the 2000 mg dose group compared to the other groups. This difference remained within normal parameters for blood pressure and was not considered clinically significant.

Sponsor's Conclusions:

1. Administration of relatively large oral doses of lanthanum carbonate ranging from 250mg to 2000mg resulted in the attainment of extremely low (sub ng/mL) plasma levels of lanthanum.
2. Plasma concentrations increased with dose but not in a linearly proportional manner. A two, four and eight fold increase in dose resulted in a 1.4. 1.8 and 2.4 fold increase in mean Cmax. Mean AUC0-

12h increased 1.5, 2.3 and 3.5 over the same dosage range. Due to individual variability not all these differences were statistically significant.

3. Tmax occurred at approximately 3.5 hours post dosing although after the highest dose this was somewhat delayed to 6 hours. This may have been due to dissolution rate limited absorption.
4. Urinary excretion of lanthanum over the 24h post dose collection period accounted for a relatively small proportion of the administered dose with a mean of 5.94×10^{-5} %.
5. The proportion of the administered dose recovered was inversely related to dose but not in a directly proportional manner. After the lowest dose of 250ng/ml, 8.58×10^{-5} % was recovered in 24h compared to only 3.82×10^{-5} % over the same period for the highest dose. This may have reflected less extensive absorption at the highest dose.

Reviewer Comments:

1. The information presented in this study showing that the absorption of lanthanum is insignificant after oral administration (very low levels of lanthanum in plasma and urine) cannot be considered definitive. Animal data have show that lanthanum carbonate is absorbed and is deposited in tissues from which is eliminated very slowly. The only way to determine how much lanthanum is absorbed and excreted is by performing a mass balance study using radiolabeled lanthanum.
2. The sampling scheme was not optimal and Cmax might not be captured.
3. The types of meals given in this study were not included.
4. It should be noted that the ECG information for this study was not included in the report.
5. Appropriate assay validation and quality control samples information was provided.

Study LAM-IV-109

Title:

A Phase I, Double-Blind, Placebo Controlled, Multiple Dose Study To Assess The Pharmacokinetics And Safety Of Lanthanum Carbonate And To Determine The Reduction In Urinary Phosphate Excretion In Healthy Male Subjects.

Investigator: [redacted]

Study Period/Site: June 22, 1999-July 27, 1999.[redacted]

Study Objectives:

- ***Primary:*** To evaluate the safety and tolerance of lanthanum carbonate when administered with food in a three times per day dosing regimen.
- ***Secondary:*** To evaluate the rate and extent of absorption of lanthanum in the presence of food and to evaluate the effect of lanthanum carbonate on urinary phosphorus excretion following 5 days of treatment.

Study Population:

Nine healthy male Japanese subjects were enrolled in the study with 6 randomized to lanthanum and 3 to placebo. The demographic characteristics of the subjects are presented next.

ITEM	LANTHANUM CARBONATE		PLACEBO	
	NO. OF SUBJECTS	MEAN (SD)	NO. OF SUBJECTS	MEAN (SD)
Age	6	23.3 (1.75)	3	22.7 (1.53)
Height (cm)	6	168.9 (4.19)	3	167.8 (7.18)
Body Weight (kg)	6	60.2 (6.53	3	60.6 (1.08)
Body Mass (BMI)	6	21.1 (2.11)	3	21.6 (1.99)

Study Design:

This was a double-blind, placebo controlled, multiple dose study conducted in 9 healthy male volunteers to investigate the safety, tolerance and pharmacokinetics of lanthanum and its effect on urinary phosphorus excretion in a Japanese population. On each of the five dosing days subjects received either 1000mg of lanthanum (1908mg lanthanum carbonate) or placebo three times per day immediately after food. Subjects were confined to the [redacted] Clinic for the duration of the study and a standard phosphate controlled diet administered to enable examination of urinary phosphorus excretion as a surrogate endpoint of binding of dietary phosphate by lanthanum carbonate.

Subjects received 5 consecutive days of treatment with either lanthanum carbonate or placebo.

Treatments and Mode of Administration:

- The test product was lanthanum 250 mg chewable tablet, Lot No. 96156 by manufactured [redacted] (containing lanthanum as 477 mg lanthanum carbonate).
- The reference product was a placebo inert tablet, which was physically indistinguishable from lanthanum 250 mg chewable tablets.

Four tablets of study drug (lanthanum carbonate or placebo) were taken immediately after a meal at 9:00, 13:00, and 17:00 hours with a glass of water (150 ml).

Assessments:

- ***Pharmacokinetics:*** Blood samples (9 ml) for the determination of plasma lanthanum were taken on study Day-1 and -5 at 9:00, 11:00, 13:00, 15:00, 17:00, and 21:00 hours. On Days-2, 3, 4, 5, and 7 at 9:00 and 17:00 hours and on Day-8 at 17:00 hours.
  Urine was accumulated from 9:00 PM the day prior to first administration to 9:00 PM of each day of the study period (Days 1 to 8) and pooled. Approximately 60 ml of each day's accumulated sample was frozen and stored.

  The following pharmacokinetic parameters were determined; Cmin, Cmax, AUC0-24, Tmax on days 1 and 5. AUC0-inf and T1/2 on day 5, accumulation ratio, and amount of lanthanum excreted in urine.

- ***Safety:*** subjects were evaluated for vital signs, ECGs, physical examination, clinical laboratory parameters, and adverse events.

- ***Pharmacodynamics:*** Urinary phosphorus excretions at baseline and during the treatment period were evaluated. In addition, creatinine clearance was calculated at baseline, treatment days 1 to 5 and study day 6 (1 day posy-treatment) as a measure of renal function, ensuring that any decrease in urinary phosphorus excretion was not a result of impaired renal function.

Bioanalytical methods:

Plasma and urine samples were analyzed for lanthanum content by fully validated [ ] assays at [ ]

Plasma: A method was developed to determine concentrations of lanthanum (La) in plasma by [ ] using — as an internal standard. This assay involves [ ] The concentration of La was determined by comparing the ratio of the analyte response to the internal standard response with a standard curve defined by calibration standards.

Urine: A method was developed to determine concentrations of La in human urine by [ ] using — as an internal standard. A ten-fold dilution of the sample with dilute nitric acid (1 %) was used for the sample preparation step. The La concentration was determined by comparing the ratio of the analyte response to the internal standard response with a standard curve defined by calibration standards.

The above analytical methods were validated for the concentration ranges [ ] ng/ml of La in plasma and [ ] ng/mL of La in urine. The methods were linear, accurate, and precise over this concentration ranges. The average within-day precision was <10% RSD for all concentrations. The average within-day accuracy was within 10% of the theoretical value for all concentrations in plasma and urine except the [ ] ng/ml in plasma that was <20%. The absolute recovery comparing aqueous calibration standards to a full calibration curve prepared in plasma was within 15% and in urine was within 10%, for each point. The correlation coefficients of the calibration curves for all validation run days was >0.9999 for the matrix calibration curves. The stability of refrigerated processed extracts of spiked plasma was tested over a 7 day period against freshly prepared spiked plasma. Recovery was within 10% at all concentrations ([ ] ng La/ml).

Statistical methods:

- ***Pharmacokinetics:*** The lanthanum plasma concentration data were explored using non-compartmental methodology. For the non-compartmental analysis, Cmax, Tmax, AUC(0-12h) and AUC(0-24h) were calculated for both Day 1 and Day 5 data. For Day 5 data, AUC(0-inf) was also calculated. The terminal elimination rate constant was calculated by linear regression of those concentrations visually determined to be in the log-linear decline phase following the final dose on Day 5.

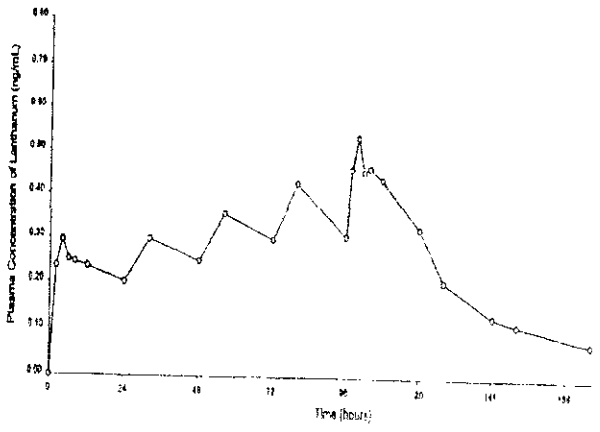
  The accumulation ratio was calculated as the ratio of the Cmin values after the first dose on Day 5 to that on Day 1 (trough values), where the trough value was taken to be the 24-hour value on both days.

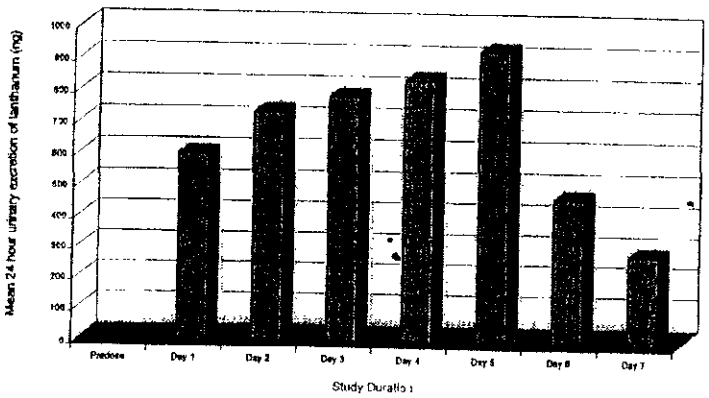
  The percentage of the dose recovered in the urine was calculated from the ratio of the cumulative amount of drug recovered up to the end of the collection period on Day 7, to the total dose administered over the 5-Day period.
- ***Safety:*** Any change in the value over time was compared with the baseline value to determine if the change was statistically significant. A significance level of 5% (two-sided, $P \leq 0.05$) was employed.
- ***Pharmacodynamics:*** For urinary phosphorus and creatinine clearance, the changes between day 1 and day 6 within each treatment group and between treatment groups within each day were compared using a paired t-test

Results:

Pharmacokinetics: Due to the limited blood-sampling schedule for plasma pharmacokinetic analysis employed in this study, reflected in just one sampling point between doses, the actual maximum and minimum concentrations (Cmax/Cmin) of lanthanum in plasma could not be determined. Therefore references to Cmax and Cmin in this report relate to the observed highest/lowest concentrations of lanthanum in plasma. Similarly the timings for Tmax are those at which the highest plasma lanthanum concentrations were observed and may not reflect the true Tmax values.

The mean plasma lanthanum pharmacokinetic parameters and mean urinary excretion of lanthanum following repeat oral administration of lanthanum carbonate (3000mg lanthanum/day) for 5 days are illustrated below.





A summary of the mean lanthanum pharmacokinetic parameters following repeat oral administration of lanthanum carbonate for 5 days is presented in the next table.

	PHARMACOKINETIC PARAMETERS FOR PLASMA LANTHANUM										
	Cmax (ng/ml)		Cmin (ng/ml)		Tmax (hours)		AUC(0-12) (ng.h/ml)		AUC(0-24) (ng.h/ml)		AUCss (0-inf) (ng.h/ml)
	Day 1	Day 5	Day 1	Day 5	Day 1	Day 5	Day 1	Day 5	Day 1	Day 5	-
Mean	0.299	0.533	0.202	0.324	4	4	2.8	5.44	5.39	9.99	22.0
SD	0.115	0.154	0.081	0.078	NA	NA	1.11	1.20	2.14	2.16	3.10
CV%	38.5	28.9	40.4	24.1	NA	NA	40.0	22.1	39.7	21.6	14.1
	EXCRETION OF LANTHANUM IN URINE										
	Accumulation Factor		Steady-State Ratio		Half-Life (hours)		Amount Excreted in Urine (ng)		% Excreted in Urine (ng)		CL (L/h)
Mean	1.80		1.06		35.8		4603.7		3.1 x10-5		91.4
SD	0.61		0.197		1.02		1739.9		1.2 x 10-5		27.5
CV%	34.0		18.6		19.6		37 8		37.8		30.1

Administration of a cumulative 15g dose of lanthanum to healthy subjects over a 5-day period resulted in the achievement of only very low plasma levels of lanthanum. The increase in Cmax and AUC values from Day 1 to Day 5 is indicative of modest accumulation on multiple dosing. The mean (SD) accumulation factor over 5 days of dosing was 1.80 (0.61), which is in line with the observed elimination half life (T1/2) of approximately 36 hours (at cessation of multiple dosing).

Over a total seven day collection period and a total administered dose of 15g (lanthanum), the amount of lanthanum recovered in urine was extremely small being only 3.1×10^{-5} % of the dose.

Safety:

- No adverse events were noted in either the subjects administered lanthanum carbonate or placebo.
- Several clinical laboratory examinations (total protein, total bilirubin, direct bilirubin, lactate dehydrogenase, alkaline phosphatase, total cholesterol, triglycerides, blood urea nitrogen, uric acid, hemoglobin, hematocrit, eosinophils, monocytes, lymphocytes, neutrophils, activated partial thromboplastin time, and specific gravity) were determined to be out of range during the study period, but similar tendencies were observed in both the lanthanum carbonate and placebo treatment groups, with only small differences between the two groups.
- A number of vital signs parameters (body temperature, respiratory rate, systolic and diastolic blood pressure and pulse rate) showed statistically significant changes at the 5% level in the paired t-test using the baseline values as control, but as similar tendencies were observed in both lanthanum carbonate and placebo treatment groups.
- Body temperature tended to be lower in subjects receiving lanthanum carbonate, but all the values were within the normal range and no clinical significance was recognized.
- The 12-lead ECG showed no abnormalities in any of the subjects.

Pharmacodynamics:

The pharmacodynamic results are summarized in the next table.

	COMPARISON OF URINARY PHOSPHORUS EXCRETION (g/day) BY TREATMENT GROUP			
	Lanthanum Carbonate Least Squares Mean	Placebo Least Squares Mean	Difference	p-value
Day 1	0.680	0.720	-0.0400	0.6019
Day 6	0.212	0.633	-0.4217	<0.0001
	COMPARISON OF 24 HOUR CREATININE CLEARANCE (L/day) BY TREATMENT GROUP			
	Lanthanum Carbonate Least Squares Mean	Placebo Least Squares Mean	Difference	p-value
Day 1	120.783	142.867	-22.0833	0.0849
Day 6	132.333	147.467	-15.1333	0.2228

Comparison of urinary phosphorus excretion on Day-1 revealed no statistical differences between subjects administered either lanthanum carbonate or placebo. However, on Day-6, subjects administered lanthanum carbonate had significantly decreased urinary phosphorus excretion as compared to the placebo group (p-value <0.0001).

On Days-1 and 6 creatinine clearance was lower in the lanthanum carbonate treatment group as compared to the placebo group by approximately 22 and 15 L/day, respectively. However, because of variation in clearance among the subjects, no statistically significant differences were detected between the two treatment groups on either day in the t-test.

Sponsor's Conclusions:

1. Lanthanum carbonate administered to healthy male Japanese subjects in a t.i.d. dosing regimen appears to be safe and well tolerated
2. Oral administration of a cumulative 15g dose of lanthanum over a 5-day period resulted in the achievement of very low plasma levels of lanthanum. Absorption was rapid and elimination slow with a half-life of approximately 36 hours. Excretion of lanthanum via the urinary route was extremely low representing only 3.1×10^{-5} % of all the administered doses over a 7-day collection period.
3. Comparison of urinary phosphorus excretion on day 1 revealed no statistical difference between subjects administered lanthanum carbonate or placebo. However, on Day 6 subjects administered lanthanum carbonate had significantly decreased urinary phosphorus excretion as compared to the placebo group (p-value <0.0001).
4. Creatinine clearance, as a measure of renal function did not decrease between Days 1 and 6 for the lanthanum carbonate treatment group indicating that the reduction in urinary phosphorus excretion seen at Day 6 was due to binding of dietary phosphorus with lanthanum and not reduced renal function.

Reviewer Comments:

1. Regarding the low absorption of lanthanum, previous reviewer comments also apply to this study.
2. The specific meals that were given in this study were not described. Therefore, there is not information regarding the type and content (% protein, fat, carbohydrates, etc) of the meals.
3. Overall, the validation of the analytical methods for lanthanum carbonate in plasma and urine are appropriate. Also, the results for the quality control samples in plasma and urine are appropriate.

Study LAM-IV-110

Title: A Phase I, Single Center, Open-Label, Randomized, Three-Way Crossover Study Comparing the Phosphate Ion Binding of Lanthanum Carbonate Chewable Tablets When Administered Before, During, or After Food in Healthy Subjects

Investigator: [ ]

Study Period/Site: Aug 19, 1999 to Sep 02, 1999/[ ]

Study Objectives:

- The primary objective of this study was to assess the pharmacodynamics of lanthanum carbonate by the measurement of urinary phosphorus excretion following administration of a 1000 mg oral dose of lanthanum (1908 mg lanthanum carbonate) 30 minutes before, during, or 30 minutes after food.
- The secondary objective was to measure plasma and urinary lanthanum pharmacokinetics following dosing.

Study Population:

There were 36 healthy subjects meeting the inclusion/exclusion criteria enrolled in the study. A total of 35 subjects, 23 males and 12 females, completed the study. There were 35 subjects included in the pharmacodynamic and pharmacokinetic analyses and 36 included in the safety analyses. A summary of the demographic information is presented in the next table.

ITEM	FEMALE (N=13)	MALE (N=23)
Race	Caucasian	Caucasian
Age	23 (4)	26 (6)
Weight (kg)	64 (6.6)	73.9 (7.5)
Height (cm)	167 (4)	178 (6)

Study Design:

This was a randomized, open-label, three-way crossover study that was reduced to a two-way crossover study due to the outcome of the test dose. For each treatment period, subjects were randomly assigned to receive a 1000 mg dose of lanthanum chewable tablets (1908 mg of lanthanum carbonate) during or after a meal of estimated phosphorus content. Following the test dose administration on the morning of Day 1, when poor tolerability was experienced by greater than 20% of the subjects, the "before food" arm was dropped and the study became a two-way crossover. Dosing for each study period was separated by a minimum three-day washout interval.

Treatments and Mode of Administration:

The test product was lanthanum tablets each containing 250 mg of elemental lanthanum, manufactured by [ ] Lot No. 96192, expiration date 31 Jan 2001.

Treatment A - 4 x 250 mg lanthanum chewable tablets (1908 mg of lanthanum carbonate tablet) administered 30 minutes before food.

Treatment B - 4 x 250 mg lanthanum chewable tablets (1908 mg of lanthanum carbonate tablet) administered during food.

Treatment C - 4 x 250 mg lanthanum chewable tablets (1908 mg of lanthanum carbonate tablet) administered 30 minutes after food.

Each subject received a 1000 mg oral dose of lanthanum chewable tablets (1908 mg of lanthanum carbonate) three times per day for 3 days at each treatment period. The dose was administered per the study randomization schedule. Four 250 mg lanthanum chewable tablets (1908 mg of lanthanum carbonate) were given on the morning of Study Day 1. Subjects were asked to take the medication on an empty stomach 30 minutes prior to food. Since 20% or more of the subjects demonstrated poor tolerability (e.g., nausea and/or vomiting), the "before food" arm (Treatment A) of the study was dropped.

Subjects randomized to Treatment B received four lanthanum carbonate tablets (equivalent to 1000 mg of elemental lanthanum) three times a day for 3 days during meal times. Tablets were chewed and then taken with 120 mL of non-carbonated bottled water. Subjects randomized to Treatment C received four lanthanum carbonate tablets (equivalent to 1000 mg of elemental lanthanum) three times a day for 3 days 30 minutes after food consumption. Tablets were chewed and then taken with 120 mL of non-carbonated bottled water. Subjects were not permitted to lie down for the first 4 hours following administration of the drug to assure proper stomach emptying.

Meals:

All subjects received a standardized phosphorus diet (<1200 mg of phosphorus/day) for the duration of the study. The same menu and meal schedule was administered uniformly for all subjects for all dosing groups and all treatment periods. Alcohol, fruit juices, caffeine- and xanthine containing beverages were prohibited during the study.

Bioanalytical methods:

The concentration of lanthanum in plasma and urine were measured by a fully validated [ ] assay at [ ]

Assessments:

- ***Pharmacodynamic:*** The pharmacodynamic endpoint following lanthanum administration was urinary phosphorus excretion. Urinary phosphorus excretion (surrogate endpoint to study the phosphate binding of lanthanum) was evaluated at baseline, Days 1, 2, and 3 of lanthanum treatment, and Day 4 following completion of lanthanum treatment. In addition, urinary creatinine excretion and creatinine clearance (standard measure of renal function) calculations were performed.

- ***Pharmacokinetic:*** During each treatment period, blood and urine samples were collected for lanthanum analysis. blood samples (9 ml) were drawn at the following times: -15 min (pre-dose), 20, 40, 60, 80, 100, 120, 240, 345 minutes, 23.75 hours, and 71.8 hours postdose. Urine was collected on Days 1-3 (dosing days) and Day 4 (post-dose) at the following intervals: 0-4, 4-8, 8-12, 12-24 hours.

  The pharmacokinetic parameters Cmax, Tmax, AUC(0-4) and AUC(0-t) were calculated from the plasma lanthanum concentration-time data from the first dosing interval using noncompartmental methods. Urinary lanthanum excretion was evaluated at baseline and on Days 1, 2, 3, and 4. Renal clearance and percent of lanthanum dose excreted in the urine were also calculated.

- ***Safety:*** subjects were evaluated for vital signs, ECGs, physical examination, clinical laboratory parameters, and adverse events.

Results:

Pharmacodynamic: The arithmetic mean (SD) average daily urinary phosphorus excretion values and the statistical comparisons are shown in the following table.

	AVERAGE DAILY URINARY PHOSPHATE EXCRETION (MMOL)			
	Treatment C (After food)	**Treatment B** (During food)	**% Difference**	**P-Value**
First 3 days of treatment period	14.50 (5.14)	13.35 (5.74)	8.84	0.0209*
Last 2 days of treatment period	14.09 (4.90)	12.73 (5.67)	11.27	0.0150*
* Difference is statistically significant, p<0.05				

Mean creatinine clearance changed very little over time for either treatment and was about 100 ml/min each day. There was only a 3% difference in creatinine clearance between the two treatments (based on least squares means), and the difference was not statistically significant.

Pharmacokinetic: The mean (SD) plasma lanthanum pharmacokinetic parameters and statistical comparisons are shown in the following table.

PHARMACOKINETIC PARAMETERS	MEAN (SD) PLASMA LANTHANUM			
	Treatment C (After food)	**Treatment B** (During food)	**% Difference**	**P-Value**
Cmax (ng/ml)	0.233 (0.074)	0.209 (0.078)	10.36	0.0738
Tmax (hr)	4.55 (1.31)	5.09 (0.867)	-8.35	0.0847
AUC_{0-t} (ng.hr/ml)	0.882 (0.325)	0.717 (0.325)	21.53	0.0001*
C24 (ng/ml)	0.392 (0.132	0.328 (0.146)	20.16	0.0124*
C72 (ng/ml)	0.445 (0.157)	0.391 (0.162)	13.83	0.0331*
* Difference is statistically significant, p<0.05				

Urinary lanthanum excretion was very low. An average of 0.00004 percent of the lanthanum dose was excreted in the urine for both treatments. Mean renal clearance was less than 0.3 L/hr. No statistical comparisons were made.

Safety: There was a total of 41 test dose AEs and 47 treatment-emergent AEs reported during the trial. Of the 36 subjects dosed with treatment administered during food and treatment administered after food, 18 (50%) experienced AEs. Headache was the most frequently reported event. No serious AEs occurred during the trial. The Investigator discontinued 1 subject from the trial due to difficulty obtaining blood samples.

Sponsor's Conclusions:

1. Mean average daily urinary phosphorus excretion during the 3-day lanthanum treatment period was approximately 9% higher for Treatment C compared to Treatment B.
2. Mean average daily urinary phosphorus excretion during the last two days of the lanthanum treatment period was approximately 11% higher for Treatment C compared to Treatment B.
3. Mean creatinine clearance values changed very little over time and were similar between the two treatments. Lanthanum treatment had no appreciable effect on creatinine clearance.
4. The timing of food intake relative to lanthanum administration appeared to have a small effect on the systemic absorption of lanthanum. There was no statistical difference in mean plasma lanthanum Cmax or Tmax between the treatments following the first dose. However, mean AUC0-t was 22% higher for Treatment C following the first dose.
5. Mean lanthanum concentrations at 24 and 72 hours were 20% and 14% higher, respectively, for Treatment C.
6. Urinary lanthanum excretion and renal clearance were low - (approximately 0.00004% of the dose was excreted in the urine and the mean renal clearance was less than 0.3 L/hr).
7. Both treatments appeared to be safe and generally well tolerated.

Reviewer Comments:

1. As noted previously, the sponsor's conclusion of very low absorption of lanthanum after oral administration is difficult to support at this time.
2. It should be noted that the specifics regarding the type of meals given in this study were not included.
3. Overall, the validations of the analytical methods used for the determination of lanthanum in plasma and urine are appropriate. Also, the quality control data are appropriate.
4. Reviewer Comments given previously for the absorption of lanthanum, also apply to this study.

Study LAM-IV-111

Title:
A Pharmacokinetic Study in Healthy Volunteers and Dialysis Patients Following Single and Multiple-doses of Lanthanum

Investigator: [ ]

Study Period/Site: December 21, 2000-July 24, 2001/ [ ]

Study Objectives:

- To determine if the pharmacokinetic parameters of orally administered lanthanum carbonate are altered by severe renal dysfunction.
- To determine if the elimination of lanthanum carbonate is affected by hemodialysis.

Study Population:

A total of 16 subjects were planned to participate in this trial; i.e., eight subjects in the Dialysis group and eight subjects with normal renal function (Control group). Eighteen (18) subjects were actually enrolled with 10 subjects in the Dialysis group and eight subjects in the Control group, as two dialysis subjects were withdrawn (Subjects 002 and 013) for adverse events and kidney transplant, respectively, during the multiple-dose period of the study. Two additional Dialysis subjects were enrolled to replace these withdrawn patients. All available data from all enrolled subjects were included in the analyses of efficacy and safety. The next Table summarizes the demographic information.

ITEM	PARAMETER	DIALYSIS GROUP	CONTROL GROUP
Gender	Male	6	5
	Female	4	3
Race	Caucasian	1	6
	Black	4	1
	Hispanic	5	1
Age (years)	-	27-67	28-62
Weight (pounds)	-	136-253	138-236
Height (in)	-	58-72	64-74

Diagnosis and main Criteria for Inclusion:

Volunteers of either sex, 18 years of age or older, with screening calcium levels 7.9 mg/dL or higher and no clinically significant abnormal laboratory values or clinically significant uncontrolled concurrent illnesses at screening (excluding markers of pathologies associated with chronic renal failure) which, in the opinion of the investigator, should exclude a subject from participating in the study. Pregnant or lactating women were excluded, as were subjects with any significant gastrointestinal surgery or gastrointestinal disorders, subjects with serum transaminases >3 times the upper limit of normal, subjects with life threatening malignancy or current multiple myeloma, subjects known to be HIV positive, and subjects who had been exposed to an experimental drug within 30 days prior to screening. Subjects enrolled to the Dialysis group must have received hemodialysis three times per week for at least two months prior to enrollment and a hemodialysis adequacy equivalent to a Kt/V of 1.4 or greater. Subjects enrolled to the Control group must have had an estimated creatinine clearance of >80 ml/minute.

Study Design:

This study was an open-label, single and multiple-dose trial to compare the pharmacokinetics, urinary excretion, and dialysis clearance of lanthanum in patients who require chronic hemodialysis treatment versus the pharmacokinetics of lanthanum in subjects with normal renal function.

A total of 16 subjects were planned to participate in the study, eight subjects who required hemodialysis (Dialysis group) and eight subjects with normal renal function (Control group). Following a two-week screening period. All subjects were dosed on Day 0 with a single 1 g oral dose of lanthanum (given as four chewable tablets each containing 250 mg of lanthanum) following a standardized meal which was to occur within 2 hrs of the completion of the Dialysis group's hemodialysis session. Blood and urine samples were collected for 48 hours post dose in order to estimate lanthanum disposition.

Two weeks later, the Dialysis subjects were again dosed with a single 1 g dose oral dose of lanthanum. Control subjects also received a single 1 g dose of lanthanum at this time but did not undergo the pharmacokinetic sampling. Four hours after dosing the Dialysis subjects underwent hemodialysis. Blood and urine samples were collected for 48 hours post dose. A dosing and sampling schedule similar to Day 0 was performed on the Dialysis subjects, with the exception that the subjects underwent hemodialysis treatment 4- to 8-hours post dose. Upon discharge from the Phase I unit on Day 17, all subjects began taking 1 g doses of lanthanum three times daily for eleven days. After eleven days of chronic dosing all subjects underwent another session of blood and urine sampling. During this period. Dialysis subjects also underwent their routine hemodialysis procedure 4-to 8-hours post dose. All sampling during this period was continued for 72 hours following the last dose of lanthanum.

Treatments and Mode of Administration:

The Sponsor provided test drug as round, unflavored, chewable, scored tablets packaged in bottles of 100 tablets (Lot Number: 9L2748). A 250 mg lanthanum chewable tablet contains 477 mg of lanthanum carbonate.

The single dose administration consisted of 1 g lanthanum (4 tablets). During the multiple dose period, 1 g lanthanum (4 tablets) were taken immediately following a meal, three times a day for a total daily dose of 3 g lanthanum. The single dose period was followed by a two-week washout interval, another single dose period with hemodialysis, and a subsequent 11-day multiple-dose period (i.e., lanthanum three times a day), and a 72-hour follow up.

Assessments:

- ***Pharmacokinetics:***

  Single dose administration without dialysis

  Visit Days 0-2: Blood samples (9 ml) for lanthanum PK analysis were collected at 0 (pre-dose), and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 18, 24, 32, 40, and 48 hours after dose. Urine sampling for lanthanum content analysis were collected at the following periods: 0-4, 4-8, 8-12, 12-18, 18-24, 24-32, 32-40, and 40-48 hours post dose.

  Single dose administration dialysis (dialysis group only)

  Visit Days 14-16: For the dialysis subjects, blood samples were collected at 0 (pre-dose), and 1, 2, 3, and 4 hrs post dose, before dialysis. A urine sample was collected at 0-4 hrs post dose. During dialysis dialysate samples were collected at 5, 6, 7, and 8 hours. After completion of dialysis blood

samples were taken at 10, 12, 14, 18, 24, 32, 40, and 48 hours after dose. Urine samples were collected at 8-12, 12-18, 18-24, 24-32, 32-40, and 40-48 hours post dose.

Multiple dosing

All subjects took 1 g of lanthanum orally three times daily for 11 days.

Visit Days 28-31: On the day of the last dose, before the dialysis subjects' hemodialysis session, blood samples were collected at 0 (pre-dose), and at 1, 2, 3, and 4 hours post dose. A urine sample 0-4 hrs post dose was also collected. During dialysis, dialysate samples were collected at 5, 6, 7, and 8 hours. After completion of dialysis blood samples were taken at 10, 12, 14, 18, 24, 32, 40, 48, 56, 64, and 72 hours after dose. Urine samples were collected at 8-12, 12-18, 18-24, 24-32, 32-40, and 40-48 hours post dose.

Extent (AUC) and rate (Cmax) of drug absorption and time-to-peak concentration (Tmax) for plasma and urine lanthanum were compared between the Dialysis and Control groups. Urinary excretion of lanthanum was calculated from the lanthanum concentrations measured in the interval urine collections during the pharmacokinetic sampling periods following single and multiple-doses. The pharmacokinetic parameters of lanthanum were estimated using standard non-compartmental methods.

The clearance of lanthanum resulting from the dialysis procedure was based on the extraction of lanthanum from blood across the dialyzer membrane. The clearance calculation was based on the difference between the rates at which the lanthanum enters and leaves the dialyzer membrane and was dependent upon blood flow and lantharum blood concentration into and out of the dialyzer membrane.

- ***Safety:*** Safety parameters included adverse events (AE), clinical laboratory tests (chemistry, hematology), physical examinations, vital signs, phosphorus levels for control subjects, and pregnancy tests for women of childbearing potential.

Bioanalytical Methods:

Plasma, urine, and dialysate samples were analyzed for lanthanum content by fully validated [redacted] at [redacted]

Plasma samples were [redacted] Urine samples were diluted one part urine to nine parts La-free water and measured for La content using [redacted] Dialysate samples were diluted one part dialysate to one part one percent nitric acid and measured for La content using [redacted] The La content of the samples ranged from [redacted] ng/mL plasma, [redacted] ng/mL urine, and [redacted] ng/mL dialysate.

The analytical methods were validated for the concentration ranges [redacted] ng/ml of La in plasma, [redacted] ng/mL of La in urine, and [redacted] ng La/ml. The methods were linear, accurate, and precise over this concentration range. The average within-day precision was <10% RSD for all plasma and urine concentrations and <15% RSD for all dialysate concentrations. The average within-day

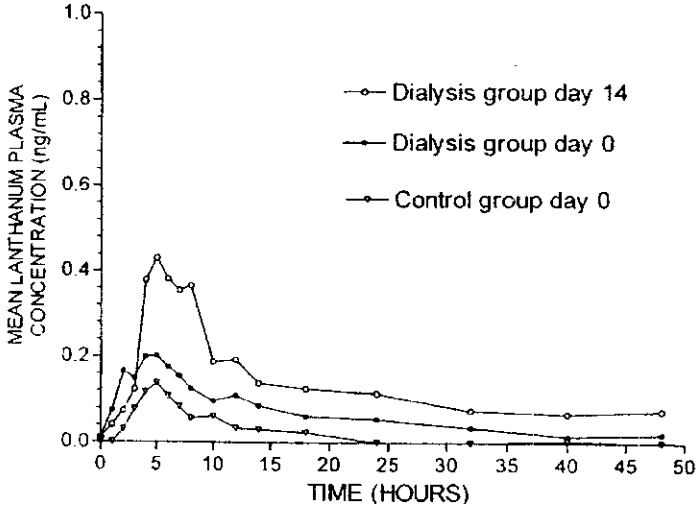
accuracy was within 10% of the theoretical value for all concentrations in urine & plasma (except the [ ] ng/ml in plasma that was <20%), and for all dialysate concentrations it was within 15%. The absolute recovery comparing aqueous calibration standards to a full calibration curve prepared in plasma was within 15% and in urine was within 10%, for each point. For dialysate standards the absolute recovery was poor, ranging between 72% for the lowest standard of 0.0125% to 120% for the [ ] ng/ml standard. Therefore, matrix standards were always required for the assay of clinical samples. The correlation coefficients of all the calibration curves of plasma, urine and dialysate validation run days were >0.9999 for the matrix calibration curves.

Results:

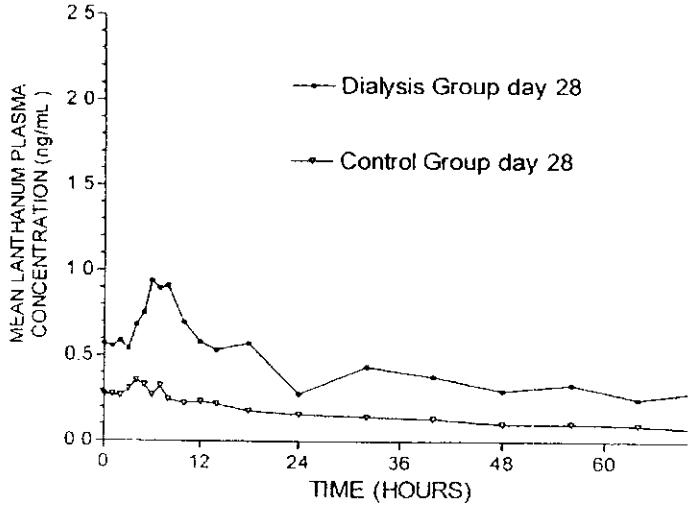
Plasma Pharmacokinetics:

The mean lanthanum concentrations after single and multiple dose administrations are illustrated below.

The Mean Lanthanum Plasma Concentrations for Control (Day 0) and Dialysis Group (Day 0 and Day 14) following Single Dose Administration



The Day 28 Mean Lanthanum Plasma Concentrations for Control and Dialysis Groups following Multiple Dose Administration



Pharmacokinetic parameters of plasma lanthanum concentrations are presented in the next table.

MEAN (SD) PHARMACOKINETIC PARAMETERS FOR LANTHANUM						
PK Parameters	1 g Single Dose Without Dialysis		1 g Single Dose With Dialysis		Following Multiple Doses of 1 g tid	
	Dialysis Subjects	Control Subjects	Without Dialysis	With Dialysis	Dialysis Subjects	Control Subjects
AUC_{0-t} (ng.h/ml)	3.099 (2.888)	1.123 (1.524)	3.099 (2.888)	6.361 (6.622)	31.049 (40.469)	10.953 (4.111)
Cmax (ng/ml)	0.296 (0.177)	0.179 (0.169)	0.296 (0.177)	0.559 (0.505)	1.055 (1.037)	0.424 (0.171)
Tmax (hours)	4.889 (3.060)	4.125 (1.553)	4.889 (3.060)	4.125 (1.553)	9.500 (9.134)	5.500 (3.742)

Following the single dose administration of 1 g lanthanum without dialysis, the mean AUC and Cmax were roughly 3-fold higher for the Dialysis group than the corresponding parameters for the Control Group. The Tmax value was slightly longer with dialysis (5.6 hr) than without dialysis (4.9 hr).

Following multiple dose administration of 1 g lanthanum tid for 11 days, the mean AUC and Cmax for the Dialysis subjects were roughly 3-fold higher than the corresponding parameters for the Control subjects. The Tmax was 9.5 hr for the Dialysis subjects versus 5.5 hr for the Control subjects.

Within the Control subjects, AUC following multiple dose administration versus single-dose administration revealed a ratio of approximately 10:1. Similarly, the ratio for the mean AUC following multiple doses versus single dose was about 10:1 for the Dialysis subjects.

Urine & Dialysate Pharmacokinetics:

The next table presents a summary of urine and dialysate PK parameters after single and multiple administration of lanthanum carbonate.

Summary Table of Urine and Dialysate Pharmacokinetic Parameter for All Subjects Following Single and Multiple Oral Doses of Lanthanum Carbonate (1 g Lanthanum)

Group	Day	Number	$Dose_{EXCR}$	$Rate_{MAX}$	t_{MAX}	X_D	AUC_{DIAL}	$CL_{P,D}$
			(%)	(ng/h)	(h)	(ng)	(ng•h/L)	(L/h)
Control Group	0	8	0.0000343 ± 0.0000382	37.891 ± 40 380	9.88 ± 7.97	ND	ND	ND
Control Group	28	8	0.0001480 ± 0.0000685[a]	71.302 ± 29.208[a]	2.5 ± 1.41[a]	ND	ND	ND
Dialysis	0	10	0.0000544 ± 0.0001325	49.995 ± 121.498	10.50 ± 12.26	ND	ND	ND
Dialysis	14	10	0.0000034 ± 0.0000066	2.577 ± 4.803	34.33 ± 16.74	144.950 ± 293.223	1.3366 ± 1.1035	0.126 ± 0 310
Dialysis	28	8	0.0000055± 0.0000040	4.556 ± 3.730	15.25 ± 11.53	238.615 ± 353.061	2.9988 ± 3.6372	0.272 ± 0.560

[a]P<0.05 as compared with Day-0 Control Group using paired Student's t-test

ND = Not determined due to subjects not undergoing dialysis

Dialysate Lanthanum Pharmacokinetics:

- On Day 0, the mean recovery in urine for Control subjects was 3.43×10^{-5} % compared with 5.43×10^{-5} % in the Dialysis Group subjects with urine output. Please note that is difficult to derive any conclusion from this information since there were only four subjects in the Dialysis Group and in one of them very high levels of lanthanum were recorded in the urine (3.25×10^{-5} %).
- On Day 8, the mean recovery of the control groups was 0.148×10^{-5} %, 0.55×10^{-5} % in the dialysis group and 0.238×10^{-5} % in the dialysate.
- On Day 14, three subjects had urine output with a mean value of 0.339×10^{-5} %. The mean quantity of lanthanum recovered in the dialysate fluid (1.45×10^{-5} %) was greater than that observed for urine. The dialysis process involves the use of large volumes and possibly for some subjects the limit of quantitation of the assay (— ng/mL) has been challenged. Such a situation would lead to underestimation of the amount excreted in the dialysis fluid.

Safety:

Fourteen (14) of the 18 enrolled subjects reported a total of 59 adverse events during the study, four of which were pre-existing. The number of adverse events for the Dialysis group was 45/59 (76%) and 14/59 (24%) for the Control group. Most adverse events (80%) were judged to be unrelated or unlikely to be related to study medication. Nearly all events were of mild or moderate severity (97%) and resolved before study exit. The most frequently reported adverse events were headache, vomiting, and nausea.

Lanthanum carbonate appeared to be well tolerated by both the Dialysis and Control subjects. There were no deaths. One serious adverse event of kidney transplant was reported for a Dialysis subject. Two Dialysis subjects withdrew one due to the kidney transplant and one for adverse events of itching and nausea. No statistically significant or clinically meaningful changes in vital signs were observed for either of the groups.

Sponsor's Conclusions:

1. Lanthanum pharmacokinetics in this study were highly variable and this variability was even higher in subjects with compromised renal function. Although the mean rate (Cmax) and extent of exposure (AUC) were higher in the Dialysis Group than the Control Group following both single and multiple dosing the high variability in the pharmacokinetic data resulted in the statistical testing not being able to ascertain differences between the group means.
2. Lanthanum carbonate appeared to be well tolerated by both the Dialysis and the Control subjects. The number of adverse events in the Dialysis group was higher than the number of events reported for the Control group. The most frequently reported events were headache, vomiting, and nausea.
3. Mean phosphorus levels for the control subjects indicated a 10% mean decrease four days after the start of the multiple dosing regimen and a mean decrease of 3%, 11 days after the start of the multiple doses.
4. Overall, lanthanum carbonate was well-tolerated by both study groups.

Reviewer Comment:

1. The overall results from this study indicate that the levels of lanthanum in dialysis patients were about 3 times higher than control subjects and the amount of lanthanum eliminated in the dialysate was minimum. Thus, it could be expected that patients with compromised renal function would have higher exposure and accumulation of lanthanum.

C. ATTACHMENT 3

Includes:

- **Summary of a Protein Binding Study:**
  Study No. V00117-LAM-IIIG

- **Summary of In-Vitro Metabolic Studies:**
  Study No. SRU 006/002701 (Inhibition of CYP450)
  Study No. No. V00160-LAM-IIIG (DDI in Gastric Fluid)

- **Summary of In-Vivo Drug-Interaction Studies:**
  Study No. LAM-IV-112 (DDI with Citrates)
  Study No. LAM-IV-113 (DDI with Warfarin)
  Study No. LAM-IV-114 (DDI with Digoxin)
  Study No. LAM-IV-115 (DDI with Metoprolol)

- **Sponsor's Assessment of the Potential of Lanthanum Carbonate to Interact with Co-Prescribed Medicines in a Renal Dialysis Patient Population**

STUDY REPORT V00117-LAM-IIIG

Title: "*In vitro* Protein Binding Study: Mouse, Rat, Rabbit, Dog, Human Plasma, and Human Alpha1-Acid Glycoprotein, Transferrin, and Albumin"

Study Objective:
The objective of this study was to determine the extent of binding of lanthanum to human albumin, human α1-acid glycoprotein (α1-AGP), human transferrin and proteins in the plasma of mouse, rat, rabbit, dog and humans over a concentration range of 0.1 to 250 ng/ml.

Study Design: *In vitro* study.

Methods:
The laboratory animal species selected were those used in the pre-clinical safety evaluation of the test compound. The data generated will facilitate the extrapolation of plasma exposure data from animals to man. The range of concentrations encompasses the plasma concentrations measured in studies carried out to support the clinical and pre-clinical development of lanthanum carbonate.

Aliquots of plasma or protein solutions were fortified with lanthanum at concentrations ranging from 0.1 to 250 ng/ml, [

]

Measurement of Lanthanum:
Concentrations of lanthanum in non-centrifuged fortified plasma and protein samples and in the ultracentrifugated supernatants were measured by validated [ ] methods at [ ]

Results:
Please note that this review only presents the human plasma protein binding data.

PLASMA PROTEIN BINDING OF LANTHANUM IN VITRO

Human: Concentrations of lanthanum in the ultracentrifuge supernatants (i.e. the unbound lanthanum concentration) of the lower human plasma spike concentrations of 0.1, 0.5 and 2.5 ng/ml were below the limit of detection of the analytical method (i.e. — g/ml), so the true extent of binding of lanthanum to the plasma proteins in vitro at these levels could not be calculated. At nominal lanthanum spike concentrations of 10, 50 and 250 ng/ml, the unbound lanthanum level was measurable and the mean extent of binding of lanthanum to the human plasma proteins determined to be 99.0, 99.3 and 99.7% respectively.

BINDING OF LANTHANUM TO SPECIFIC PLASMA PROTEINS IN VITRO

Human α_1-acid glycoprotein (AGP): Concentrations of lanthanum in the ultracentrifuge supernatants (i.e. the unbound lanthanum concentration) of the AGP spike concentrations of 0.1, 2.5 and 250 ng/ml were below the limit of detection of the analytical method (i.e. — ng/ml), so the true extent of binding

of lanthanum to the protein in vitro at these levels could not be calculated. At nominal lanthanum spike concentrations of 0.5, 10 and 50 ng/ml, the unbound lanthanum level was measurable and the mean extent of protein binding of lanthanum to AGP determined to be 75.5, 98.8 and 99.8% respectively.

Human Serum Albumin (HSA): Concentrations of lanthanum in the ultracentrifuge supernatants (i.e. the unbound La concentration) of all the HSA spike concentrations of 0.1, 0.5, 2.5, 10, 50 and 250 ng/ml were below the limit of detection of the analytical method (i.e. — ng/ml), so the true extent of binding of lanthanum to the protein in vitro at these levels could not be calculated. However, if the unbound concentration is taken to be this limit of detection for the former five concentrations and — ng/ml (the limit of detection of the diluted samples) for the 250 ng/ml concentration, the extent of binding of lanthanum to HSA at the above concentrations was calculated to be 95.3, 96.8, 98.7, 99.6, 99.9 and 99.9%, respectively.

Human Transferrin: Concentrations of lanthanum in the ultracentrifuge supernatants (i.e. the unbound lanthanum concentration) of the transferrin spike concentrations of 2.5, 10 and 250 ng /ml were below the limit of detection of the analytical method (i.e. — ng/ml), so the true extent of binding of lanthanum to the protein in vitro at these levels could not be calculated. At nominal lanthanum spike concentrations of 0.1, 5 and 50 ng/ml, the unbound lanthanum level was measurable and the mean extent of protein binding of lanthanum to transferrin determined to be 40.0, 57.4 and 99.7%, respectively.

Sponsor's Conclusion:

The results of this study have shown that, where lanthanum levels were measurable in the ultracentrifuge supernatant, lanthanum was extensively (i.e. >99%) bound to human plasma proteins in vitro over the concentration range 0.1-250 ng/ml. At the spiked lanthanum concentration of 250 ng/ml, the extent of binding of lanthanum to human serum albumin, human α_1-acid glycoprotein, and human transferrin in vitro was >99.7 %. There was no evidence of a concentration-dependent reduction in binding over the range investigated

Reviewer Comment:

The study was well designed and sponsor conclusions are appropriate.

STUDY REPORT SRU 006/002701

Title:
"Potential Inhibition of Cytochromes P450 in Human Liver Microsomes"

Investigators: [redacted]

Study Site: [redacted]

Study Objectives:
The goal of this investigation was to characterize, with subcellular preparations, the potential interactions of lanthanum with substances metabolized by human hepatic cytochrome P450 (CYP) isoforms.

Microsomes
Human liver microsomes used in this study were from a pool of donors designated HHM-0218. These microsomes were obtained from [redacted]

Study Design:
Lanthanum carbonate was investigated for its potential to inhibit human liver cytochrome P450. The compound was separately incubated, at concentrations of 10 mcg/ml and 40 mcg/ml (approximately 5.2 mcg and 21.0 mcg elemental lanthanum per ml, respectively), with pooled human liver microsomes either with or without a 15 minute pre-incubation period prior to the introduction of a range of substrates, each selective for one specific isoform of cytochrome P450. The effects of the test compound on the rate of metabolism of these substrates were compared with those elicited by a range of isoform-selective chemical inhibitors, as follows.

Activity (related P450)	Selective Inhibitor (concentration)
• 7-ethoxyresorufin O-deethylase (CYP1A2)	Furafylline (30 mcM)
• Tolbutamide-methyl hydroxylase (CYP2C9/10)	Sulphaphenazole (20 mcM)
• S-Mephenytoin 4'-hydroxylase (CYP2C19)	Tranylcypromine (100 mcM)
• Debrisoquine 4-hydroxylase (CYP2D6)	Quinidine (5 mcM)
• Testosterone 6β-hydroxylase (CYP3A4/5)	Troleandomycin (100mcM)

RESULTS:
The following table presents the overall results from the microsomal incubations, as the mean percent of inhibition of enzyme activities of the pooled donors, relative to appropriate control values.

ACTIVITY	% INHIBITION				
	Selective Inhibitor	Lanthanum Carbonate			
		10 mcg/ml		40 mcg/ml	
		0 min pre-inc	15 min pre-inc	0 min pre-inc	15 min pre-inc
7-ethoxyresorufin O-deethylase	92	20	21	38	44
Tolbutamide-methyl hydroxylase	90	0	0	17	0
S-Mephenytoin 4'-hydroxylase	73	0	11	7	21
Debrisoquine 4-hydroxylase	68	6	10	2	0
Testosterone 6β-hydroxylase	57	0	0	0	0

7-ETHOXYRESORUFIN O-DEETHYLASE ACTiVITY: The selective CYPIA2 inhibitor, furafylline, inhibited this activity by 92% in the pooled human microsomes following a 15-minute pre-incubation. For lanthanum carbonate, an apparently dose- related inhibition of the activity was noted, both with and without a 15 minute pre-incubation period. The greatest degree of inhibition seen was 44%, at the higher dose level with a 15 minute pre- incubation period, which was similar to that found without any pre-incubation.

TOLBUTAMIDE METHYL HYDROXYLASE ACTIVITY: The selective CYP2C9/l0 inhibitor. sulphaphenazole. inhibited this activity by 90% using the pooled microsomes in the absence of a pre-incubation period. Slight inhibition (of 17%) was observed with the test compound at the higher dose level without pre-incubation. However. no inhibition by lanthanum carbonate was noted at either dose level when the compound was pre-incubated for 15 minutes prior to addition of substrate or at the lower dose level without pre-incubation.

S-MEPHENYTOIN 4'-HYDROXYLASE ACTIVITY: The selective CYP2C19 inhibitor, tranylcypromine, inhibited this activity by 73% in the pooled human microsomes following 15 minutes pre-incubation. There was no significant inhibition by lanthanum carbonate either with or without a pre-incubation period at either dose level, the maximum inhibition observed being 21 % at the higher dose level following pre-incubation.

DEBRISOQUINE 4-HYDROXYLASE ACTiVITY: The selective CYP2D6 inhibitor, quinidine, inhibited this activity by 68% in the pooled human microsomes without any pre-incubation. There was no significant inhibition by lanthanum carbonate either with or without 15 minutes pre-incubation at either dose level, the maximum inhibition observed being 10% at the lower dose level following a pre-incubation period.

TESTOSTERONE 6/3.HYDROXYLASE ACTMTY: The selective CYP3A4/5 inhibitor, troleandomycin, inhibited this activity by 57% in the pooled human microsomes following a 15-minute pre-incubation period. However, no inhibition by lanthanum carbonate was observed either with or without pre-incubation at either dose level.

DISCUSSION:

In the present study, the potential inhibitory properties of lanthanum carbonate were investigated by separately incubating the compound with human liver microsomes pooled from six individual donors and a range of substrates, each selective for a particular isoform of cytochrome P450. Specifically, 7-ethoxyresorufin O-deethylase, tolbutamide methyl hydroxylase, S-mephenytoin 4/-hydroxylase, debrisoquine 4-hydroxylase and testosterone 6P-hydroxylase were used as catalytic markers for P450s 1A2, 2C9/10, 2CI9, 2D6, and 3A4/5, respectively (Parkinson, 1996). Parallel incubations were performed using known chemical inhibitors of P450, each selective for a particular isoform (furafylline, sulphaphenazole, tranylcypromine, quinidine and troleandomycin, respectively). These compounds were included to demonstrate that the isoforms concerned were sensitive to inhibition under the assay conditions used. Concentrations of lanthanum carbonate of 10 mcg/ml and 40 mcg/ml were selected as these reflect the concentrations found in rat liver and in rat intestine, respectively (information supplied by the Sponsor). In addition, two pre-incubation regimes were employed with the test compound. Firstly, the test compound was added to the incubation mixture immediately before the selective substrate used to initiate the reaction, and secondly, the test compound was pre-incubated for about 15 minutes prior to addition of the selective substrate. This latter method was designed to accommodate the possibility of the test compound requiring metabolic activation to exert an inhibitory effect.

It was found that lanthanum carbonate did not elicit a significant inhibitory effect on any of the catalytic probes investigated that was greater than that seen with the corresponding selective inhibitor. Moderate inhibition of CYPIA2 was observed but although this was concentration-dependent, it did not require, or was not significantly potentiated by, a 15-minute pre- incubation. This is indicative of reversible, non-mechanism based inhibition. Further, since the maximum liver concentration of lanthanum carbonate previously observed in vivo in rat was found to be approximately 10 mcg/ml, and this concentration in the assay elicited a maximum inhibition of 21 %, it is considered unlikely that this effect will have any clinical significance.

Sponsor's Conclusion:

The results obtained from this study indicate that lanthanum carbonate was not acting as a significant inhibitor of any of the cytochromes P450 examined, in incubations with human liver microsomes.

Reviewer Comments:

- The results of this study showed that lanthanum carbonate at concentrations of 10 and 40 mcg/ml do not have relevant inhibitory effects on any of the CYP450 isoenzymes tested (1A2, 2C9/10, 2C19, 2D6, & 3A4/5).
- In general, clinically significant drug-interactions depend on the mode of inhibition and on the concentration achieved in vivo, thus, the results from in vitro metabolic studies are meaningful only if clinically relevant concentrations of the studied drug are used in these tests. Please note that CYP3A4 is also the dominant microsomal P450 in the mucosal epithelial barrier of the small intestine, its expression is higher in the proximal (duodenum-jejunum) small bowel. The mean level of duodenal mucosal microsomal CYP3A is about 44% oft hat in the human liver. Therefore, in this case, animal data had shown that after chronic oral administration of lanthanum carbonate, the concentrations of lanthanum in the GI were up to 3700 mcg/g Thus, the provided in vitro metabolic information is incomplete, because the inhibitory effect of higher concentrations of lanthanum on gastrointestinal-CYP3A4, is unknown.

STUDY No. 308017388/A (Shire No. V00160-LAM-IIIG)

Title: "Lanthanum Carbonate: In Vitro Drug Interaction Study in Gastric Fluid".

Principal Investigator/Study Site: /Shire Pharmaceutical Development Ltd, East Anton, Andover, Hampshire, UK

Study Objectives:

To establish, by in vitro experiments, whether coadministration of six concurrently used medications (con meds) with lanthanum carbonate or calcium carbonate was likely to result in precipitation of an adduct or other species.

Background:

Lanthanum carbonate is being developed as a dietary phosphate binding agent for patients with end stage renal disease. It is intended to administer the new phosphate binding preparation as a chewable tablet at doses containing up to 3,000 mg lanthanum in divided doses with meals. The drug acts locally within the gut tract by binding to phosphate to form a highly insoluble salt that is then eliminated in the feces.

Six commonly used concomitant medications have been identified and this investigation was to check for the potential of local interactions between the lanthanum active and these agents.

Samples.

- Lanthanum carbonate: Lot No. 33842, PMID18983, Amount 150 g, Dosage 1.5 g lanthanum active
- Calcium Carbonate: Lot No. 128H01971, Amount 100g, Dosage 2.25 g Calcium active

The following materials were purchased from

- Warfarin Sodium Salt: LotNo.10K1147, purchased, Dosage 10mg
- Digoxin Base: Lot No. 50K14V, purchased, Dosage 1.5 mg
- Furosemide Base: Lot No. 69H 1237, purchased, Dosage 80 mg
- Phenytoin Sodium Salt: Lot No. 24H0073, purchased, Dosage 500 mg
- Metoprolol, Tartrate Salt: Lot No. 100KI483, purchased, Dosage 400 mg
- Enalapril, Maleate Salt: Lot No. 109H1258, purchased, Dosage 40 mg

Dosages are the maximum single doses recommended in the ABPI.

Methods:

Representative sub-samples of each of the con med actives were examined by These were then analyzed by using a microscope accessory Each spectrum was acquired over scans, using a detector at a resolution of

Subsamples from the second series of experiments were mounted on microscope slides at room temperature and examined by transmitted light microscopy [ ] and records were made of typical regions [ ]

Subsamples selected for X-ray microanalysis were mounted on [ ] applied to a [ ] imaged by scanning electron microscopy [ ] using an [ ] and analyzed using X-ray microanalysis [ ]

Results:

When solutions prepared from lanthanum carbonate (17.3 g) and simulated gastric fluid, SGF (1.8 L and 0.6 L), were clarified by centrifugation (12,000 rpm, 15 min) followed by filtration [ ] and allowed to cool below 37°C substantial precipitation occurred. It was, therefore, necessary to maintain lanthanum-containing solutions at 37°C throughout the experiment. This was also done for the corresponding solution prepared using calcium carbonate (33.7 g) and SGF (1.8 L).

When the solubility of the dosage levels of the con med drugs in SGF (100 ml) at 37°C was investigated, only digoxin, metoprolol, and enalapril dissolved completely. Furthermore, there were slight indications of precipitation after 1 hr in the case of digoxin. Warfarin, furosemide and phenytoin were, at best, only partially soluble in SGF.

The precipitates were concentrated by centrifugation (except for digoxin/lanthanum/SGF (300 ml) and metoprolol/lanthanum/SGF (300 ml) which were lost by tube breakage during centrifugation) and examined by light microscopy and ~ microspectroscopy

[ ]of precipitates

- The precipitates obtained in the case of warfarin yielded spectra, which differed from that of warfarin itself. Of these, the precipitate obtained with lanthanum/SGF (100 ml) was identified as lanthanum chloride ($LaCl_3$) on the basis of comparison with an authentic spectrum of the salt and the fact that X-ray microanalysis of the precipitate showed large peaks corresponding to lanthanum and chlorine. The precipitate obtained with lanthanum/SGF (300 ml) was mainly $LaCl_3$ but some organic material (which did not have the ~ spectrum of warfarin) was present, on the basis of the — data.
- The precipitate obtained in the case of digoxin and lanthanum/SGF (100 ml) was also $LaCl_3$.
- All the precipitates obtained in the case of furosemide yielded ~ spectra appropriate for furosemide itself. This was rationalized on the basis of the insolubility of furosemide in SGF.
- Phenytoin yielded the same precipitate with both 100 ml and 300 ml of lanthanum/SGF and with calcium/SGF. The ~ spectrum, which differed from that of phenytoin itself, was considered to correspond to a reaction product of phenytoin and SGF alone.
- The precipitate obtained from metoprolol and lanthanum/SGF (100 ml) yielded a — spectrum and differed from any of the others observed in this series of experiments. X-ray microanalysis suggested that the precipitate consisted of hydrated $LaCl_3$.
- The precipitates obtained for enalapril consisted of $LaCl_3$.

Sponsor's Conclusion:

There was no evidence, from these experiments, to suggest that therapeutic doses of lanthanum carbonate increased the likelihood of precipitation, in the stomach, of insoluble complexes incorporating any of the six concomitant medications that were selected.

Reviewer Comments:

- The overall results of this in vitro study showed that the probability of concomitant drugs in having a chemical interaction (precipitation) with lanthanum carbonate at the gut level is low.
- Also, the results showed that lanthanum carbonate reacts with the gastric fluid, therefore, at the gut level lanthanum carbonate will react not only with phosphate to form lanthanum phosphate, but also with HCl to form lanthanum chloride. Lanthanum chloride is a more soluble salt than lanthanum carbonate and it could be expected that its absorption would be higher.

APPEARS THIS WAY
ON ORIGINAL

Study LAM-IV-112

Title: A Phase I, Single Center, Open-Label, Randomized, Three Way Crossover Study to Assess the Effects of Co-Administration of Citrate on the Systemic Absorption of Lanthanum Following a Single Oral Dose.

Investigator: [redacted]

Study Period/Site: October 2000 - December 2000 [redacted]

Study Objectives:

- ***Primary:*** to assess whether the systemic absorption of lanthanum was affected when lanthanum carbonate tablets were concomitantly administered with citrate-containing compounds.
- ***Secondary:*** to characterize the plasma and urine profiles of lanthanum following a single dose and to assess the safety and tolerability of lanthanum carbonate.

Study Population:

Twenty-five subjects aged between 18 and 55 years, 12 males and 13 females were enrolled into this clinical study. One female subject withdrew consent during period I and was replaced. Twenty-four subjects successfully completed the study and were analyzed for pharmacokinetics. All 25 subjects randomized into the trial were analyzed for safety and tolerability. A summary of the demographic information is presented in the next table.

ITEM	FEMALE (N=13)	MALE (N=23)
Age	33.5 (9.4)	34.4 (7.5)
Weight (kg)	62.0 (6.3)	77.0 (7.0)
Height (cm)	166 (6)	180 (5)

Study Design:

This was a randomized, open-label, three-way crossover study. For each treatment-period subjects were randomly assigned to receive a 1000 mg dose of lanthanum chewable tablets (1908mg of lanthanum carbonate) either alone, with 200ml of orange juice or with 2 Effercitrate tablets (total 3g of potassium citrate and 0.5g of citric acid) dissolved in 200ml water. All doses were administered 5 minutes after a meal of low phosphorus content. There were at least 14 days between each of the dosing days.

Treatments and Mode of Administration:

The test product was a lanthanum 250mg chewable tablet (containing lanthanum as 477mg lanthanum carbonate) for oral administration (Batch number 96190). The Effercitrate soluble tablets (3g of potassium citrate and 0.5 g of citric acid) were from [redacted] Batch No. 76, and the orange juice was brand [redacted]

Subjects were randomized immediately before the first dose of study medication. All subjects received 3 single doses of lanthanum 1000 mg over a study period of a maximum of 40 days. The following treatments were given:

- ***Treatment A:*** 4 x 250mg lanthanum chewable tablets (1908mg of lanthanum carbonate/tablet) administered 5 minutes after food with 200ml room temperature non- carbonated water.

- ***Treatment B:*** 4 x 250mg lanthanum chewable tablets (1908 mg lanthanum carbonate tablet) + 200ml room temperature orange juice administered 5 minutes after food.
- ***Treatment C:*** 4 x 250mg lanthanum chewable tablets (1908mg of lanthanum carbonate tablet) + 2 x Effercitrate tablets dissolved in 200ml room temperature non- carbonated water (3g of potassium citrate and 0.5g of citric acid) administered 5 minutes after food.

There were at least 14 days between dose administrations. Each study period lasted 8 days, from check-in the evening prior to dosing until 144 hours post dosing. The study took place in the [ ] under full medical and nursing supervision.

Assessments:

- ***Pharmacokinetics:***
  Plasma: Blood samples (7 ml) for lanthanum PK were collected at each study-period at pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 36, 48, 72, 96, 120, and 144 hours post dose.
  Urine: urine samples were collected during each treatment period at the following times: pre-dose,0-3, 3-6, 6-9, 9-12, 12-24, 24-48, and 48-72 hours.

  The following pharmacokinetic parameters were assessed AUC(0-t), AUC(0-inf), Cmax, Tmax, terminal half- life (T1/2), relative bioavailability (Frel), amount of drug excreted in urine from 0-72 hrs (Ae), and Renal clearance (CLr).

- ***Safety:*** subjects were evaluated for vital signs, ECGs, physical examination, clinical laboratory parameters, and adverse events.

Bioanalytical Methods:

The levels of lanthanum in plasma and urine were measured by fully validated [ ] assays at [ ]

Plasma samples were heated at 60°C in the presence of dilute hydrochloric acid using a hot water bath. [ ]. Urine samples were diluted one part urine to nine parts La-free water and measured for La content using [ ] The La content of the samples ranged from [ ] ng La/mL plasma and [ ] ng La/mL urine.

Statistical methods:

Safety: Adverse events, laboratory tests and vital signs are listed and out of range values flagged in order to detect differences between treatment groups.

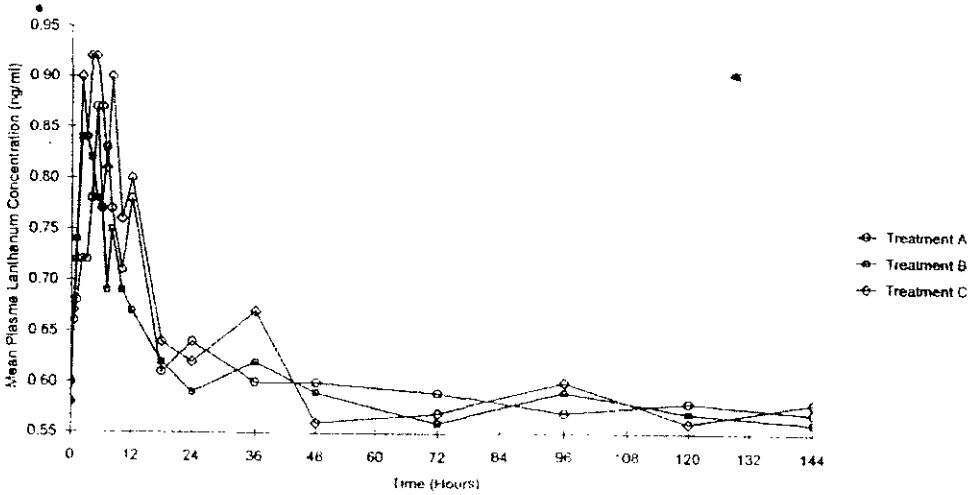
Pharmacokinetics: The hypothesis was that there are no differences in the bioavailability of 1000mg lanthanum (1908mg lanthanum carbonate) chewable tablets when administered alone and in combination with citrate. Individual and mean plasma concentrations of lanthanum were tabulated at each time-point following each treatment and summary statistics are presented. Individual plasma concentration/time curves were drawn on linear/linear and linear/log scale. Mean plasma concentrations vs time profiles are presented on linear/linear plot for all three treatments. Individual pharmacokinetic parameters and the mean, SD, maximum, and minimum values were tabulated for each treatment. Following logarithmic

transformation, the AUC0-inf and Cmax values were subjected to analysis of variance (ANOVA), Tmax was analyzed using a Kruskal-Wallis Test.

Pharmacokinetic Results:

Plasma: It should be noted that the analytical results showed that the batch of plasma collection tubes used during the study were contaminated by lanthanum. Both the 7 and 10 ml vacutainers were contaminated with lanthanum. The mean quantity of lanthanum found in the 7 and ml vacutainers was 5.87 (range — ng) and 5.43 (range —), respectively. Due to this contamination, the analysis of the plasma samples was made by using the data with no correction made for the contamination and by subtracting the baseline lanthanum concentration.

The mean concentration time-profile and mean PK parameters for lanthanum without adjustment following all administrations are presented next.



Note: Calculated from results without adjustment for lanthanum contamination
Treatment A - 4 x 250mg lanthanum chewable tablets
Treatment B - 4 x 250mg lanthanum chewable tablets + 200ml room temperature orange juice
Treatment C - 4 x 250mg lanthanum chewable tablets + 2 x Effercitrate tablets in 200ml water

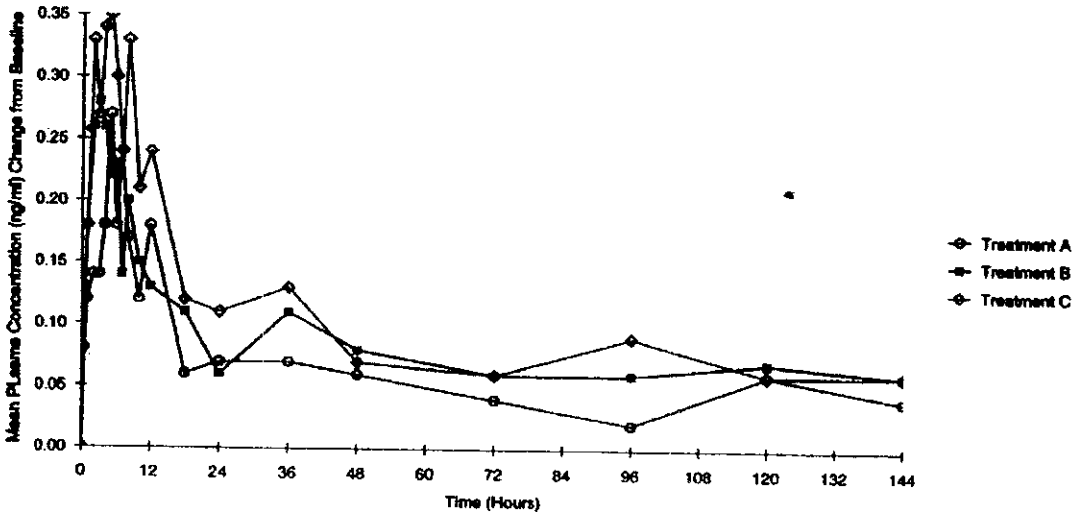
MEAN (SD) PHARMACOKINETIC AND STATISTICAL RESULTS USING DATA WITHOUT ADJUSTMENT FOR LANTHANUM CONTAMINATION							
PK PARAMETER	REFERENCE	TEST 1	TEST 2	RATIO (%) TEST 1/REF	90% CI TEST 1/REF	RATIO (%) TES T2/REF	90% CI TEST 2/REF
Cmax (ng/ml)	0.98 (0.16)	1.0 (0.19)	1.10 (0.23)	102.7	94.8-111.2	111.9	103.3-121.2
AUC0-t (ng.h/ml)	87.44 (14.35	87.34 (16.40)	88.40 (12.92)	98.6	92.7-105.0	101.4	95.3-107.9
Tmax (hours)	9.13 (13.95)	10.0 (13.62)	10.79 (19.69)	-	-	-	P=0.6017

Reference = 250 mg lanthanum chewable tablets
Test 1 = 250 mg lanthanum chewable tablets + 200 ml Orange juice
Test 2 = 250 mg lanthanum chewable tablets + 2 x Effercitrate tablets

The statistical results for the data without adjustment for lanthanum contamination showed that the 90% CI for Cmax and AUC0-t fell within the 80% to 125% range defined for bioequivalence with regard to

treatments B (lanthanum + orange juice) and C (lanthanum + Effercitrate) and lanthanum administered alone. The Kruskal-Wallis Test did not show a statistically significant difference (p=0.6017) between any treatments with regard to Tmax at the 5% level.

With respect to the PK analysis for the corrected data, the baseline levels of lanthanum were subtracted from each of the post dose samples. Baseline lanthanum concentration was defined as the concentration of lanthanum present in the pre-dose plasma sample (including the contribution from contamination) for the first treatment period of the study. The mean plasma lanthanum concentration-time profile and mean PK parameters using baseline corrected plasma lanthanum data are presented below.



Note: Calculated from results with adjustment for lanthanum contamination.

Treatment A - 4 x 250mg lanthanum chewable tablets

Treatment B - 4 x 250mg lanthanum chewable tablets + 200ml room temperature orange juice

Treatment C - 4 x 250mg lanthanum chewable tablets + 2 x Effercitrate tablets in 200ml water

MEAN (SD) LANTHANUM PHARMACOKINETIC PARAMETERS USING BASELINE CORRECTED DATA				
	Cmax (ng/ml)	Tmax (h)*	AUC0-72 (ng.h/ml)	AUC0-t (ng.h/ml)
Lanthanum	0.38 (0.15)	5.52 (1-72)	5.99 (5.24)	8.25 (7.57)
Lanthanum + Orange Juice	0.43 (0.20)	5.00 (1-48	7.40 (6.23)	11.94 (10.92)
Lanthanum + Effercitrate	0.53 (0.20)	5.00 (1-96)	9.05 (5.56)	13.64 (10.59)

* Median (range)

Using baseline corrected data the peak plasma concentrations were achieved between 5-6 hrs with a Cmax in the range of 0.38-0.52 ng/ml. The overall extent of absorption was in the range of 8.25-13.64 ng.h/ml

Urine: Please note that due to the lanthanum contamination, the sponsor decided that the results from plasma and urine samples were not comparable and an analysis of urine PK was not appropriate, therefore, urine PK was not discussed in the report.

Safety Results:

There were forty adverse events reported during this clinical study. Eight subjects following administration of lanthanum carbonate alone reported fourteen adverse events. There were four moderate adverse events and all other events were considered to be mild in severity. Two events of nausea were considered 'likely' to be related to the study medication.

Twelve subjects following co-administration of lanthanum carbonate with orange juice reported nineteen adverse events. Seven of the events were considered to be moderate in severity and all other events were mild in severity. Eight events were considered 'likely' to be related to the study medication; nausea (3), headache (3), dizziness (I) and vomiting (1).

Three subjects following co-administration of lanthanum carbonate with Effercitrate tablets reported seven adverse events. One event of nausea was considered to be severe, five events were moderate in severity and the one remaining event was mild in severity. All seven adverse events were considered 'likely' to be related to the study medication; nausea (3), headache (2) and vomiting (2).

All adverse events, with the exception of one, completely resolved. Subject 121 was reported as having thrombocythaemia, which was moderate in severity and classed as 'unlikely' to be related to the study medication. The following table presents a summary of adverse events by treatment and relationship to medication.

ADVERSE EVENTS BY TREATMENT AND RELATIONSHIP TO MEDICATION								
	250 mg Lanthanum Chewable Tablets		250 mg Lanthanum Chewable Tablets + 200 ml Orange Juice		250 mg Lanthanum Chewable Tablets + 2 x Effercitrate Tablets		All Treatments	
	N	%	N	%	N	%	N	%
Likely	2	5.00	8	20.0	7	17.5	17	42.5
Unlikely	11	27.5	11	27.5	0	-	22	55.0
Definitely No	1	2.500	0	-	0	-	1	2.50
Total	14	35.0	19	47.5	7	17.5	40	100.0

There were no clinically significant abnormalities found in this study for the biochemistry or urinalysis laboratory parameters, in the vital sign and ECG recordings nor significant physical examination findings.

Sponsor's Conclusions:

- The pharmacokinetic data indicated that the peak plasma concentration (Cmax) and the extent of absorption (AUC0-t) from all treatment groups using baseline uncorrected data were bioequivalent.
- There were no significant differences in absorption of lanthanum when administered alone or in the presence of citrate compounds.
- Lanthanum carbonate was safe and well tolerated by all subjects in the study, when given alone or co-administered with citrate compounds.

Reviewer Comments:

1. The results of this study showed that plasma and urine levels of lanthanum are not affected by concomitant administration of citrate containing products. Thus, it could be assumed that there is no chemical interaction at the gut level and the absorption of lanthanum is not affected. However, as previously mentioned plasma/urine levels do not represent lanthanum's total body exposure and is difficult to predict if the concomitant administration of lanthanum & citrates would affect (increase/decrease) the levels of lanthanum in relevant tissues (bone, liver, kidney, etc.).
2. The overall safety data showed that the number of adverse events likely to be related to the medication is higher when lanthanum is co-administered with citrates (orange juice or effercitrate)
3. Overall, the validation of the analytical methodologies used to assay lanthanum carbonate in plasma and urine are appropriate. Also, the quality control samples data are appropriate.

APPEARS THIS WAY
ON ORIGINAL

Study LAM-IV-113

Title: A Phase I, Single Center, Open Label Randomized Crossover Study to Assess the Effects of Lanthanum Carbonate on the Pharmacokinetic Parameters of Warfarin Following a Single Oral Dose

Investigator: [redacted]

Study Period/Site: February, 200 1 to March, 200 1[redacted]

Study Objectives:

- ***Primary:*** To assess whether the pharmacokinetic parameters of warfarin were affected when lanthanum carbonate was administered concomitantly.
- ***Secondary:*** To assess the safety and tolerability of lanthanum carbonate and warfarin when administered concomitantly.

NOTE: Warfarin is a chiral narrow-therapeutic anticoagulant, which has been shown to be involved in a number of drug-drug interactions. In humans, warfarin is eliminated almost entirely by hepatic cytochrome P450 (CYP) enzymes, in a partially stereospecific manner. (S)-warfarin, which is approximately 5 times more potent as an anticoagulant than (R)-warfarin, is stereoselectively metabolized by CYP2C9, mainly to 7-(S)- hydroxywarfarin. CYP3A4 seems to be involved in the metabolism of (R)-warfarin, with 6-(R)-hydroxywarfarin as the major metabolite (Park, 1988). The half- life of the (R)-enantiomer (about 45 hours) appears to be longer than that of the (S)-enantiomer (about 30 hours). The stereoselective interaction of warfarin and the CYP system has led to the use of warfarin as a stereochemical probe in interaction studies.

Study Population:

Fourteen healthy Caucasian males aged between 18 and 35 years, with body weight between 60 and 80 kg meeting the inclusion/exclusion criteria were enrolled into the trial to ensure that 12 subjects completed the study. All 14 subjects completed the study, were analyzed for PK, safety and tolerability. A summary of the demographic data is presented next.

	SUMMARY OF DEMOGRAPHIC DATA -		
Parameter	**Age (years)**	**Height (cm)**	**Weight (kg)**
Mean (SD)	23.6 (3.41	180.4 (5.12)	72.9 (5.59)

Study Design:

This was an open label, randomized, two-way crossover study. Subjects were randomly assigned to receive either 10 mg warfarin alone or 10 mg warfarin taken 30 minutes after a fourth dose of 1000 mg lanthanum (1908 mg lanthanum carbonate). After completion of the first treatment period the subjects were crossed over to receive the other treatment. There were 14 days between each of the warfarin dosing days.

Study products, dose and mode of administration:

- Four 250 mg lanthanum chewable tablets, Lot No. 90378 (each tablet containing lanthanum as 477 mg lanthanum carbonate, Shire pharmaceuticals).

- One 10 mg warfarin (2 x 5 mg [ ] tablets, Lot No. 503603, [ ] is a single oral dose. A 10 mg dose of warfarin was chosen for this study because 10 mg is the highest recommended dose in clinical practice.

Treatment A = A single oral dose of warfarin 10 mg 30 minutes after the end of breakfast on Day 1 or Day 16.

Treatment B = Oral lanthanum 1000 mg, immediately after meals on Day 0 or Day 15 (3 doses) and then on Day 1 or Day 16, a single dose of lanthanum 1000 mg immediately after breakfast, followed by a single dose of warfarin 10 mg 30 minutes later.

Assessments:

Safety: All subjects were evaluated for vital signs, 12- lead ECGs, physical examinations, clinical laboratory parameters and adverse events.

Pharmacokinetics: Blood samples for warfarin analysis were taken for each treatment at the following times: pre dose (-5 min), and 2, 3, 4, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours after dose. Please note that lanthanum concentrations in plasma and urine were not measured in this trial.

Plasma pharmacokinetic parameters including the area under the plasma concentration vs. time curve (AUC), the maximum observed concentration (Cmax), the time to maximum observed concentration (Tmax) and plasma half- life (t1/2) were calculated from the drug concentration- time data for warfarin using non-compartmental methods for warfarin taken alone or taken with lanthanum carbonate.

Analytical: The (R)- and (S)- warfarin concentrations were determined in plasma by [ ] The correlation coefficients of the calibration curves were at least [ ] for both analytes, demonstrating assay linearity. The lower and upper limits of quantification were [ ] ng/ml for both analytes. The precision (CV%) for the 150 ng/ml, 1500 ng/ml, and 3200 ng/ml levels, based on the quantity control results, was below 6% for both analytes. The accuracy (bias) was between [ ] % for both analytes. The data presented on assay specificity, linearity, precision and accuracy indicate that the (R)- and (S)-warfarin concentration in plasma samples are reliable. The analytical site was [ ]

Statistical Methods:

Safety: Adverse events were listed, tabulated, coded using the WHO- ART dictionary, and were evaluated for differences in frequency and percentage of subjects among the treatment groups.

Pharmacokinetics: Individual pharmacokinetic parameters for warfarin were determined using non-compartmental methods. The parameters included the AUC, Cmax, T max, and T1/2.

RESULTS:

Safety: The safety results presented indicate that lanthanum carbonate and warfarin, when administered concomitantly appeared to be generally well tolerated in healthy adult subjects. There were no withdrawals from the study due to adverse events; no serious adverse events and no safety concerns were raised in this trial. Two subjects reported a total of five adverse events. Headache and light-

headedness were reported after Treatment A (warfarin alone). Hypoglycemia, joint stiffness and vasovagal syncope were reported after Treatment B (co-administered warfarin and lanthanum carbonate).

There were no clinically significant abnormalities found in this study for any laboratory parameter, in the vital sign and ECG recordings nor significant physical examination findings.

Pharmacokinetics: The 90% confidence intervals for all PK parameters were within the bioequivalence criteria for a log-transformed data. Therefore, it can be concluded that these pharmacokinetic parameters of warfarin were not affected by lanthanum carbonate. The following table summarizes the PK and statistical results.

	MEAN (SD) PHARMACOKINETIC PARAMETERS & STATISTICS FOR WARFARIN					
	R-Warfarin Enantiomer			S-Warfarin Enantiomer		
PARAMETER	Treatment A	Treatment B	90% CI	Treatment A	Treatment B	90% CI
$AUC_{0\text{-last}}$ (ng.h/ml)	27222.8 (4404.5)	26400.4 (5172.6)	92.0-102.6	15900.8 (4904.4)	14962.5 (4150.1)	90.2-99.6
$AUC_{0\text{-inf}}$ (ng.h/ml)	31056.9 (4889.8)	30476.9 (5681.2)	91.8-100.4	18831.8 (5413.2)	17776.9 (4641.8)	90.2-100.0
Cmax (ng/ml)	558.0 (43.12)	556.9 (65.74)	95.4-103.6	537.64 (60.52)	541.6 69.66)	97.0-104.2
Tmax (hours)	3.00 (0.555)	3.29 (0.995)	-	2.71 (0.611)	2.86 (0.770)	-
T1/2 (hours)	45.33 (7.52)	44.82 (8.66)	-	32.32 (5.83)	30.81 (6.60)	-

Sponsor's Conclusions:

- The study demonstrates that the pharmacokinetic parameters of warfarin were not affected when lanthanum carbonate was concomitantly administered (i.e., lanthanum carbonate did not affect the absorption of warfarin) and both treatments were well tolerated and appear to be safe in healthy adult subjects when administered concomitantly.
- The administered dose of warfarin does not need to be adjusted in the presence of lanthanum in the clinical environment.

Reviewer Comments:

1. Although the results of this study showed that lanthanum carbonate and warfarin do not interact from the pharmacokinetic viewpoint, it should be noted that in this study the pharmacodynamic interaction (bleeding time or prothrombin time) between these drugs was not assessed. The sponsor should have assessed the PD endpoints in this study.
2. Please note that the possibility of having a PK and/or PD interaction between these drugs under chronic conditions is unknown (high accumulation of lanthanum in several organs/tissues-non linear kinetics). If possible, it is recommended that the sponsor screens for a PD-interaction (i.e., increase in bleeding/prothrombin time), the data of those patients taking warfarin in addition of lanthanum in the Phase II/III trials.
3. Overall, the validation of the analytical methodology and quality control samples used to assay (S)- and (R)-warfarin in this study are appropriate and acceptable.

Study LAM-IV-114

Title: A Phase I, Single Center, Open Label Randomized Crossover Study to Assess the Effects of Lanthanum Carbonate on the Pharmacokinetic Parameters of Digoxin Following a Single Oral Dose.

Investigator: [redacted]

Study Period/Site: March 13,2001 to April 6, 2001 [redacted]

Study Objectives:

- ***Primary:*** To assess whether the pharmacokinetic parameters of digoxin were affected when lanthanum carbonate was administered concomitantly.
- ***Secondary:*** To assess the safety and tolerability of lanthanum carbonate and digoxin when administered concomitantly.

Study Population:

Fourteen healthy Caucasian males aged between 18 and 35 years, with body weight between 60 and 80 kg were enrolled into the trial to ensure that 12 subjects completed the study. All 14 subjects completed the study, were analyzed for PK, safety and tolerability. A summary of the demographic data is presented next.

	SUMMARY OF DEMOGRAPHIC DATA		
Parameter	**Age (years)**	**Height (cm)**	**Weight (kg)**
Mean (SD)	22.9 (2.37)	177.5 (6.67)	71.8 (4.54)

Study Design:

This was an open- label, randomized, two- way crossover study. Subjects were randomly assigned to receive either 0.5mg digoxin alone or 0.5mg digoxin taken 30 minutes after a fourth dose of 1000 mg lanthanum (1908mg lanthanum carbonate). After completion of the first treatment period, the subjects were crossed over to receive the other treatment. There were 14 days between each of the digoxin dosing days.

Study products, dose and mode of administration:

- Four 250 mg lanthanum chewable tablets (each tablet containing lanthanum as 477 mg lanthanum carbonate, Batch No.: 90378, Shire pharmaceuticals).
- Digoxin 0.5 mg (2 x 0.25 mg [redacted] tablets, Batch No. A010204, [redacted] as a single oral dose.

Treatment A = A single oral dose of digoxin 0.5 mg 30 minutes after the end of breakfast.

Treatment B = Oral lanthanum 1000 mg, immediately after meals on one day (three doses) and then on the following day, a single oral dose of lanthanum 1000 mg immediately after the end of breakfast followed by a single oral dose of digoxin 0.5 mg, 30 minutes later.

Assessments:

Safety: All subjects were evaluated for vital signs, 12-lead ECGs, physical examinations, clinical laboratory parameters and adverse events.

Pharmacokinetics: Blood samples for digoxin analysis were taken for each treatment at the following times: -5 (pre-dose), and at 0.33, 0.66, 1, 1.33, 1.66, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours after dose. Serum pharmacokinetic parameters including the area under the serum concentration vs. time curve (AUC), the maximum observed concentration (Cmax), the time to maximum observed concentration (Tmax), and serum half- life (T1/2) were calculated from the drug concentration-time data using non-compartmental methods for digoxin taken alone and taken with lanthanum carbonate.

Analytical: Serum concentrations of digoxin were assayed using a validated immunoassay at [ ] The digoxin assay is a [ ] assay.

Statistical Methods:

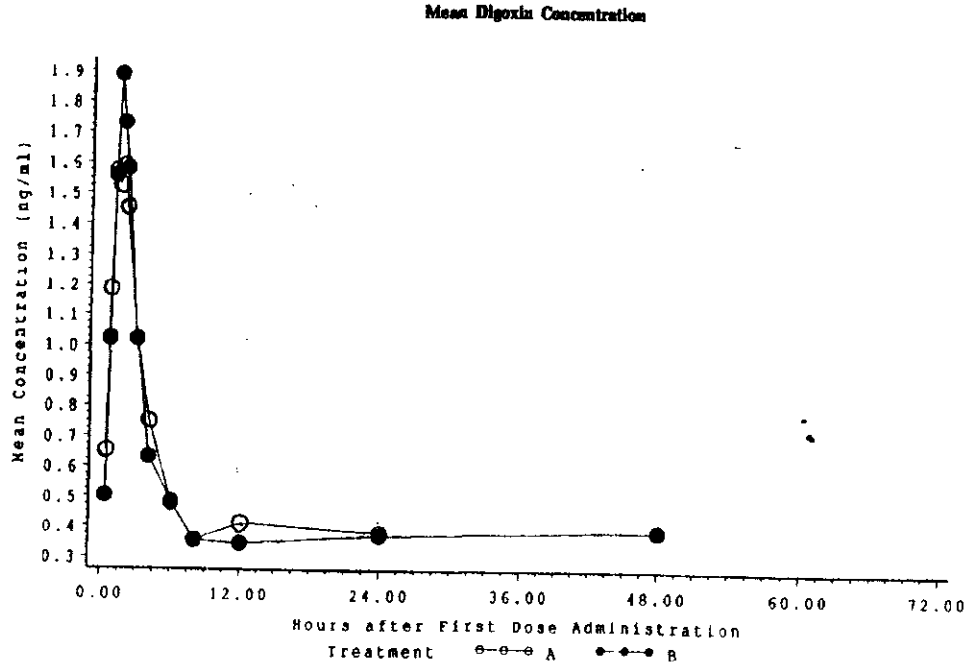
Safety: Adverse events were listed, tabulated, coded using the WHO- ART (98.3) dictionary, and were evaluated for differences in frequency and percentage of subjects among the treatment groups.

Pharmacokinetics: Individual pharmacokinetic parameters for digoxin alone and with lanthanum carbonate were determined using non-compartmental methods. The parameters included the AUC, Cmax, Tmax and T1/2.

RESULTS:

Safety: There were no serious adverse events in this study. There were no clinically significant changes in laboratory parameters in either treatment group, no clinically significant abnormalities in the vital signs or ECG recordings, and no abnormal physical examination findings throughout the study.

Pharmacokinetics: The mean plasma concentration vs. time profiles for digoxin after treatment A and B are illustrated in the next Figure.



The PK and statistical results are summarized in the next table.

PARAMETER (N=14)	MEAN (SD) PHARMACOKINETIC PARAMETERS & STATISTICS FOR DIGOXIN		
	Treatment A	Treatment B	90% CI
$AUC_{0\text{-last}}$ (ng.h/ml)	7.67 (4.11)	9.12 (6.92)	93.9-124.8
Cmax (ng/ml)	2.04 (0.456)	2.23 (0.527)	99.4-119.5
Tmax (hours)	1.55 (0.769)	1.52 (0.581)	-
T1/2 (hours)	11.43 (15.65)	14.79 (19.04)	-

The 90% confidence intervals for Cmax, and AUC0-last were within the bioequivalence criteria for a log-transformed data. The data for the primary parameter AUC0-inf was considered unreliable due to the wide variability in the individual profiles during the terminal arm of the excretion phase and is not reported.

Sponsor's Conclusions:

1. This study shows that co-administration of lanthanum carbonate results in a small increase in the bioavailability of orally administered digoxin.
2. The data from this study suggests that no additional precautions than those applying to digoxin alone are necessary when lanthanum carbonate and digoxin are administered concomitantly.
3. The safety results of this study demonstrate that lanthanum carbonate and a single oral dose of digoxin were well tolerated and appear to be safe in healthy adult subjects when administered concomitantly.

Reviewer Comments:

1. The co-administration of multiple 1000 mg oral doses of lanthanum carbonate did not have an effect on the pharmacokinetics associated with a single 0.5 mg oral dose of digoxin.
2. The assay information for digoxin is appropriate.

Study LAM-IV-115

Title: A Phase I, Single Center, Open Label Randomized Crossover Study to Assess the Effects of Lanthanum Carbonate on the Pharmacokinetic Parameters of Metoprolol Following a Single Oral Dose

Investigator: [ ]

Study Period/Site: April 2, 2001 to April 18, 2001 [ ]

Study Objectives:

- ***Primary:*** To assess whether the pharmacokinetic parameters of metoprolol were affected when lanthanum carbonate was administered concomitantly.
- ***Secondary:*** To assess the safety and tolerability of lanthanum carbonate and metoprolol when administered concomitantly.

Study Population:

Fourteen healthy Caucasian males aged between 18 and 35 years, with body weight between 60 and 80 kg were enrolled into the trial to ensure that 12 subjects completed the study. Two subjects withdrew following the completion of the first period for non- medical reasons. All 14 subjects were analyzed for safety and tolerability. The 12 subjects that completed the study were analyzed for pharmacokinetics. A summary of the demographic data is presented next.

	SUMMARY OF DEMOGRAPHIC DATA (N=14)		
Parameter	Age (years)	Height (cm)	Weight (kg)
Mean (SD)	24.0 (4.28)	174.9 (5.68)	74.4 (5.02)

Study Design:

This was an open- label, randomized two- way crossover study. Subjects were randomly assigned to receive either 100 mg metoprolol orally alone or 100 mg metoprolol orally taken 30 minutes after a fourth oral dose of 1000 mg lanthanum (1908 mg lanthanum carbonate). After completion of the first treatment period the subjects were crossed over to receive the other treatment. There were eight days between the two metoprolol dosing days.

Study products, dose and mode of administration:

- Four 250 mg lanthanum chewable tablets (each tablet containing lanthanum as 477 mg lanthanum carbonate, Shire pharmaceuticals), Batch No. 90378.
- One 100 mg metoprolol (100 mg [ ] tablets, containing metoprolol as 100 mg metoprolol tartrate, [ ] Batch No. U37683.

Treatment A = A single oral dose of metoprolol 100 mg, 30 minutes after the end of breakfast.

Treatment B = Oral lanthanum 1000 mg, immediately after meals (3 doses) on one day, then on the following day a single oral dose of lanthanum 1000 mg immediately after breakfast, followed by a single dose of metoprolol 100 mg 30 minutes later.

Assessments:

Safety: All subjects were evaluated for vital signs, 12- lead ECGs, physical examinations, clinical laboratory parameters and adverse events.

Pharmacokinetics: Blood samples for metoprolol analysis were collected after each treatment at the following times: -5 (pre-dose), 1, 1.33, 1.66, 2, 2.33, 2.66, 3, 4, 6, 8, 12, and 24 hours after dosing.
Plasma pharmacokinetic parameters including the area under the plasma concentration vs. time curve (AUC), the maximum observed concentration (Cmax), the time to maximum observed concentration (Tmax) and plasma half-life (T1/2) were calculated from the drug concentration-time data for metoprolol taken alone and with lanthanum carbonate using non-compartmental methods.

Analytical: The measurement of metoprolol in plasma samples was conducted at the [ ] using a validated high performance liquid chromatography method.

Statistical Methods:

Safety: Adverse events were listed, tabulated, coded using the WHO- ART (98.3) dictionary, and were evaluated for differences in frequency and percentage of subjects among the treatment groups. Laboratory tests and vital signs were listed and out- of- normal- range values flagged in order to detect differences between the two treatment groups.

Pharmacokinetics: Individual pharmacokinetic parameters for metoprolol alone and with lanthanum carbonate were determined using non-compartmental methods. The parameters included area under the curve (AUC), maximum observed plasma concentration (Cmax), time to the maximum observed concentration (T max) and plasma half- life (T1/2).

RESULTS:

Safety: The safety results indicate that lanthanum carbonate and metoprolol, when administered concomitantly appeared to be safe for healthy adult subjects. There were no deaths, serious adverse events or withdrawals due to adverse events in this study. One adverse event, a moderate headache, was reported in this study after Treatment B (co- administered lanthanum carbonate and metoprolol) and was considered to be unlikely to be related to the study medication at the time of the assessment. There were no clinically significant changes in laboratory tests in either treatment group and no clinically significant abnormalities in vital signs; ECG readings or physical examinations were observed during this study.

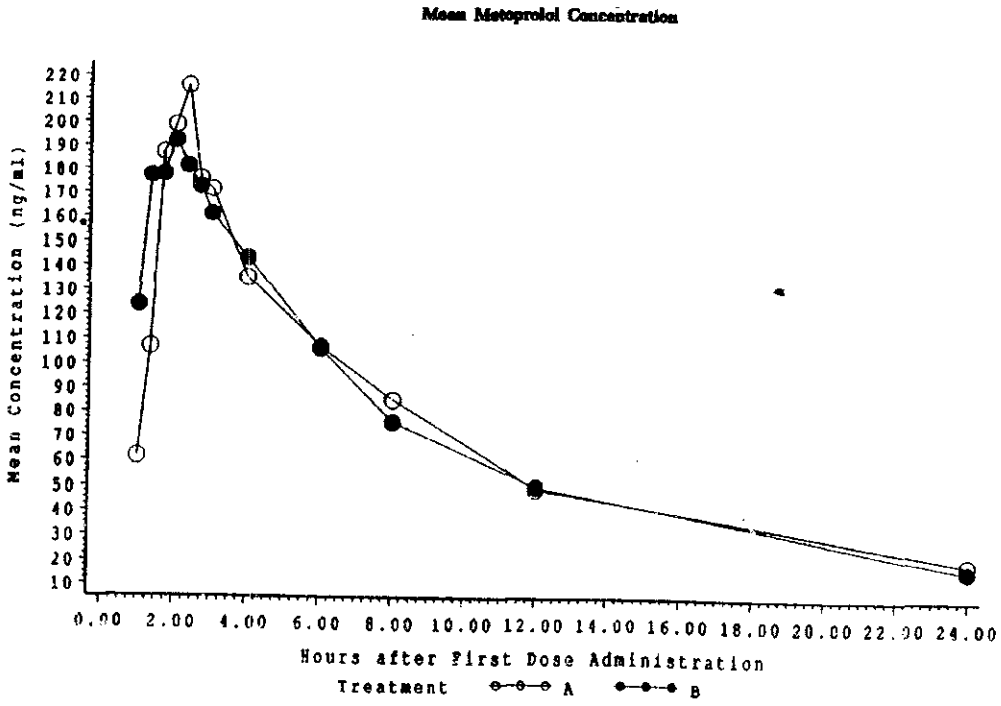
Pharmacokinetics: A summary of PK and statistics for metoprolol is presented in the next table.

PARAMETER	MEAN (SD) PHARMACOKINETIC PARAMETERS & STATISTICS FOR METOPROLOL		
	Treatment A	Treatment B	90% CI
$AUC_{0\text{-last}}$ (ng.h/ml)	1459.23 (922.01)	1391.59 (953.8)	86.9-103.4
$AUC_{0\text{-last}}$ (ng.h/ml)*	1731.97 (1002.44)	1546.57 (1090.49)	88.8-107.9
Cmax (ng/ml)	269.93 (119.45)	234.76 (106.57)	73.3-112.6
Tmax (hours)	1.95 (-)	2.08 (0.843)	90.3-104 8
T1/2 (hours)	4.68 (-)	4.51 (1.488)	95.4-110.8

*n =11

The 90% confidence intervals for AUC0-inf and AUC0-last were within the bioequivalence acceptance range of 80-125% for log-transformed data, although the 90% confidence interval for Cmax was marginally outside this range.

The mean metoprolol concentrations vs. time after treatment A and B are illustrated in the next Figure.



Sponsor's Conclusions:

- The extent of absorption of metoprolol, as determined by AUC0-inf and AUC0-last, was not affected by co-administration of lanthanum carbonate. The rate of absorption of metoprolol, as determined by Cmax, was slightly decreased when co-administered with lanthanum carbonate.
- The safety results of this study show that both lanthanum carbonate and metoprolol were well tolerated and appear to be safe in healthy male adult subjects when administered concomitantly.

Reviewer Comments:

1. This reviewer agrees with the sponsor conclusions, the co-administration of multiple 1000-mg oral doses of lanthanum carbonate did not have any effect on the pharmacokinetics associated with a single 100-mg oral dose of metoprolol.
2. The analytical information for metoprolol is appropriate.

AN ASSESSMENT OF THE POTENTIAL OF FOSRENOL (LANTHANUM CARBONATE) TO INTERACT WITH CO- PRESCRIBED MEDICINES IN A RENAL DIALYSIS PATIENT POPULATION

Background:

On November 1, 2002 an Original Amendment (N000-BM) to the NDA was submitted to the Agency in response to the request made by the Division of Cardio-Renal Drug Products to provide information on the potential of Fosrenol (lanthanum carbonate) to interact with concomitant medications in renal dialysis patients. The Amendment provided an assessment of the potential of Fosrenol to interact with drugs prescribed in ESRD, using as its basis those prescribed during Phase 2 and 3 clinical studies with Fosrenol. A conservative assessment was made of those most likely to be of interest, and concern, from the point of view of possible interactions with Fosrenol. Commonly used drugs and pharmaceutical preparations that were unlikely to have any adverse effects as a result of potential interactions with Fosrenol were excluded from further consideration. A summary of the sponsor's assessment is presented next.

1. Assessment of DDI to Fosrenol Co-Administration Based on Theoretical Mechanisms:

- ***Altered Plasma Protein Binding:*** Drugs may be displaced from protein binding sites when two protein bound drugs are given concurrently. From experiments with lanthanum carbonate, it has been shown that lanthanum is extensively (>99%) bound to human plasma and to the same extent to human α1-acid glycoprotein, serum albumin and transferritin. Due to the high degree of binding, it is considered to be very unlikely that the lanthanum cation will share, and interact with, the same binding sites as those utilized by more structurally complex drug molecules.

- ***Altered Tissue Binding:*** Tissue distribution studies in rats and dogs have shown that the small fraction of lanthanum systemically available following an oral dose is widely distributed throughout the body. For many tissues, the tissue:plasma concentration ratio is greater than 1, indicating binding and accumulation. Further studies have shown that there is a steady clearance of lanthanum from most tissues, but at a much slower rate from the stomach, parts of the upper small intestine and bone.

- ***Altered Metabolism:*** Lanthanum carbonate, as an inorganic metal salt, is not itself metabolized. Nor a substrate for cytochrome P450. Results of an in vitro metabolic study showed that lanthanum is not an inhibitor of CYP1A2, CYP2C9/10, CYP2C19, CYP2D6 and GYP-3A4/5. The same data also provide evidence that lanthanum carbonate does not affect drug metabolism by acting as a 'metal poison'. It is of note that the concentrations of lanthanum used in the in vitro studies were up to 40mcg/ml, about 4 times higher that the concentrations found in the liver of dogs in a long-term toxicity study. This suggests that lanthanum is unlikely to have an affect upon drug metabolizing enzyme systems.

- ***Altered Urinary Excretion:*** There are a number of mechanisms by which interactions between drugs can result in altered urinary excretion and possible adverse pharmacokinetic consequences. However, consideration of such interactions is not relevant with Fosrenol as the target population have chronic renal failure and are receiving dialysis. Further, based on animal data, lanthanum is excreted predominantly by non-renal mechanisms.

- ***Altered Biliary Excretion:*** Experiments in rats have shown that absorbed lanthanum is excreted predominantly in the bile. Assuming an analogous profile in man, the potential for possible interactions should be considered. Although a relatively minor excretory route for most drugs under normal circumstances, it is possible that, in the patients to whom Fosrenol will be administered, biliary excretion might become of greater importance in compensation for compromised renal clearance. Little is known about the mechanism by which La^{3+} is excreted into the bile, although there is some evidence to suggest that it is not by passive diffusion. For a significant number of drugs, entry into the hepatocyte, and then to the canalicular system, is achieved by a variety of carrier systems.

- ***Altered Gastrointestinal Absorption***
  Complexation: It is well known that cations such as Ca^{2+}, $Al^{3}+$, Mg^{2+} and Fe^{2+} can form non-absorbable chelates with compounds such as the fluoroquinolone and tetracycline antibiotics, with changes in pharmacokinetic parameters being the result. There is no direct in vitro evidence available to assess the efficacy of La^{3+} cations as a chelator of drugs and the initiator of interactions at this level. Whereas the likelihood for any significant chelation interaction is small, there is a theoretical possibility that an interaction at this level could occur. It would be prudent to recommend that compounds known to interact with cations in this way, should not be taken within 2 hours of dosing with lanthanum carbonate.

  Altered Motility: Changes in gastrointestinal motility may affect the pharmacokinetics of orally administered drugs by altering the rate of delivery to and residence time at the absorption site. However, since the overall effect of lanthanum on gastrointestinal motility is small, as assessed by the charcoal meal, it is considered that this mechanism is unlikely to be of any significance.

  Another possible mechanism whereby drug availability might be affected is emesis. Phase I studies have shown that administering lanthanum carbonate immediately after food greatly reduces vomiting. Instructing patients to take Fosrenol immediately after food, which in any event is essential for effective dietary phosphate binding to occur, will greatly reduce the risk of emesis-associated interactions.

  Altered pH: Although lanthanum carbonate is to be given with food, the relatively large doses administered could have the affect of lowering the acidity of the gastric contents. Under these circumstances, there is a theoretical potential for an effect upon the absorption of some weak acids and bases, most likely weak bases, whose degree of ionization might be affected by such changes in pH.

  Altered Absorption of Lanthanum:. Any changes in the extent of absorption of Fosrenol, produced by interactions with co-administered drugs, could increase this exposure.

2. Assessment of Potential Interactions Between Fosrenol and Concomitant Medications in Patients with End Stage Renal Disease:

- ***Antibiotics:*** As a therapeutic class, the mechanism of drug- drug interaction most commonly cited with antibiotics is that of chelation with metal cations following the administration of antacids such as magnesium and aluminium hydroxides. There is a theoretical possibility that an interaction at this level

could occur and it would be prudent to recommend that known to interact with cations in this way should not be taken within 2 hours of dosing with lanthanum carbonate.

- ***Calcium Channel Antagonists (Felopidine, lacidipine, nitrendipine, verapamil):*** The major source of clinically significant interactions reported between calcium channel antagonists and other drugs is at the level of cytochrome P450 mediated metabolism. This family of drugs is metabolized by CYP3A4, which makes them susceptible to interactions with drugs that either inhibit or induce CYP3A4. Given that the potential for lanthanum carbonate to interact with cytochrome P450 is considered to be low, it is unlikely that there will be any clinically significant interactions between Fosrenol and calcium channel antagonists.

- ***H2 Blockers (Ranitidine, famotidine, nizatidine, cimetidine):*** Given that the potential for lanthanum carbonate to interact with cytochrome P450 is considered to be low, it is unlikely that there will be any clinically significant interactions between Fosrenol and H2-antagonists at the level of altered metabolism. Neither would it be anticipated that the theoretical gastric acidity lowering potential of lanthanum carbonate would exacerbate similar effects of this therapeutic class.

- ***Proton Pump Inhibitors (Omeprazole, lansoprazole, pantoprazole):*** Given that the potential for lanthanum carbonate to interact with cytochrome P450 is considered to be low, it is unlikely that there will be any clinically significant interactions between Fosrenol and these proton pump inhibitors. Neither would it be anticipated that the theoretical gastric acidity lowering potential of lanthanum carbonate would exacerbate similar pronounced effects of omeprazole, lansoprazole and pantoprazole. By the increase in gastric pH caused by proton pump inhibitors, there is a theoretical potential for the solubility of lanthanum carbonate to be decreased. Lanthanum ions in solution are required for phosphate binding. However, this potential effect is ameliorated by the fact that Fosrenol will always be taken with food.

- ***ACE Inhibitors (Lisinopril, enalapril, captopril, fosinopril, quinapril, ramipril, benazepril):*** Considering this overall profile with that of Fosrenol, it would appear that the most likely theoretical interaction between ACE inhibitors and Fosrenol may be at the level of reduced absorption. However, such an interaction is unlikely to be of any clinical significance.

- ***Beta-adrenergic Blockers (Atenolol, celiprolol, propranolol, sotalol, carvedilol, labetolol, bisoprolol):*** The major source of clinically significant interactions reported between beta-blockers and other drugs is at the level of cytochrome P450 mediated metabolism. The pharmacokinetics of beta-blockers is strongly affected by cytochrome P450 inducers and inhibitors. Given that the potential for lanthanum carbonate to interact with cytochrome P450 is considered to be low, it is considered unlikely that there will be any clinically significant interactions between Fosrenol and beta- blockers.

- ***Oral Hypoglycaemics (Glipizide, glibenclamide):*** Two major sources of pharmacokinetic interactions have been documented with this class of compound. These are by protein binding displacement and by interactions at the cytochrome P450 level, with CYP2C9 being the major isoform involved. The potential for lanthanum carbonate to have significant interactions with the hypoglycaemics either by perturbing their plasma protein binding or affecting their metabolism by cytochrome P450 is considered to be low.

- ***Antidepressants***

  -Selective Serotonin Reuptake Inhibitors (Setraline. paroxetine. fluoxetine): Of particular relevance to the assessment of any possible interactions of these compounds with Fosrenol is their plasma protein binding and cytochrome P450 mediated metabolism. All three are very tightly bound (> 95%) to plasma proteins, and interactions with other drugs by this mechanism have been reported. All three are extensively metabolized by cytochrome P450, the predominant isoform involved is CYP2D6. The potential for lanthanum carbonate to have significant interactions with these SSRIs either by perturbing their plasma protein binding or affecting their metabolism by cytochrome P450 is considered to be low.

  -Tricyclic Related Antidepressants (Amitriptyline, trazodone): Both amitriptyline and trazodone are extensively metabolized by cytochrome P450: for amitriptyline the isoform of most importance is CYP2D6 while for trazodone is CYP3A4. Given that the potential for lanthanum carbonate to interact with cytochrome P450 is considered to be low, it is unlikely that there will be any clinically significant interactions between Fosrenol and either amitriptiline or trazodone.

- ***Anticonvulsant (Gabapentin):*** The only major source of pharmacokinetic interactions which has been documented with gabapentin, which is of relevance to its co- administration with Fosrenol, is the reduction in its absorption seen following treatment with antacids such as magnesium hydroxide and aluminium hydroxide. The possibility of an interaction between Fosrenol and gabapentin at the level of reducing absorption by binding exists.

- ***Adrenergic Receptor Agonists and Antagonists (Doxazosin, clonidine, midodrine, moxonidine, terazosin):*** With all five compounds, the interaction literature focuses very much upon the pharmacological consequences, cardiac and renal, of co-administration with other drugs. The possible mechanisms for interactions between doxazosin, clonidine, midodrine, moxonidine, terazosin and Fosrenol are via plasma protein binding and cytochrome P450 mediated metabolism. In both cases, it is unlikely that Fosrenol co-administration would elicit any clinically significant effects.

- ***Cardiac Glycosides (Digoxin, digitoxin):*** It is possible that Fosrenol administration could perturb the pharmacokinetics of digoxin and digitoxin by reducing the extent of their absorption. This, together with the compromised renal sufficiency of the target population, indicates careful monitoring of those patients where co-administration is necessary. It has also been shown that the absorption of the cardiac glycosides is affected by the administration of antacids such as magnesium hydroxide and aluminium hydroxide. Interactions between Fosrenol and the cardiac glycosides cannot be ruled out.

  It should be noted that the results from a drug interaction study showed that concomitant administration of Fosrenol and digoxin, did not affect the pharmacokinetics of digoxin. The data from this study suggest that no additional precautions beyond those applying to administration of digoxin alone are necessary when lanthanum carbonate and digoxin are administered concomitantly.

- ***Antiarrhythmic (Amiodarone):*** Interactions with amiodarone are extensive and are mainly based upon two mechanisms, the high degree of plasma protein binding of the compound and its extensive metabolism by cytochrome P450. Amiodarone is a substrate for CYP3A4 and also an inhibitor of CYP1A2, CYP2C9/10 and CYP2C18/19. As the potential for lanthanum carbonate to produce clinically significant effects by interacting at the protein binding and cytochrome P450 levels is low,

there is little likelihood of adverse reactions resulting from the co-administration of amiodarone and Fosrenol.

- ***3-Hydroxy- 3-methylglutaryl Coenzyme A Reductase Inhibitors (Atorvastatin, simvastatin, pravastatin, lovastatin):*** Simvastatin and lovastatin are extensively metabolized by cytochrome P450 3A4, pravastatin, on the other hand, is metabolized by non CYP-dependent processes. Given that the potential for lanthanum carbonate to interact with cytochrome P450 is considered to be low, it is thought unlikely that there will be any clinically significant interactions between Fosrenol and members of the statin family.

- ***Angiotensin II Receptor Antagonists (Losartan, irbesartan, candesartan):*** The major source of clinically significant interactions reported between losartan, irbesartan, candesartan and other drugs is at the level of cytochrome P450 mediated metabolism, the most important isoforms of which are CYP2C9 and CYP3A4. The pharmacokinetics of all three are affected by inducers and inhibitors of these isoforms. Given that the potential for lanthanum carbonate to interact with cytochrome P450 is considered to be low, it is unlikely that there will be any clinically significant interactions between Fosrenol and angiotensin II receptor antagonists.

- ***5-HT$_4$ Receptor Agonist (Cisapride):*** Cisapride is metabolized mainly via the cytochrome P450 3A4 enzyme and adverse interactions have been noted when its metabolism has been perturbed by co-administration of inhibitors of this isoform. It has also been shown that the acceleration of gastric emptying caused by cisapride can affect the rate of absorption of other drugs.

  The low potential of lanthanum carbonate to interact with CYP 3A4, and any other isoform of cytochrome P450, makes it unlikely that there will be any interactions between these two drugs. Conversely, the mode of action of Fosrenol makes it improbable that this will be affected adversely by any acceleration of gastric emptying elicited by cisapride.

- ***Thyroid Hormones (Levothyroxin):*** Two major sources of pharmacokinetic interactions have been documented with levothyroxine, which are of relevance to its co-administration with Fosrenol. These are by protein binding displacement, the thyroid hormones being very highly protein bound, and by a reduction in its absorption following treatment with antacids such as magnesium hydroxide and aluminium hydroxide. Whereas the potential of lanthanum carbonate to perturb the plasma protein binding of levothyroxine, and other thyroid hormones, is low, the possibility of an interaction at the level of reducing absorption by binding exists. It will be probable that plasma thyroxine levels will be measured in these patients and any reduction in circulating levels seen can be corrected by an increase in dose if required.

- ***Anti-histamines (Fexofenadine, cyproheptadine, clemastine, dimetindine):*** There are reports of reduced absorption of these four by the co- administration of aluminium hydroxide and magnesium hydroxide containing gels. Thus, there is a possibility that co-administration of some anti- histamines with Fosrenol may result in an effect upon their absorption. Given that antihistamines are dosed to effect, clinically, a reduction in absorption, if it occurs, may be countered by additional dosing as required.

- ***Thrombolytic (Clopidogrel):*** The major source of interactions with clopidogrel resides in its metabolism by cytochrome P450, predominantly through the CYP1A subfamily. The low potential of lanthanum carbonate to interact with cytochrome P450 makes it unlikely that there will be any interaction following co- administration of Fosrenol and clopidogrel.

- ***Benzodiazepines (Temazepam, clonazepam, lorazepam, diazepam, alprazolam):*** The benzodiazepines are extensively metabolized by various isoforms of cytochrome P450; CYP3A4 and CYP2C19 being particularly important. The most clinically significant interactions reported with these compounds are those, which involve changes in metabolic clearance via CYP-mediated processes. The low potential of lanthanum carbonate to interact with cytochrome P450 makes it unlikely that there will be any interactions with the various benzodiazepines.

- ***Anxiolytics (zolpidem):*** The major source of interactions with zolpidem resides in its metabolism by cytochrome P450. The major, but not the sole isoform, mediating zolpidem metabolism is CYP3A4, with contributions from CYP1A2 and CYP2D6. Interactions with zolpidem through cytochrome P450 mechanisms are unlikely.

- ***Non- steroidal Anti- inflammatory (Naproxen):*** There are two potential sources of pharmacokinetic interactions that are of relevance to its co-administration with Fosrenol. These are by protein binding displacement, naproxen being very highly protein bound, and interactions with cytochrome P450. Naproxen is a substrate for both CYP2C9 and CYP1A. As the potential for lanthanum carbonate to produce clinically significant effects by interacting at the protein binding and cytochrome P450 levels is low, there is little likelihood of adverse reactions resulting from the co- administration of naproxen and Fosrenol.

- ***Oral Anticoagulants (Warfarin, fenprocoumon):*** In common with other coumarin derivatives, warfarin and fenprocoumon combine three unfavourable properties that make them susceptible to potentially very serious drug- drug interactions. High plasma protein binding, cytochrome P450 dependent metabolism via CYP2C9 and a narrow therapeutic range.

  An interaction study co-administering warfarin with Fosrenol was undertaken in healthy volunteers. There were no changes in the pharmacokinetics of either the R- or S-enantiomers of warfarin.

- ***Loop Diuretics (Furosemide and torasemide):*** Given the severely compromised renal function of the patients for whom Fosrenol will be indicated, it is considered that any possible interactions between lanthanum carbonate and loop diuretics is not clinically relevant.

- ***Lipid Lowering Fibrates (Gemfibrozil):*** In common with other fibrates, gemfibrozil combines two properties which are relevant to their potential for drug- drug interactions. High plasma protein binding and cytochrome P450 dependent metabolism via CYP3A4. Gemfibrozil is also a potent inhibitor of CYP2C9. As the potential for lanthanum carbonate to produce clinically significant effects by interacting at the protein binding and cytochrome P450 levels is low, there is little likelihood of adverse reactions resulting from the co-administration of gemfibrozil and Fosrenol. An analogous conclusion may be drawn about the possibility of interactions with other fibrates.

- ***Antiemetic (Ondansetron):*** The major source of interactions with ondansetron resides in its extensive metabolism by multiple forms of cytochrome P450. Thus, it is unlikely that there will be any interaction following co- administration of Fosrenol and ondansetron.

- ***Laxatives and Antidiarrhoeals:*** The patients enrolled were taking a wide variety of drugs and preparations that have affects upon gastrointestinal motility. Given the properties and mechanisms of actions of these compounds, it is difficult to envisage that lanthanum carbonate will have any significant impact upon their effectiveness. Conversely, as any motor disturbances will affect the transit of food as well as lanthanum carbonate, it is improbable that the phosphate binding effectiveness of Fosrenol would be adversely affected by the actions of laxatives or antidiarrheals.

- ***Polystyrene Sulphonate Resins:*** These resins are not selective in the cations they exchange and it is possible that there could be some binding of lanthanum cations if the resins and Fosrenol are administered together. If this were the case, then a decrease in phosphate binding could result. The magnitude of the effect would depend upon the relative affinities of lanthanum for phosphate or the anionic sites on the resins. As a precaution for any possible interactions, it would be prudent to separate doses of Fosrenol and any resins by several hours.

- ***Antacids and Other Preparations:*** Amongst the concomitants administered during the Fosrenol trials were a relatively large number of antacid preparations containing magnesium, calcium and aluminium salts in various forms. Additionally there were various preparations of iron. There is a theoretical possibility of interactions between lanthanum ions and these metals through either adsorptive or ionic mechanisms such that the free concentration of lanthanum ions in solution would be decreased. However, given that Fosrenol will always be taken with food, it is considered very unlikely that interactions of this type would have any impact upon the effectiveness of Fosrenol as a phosphate binder.

- ***Vitamins:*** Although the effects of Fosrenol on the absorption of vitamin supplements has not been investigated directly, treatment with Fosrenol was shown not to affect vitamin D usage in Phase 3 clinical studies (Studies LAM- IV- 301 and LAM- IV- 307). Further, in a subset of patients (100) in Study LAM- IV- 307, blood levels of: Vitamin A, Vitamin D3 (calcidiol and calcitriol), Vitamin E, Vitamin K, serum folate, and Vitamin B12 were unaffected by Fosrenol treatment. No significant differences were noted between lanthanum and standard therapy groups when changes from screening visit to a follow-up visit were analyzed, suggesting that Fosrenol does not alter the absorption of these vitamins from the diet.

Sponsor's Overall Conclusions:

1. The potential for drug-drug interactions between Fosrenol and co-administered medications has been reviewed. It is concluded that, of the theoretically possible mechanisms, those affecting absorption are the most likely to occur. In these instances, the interaction will be physico-chemical, resulting from chelation and binding, rather than from anything related to drug transport mechanisms.
2. It is considered very unlikely that Fosrenol will precipitate any interaction by the perturbation of plasma protein binding or cytochrome P450 mediated metabolism, two very common sources of adverse drug- drug interaction.
3. Within the ESRD clinical setting, evaluating drugs prescribed during Phase 2 and 3 studies with Fosrenol, it is considered that, overall, the potential for any clinically significant drug-drug interactions

is very low. However, there is a theoretical possibility that co-administration of Fosrenol with antibiotics, gabapentin, cardiac glycosides, anti-histamines and levothyroxin might result in changes in pharmacokinetic profiles. It would be prudent to exercise caution when considering such combinations.

Reviewer Comments:

1. Please note that CYP3A4 is also the dominant microsomal P450 in the mucosal epithelial barrier of the small intestine, its expression is higher in the proximal (duodenum-jejunum) small bowel. The mean level of duodenal mucosal microsomal CYP3A is about 44% oft hat in the human liver. Thus, following chronic administration the effect of high concentrations of lanthanum may have on CYP 3A4 (inhibition/induction) and the consequences of drug interactions at the GI level, is unknown.
2. It should be noted that p-glycoprotein was not included in their drug-interactions assessment. Also, note that the sponsor did not conduct an in vitro study to evaluate if lanthanum inhibits/induces p-glycoprotein. P-glycoprotein recognition is a critical determinant in drug absorption and disposition and in the potential consequences of drug interactions between substrates/or inhibitors of this protein. Thus, it is important to know this information in order to avoid co-administration of lanthanum with medications that may be affected by p-glycoprotein at the GI level.

APPEARS THIS WAY
ON ORIGINAL

D. ATTACHMENT 4

Includes:

NOTE: The following Clinical Studies were evaluated only with respect to plasma lanthanum levels. The medical officer of DCRDP evaluated the efficacy and safety information.

- Summaries of Individual Clinical Studies:

Study No. LAM-IV-202

Study No. LAM-IV-204

Study No. LAM-IV-301

Study No. LAM-IV-302

Study No. LAM-IV-307

Clinical Study LAM-IV-202

Title: A Phase II, Dose Ranging, Placebo Controlled Parallel Group Study to Assess The Efficacy and Safety of 'Lambda' For Reduction of Gastrointestinal Phosphate Absorption in Patients Receiving Hemodialysis or Continuous Ambulatory Peritoneal Dialysis (CAPD).

Investigators: Dr. A. Hutchison (PI) plus seven supporting investigators.

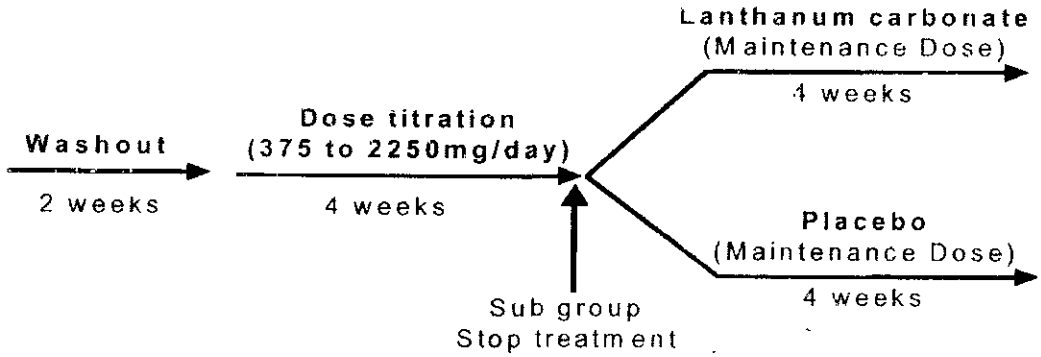
Study Period/Site: June 1997 to June 1999 / Renal Unit, Manchester Royal Infirmary, Manchester plus seven other renal medicine departments at hospitals in the UK.

Study Objectives:

- To determine an efficacious dose of lanthanum for reduction and maintenance of serum phosphate at a level between 1.3 mmol/ L and 1.8 mmo1/ L
- To evaluate the absorption and safety profile of lanthanum carbonate in hemodialysis and CAPD patients to collect data on dose and frequency of established phosphate binder compared to effective doses of lanthanum in this patient population.

Study Design:

Washout phase followed by open dose titration period of 4 weeks (Part 1) followed by double- blind placebo- controlled comparative phase of 4 weeks (Part 2). The overall study design is presented next.



A total of 59 patients were dose-titrated with lanthanum carbonate. The final titrated doses at the end of Part 1 in mg of lanthanum were 250 mg/ day for one patient, 375 mg/ day for 9 patients, 750 mg/ day for 15 patients, 1500 mg/ day for 20 patients and 2250 mg/ day for 13 patients. One patient titrated to 750 mg before withdrawal was assigned a dose of 'other'. Fifty patients completed dose titration and 36 entered Part 2; 17/36 patients were treated with lanthanum carbonate and 19/36 with placebo. Two placebo patients withdrew from the study. A subgroup analysis was conducted on the patients receiving CAPD, 39/ 59. Of the 39 who were dose titrated, 31 completed Part 1 and 21 entered Part 2.

Study Population:

An initial 12 patients in Part 1 (a pilot group) and then sufficient patients enrolled to Part 1 to achieve 46 patients in Part 2 (23 per group). Studied: a total of 59 treated patients (40 M, 19F, aged 21.9- 79.8, mean

54.7 years) in Part 1 and 36 in Part 2 (17 (10 M, 7 F, aged 29.7- 79.8, mean 57.0 years) treated with lanthanum carbonate and 19 (10 M, 9 F, aged 31.8- 78.3, mean 53.3 years) treated with placebo).

Diagnosis and Main Criteria for Inclusion: Patients who had been receiving either CAPD or hemodialysis for >6 months with serum phosphate level >1.8 mmol/L following washout of previous phosphate binders. Male or female aged 18 or above. Sexually active females of childbearing potential could enter if contraceptive precautions were deemed adequate.

Products, Dose and Mode of Administration:
Study drug was supplied as round, chewable tablet containing 125 mg (Lot No. 22923) or 250 mg (Lot No. 22923) of lanthanum. The placebo tablets (Lot No. 22922) were identical in appearance to the active tablets, but contained [redacted]

- ***Test Part 1:*** oral lanthanum at a starting dose of 375 mg lanthanum/ day (in three divided doses) titrated up to 2250 mg lanthanum/ day as necessary to control serum phosphate.
- **Test Part 2:** oral lanthanum at the titrated dose. Treatment taken with meals.
- **Oral placebo** (Part 2 only)

Patients were titrated on a weekly basis depending on their serum phosphate levels from a total daily dose of 375 mg lanthanum up to a maximum of 2250 mg lanthanum as shown below.

Lanthanum dosing schedule

Visit	Lanthanum dose (mg/day)
1	375
2	750 or 250
3	1500
4	2250

Tablets were to be taken with food at each of the three meals, breakfast, lunch and dinner. If serum phosphate levels were controlled after the first dose, it was possible to titrate down to 250 mg daily at the first titration visit and down-titration at subsequent visits was permitted at the discretion of the investigator by reducing the frequency of dosing to twice or once daily with food. The duration of treatment for Part 1 was 4 weeks (from week 1 to week 5) and for Part 2 was 4 weeks (week 5 to week 9)

A blood sample was taken for subsequent plasma lanthanum determination at visits 0, 1, 3, 5, 7 and 9. For the initial sub-group that only participated in Part 1, samples were also taken at visits 2 and 4. Serum lanthanum was assayed by [redacted] using a validated [redacted] assay. The limit of quantification was [redacted] ng/g.

RESULTS:

Lanthanum Concentrations: At week 4, 24 patients (52%) had serum lanthanum levels above the limit of quantification [redacted] ng/g). Levels above the LOQ in individual patients ranged from [redacted] ng/g. At week 9, 9/16 patients in the lanthanum carbonate group and 4/16 in the placebo group had detectable plasma lanthanum levels. The detectable levels in the lanthanum carbonate group ranged from [redacted]

ng/g and those in the placebo group from [redacted] ng/g. The following table lists the mean lanthanum plasma levels during Part 1 and 2 of the study.

MEAN (SD) LANTHANUM PLASMA LEVELS (NG/G)*							
	Part 1: Safety Population			Part 2: Safety Population			
	All Patients	CAPD Patients		All Patients		CAPD Patients	
	Lanthanum	Lanthanum		Lanthanum	Placebo	Lanthanum	Placebo
Screening	n = 2 0.50 (0.0)	n = 2 0.5 (0.0)	Week 1	n = 16 0.53 (0.104)	n = 18 0.59 (0.20)	n = 10 0.55 (0.13)	n = 10 0.61 (0.25)
Week 1	n = 54 0.54 (0.131)	n = 36 0.55 (0.15)	Week 5	n = 2 0.8 (0.424)	n = 4 0.61 (0.202)	-	n = 3 0.64 (0.23)
Week 2	n = 51 0.57 (0.237)	n = 31 0.54 (0.1)	Week 6	n = 16 0.71 (0.307)	n = 17 0.65 (0.252)	n = 9 0.74 (0.263)	n = 10 0.73 (0.306)
Week 3	n = 10 0.70 (0.239)	n = 10 0.70 (0.239)	Week 7	n = 1 0.50	n = 1 0.73	n = 1 0.50	n = 1 0.73
Week 4	n = 46 0.74 (0.573)	n = 29 0.84 (0.698)	Week 8	n = 16 0.61 (0.157)	n = 16 0.68 (0.622)	n = 9 0.72 (0.263)	n = 9 0.51 (.014)
Week 5	n = 11 0.78 (0.452)	n = 8 0.81 (0.504)	Week 9	n = 16 0.89 (0.843)	n = 16 0.52 (0.053)	n = 9 0.70 (0.254)	n = 9 0.53 (0.086)
			Last Visit	n = 17 0.87 (0.82)	n = 19 0.53 (0.079)	n = 10 0.70 (0.254)	n = 11 0.53 (.086)

*

Sponsor's Conclusion:

- Lanthanum was detectable in serum at mean levels of around 0.7 ng/ g. However, at each visit, an appreciable proportion of lanthanum carbonate treated patients had no detectable lanthanum. (The limit of quantification was [redacted] g/g). The highest non-artefactual lanthanum level seen in an individual was [redacted] ng/g; the patient was titrated to 1500 mg/ day.

Reviewer Comments:

1. This is a clinical study designed to evaluate the efficacy and safety of lanthanum carbonate; therefore, this reviewer will comment only on the lanthanum plasma levels data.
2. It should be noted that one patient (No. 313) had very high lanthanum values of [redacted] ng/g. The sponsor believed to be artefactual and these values were not included in the data summaries.
3. Please note that in this study, the sponsor is reporting lanthanum concentrations in ng/g instead of ng/ml.
4. The assay validation and quality control samples information was not included in the study report.

Clinical Study LAM-IV-204

Title: A Dose Ranging, Placebo- controlled Group Study to Assess the Efficacy and Safety of Lanthanum Carbonate for Reduction of Serum Phosphate in Chronic Renal Failure Subjects Receiving Hemodialysis.

Principal Investigator/Study Period/Sites: William Finn, MD Univ. of North Carolina Chapel Hill, NC. April 6, 1998 - November 11, 1998 / 10 study centers

Study Objectives:

- ***Primary:*** To compare changes in serum phosphate levels from baseline to the end of treatment for four fixed doses of lanthanum and placebo.
- ***Secondary:***
  - To determine the minimum effective dose and maximum clinically effective dose
  - To determine the time at which a significant reduction in serum phosphate was first achieved, and whether this reduction was sustained until the end of treatment for each dose group
  - To evaluate the tolerability and safety of lanthanum carbonate
  - To determine the effects of lanthanum carbonate withdrawal on serum phosphate level
  - To evaluate the effects of dietary phosphorous and calcium intake on changes in serum phosphate levels.

Study Design:

This was a randomized, double- blind, placebo- controlled, parallel group, dose ranging study of lanthanum carbonate in chronic renal failure subjects receiving hemodialysis. This study consisted of three phases: A one to three week single- blind placebo run- in phase during which subjects stopped all phosphate binding medication. To be eligible to enter the double- blind treatment phase subjects' serum PO4 had to be > 5.6 mg/ dL. Eligible subjects were then randomized to six weeks of double- blind study drug treatment, followed by a final two- week, single- blind placebo run- out phase.

Study Population:

The protocol called for a total of 150 subjects (30/ treatment group). One hundred and ninety- six subjects were enrolled and entered the placebo run- in phase. Of these, 145 met the criteria for randomization to the double- blind treatment phase (placebo 32; La-225 28; La-675 29; La-1350 30; and La-2250 26). One subject in the La-225 group was withdrawn in the first week of double- blind treatment to have a kidney transplant and thus the ITT population consisted of 144 subjects.

Diagnosis and Main Criteria for Inclusion: Subjects of either sex, 18 years and older with end stage renal disease, and who had been undergoing dialysis for at least 6 months, were enrolled in the placebo run- in phase.

Test Product, Dose and Mode of Administration, Batch Number:

Study drug was supplied as identical, round, chewable tablets containing 25 mg, 75 mg,150 mg or 250 mg of lanthanum. The placebo tablets were identical in appearance to the active tablets, but contained

[redacted]

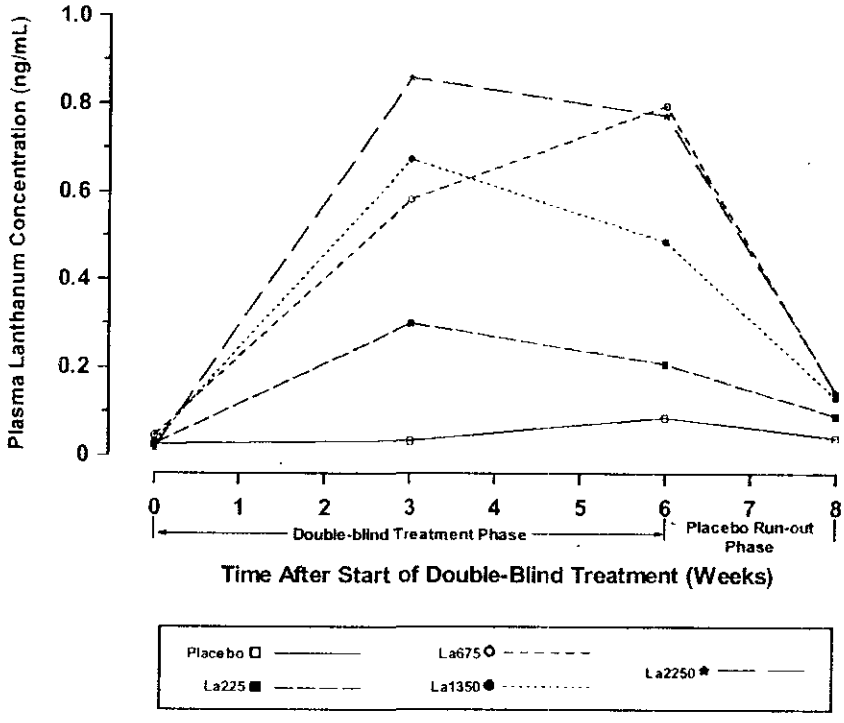
Study Drug	Lot No.
Placebo tablet	28494, 28495, 28527
Lanthanum 25 mg tablet	28496
Lanthanum 75 mg tablet	28497
Lanthanum 150 mg tablet	28768
Lanthanum 250 mg tablet	28540

Subjects were randomized to one of the following doses: placebo: 9 placebo tablets daily; La-225: 9 lanthanum 25 mg tablets daily; La-1350: 9 lanthanum 75 mg tablets daily; La-2250: 9 lanthanum 150 mg tablets. Daily doses were administered BID or TID with meals; subjects who took only two meals per day took a larger number of tablets with the heavier meal.

The placebo run- in phase lasted from one to three weeks, until subjects' serum PO4 was >5.6 mg/ dL. Double- blind treatment lasted for 6 weeks and this was followed by a two- week placebo run- out phase.

RESULTS:

Lanthanum Concentrations: Blood samples were drawn for measuring plasma lanthanum levels at the first weekly dialysis session at visits 1, 3 and 6 (random treatment phase) and at visit 9 (the final visit). The blood samples taken at the first dialysis session of Visit 1, were obtained pre-dose and the plasma levels from these samples served as the baseline values. The mean lanthanum levels in plasma ranged between 0.2 and approximately 1.1 ng/ mL for patients on active drug, compared to less than 0.1 ng/ mL for either patients on placebo or the pre-dose measurement. The lanthanum serum concentration versus time profile for each lanthanum treatment group is illustrated in the next Figure.



Reviewer Comments:

1. The overall results of this study showed that there was a minimum increase in plasma lanthanum with dose and following chronic administration of lanthanum carbonate for 6 weeks there was not accumulation in plasma with time.
2. The analytical information was not included in the study report.

Clinical Study LAM-IV-301

Title: A Phase III, Open Label, Comparator Controlled Parallel Group Study to Assess the Efficacy and Safety of Lanthanum Carbonate for Reduction of Gastrointestinal Phosphate Absorption and Maintenance of Control of Serum Phosphate in Chronic Renal Failure Patients Receiving Hemodialysis.

Investigator: Dr. A. Hutchison, Department of Renal Medicine Manchester Royal Infirmary Oxford Road, Manchester, UK.

Study Period:
Enrolment: September 1998 to March 1999 Treatment: September 1998 to April 2000. Study Parts 1- 4 are reported here, Part 5 is ongoing.

Study Sites:
The study was conducted at 67 centers in four countries: Belgium (11), The Netherlands (5) Germany (37) and United Kingdom.

Study Objectives:

- ***Primary:*** To assess the reduction of serum phosphate by dosing with lanthanum carbonate compared to calcium carbonate, an established phosphate binder.
- ***Secondary:***
  - To investigate the following parameters in hemodialysis patients:
  - Maintenance of control of serum phosphate to =1.80 mmol/ L (= 5.6 mg/ dL)
  - Long- term absorption profile of lanthanum in hemodialysis patients,
  - Effects of lanthanum carbonate on serum calcium and PTH levels
  - Use of vitamin D therapy in patients taking lanthanum carbonate compared to calcium carbonate
  - Long- term safety and tolerability of lanthanum carbonate

Study Population:
1013 hemodialysis patients were screened, 805 patients were randomized 2:1 to lanthanum carbonate or calcium carbonate (Enrolled: 805, Intent to treat: 767, Per-protocol analysis: 519).

Inclusion criteria: Patients who had been receiving hemodialysis for 3 consecutive months with serum phosphate level >1.80mmol/L following a washout of previous phosphate binders. Male or female patients aged 18 years or above. Females of childbearing potential could be included if contraceptive precautions were deemed adequate.
Exclusion criteria: Significant hypercalcemia (>ULN), severe hyperparathyroidism (serum PTH >1000pg/ mL), significant gastrointestinal disorders (past or present malignancy, Crohn's disease, active peptic ulcer, ulcerative colitis) women with a positive pregnancy test at screening or who were lactating.

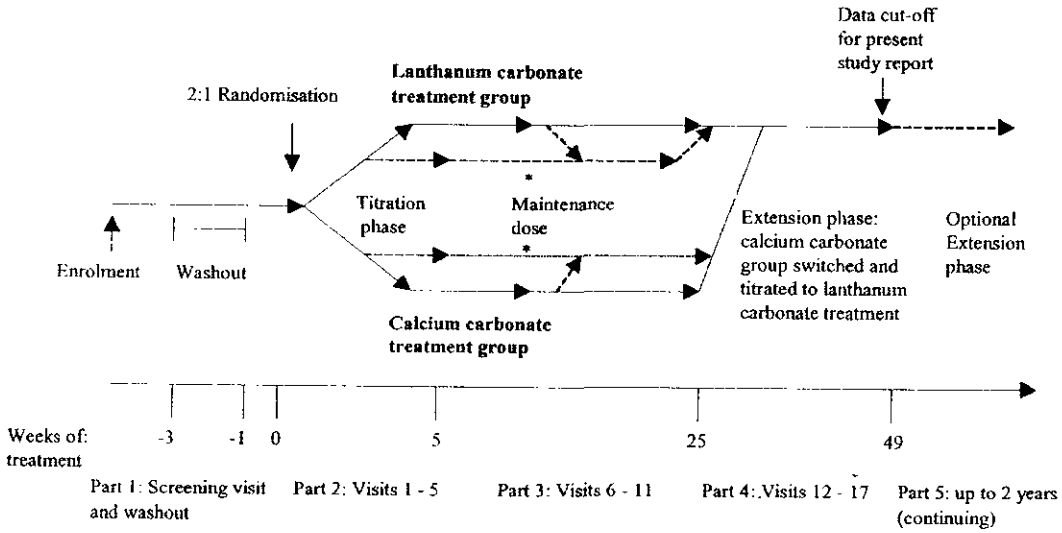
Overall Study Design:
This was an open-label, randomized, active comparator-controlled, parallel-group study of lanthanum carbonate in chronic renal failure patients receiving hemodialysis. Patients were randomized in Part 2 in a 2: 1 ratio to either lanthanum carbonate or calcium carbonate respectively and titrated as required from 375mg- 3000mg elemental lanthanum or 1500mg-9000mg elemental calcium, in order to achieve a phosphate level of = 1.8mmo / L. In order to account for any significant changes in dietary phosphate

intake during the study, a sub- population of patients was monitored during part 3 of the study for dietary phosphate intake. Two hundred patients were anticipated to have two dietary assessments.

Study Parts 1 to 3 were designed for the assessment of efficacy and safety. Parts 4 and 5 were designed primarily for the assessment of safety. A summary of procedures to be carried out during each part were as follows:

- **Part1:** A 1 to 3- week screening and washout period to allow serum phosphate levels to return to pre- treatment levels
- **Part 2:** Randomization followed by a 5-week dose titration period on either lanthanum carbonate or calcium carbonate.
- **Part 3:** A 20- week treatment phase (either lanthanum carbonate or calcium carbonate, as randomized) for patients achieving control of serum phosphate in Part 2.
- **Part 4:** A 24- week extension phase during which all patients were treated with lanthanum carbonate. This period included a titration of up to 5 weeks for the patients who were new to lanthanum carbonate as they had received calcium carbonate in Parts 2 and 3.
- **Part 5:** An optional 2- year extension phase (ongoing and not reported here).

The study design is summarized in the next Figure.



*: Patients in either treatment group whose serum phosphate levels were not controlled during titration (Part 2), or were subsequently found not to be controlled, skipped all or part of study Part 3 and were reintroduced into study Part 4.

Duration of Treatments:

Part 1: One to three week washout followed by,

Part 2: Five- week dose titration on either lanthanum carbonate or calcium carbonate.

Part 3: Twenty- week open label parallel group phase: maintenance dose of lanthanum carbonate or calcium carbonate.

Part 4: Open- label extension to the study: patients on calcium were titrated to a dose of lanthanum carbonate. All patients received lanthanum carbonate for a further 24 weeks.

Part 5: Optional extension. All patients received lanthanum carbonate for an additional period of up to 2 years.

Study Products, dose and mode of administration:

Test: Chewable tablets containing 125 mg or 250 mg lanthanum, as lanthanum carbonate oral route, batch numbers: 96155, 96156, 96157, 96173, 96170, 96174, 96185, 96189, 96190, 96191, 96192, 90378 and 90379.

Reference: Calcium carbonate tablets containing 500 mg calcium as calcium carbonate, batch numbers: 10002461, 806216.

Patients had one study visit each week over the 5-week titration period. At the randomization visit (visit 1, treatment week 0), the patient was allocated to either a daily dose of 375 mg lanthanum or 1500 mg calcium according to the randomization schedule. The schedule randomized the treatments in blocks of three with a 2:1 ratio of lanthanum carbonate to calcium carbonate. Total daily dose was titrated as necessary from 375 mg lanthanum or 1500 mg calcium, up to a maximum of 3000 mg lanthanum or 9000 mg calcium, as shown below, in order to reduce phosphate to target level defined as <1.80 mmol/L (<5.6 mg/dL). Patients were maintained on the dose found to control serum phosphate levels.

Visit No.	Weeks on treatment	Daily Dose Calcium (mg)	Tablet Strength (mg)	Daily Dose Lanthanum (mg)	Tablet Strength (mg)
1	0	1500	500	375	125
2	1	3000	500	750	250
3	2	4500	500	1500	250
4	3	6000	500	2250	250
5	4	9000	500	3000	250

It was possible to titrate up or down a dose by altering the number of tablets taken to one, two, three, four or six per meal. If phosphate levels fell to below 1.00 mmol/L (3.1 mg/dL) at the starting dose, the total daily dose could be reduced to 250 mg lanthanum or 1000 mg calcium.

RESULTS:

Lanthanum Concentrations: Plasma levels of lanthanum were measured at visits 0, 6, 9,11 14 and 17 (after 0, 5, 17, 25, 37, and 49 weeks of treatment). The lower limit of detection of the — assay for lanthanum in plasma was — ng/mL. Values below the lower limit of detection were replaced by zero in the summary tables.

The highest mean plasma concentration was 0.67 ng/mL which occurred at visit 11 in the 2250 mg lanthanum group. Background levels were often detected in patients at screening or in the calcium group. In general, there was minimal increase in plasma lanthanum concentration with dose, and there was no accumulation with time.

Summary of lanthanum levels by visit and dose level in lanthanum-treated patients at visits 0, 6, 9, 11, 14 and 17 (ITT population).

Visit No. (Weeks treated)	Serum lanthanum levels (ng/mL) by lanthanum dose level														p-value for comparison between dose levels**
	n	Screen mean, (SD) median range	n	375 mg mean, (SD) median range	n	750 mg mean, (SD) median range	n	1500 mg mean, (SD) median range	n	2250 mg mean, (SD) median range	n	3000 mg mean, (SD) median range	
0 (0)	505	0.0112 (0.0632) 0 0-0.95													
6 (5)			18	0.37 (0.310) 0.28	54	0.39 (0.230) 0.36	105	0.47 (0.278) 0.42	117	0.58 (0.504) 0.48	157	0.55 (0.537) 0.42			0.015
9 (17)			7	0.32 (0.286) 0.29	36	0.50 (0.307) 0.43	76	0.48 (0.328) 0.40	59	0.62 (0.516) 0.50	59	0.60 (0.509) 0.55			0.134
11 (25)			5	0.23 (0.174) 0.24	36	0.38 (0.251) 0.34	70	0.49 (0.348) 0.43	51	0.67 (0.645) 0.47	57	0.49 (0.395) 0.40			0.040
14 (37)			2	0.08 (0.106) 0.08	27	0.52 (0.259 0.48	69	0.54 (0.304) 0.53	61	0.61 (0.376) 0.52	125	0.51 (0.407) 0.43			0.043
17 (49)			1	0 (0) 0	28	0.45 (0.225) 0.42	69	0.61 (0.369) 0.55	49	0.65 (0.449) 0.47	119	0.53 (0.386) 0.48			0.053
p-value*				0.130		0.478		0.043		0.775		0.756			

Non-detectable values were replaced with a zero and included in the summary statistics
*:p-value from comparisons of Visit 6 and last recorded value (Wilcoxon rank sum test)
**: p-value from comparisons between doses (Kruskal-Wallis test)

Summary of lanthanum levels by visit and dose level in calcium carbonate treated patients at visits 0, 6, 9 and 11 (ITT population)

Visit No. (Weeks treated)	Serum lanthanum levels (ng/mL) by calcium dose level														p-value between dose levels**
	n	Screen mean, (SD) median range	n	1500 mg mean, (SD) median range	n	3000 mg mean, (SD) median range)	n	4500 mg mean, (SD) median range	n	6000 mg mean, (SD) median range	n	9000 mg mean, (SD) median range	
0 (0)	254	0.01 (0.044) 0 0-0.46													
6 (5)			49	0.03 (0.084) 0	56	0.03 (0.094) 0	48	0.02 (0.040) 0	23	0.007 (0.017) 0	32	0.01 (0.034) 0			0.623
9 (17)			39	0.02 (0.041) 0	37	0.03 (0.099) 0	26	0.01 (0.028) 0	15	0 (0) 0	13	0.004 (0.014) 0			0.364
11 (25)			33	0.01 (0.027) 0	35	0.01 (0.028) 0	16	0.005 (0.014) 0	13	0.009 (0.022) 0	13	0 (0) 0			0.601
p-value*				0.673		0.179		0.731		0.928		0.142			

Summary of lanthanum levels by visit and dose level during study Part 4 in patients treated with calcium in study Parts 2&3 then switched to lanthanum (ITT population).

Visit No.	Serum lanthanum levels (ng/mL) by lanthanum dose level										p-value for comparison between dose levels**
	n	375 mg mean, (SD)	n	750 mg mean, (SD)	n	1500 mg mean, (SD)	n	2250 mg mean, (SD)	n	3000 mg mean, (SD)	
14 (37)	4	0.25 (0.261) 0.21	12	0.24 (0.222) 0.19	31	0.62 (0.509) 0.49	27	0.36 (0.257) 0.31	58	0.44 (0.315) 0.36	0.006
17 (49)	2	0.35 (0.035) 0.35	5	0.35 (0.228) 0.30	25	0.61 (0.499) 0.47	17	0.34 (0.229) 0.28	58	0.47 (0.476) 0.38	0.166
p-value*	.	0.817		0.292		0.993		0.895		0.963	

Non-detectable values were replaced with a zero and included in the summary statistics
*:p-value from comparisons of Visit 14 and 17 (Wilcoxon rank sum test)
**: p-value from comparisons between doses (Kruskal-Wallis test)

Sponsor's Conclusion:

- Serum calcium levels were higher in the calcium carbonate treated patients than the lanthanum well tolerated.

Reviewer Comments:

1. This study also showed that in general there is minimal increase in plasma lanthanum concentration with dose and there is no accumulation in plasma with time.
2. Analytical information for the assay of lanthanum carbonate in plasma was not provided.

APPEARS THIS WAY
ON ORIGINAL

Clinical Study LAM-IV-302

Title: A Phase III, Dose Titration, Randomization, Double Blind, Placebo Controlled Parallel Group Study to Assess the Efficacy and Safety of Lanthanum Carbonate for Reduction and Maintenance of Serum Phosphorus Levels in Chronic Renal Failure Patients Receiving Hemodialysis.

Investigator/Study Sites: Multi-investigators/Multi-center study (14 different sites).

Study Period:
Enrolment: September 1998 to March 1999 Treatment: September 1998 to April 2000. Study Parts 1- 4 are reported here, Part 5 is ongoing.

Study Objectives:

- ***Primary:*** To assess the maintenance and control of serum phosphorus levels within the clinical acceptable limits defined as >5.9 mg/L by continued use of lanthanum carbonate compared to placebo in chronic renal failure patients receiving hemodialysis and with hyperphosphatemia which was defined as serum phosphorus >5.9 mg/dL.

- ***Secondary:***
  - To assess the serum phosphorus profile during the dose titration phase
  - To assess the effect of lanthanum carbonate on calcium-phosphorus product and serum calcium levels
  - To investigate the effect of lanthanum carbonate on parathyroid hormone.
  - To assess the plasma lanthanum concentrations and any changes occurring over time
  - To evaluate the safety and tolerability of lanthanum carbonate

Study Population:
A total of 120 patients of either sex, 18 years and older with end stage renal disease, and who had been undergoing dialysis 3 times weekly for at least 2 months, were enrolled in the washout phase.

The protocol called for patients to be dose titrated with the intention of having 80 patients, whose serum phosphorus was >5.9 mg/ dL at the end of titration, randomized into the drug maintenance phase (40 per treatment arm). One hundred and sixty- three patients were enrolled and entered the washout phase. Of these, 126 met the criteria for dose titration and entered the open-label lanthanum titration phase. Of the 126 patients, 94 completed the dose titration and were randomized to the drug maintenance phase. All but one were included in the intent- to- treat population (N= 93) which was used as the primary efficacy population (lanthanum: 49; placebo: 44). One patient was excluded from the ITT population because of the lack of post-randomization serum phosphorus levels. All of the 163 study participants were evaluated for safety.

Study Design:
This was a randomized, double-blind, placebo- controlled, parallel group study to assess the ability of lanthanum carbonate to control serum phosphorus in chronic renal failure patients receiving hemodialysis. This study consisted of three phases: a one to three week washout during which patients stopped all phosphorus binding medication, a 6-week open- label dose titration, and a 4-week double blind randomized drug maintenance phase with a placebo arm. To be eligible to enter the open-label

dose titration phase patients' serum PO4 had to be > 5.9 mg/dL after washout. Eligible patients were then titrated to the optimal dose of lanthanum required to reduce their serum phosphorus to <5.9 mg/dL using 5 pre-defined dose levels for six weeks. The five daily doses were lanthanum 375 mg, 750 mg, 1500 mg, 2250 mg, and 3000 mg, given BID or TID with food. The start dose was 750 mg per day. Patients who completed the 6-week titration were then randomized to receive either lanthanum or placebo for 4-week maintenance treatment.

Study Products/Dose and Mode of Administration:

Study drug was supplied as identical, round, chewable, scored tablets containing 250 mg (Batch No. 9F2700) of lanthanum.

Placebo tablets (Batch No. 9D2751) were used in this study during drug maintenance period. These tablets were identical in appearance to the active tablets, but contained [ ]

Five daily doses were used, including 375 mg, 750 mg, 1500 mg, 2250 mg, and 3000 mg. Patients started on 750 mg per day. Doses were adjusted weekly with the intention to reduce serum phosphorus level <5.9 mg/ dL. The final daily dose at the end of titration was used throughout the maintenance phase. Daily doses were administered BID or TID with food; patients who took only two meals per day took a larger number of tablets with the heavier meal. The washout phase was two to three weeks, until patients' serum PO4 was >5.9 mg/dL. Dose titration lasted for 6 weeks and the randomized double- blind maintenance treatment lasted for 4 weeks.

RESULTS:

Lanthanum Concentrations: Plasma lanthanum levels were measured at pre-dose, study week 4 (middle of dose-titration), study week 7 (end of titration), and study week 11 (end of study). Prior to dosing, the mean lanthanum levels in plasma ranged between 0.014 and 0.098 ng/mL. The mean lanthanum concentration increased to the range of 0.346 to 0.776 ng/mL at the time of three weeks into dose titration, and remained at the same level until the end of dose titration (6 weeks in treatment). After being randomized and 4 weeks off lanthanum, the mean lanthanum levels decreased to 0.200 ng/mL for patients on placebo. The plasma lanthanum levels remained at the same level around 0.640 ng/mL for patients with continued use of lanthanum. These findings indicate that with the chronic use of lanthanum up to 3000 mg per day, the mean concentration of plasma lanthanum were in the range of 0.346 to 0.776 ng/mL, approximately a ten-fold increase from the baseline level of around 0.014 to 0.098. Four weeks off the drug, lanthanum was still apparent in plasma.

Treatment	MEAN (SD) PLASMA LANTHANUM CONCENTRATIONS (NG/ML)			
	Time in Study			
	Pre-Study	Week 4	Week 7	Week 11
Lanthanum	n = 45 0.014 (0.048)	n = 50 0.776 (1.054)	n = 47 0.753 (1.147)	n = 48 0.640 (0.602)
Placebo	n = 39 0.030 (0.084)	n = 42 0.590 (0.482)	n = 42 0.670 (729)	n = 39 0.200 (0.207)

Sponsor's Conclusions:

- With the use of lanthanum up to 3000 mg per day, the mean concentration of plasma lanthanum were in the range of 0.346 to 0.776 ng/mL, approximately a ten fold increase from the baseline level of around 0.014 to 0.098 ng/mL. Four weeks off the drug, lanthanum was still apparent in plasma.

Reviewer Comments:

1. This study also showed that in general there is minimal increase in plasma lanthanum concentration with dose and there is no accumulation in plasma with time. However, it is important to note that 4 weeks after stopping its administration, lanthanum was still apparent in plasma, most probable due to its clearance from tissues.
2. Analytical information for the assay of lanthanum carbonate in plasma was not provided.

Clinical Study LAM-IV-307

Title: An Open Label, Randomized, Multicenter, Phase III, Comparator Controlled Parallel Group Study to Assess the Long- Term Safety and Efficacy of Lanthanum Carbonate in Chronic Renal Failure Patients Receiving Hemodialysis.

Investigator/Study Sites: Multi-investigators/Multi-center study (96 different sites).

Study Period:
First enrollment date: July 29, 1999. Date of interim data cut-off, October 31, 2001

Overall Study's Purpose:
The purpose of this 2- year study was to compare the long- term safety of lanthanum carbonate with that of standard therapy, in patients with end stage renal disease, when used for the reduction and control of hyperphosphatemia. The study also gather information on the efficacy of long-term maintenance of serum phosphorus within a clinically acceptable range, assessment of patients' mental status over time and palatability of the lanthanum tablet.

Study Objectives:

- ***Primary:*** To evaluate long- term safety of lanthanum carbonate in chronic renal failure patients with hyperphosphatemia on hemodialysis. Safety was evaluated by monitoring biochemical and hematological parameters, adverse events (AEs), vital signs, physical examinations, and cognitive function assessments.
- ***Secondary:***
  - To assess the maintenance of control of serum phosphorus (PO4) with long-term use of lanthanum carbonate.
  - To assess the long-term effect of lanthanum carbonate on the calcium- phosphorus product (Ca PO4) and calcium levels.
  - To investigate the long- term effect of lanthanum on parathyroid hormone (PTH) levels.
  - To measure plasma lanthanum levels and changes over time.
  - To evaluate the palatability of lanthanum carbonate.
  - To measure differences in the cognitive function between patients treated with lanthanum carbonate and standard therapy.
  - To measure differences in bone mineralization between patients treated with lanthanum carbonate and standard therapy

Study Population:
The protocol called for a total of at least 500 patients randomized to each arm. As of the data cut-off date of October 31, 2001, a total of 1,345 patients enrolled with 1,228 patients being randomized to treatment (616 lanthanum versus 612 standard therapy), 110 patients being terminated prior to randomization, and 7 patients still in the washout phase. All participants were included for safety evaluation and the intent- to-treat population included 1,203 patients (600 lanthanum versus 603 standard therapy).

Diagnosis and Main Criteria for Inclusion: Patients of either sex, at least 12 years of age, with chronic renal failure, who had undergone hemodialysis for chronic renal failure three times per week for at least

the previous two months, and who currently required phosphate binders for the treatment of hyperphosphatemia (hyperphosphatemia was defined as a PO4 >5.9 mg/dL), were eligible for enrollment.

Overall, the demographic characteristics of the Lanthanum and Standard Therapy Groups were similar to each other and to those of all enrolled patients. Fifty six percent (56%) and 60% of the patients randomized to lanthanum and to standard therapy were male, 45% and 47% were Caucasian, 45% and 41% were Black, and 74% and 71%, respectively, of each treatment group were between 18 and 64 years of age. The mean age was 55 years for all patients enrolled, 54 years for patients receiving lanthanum treatment, and 56 years for patients receiving standard therapy.

Study Design:

This was an open label, randomized, multicenter, Phase III, comparator controlled, parallel group study of the long- term safety of lanthanum carbonate for controlling hyperphosphatemia in chronic renal failure patients undergoing hemodialysis three times per week. The study consisted of three phases: a screening and one- to three-week washout phase (Part 1), followed by a six- week dose-titration phase (Part 2), and finally, a long-term maintenance phase (Part 3), for a total of 24 months of study participation. To be eligible to enter the dose-titration phase, patients' PO4 levels had to be >5.9 mg/ dL. Eligible patients were randomized in a 1:1 ratio to receive either lanthanum carbonate or their pre- study standard phosphate binder.

All patients had PO4 levels assessed weekly and their phosphate binder dose titrated for a period of six weeks. Patients randomized to the lanthanum arm received a starting dose of 750 mg daily unless, at the discretion of the Investigator, the patient required a starting daily dose of 1500 mg lanthanum. Doses were titrated as necessary up to a maximum of 3000 mg/ day, and were adjusted based on the results of the PO4 levels taken at the first dialysis session of the week. If the patient's PO4 level dropped below 3.1 mg/dL the patient's lanthanum dose could have been reduced to 375 mg per day. Patients randomized to standard therapy had their dose of phosphate binder titrated according to the drug's label and current clinical practice. On completion of titration, all patients received their dose of phosphate binder up to 24 months of treatment.

Products, Dose and Mode of Administration:

- ***Arm A:*** Study drug was supplied as round, unflavored, chewable, scored tablets, containing 250 mg of lanthanum (Batch Nos.: 9C2735, 9C2736, 9C2737, 9F2700, 9F2799, 9G2712, 9L2745, 9L2744, 9L2746, 9L2748, 9L2749, 9L2750 and 9L2751).
- ***Arm B:*** Patients randomized to standard therapy continued taking their prescribed phosphate binder at the optimal dose required to control their PO4 levels at <5.9 mg/ dL. Patients were allowed to switch phosphate binders throughout the study and could also take a combination of binders in order to achieve optimal PO4 control.

Five daily doses of lanthanum were used: 375 mg, 750 mg, 1500 mg, 2250 mg, and 3000 mg. Patients received a starting dose of 750 mg/ day lanthanum, however patients could start with a dose of 1500 mg/ day lanthanum at the discretion of the Investigator. Doses were adjusted weekly with the intention of reducing PO4 levels to <5.9 mg/ dL. Doses were administered two or three times daily with food; patients who ate only two meals per day took a larger number of tablets with the heavier meal. The dose was increased or decreased no more than two levels at one study visit. All patients received phosphate

binder for up to 24 months. The washout phase was one to three weeks (Part 1), dose titration lasted for six weeks (Part 2), and maintenance treatment lasted for 24 months (Part 3).

RESULTS:

Lanthanum Concentrations: Blood samples were drawn and assayed for lanthanum at Screening, Weeks 3, 7 (maintenance baseline), 14, 26, and 52. The mean concentrations are listed in the next Table.

	MEAN (SD) PLASMA LANTHANUM LEVELS					
	Screening	Week 3	Week 7	Week 9	Week 12	Week 15
Lanthanum (ng/ml)	n = 591 0.0	n = 576 0.4 (0.76)	n = 519 0.5 (0.85)	n = 446 0.6 (0.87)	n = 362 0.6 (0.75)	n = 265 0.6 (1.15)

The mean plasma lanthanum level at screening was below the limit of quantification. By Week 3 (the mid point of the titration phase) the mean plasma lanthanum concentration was 0.4 ng/ mL and at the start of the maintenance period (Week 7) the mean was 0.5 ng/mL. At the remaining visits at which lanthanum levels were measured, the mean was 0.6 ng/mL. There was no plasma accumulation with time. The large standard deviations accompanying these values (ranging between 0.8 and 1.15) were indicative of the wide range in dose being received by the lanthanum treated subjects.

Sponsor's Conclusions:

- The mean plasma lanthanum level at screening was below the limit of quantification (ng/mL). These levels indicate background levels are present in the population, the origins of which are believed to be dietary and environmental.
- Although some accumulation was observed, plasma lanthanum concentrations remain low following long-term administration of up to 3000 mg/ day lanthanum. No specific plasma levels, which could be regarded as toxic or likely to endanger health, have been defined.

Reviewer Comments:

1. This study also showed that in general there is minimal increase in plasma lanthanum concentration with dose and there is no accumulation in plasma with time. However, as previously noted, lanthanum plasma concentrations are not representative of lanthanum's exposure, thus, plasma levels are not relevant from the clinical safety viewpoint.
2. Analytical information for the assay of lanthanum carbonate in plasma was not provided.

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/s/

Angelica Dorantes
1/10/03 04:46:23 PM
BIOPHARMACEUTICS

Patrick Marroum
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BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

IND 55,054 [N(PC)091] **SUBMISSION DATE:** January 31, 2001
Lanthanum Carbonate Hydrate

Shire Laboratories **REVIEWER:** Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: PROTOCOL AMEDMENT

BACKGROUND:
This is a review of an amendment to a protocol (Protocol LAM-IV-111) submitted to the IND. The original protocol was reviewed with OCPB comments on January 30, 2000. Lanthanum carbonate binds dietary phosphate in the gut to form lanthanum phosphate causing a reduction in the absorption of phosphate systemically. The sponsor is developing lanthanum carbonate as a phosphate-binding agent for [redacted]

SYNOPSIS:
Protocol LAM-IV-111– "*A Pharmacokinetic Study in Healthy Volunteers and Dialysis Patients Following Single and Multiple Doses of Lanthanum*": This is an open label, single and multiple dose study in 16 subjects {8 with normal renal function (control subjects) and 8 receiving hemodialysis (study subjects)} to determine if the PK of orally administered lanthanum carbonate are altered by severe renal function and if the elimination of lanthanum is affected by hemodialysis. The study consists of 5 parts: a screening period (Part 1), single dose PK study (Part 2), PK during dialysis (Part 3), multiple dosing phase (Part 4) and a multiple dose PK phase (Part 5). On day 2 of the study (Part 2) each subject will receive a single oral dose of 1 g of lanthanum carbonate; within two hours following dialysis in the study subjects. Blood samples will be collected at 0 (predose), 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 18, 24, 32, 40, and 48 hours post dose and urine samples will be collected at 0-4, 4-8, 8-12, 12-18, 18-24, 24-32, 32-40 and 40-48 hours post dose. On day 14 of the trial (Part 3), each subject will receive a single oral dose of 1 g of lanthanum carbonate; prior to the standard 4-hour dialysis procedure in the study subjects. Blood samples will be collected from the study subjects at 0 (predose), 1, 2, 3, 5, 6, 7, 8, 10, 12, 14, 18, 24, 32, 40, and 48 hours post dose and urine samples will be collected at 0-4, 8-12, 12-18, 18-24, 24-32, 32-40 and 40-48 hours post dose. Blood samples and dialysate samples will be taken during the dialysis procedure at times corresponding to 5, 6, 7, and 8 (hourly during dialysis) hours post dose. On days 17 to 27 of the study (Part 4) each subject will receive 1000 mg of lanthanum carbonate three times daily. On day 28 of the study (Part 5) each subject will receive a single oral dose of 1 g of lanthanum carbonate. Urine samples will be collected at 0-4, 4-8, 8-12, 12-18, 18-24, 24-32, 32-40 and 40-48 hours post dose from control subjects and any patients with residual renal function. Blood samples will be collected from control subjects at 0 (predose), 1, 2, 3, 4, 5, 6, 7, and 8 hours post dose. Blood samples will be collected at 0 (predose), 1, 2, 3 and 4 from the patients after which they will begin their standard 4-hour dialysis procedure. Blood samples and dialysate samples will be taken during the dialysis

procedure at times corresponding to 5, 6, 7, and 8 (hourly during dialysis) hours post dose. Blood sampling will then continue at 10, 12, 14, 18, 24, 32, 40, 48, 56, 64 and 72 hours post dose.

PK parameters will be estimated and comparison will be made between the parameters for control and study subjects and pre and during hemodialysis for study subjects.

CONCLUSION:
The Division of Pharmaceutical Evaluation I has reviewed the sponsor's proposed protocol amendments and finds them satisfactory.

RECOMMENDATION:
No further action is indicated at this time.

/S/

Emmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation I

/S/

FT Initialed by A. Dorantes. Ph.D. ----------

cc: IND 55-054, HFD-110, HFD-860 (Fadiran, Mehta), BIOPHARM – CDR.

/s/

Emmanuel Fadiran
2/9/01 08:41:07 AM
BIOPHARMACEUTICS

Angelica Dorantes
2/9/01 12:47:07 PM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 860)** **Tracking/Action Sheet for Formal/Informal Consults**

From: **Elena V. Mishina, Ph.D.**

To: DOCUMENT ROOM (LOG-IN and LOG-OUT)
Please log-in this consult and review action for the specified IND/NDA submission

DATE: 9/05/01	IND No.: 55054/112	NDA No.	DATE OF DOCUMENT **9/04/2001**	
NAME OF DRUG **Lanthanum Carbonate Hydrate**	PRIORITY CONSIDERATION		Date of informal/Formal Consult:	

NAME OF THE SPONSOR: **Shire Pharm. Development Inc.**

TYPE OF SUBMISSION

• CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☒ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☒ MEETING PACKAGE /Pre-NDA	☐ OTHER *(SPECIFY BELOW)*:
☐ PHASE IV RELATED		

REVIEW ACTION

☒ NAI (No action indicated)	☐ Oral communication with	☐ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☒ See comments below
☐ Medical ☐ Chemist ☐ Pharm-Tox	☐ Comments communicated in	☐ See submission cover letter
☐ Micro ☐ Pharmacometrics ☐ Others	meeting/Telecon. see meeting minutes	☐ OTHER *(SPECIFY BELOW)*:
(Check as appropriate and attach e-mail)	dated: [ ]	[ ]

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☒ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:

1. **In response to the Agency's request, the sponsor has developed a plausible method of tablet dissolution (USP Apparatus II, [ ] % at ~ minutes).**
2. **For the future NDA submission, the Agency requested the sponsor to submit in electronic format (MSWord) the Summary of Human Pharmacokinetics.**

SIGNATURE OF REVIEWER: Elena V. Mishina, Ph.D. Date 9/18/01

SIGNATURE OF TEAM LEADER: Patrick J. Marroum, Ph.D. Date 9/18/01

CC.: HFD # [ ]; TL: [ ]; DD: [ ]

Project Manager: _____ **Date** _____

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

/s/

Elena Mishina
9/18/01 05:19:32 PM
BIOPHARMACEUTICS

Patrick Marroum
9/18/01 05:39:14 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

IND 55,054 [N(IM)086] **SUBMISSION DATE:** January 4, 2001
Lanthanum Carbonate Hydrate

Shire Laboratories **REVIEWER:** Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: NEW PROTOCOL

BACKGROUND:
This is a review of a new protocol (Protocol LAM-IV-113) submitted to the IND. Lanthanum carbonate binds dietary phosphate in the gut to form lanthanum phosphate causing a reduction in the absorption of phosphate systemically. The sponsor is developing lanthanum carbonate as a phosphate-binding agent for [redacted].

[redacted]. Studies conducted by the sponsor have indicated little absorption of lanthanum carbonate from the GI tract and plasma levels have remained low as it appears to pass through the GI tract and is eliminated in the feces. Phase II and III trials with lanthanum carbonate completed to date by the sponsor have shown that a small but important proportion of patients with end stage renal disease use warfarin. The sponsor therefore decided to study the effect of lanthanum carbonate on warfarin pharmacokinetics. The study will be conducted in [redacted] but the sponsor intends to include the results of the study in the planned NDA.

SYNOPSIS:
Protocol LAM-IV-113– "A Phase I, Single Center, Open Label Randomized Crossover Study to Assess the Effects of Lanthanum Carbonate on the Pharmacokinetics of Warfarin Following a Single Dose": This is an open label, randomized two-way crossover study in twelve healthy volunteers and a washout period of fifteen days. Subjects will be randomly assigned to receive either 10 mg warfarin alone or 10 mg warfarin taken 30 minutes after the fourth dose of 1000 mg lanthanum (1908 mg lanthanum carbonate).
Blood samples will be collected prior to the dose of warfarin (-5 minutes) and at 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours post dose for warfarin analysis. PK parameters (AUC, C_{max}, T_{max}, and $t_{1/2}$) will be determined using non-compartmental methods. Difference between treatment groups for the PK parameters on a log scale will be calculated using analysis of variance (ANOVA), along with 90% confidence intervals of the mean difference. It will be considered that the PK of warfarin are not affected when lanthanum carbonate is administered concomitantly if the 90% confidence intervals for the ratio of the two treatments are within 80-125% for AUC and Cmax.

Attached is a summary of the study protocol.

COMMENT CONVEYED TO THE SPONSOR:

1. The sponsor has made gender an inclusion criterion for the study. The sponsor is reminded that the Agency's "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs" does not allow gender to be an inclusion criterion for this study.
2. Sampling times: Following oral administration of warfarin maximal plasma concentrations are reached in 1 to 9 hours. It is recommended that the sponsor include 0.5 and 1 hour sampling times for warfarin analysis for this study.

CONCLUSION:

The Division of Pharmaceutical Evaluation I has reviewed the sponsor's protocol and conveyed the comments above to the sponsor through a telephone conversation between the reviewer and Tami T. Martin (Vice President, Regulatory Affairs, Shire Laboratory) on January 26, 2001. No further action is indicated at this time.

/S/

Emmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation I

FT Initialed by A. Dorantes, Ph.D. ----------

cc: IND 55-054, HFD-110, HFD-860 (Fadiran, Mehta), BIOPHARM – CDR.

SUMMARY

TITLE	A Phase I, Single Centre, Open Label Randomised Crossover Study To Assess The Effects Of Lanthanum Carbonate On The Pharmacokinetic Parameters Of Warfarin Following A Single Oral Dose.
INVESTIGATORS	– Principal Investigator – Co-Investigator – Co-Investigator
TRIAL LOCATION	
OBJECTIVES	Primary: To assess whether the pharmacokinetic parameters of warfarin are affected when lanthanum carbonate is administered concomitantly. Secondary: To assess the safety and tolerability of lanthanum carbonate and warfarin when administered concomitantly.
TRIAL DESIGN	This will be an open label, randomised two-way crossover study. Subjects will be randomly assigned to receive either 10mg warfarin alone or 10mg warfarin taken 30 minutes after the fourth dose of 1000mg lanthanum (1908mg lanthanum carbonate). After completion of the first treatment period the subjects will crossover to receive the other treatment. Subjects will be confined for 36 hours prior to dosing with warfarin and 48 hours after dosing with warfarin during both study periods. There will be outpatient visits on the five consecutive days following discharge. There will be 15 days between the two dosing days.
TRIAL POPULATION Diagnostic admission criteria Number	Healthy Caucasian males aged between 18 and 35 years, with body weight between 60kg and 80kg and within 15% of the ideal weight for their height and estimated frame. No clinically significant abnormal findings on the physical examination, ECG, medical history, or clinical laboratory results during screening. Fourteen (14) healthy male subjects will be enrolled, to ensure that twelve (12) complete the trial.

TRIAL PRODUCT	Lanthanum 250 mg chewable tablets (477 mg of lanthanum carbonate)
EVALUATION CRITERIA	Pharmacokinetic parameters – AUC_{last}, $AUC_{(0-\infty)}$, C_{max}, $t_{1/2}$ and t_{max} will be calculated from the drug concentration-time data for warfarin using non-compartmental methods. Safety - Biochemistry/haematology/ECG/vital signs, adverse event reporting and physical examination.
DURATION OF TRIAL	Maximum of 27 days
PLANNED TRIAL DATES Recruitment Phase Treatment Phase Study Completion Date	 Q1 2001 Q1 2001 Q1 2001

/s/

Emmanuel Fadiran
1/26/01 12:32:58 PM
BIOPHARMACEUTICS

Angelica Dorantes
1/29/01 11:35:54 AM
BIOPHARMACEUTICS

Clinical Pharmacology and Biopharmaceutics Review

IND: 55,054
Serial # P (PN) 072

Submission Date:
September 28, 2000

Compound: Lanthanum Carbonate Hydrate

Formulation (s): [ ] Chewable Tablets

Sponsor: Shire Laboratories, Inc.
Rockville, MD

Type of Submission: PK Protocol

Indications: [ ]

Reviewer: Sayed Al-Habet, Ph.D.

Date Review: October 11, 2000

Background:

Lanthanum is phosphate binder and is being developed for [ ] It is proposed to be given orally to reduce the absorption of phosphate in the GI tract. The sponsor has submitted a PK protocol (#LAM-IV-112) to investigate the effect of the co-administration of citrate on the absorption of the drug (see Attachment 1 for the protocol summary).

Briefly, this is a three-way crossover design in healthy subjects. The dose of lanthanum is 1000 mg chewable table to be given as follows:

1. After 5 minutes of food with 200 ml water.

2. After 5 minutes of food with 200 ml orange juice.

3. After 5 minutes of food with two Effercitrate tablets dissolved in 200 ml water (i.e., 3 gram of potassium citrate and 0.5 gram of citric acid).

On October 16, 2000 the sponsor was contacted (Tami Martin) and was requested to consider eliminating the orange juice arm from the protocol and replacing it with an arm in which Lanthanum be administered with two Effercitrate tablets after overnight fast.

Recommendation:

Since the protocol was discussed with the sponsor, no further action is necessary.

Reviewer

Sayed Al-Habet, Ph.D.
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT Initialed by Patrick Marroum, Ph.D. ----------

cc: IND # 55,054, HFD-110, HFD-860 (Al-Habet and Mehta), Drug file (Biopharm File, Central Document Room).

Redacted 3

page(s) of trade secret and/or confidential commercial information (b4)

Clinical Pharmacology/Biopharmaceutics Review

IND: 55-054
Serial # N-010
Lanthanum Carbonate Hydrate
Shire Laboratories Inc.
Submission Date: March 22, 1999

Reviewer: Thomas A. Parmelee, Pharm.D.

Type of Submission: Study LAM-IV-205, A dose-titration, safety assessment of lanthanum in an extension study of protocol LAM-IV-204.

BACKGROUND

High phosphate serum levels in patients with chronic renal failure seem to play an important role in the genesis of renal osteodystrophy. Treatment of hyperphosphatemia has generally been accomplished through the use of aluminum- or calcium-based phosphate binding agents. These agents produce insoluble phosphates, which are not absorbed in the GI tract. Due to the safety concerns involving the use of aluminum and calcium salts, the sponsor hopes to establish a new phosphate binder with an improved safety profile compared to current therapies.

Studies have shown that the rare earth salt, lanthanum carbonate, has been effective in binding phosphate. It is believed that lanthanum carbonate has a very low bioavailability for systemic lanthanum absorption, as well as a low toxicity profile. Lanthanum phosphate is extremely insoluble in aqueous solutions. Study LAM-IV-204 is a Phase 2, double-blind, placebo controlled dose-ranging study of 4 doses of lanthanum that is currently on-going in hemodialysis patients. The study protocol LAM-IV-205, that is the subject of this review, is an extension study of LAM-IV-204, intended to provide additional safety data on the long-term use (i.e. 12 months) of lanthanum carbonate. The study population will comprise the patients enrolled in LAM-IV-204. This study will allow the patients in LAM-IV-204 the opportunity to continue treatment with lanthanum carbonate.

The sponsor believes that the clinically relevant doses for the average renal patient on an average diet is between 300-2250 mg of lanthanum/day. This is the dosage range that will be tested in this study, with dosage adjustment dependent upon the patient's serum phosphate levels. A review of the study protocol is attached as Appendix 1.

COMMENTS

1) It is not clear whether or not lanthanum is clinically absorbed (and to what extent) into the systemic circulation. The lanthanum blood draws proposed by the sponsor will not adequately show the absorption profile of this agent.

Clinical Pharmacology/Biopharmaceutics Review

IND: 55-054
Serial # N-010
Lanthanum Carbonate Hydrate
Shire Laboratories Inc.
Submission Date: March 22, 1999

Reviewer: Thomas A. Parmelee, Pharm.D.

Type of Submission: Study LAM-IV-205, A dose-titration, safety assessment of lanthanum in an extension study of protocol LAM-IV-204.

BACKGROUND

High phosphate serum levels in patients with chronic renal failure seem to play an important role in the genesis of renal osteodystrophy. Treatment of hyperphosphatemia has generally been accomplished through the use of aluminum- or calcium-based phosphate binding agents. These agents produce insoluble phosphates, which are not absorbed in the GI tract. Due to the safety concerns involving the use of aluminum and calcium salts, the sponsor hopes to establish a new phosphate binder with an improved safety profile compared to current therapies.

Studies have shown that the rare earth salt, lanthanum carbonate, has been effective in binding phosphate. It is believed that lanthanum carbonate has a very low bioavailability for systemic lanthanum absorption, as well as a low toxicity profile. Lanthanum phosphate is extremely insoluble in aqueous solutions. Study LAM-IV-204 is a Phase 2, double-blind, placebo controlled dose-ranging study of 4 doses of lanthanum that is currently on-going in hemodialysis patients. The study protocol LAM-IV-205, that is the subject of this review, is an extension study of LAM-IV-204, intended to provide additional safety data on the long-term use (i.e. 12 months) of lanthanum carbonate. The study population will comprise the patients enrolled in LAM-IV-204. This study will allow the patients in LAM-IV-204 the opportunity to continue treatment with lanthanum carbonate.

The sponsor believes that the clinically relevant doses for the average renal patient on an average diet is between 300-2250 mg of lanthanum/day. This is the dosage range that will be tested in this study, with dosage adjustment dependent upon the patient's serum phosphate levels. A review of the study protocol is attached as Appendix 1.

COMMENTS

1) It is not clear whether or not lanthanum is clinically absorbed (and to what extent) into the systemic circulation. The lanthanum blood draws proposed by the sponsor will not adequately show the absorption profile of this agent.

The above comment was conveyed to the sponsor on April 12, 1999 via a teleconference call with Tami T. Martin and others in the Regulatory Affairs group. The sponsor said that a phase I study conducted in Japan had data showing more frequent blood draws to determine lanthanum levels. Attached is a copy of this information submitted by the sponsor via fax on April 13, 1999.

2) The blood sampling for lanthanum levels is more frequent in this phase I study, but may still not rule out the possibility of lanthanum absorption. This dose-escalation study (LAM-IV-108), involving single-dose administration of lanthanum on alternating days, increases the dose of lanthanum from 262 mg to 2096 mg. Sampling times for blood lanthanum levels are scheduled at 2 hr., 4 hr., 6 hr., and 12 hr. following dose administration. If the compound has a short half-life, for example, this sampling schedule may not elucidate drug absorption or provide any information regarding the pharmacokinetic profile of lanthanum carbonate.

Since the sponsor has not addressed the issue of lanthanum absorption, it is recommended that the sponsor attempt to collect information that looks at this very important question.

Another teleconference was held with the sponsor (via Sandy Geroux) on April 15, 1999. The comments above were conveyed to the sponsor during this interaction.

RECOMMENDATION

/S/

Thomas A. Parmelee, Pharm.D.

RD/FT by Patrick Marroum, Ph.D.

CC: IND 55-054, HFD-110, HFD-860 (Mehta, Parmelee), CDER document room: Attn. Barbara Murphy

APPENDIX 1

"LONG TERM, OPEN LABEL EXTENSION STUDY OF PROTOCOL LAM-IV-204"

PROTOCOL: **LAM-IV-205**

SPONSOR: Shire Laboratories Inc.
1550 East Gude Drive
Rockville, MD 20850

INVESTIGATOR AND STUDY SITE:

Lead Investigator: William Finn, M.D.
Division of Hypertension and Nephrology
CB# 7155, 349 MacNider Hall
University of North Carolina
Chapel Hill, NC 27599-7155

Trial Locations: 5-7 centers in USA

OBJECTIVES:

1) Primary Objective: To assess the safety of lanthanum carbonate in hemodialysis patients who have participated in the previous study (LAM-IV-204), and wish to continue with the treatment.

2) Secondary Objectives: To gather titration data on study participants and monitor the tolerability profile of lanthanum carbonate following up to 12 months of treatment.

FORMULATIONS:

Chewable tablets containing 150mg or 250mg lanthanum.

STUDY DESIGN:

This study is an open-label, long-term (12-month), safety assessment of lanthanum carbonate as a continuation or extension study of protocol LAM-IV-204. Subjects with chronic renal failure who have participated in LAM-IV-204 are eligible for this study. A maximum of 150 subjects may participate and include men and non-pregnant women, or women using effective birth control.

Patients who have completed LAM-IV-204 will be directly enrolled into this study. The final study visit for LAM-IV-204 (week 9) will be study visit 1 (week 1) for LAM-IV-205. The data collected at the final visit of LAM-IV-204 will be considered baseline values for this study (LAM-IV-205 week 1). Patients who have discontinued

LAM-IV-204 prior to completion or patients who have successfully completed that study before establishing LAM-IV-205 may be enrolled in this study if their phosphate levels are between 2 and 10 mg/dl.

Lanthanum carbonate will be administered at the initial dose of 300 mg/day. Other doses to be studied are 450 mg/day, 900 mg/day, 1350 mg/day, 1500 mg/day, and 2250 mg/day. Adjustment of dose levels will occur at study visits 2, 3, 4, 5, and 6 (corresponding to weeks 2, 3, 4, 6, and 8) as necessary. After visit 6 (week 8), the patient's dose may be adjusted at any time. The dosage adjustment will depend on phosphate levels:

Phosphate Level	Dosage Adjustment
Within normal range	No change in dose
Above normal range	Increase to next higher dose
Remains above normal	Increase to 2nd higher dose
Below normal range	Decrease to next lower dose-withdraw if at 300mg
Remains below normal	Decrease to 2nd lower dose level-withdraw if at 300mg

The following table shows the study procedure schedule through week 48:

Table 1: Schedule of Study Procedures

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Week Number	1	2	3	4	6	8	12	16	20	24	28	32	36	40	44	48
Informed Consent	X															
Medical History	X															
Physical Exam	X						X			X			X			X
Serum Pregnancy	X						X			X			X			X
ECG	X**						X			X			X			X
Vital signs/weight	X**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full blood profile	X			X			X			X			X			X
Calcium/Phosphate Levels		X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*
Lanthanum Blood Levels	X**						X			X			X			X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X***
Compliance		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

* Levels are to be collected at the last dialysis session prior to study visit
** For patients who complete LAM-IV-204 and roll directly over to this study
*** End of study form to be completed should the study end at 48 weeks

ASSAY:

Assay methodologies are not provided in this study protocol.

DATA ANALYSIS:

The primary endpoint for this study will be the control of pre-dialysis serum phosphate levels within the normal range using titration of lanthanum carbonate doses in response to changing levels of serum phosphate. Pre-dialysis blood samples for phosphate analysis will be taken during the last dialysis session prior to each study visit. The phosphate levels will be plotted over study visit. The distribution of the efficacy endpoints will be reported, and the variances of these distributions analyzed using analysis of variance (ANOVA) on transformed data by a procedure proposed by O'Brien. Based on the ANOVA results, variances will be further tested by Tukey's wholly significant differences (WSD).

The same analysis will be applied to a "per-protocol" population, which includes those patients whose drug compliance is at least 80% and who are in treatment for at least up to study visit 7. Various sub-group populations may also be examined, including gender, age, and other diagnoses.

Phosphate levels will be coded as "normal" or "abnormal" for each individual in the study. The coded data at each study visit will be examined, using probit analysis, to obtain an effective lanthanum dose targeted to a drug response rate of 80%. The 95% confidence interval of the effective dose (ED80) at each study visit will be reported and plotted in graphics.

Patients will be classified as "responsive" or "non-responsive", depending upon how many times their phosphate levels were coded as "normal" or "abnormal" during the late period of the study after dose titration has ceased. Descriminant analysis will be utilized to determine which variables may predict drug responsiveness. The model covariates may include dose, demographics, post-dialysis weight variation, and meal routine.

If patients are dismissed from the study because their phosphate levels drop below 2 mg/dl, or rise above 10 mg/dl, non-parametric tests may be used to examine the relationship between dose and phosphate levels.

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

IND 55,054 [N(GC)057] **SUBMISSION DATE:** April 17, 2000
Lanthanum Carbonate Hydrate

Shire Laboratories **REVIEWER:** Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: PROTOCOL AMENDMENT – RESPONSE TO COMMENTS FROM THE AGENCY

BACKGROUND:
This is a review of an amendment to protocol (Protocol LAM-IV-111) submitted to the IND. Lanthanum carbonate binds dietary phosphate in the gut to form lanthanum phosphate causing a reduction in the absorption of phosphate systemically. The sponsor is developing lanthanum carbonate as a phosphate-binding agent for [redacted][1] Protocol LAM-IV-111 was submitted to the Agency on March 20, 2000 and comments were communicated by phone to the sponsor on March 29, 2000.

SYNOPSIS:
Protocol LAM-IV-111– "Lanthanum Pharmacokinetics in Dialysis Patients Following Single and Multiple Doses": This is an open label, single and multiple dose study in 16 subjects {8 with normal renal function (control subjects) and 8 receiving hemodialysis (study subjects)} to determine if the PK of orally administered lanthanum carbonate are altered by severe renal function and if the elimination of lanthanum is affected by hemodialysis. The study consists of 5 parts: a screening period (Part 1), single dose PK study (Part 2), PK during dialysis (Part 3), multiple dosing phase (Part 4) and a multiple dose PK phase (Part 5).
The sponsor has incorporated the recommendation from the Agency that the same dose of lanthanum should be used in Parts 2 to 5 of the study and has chosen to use 1 g of lanthanum for the single dose phases and 1 g TID for the multiple dose phase in order to make it possible to compare the pharmacokinetic parameters across the phases.

CONCLUSION:
The Division of Pharmaceutical Evaluation I has reviewed the sponsor's protocol amendment and observed that the comments from the Agency have been incorporated into the amendment. No further action is indicated at this time.

Emmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation I

FT Initialed by P. Marroum, Ph.D. ----------

cc: IND 55-054, HFD-110, HFD-860 (Fadiran, Mehta), BIOPHARM – CDR.