CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-468

Medical

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Memorandum

NDA: 21-468 (Lanthanum carbonate to bind dietary phosphate)

Review date: 13 October 2004

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

This memo is to convey my general agreement with the conclusions of Dr. Karkowsky in his secondary review of the resubmission of this NDA, entered into DFS on October 12, 2004. Specifically, his review deals adequately with issues related to long-term concerns and the data that do or do not support more than a theoretical concern for such things as GI symptoms and bone effects.

In several places, Dr. Karkowsky suggests that the application should be approvable, pending a phase 4 commitment to study long-term toxicity. After many long discussions, the Division was unable to come up with a workable plan for such a phase 4 study. Controlled experience would inherit the same difficulties that plagued interpretation of long-term studies in the sponsor's development program, particularly how to handle crossovers. Synthesis of a control group [ ] was considered, but has similar difficulties for detecting any long-term and rare event. For these reasons, the Division does not make its recommendation of approval contingent upon a phase 4 commitment.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Norman Stockbridge
10/13/04 05:11:46 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
HFD 110
Medical Review of NDA 21- 468 (s 066)

Reviewer:	**A.O.Williams, M.D.**
NDA:	21-468 (submission no 066)
Study:	Resubmission
Drug:	Lanthanum Carbonate
Sponsor:	Shire Pharmaceutical Development Inc.
Proposed indication:	[redacted]
Date of NDA resubmission:	January 26, 2004
Dater Received by FDA:	January 26, 2004
Date Assigned	January 30, 2004
Medical Review Completed:	July 14, 2004

171 Pages, 68 Tables, 30 Figures, 13 Appendices

Table of Contents

List of Tables

List of Figures

List of Appendices

Executive Summary

This is a clinical review of a resubmitted NDA 21- 468.The primary clinical reviewer of the original NDA 21- 468 did not recommend Lanthanum carbonate for approval because of inadequacy of long term safety evaluation among other reasons (See page 10). This position was supported by an approvable letter that required the sponsors to address and respond to the deficiencies due to insufficient evaluation of lanthanum carbonate's safety. The deficiencies related to serious adverse events particularly those associated with discontinuations and withdrawals among patients who received Lanthanum and had stopped taking the drug. One would normally expect resolution of adverse events within a reasonable time after cessation of drug intake but because of the affinity of lanthanum of lanthanum for bones and GI the Agency sought additional information on the time to resolution of these discontinued patients. The concern of the Agency is justified because the proportion of patients on lanthanum (461/680) who discontinued for GI adverse events is very high (67.8%) compared to 327/674 (48.5%) in the long term 2 year follow up study. The critical body of information required in this resubmission include the time to resolution of the GI adverse events after the drug was discontinued, the clinical manifestations of lanthanum deposition and accumulation in bones after a reasonably long time, and the prolongation of the QT interval among the patients exposed to lanthanum. This information is considered important because of the relatively long median half life of lanthanum that is estimated to be about 3.57 years (Sponsor's estimate). The safety concerns therefore affect the gastrointestinal, cardiovascular and musculoskeletal systems including bones (See Safety Section under Summary of Clinical findings pp 29-57)). As far efficacy is concerned lanthanum has been shown to be an effective phosphate binder that reduces phosphorous levels and maintains the level at a pre-specified level of < 5.9mg/dL.

The following sentence in the approvable letter captures the essence of the deficiencies: "While it is clear that Lanthanum carbonate is effective as a phosphate binder in patients with end stage renal disease (ESRD), there has been insufficient evaluation of lanthanum carbonate's safety". A copy of the approvable letter from the Agency is underlined and reproduced below for ease of reference:

Approvable letter from FDA (February 28, 2003)
"Attention: Rick Lilley, Ph.D.
1801 Research Boulevard, Suite 600
Rockville, MD 20850

Dear Dr. Lilley:

Please refer to your new drug application (NDA) dated April 30, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosrenol (lanthanum carbonate) 250 and 500 mg Chewable Tablets.

We acknowledge receipt of your submissions dated May 21 and 22, June 7, 14, 19 and 28, July 11, 25 and 30, August 5, 14, 27 (two), 29 and 30 (three), September 10, 13, 16, 18 and 25,October 3, 8, 22, 24 and 28, November 1, 4, 11, 15, 21, 22 (two), 27 (two) and 29, December 13 (two), 16, 18, 20 (two), 23, 2002 and January 23, 27 and 28, and February 12, 2003.

We have completed the review of this application, as amended, and it is approvable. Before this

application may be approved, however, it will be necessary for you to address the following deficiencies:

1.1 CLINICAL

"While it is clear that lanthanum carbonate is effective as a phosphate binder in patients with end-stage renal disease (ESRD), there has been insufficient evaluation of lanthanum carbonate's safety.

1. 2 Adverse Events Leading to Discontinuation

It is clear that the rate of discontinuation for adverse events (especially gastrointestinal adverse events) was significantly higher for patients receiving lanthanum compared with standard phosphate binders over all periods of exposure in the clinical trials. Insufficient information is available regarding the resolution of these symptoms following lanthanum discontinuation. While in most cases such symptoms would be expected to resolve when a study drug is discontinued, given the high concentration of lanthanum in the GI tract following oral administration and the uncertainties about the rate of elimination of lanthanum in patients with ESRD, our concern is that these symptoms may not resolve quickly, presenting a real risk of malnutrition and additional injury in this population.

Resolution of this clinical issue will require data regarding the timing and extent of resolution of reported serious adverse events (especially events leading to discontinuation) in patients receiving lanthanum in the long term trials.

1.3. Long Term Safety Information

It is clear from the bone histologic examination that lanthanum is absorbed following oral administration
and is then deposited in tissue. It is deposited widely in animals, including the GI tract, bone and cardiac tissues in patients with ESRD. There is less information available, but bone deposition has been clearly demonstrated. As we do not yet know if (or when) a steady-state tissue concentration of lanthanum should be expected following chronic use, it is difficult to use the present database to assess the possibility of significant long-term toxicities resulting from tissue deposition of lanthanum. Given the history of significant, but unpredicted, long-term bone toxicity following the use of aluminum containing antacids, where toxicity was not manifest clinically for several years after initial exposure, the current database is inadequate with respect to long-term follow-up to exclude significant toxicity, including bone toxicity.

Additional long-term data will therefore be needed. Deciding on the extent and duration of long-term safety data will require additional data on the rate at which lanthanum continues to be deposited during chronic administration of lanthanum to patients with ESRD. These data will provide a basis for discussions of how to assess the long term safety of lanthanum.

1.4. Prolongation of the QT Interval on the Surface Electrocardiogram

Lanthanum appears to prolong the QT interval by a mean of 5-10 milliseconds when compared with the other phosphate binders, as shown in the LAM-IV-307 study. This effect is poorly characterized in the available trial data and additional clinical data are needed on the following:

1. Time-course of the effects of lanthanum on QT interval, including time to resolution following drug discontinuation.

2. Assessment of link between QT prolongation and risk of cardiac death in patients with ESRD. Such an assessment may be done using the available and pending data from the long-term clinical trials.

We remind you that a full response is needed to the comments and requests identified in our letter dated January 16, 2003, as you have committed to providing in your letter dated January 28, 2003.

Given the extent of the additional information needed, final labeling can not be considered at this time. As the additional information requested becomes available, revision of the proposed labeling will be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with the Division of Cardio-Renal Drug Products to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved"

End of quote

Below is a list of some reasons adduced by the reviewer-Dr Pelayo - of the original NDA for non-approval

Summary of selected grounds for recommending non-approval of original NDA

- Aluminum and Lanthanum are both trivalent cations and binders and both tend to accumulate in tissues. Aluminum toxicity was discovered late. It was reported to cause bone disease, dementia, myopathy, hypoparathyroidism and death.
- Widespread deposition of lanthanum in tissues of healthy animals with normal renal function.
- There is dose-dependent decrease in bone formation and osteomalacia in chronic renal failure rat model.
- There is compelling evidence that lanthanum is deposited in bones.
- There are a significant number of withdrawals/discontinuations in patients receiving lanthanum (284 days) compared to standard therapy (397 days). In the short-term studies 26 (8.7%) patients receiving lanthanum carbonate and 5 (5.3%) patients treated with placebo discontinued due to adverse events. Overall, 236 (16.0%) of patients treated with lanthanum

carbonate discontinued treatment during the long-term Phase II- III studies while 46 (5.1%) of patients treated with active control discontinued (p< 0.001). 26 A total of 190 patients representing 80.5% of all the discontinuations in the lanthanum carbonate group withdrew prematurely from the study because of adverse events related to the gastrointestinal system: nausea, vomiting, diarrhea and abdominal pain were the major causes leading to discontinuation in this group. The results indicate that lanthanum carbonate is significantly less well tolerated than other phosphate binders.

- Calcium carbonate is not and FDA approved drug and yet it was used as an active control drug in the comparator studies. Furthermore the safety of lanthanum that is not known was used as comparator in the safety studies.
- In conclusion, Lanthanum safety has not been adequately evaluated from the safety standpoint.

The presentation of this review is based on the recently approved CDER clinical review template. The template has been slightly modified to accommodate the special needs of this resubmitted NDA.

This reviewer consulted the original submission and its clinical review. In addition the resubmitted NDA was reviewed with the primary focus on the efforts of the sponsor in addressing the deficiencies in the approvable letter. The recommendations of this reviewer are therefore based on an overall review of both the original and resubmitted NDAs and additional submissions relating to the open label study LAM-IV-307, the 15-month and 25-month safety updates.

I. Recommendations

A. Recommendations on Approvability

Based on the lanthanum clinical program, this reviewer recommends that lanthanum carbonate in the resubmitted NDA is "approvable" for [ ] but with a caveat of caution. The reasons for the approvable recommendation and the caveat are set out below in 3 parts. The following observations seek to evaluate the potential toxicity of lanthanum carbonate based on the data provided in the original and resubmitted NDAs.

Part A:

- Post approval action should include [ ]
- Adjusted data should be provided for fractures, mortality rates and other information that may be used for claims in the label.
- The clinical trial program shows that lanthanum is effective in reducing hyperphosphatemia in patients with end stage renal disease.
- The sponsor has not addressed all the deficiencies in the approvable letter with particular reference to safety concerns affecting bones and gastrointestinal system.
- The sponsor has provided new data to clarify the limitations in the clinical data that resulted from differential discontinuations due to adverse events.
- Based on new data, there is no increase in fractures among patients treated with lanthanum for up to two years compared to patients treated with other phosphate binders in the clinical trials. The 2 year follow up period is considered inadequate for bone toxicity because lanthanum has not reached its steady state at this point in time.

Therefore the peak effects of lanthanum on bones and perhaps other tissues are therefore not known.

- The potential for lanthanum toxicity in bones after 2 years remains unknown as the steady state for lanthanum in bones has not been reached and the mean half life is more than 2 years. There is a more than >100% increase in mean plasma lanthanum concentration in patients selected for the bone sub-study between week 7 and month 24 in the LAM-IV-307 study (0.3ng /mL at wk 7 and 0.7ng/mL at month 24).
- Based on new data, there is no significant increase in GI adverse events among patients treated with lanthanum compared to patients treated with other phosphate binders in the clinical trials but most of the data submitted are unadjusted for drug exposure.
- There are no data to support the claim by the sponsor that the length of time from onset to resolution of GI adverse events among patients treated with lanthanum is different compared to patients treated with other phosphate binders in the clinical trials. In effect there are no data on "stop dates of GI adverse events" whereas there are data on "time to onset of events". As a result calculation of time to resolution is not feasible). However, there are data that the overall rates of GI adverse events are similar in both groups except in short term phase II-III placebo controlled studies (LAM-IV-202, 204, 302) that show more than 50% greater rates of GI adverse events in the lanthanum group compared to standard therapy (e.g. Nausea 10.6% vs 5.3%; vomiting 9.4% vs 4.2%; abdominal pain 9.00% vs 0.00%; lanthanum vs standard, respectively).
- According to the sponsor, there is no significant difference in the number of patients with unresolved GI adverse events among those treated with lanthanum (N= 215) compared to those treated with other phosphate binders (N=289) after more than one year of follow up (Numbers adjusted for discontinuations)

Part B:

The demonstrated propensity for lanthanum to accumulate in tissues particularly bones and its relatively long half life of lanthanum should be considered a potential risk in the light of limited and inadequate data relating to the concerns expressed by the Agency. Evaluation for toxicity may be based on actual data and in its absence surrogates may be used where appropriate. The following observations seek to evaluate the toxicity of lanthanum carbonate based on the data provided in the original and resubmitted NDAs.

Surrogates for bone pathology/toxicity

- Nothing is known now about the possible worst case scenario when lanthanum reaches steady state in bones or other organs such as liver or GI...
- Bone specific Alkaline phosphatase – The change from baseline increased continuously in patients given lanthanum compared to Standard therapy [p= 0.000 for bone specific alkaline phos. at visit 12; alk phos. that is not bone specific not bone specific shows statistically significant differences: p=0.006 at visit 3 and p=0.0009 at visit 12; Note lanthanum accumulates in the liver also].
- The transfer rate of lanthanum into bone has been calculated by the sponsor to be 1.125µg/hr and 3.675µg/hr using average and measured highest bioavailability rates. After 15 years of exposure, lanthanum concentration accumulation rates in bone would result in average and highest bioavailability of 13,922µg/kg and 45,990µg/kg, respectively.
- There is evidence that lanthanum damages bone in rats with normal renal function tests (See page 68 and Appendix 4) suggesting a direct toxic effect of lanthanum on rat bones.

- There are no biopsies of long bones from patients treated with lanthanum to assess adequately bone changes that in turn indicate interplay of periosteal gene expression which is known to increase with mechanical loading on long bones. Biopsy of long bones was not prespecified in the protocol. The distribution of bone fractures in patients on lanthanum and standard therapy suggest a greater frequency of fractures in weight bearing bones over the 2 year period.
- There are very few patients with long term exposure (>3years) to lanthanum considering the relatively long mean half life of lanthanum in bones and perhaps other tissues (3.57years). According to the sponsor, 212 patients have received lanthanum for more than 2 years but there are only 3 patients with bone biopsies in the long term follow up study – 307... The histological review of these 3 bone biopsies is not very reassuring because of artifacts of preparation. Overall, adequacy of testing for bone toxicity is unsatisfactory and inadequate on quantitative and qualitative grounds.
- Evaluation of bone toxicity utilized iliac bones because this site has been generally shown to be acceptable for monitoring bone changes in metabolic diseases. However, it has not been shown to be specific for chemically associated bone toxicity such as lanthanum.
- Total protein – The change from baseline is greater in the lanthanum group compared to standard group (p=0.007 at visit 12).
- Serum Calcium phosphate product- The change from baseline is slightly higher in lanthanum patients compared to others for the duration of 2 years follow up. (See Figure page)
- Glucose – The change from baseline is higher in lanthanum group compared to standard group (p=0.001)
- Total serum Calcium concentration- The change is lower in lanthanum patients compared to others for the duration of 2 years [p=0.001 at visit 15] (See Figure page)
- The mean values of serum phosphorous levels by visit and treatment group during the maintenance phase is above the predefined PSPL control level of ≤5.9mg/dL in both the lanthanum and standard groups but the mean values are closer to 5.9mg /dL at months 22 and 24 among the standard group compared to the lanthanum group (See Table 55)
- By the end of the titration phase the proportion of patients with controlled PSPL was significantly greater in the Standard Therapy compared to the Lanthanum group 57.5% versus 43.3% respectively; p= 0.0001.

During the original review of NDA 21-468, the lack of adequate data on significant long term toxicity from lanthanum deposition in bone was identified as a deficiency. The approvable letter that sent to the sponsor requested that the deficiency be corrected. However, the period for "long term" was not defined in number of years.
The mean exposure to lanthanum for the evaluation of bone fractures was 10.2±8.4 months for patients that received lanthanum whereas for the comparator group the mean exposure was 14.1±8.6 months. Additional longer term data on a larger number of patients exposed are therefore required to fully adequately assess bone toxicity.

Considering that the calculated period to reach steady state for lanthanum in bone is more than 10 years a two year follow up period is inadequate. A post approval [ ] proposed by the sponsor may probably compensate for this.

Part C:

GI Adverse events

- The time to resolution of GI adverse events in patients receiving lanthanum is not known and remains unknown as of June 20, 2004 based on the sponsor's table and explanation...
- According to the sponsor the majority of GI adverse events resolved within the first 3 weeks of onset. This claim is not supported by any data submitted by the sponsor and therefore fails to address one of the deficiencies in the approvable letter.
- In the open label, long term follow up safety study, LAM-IV-307, about 68% (461/680) of patients on lanthanum were withdrawn for a variety of reasons in the lanthanum group compared to about 49% (327/674) in the standard group. One hundred and five patients withdrew consent (15.4%) from the lanthanum group compared to 30 (4.5%) who withdrew consent in the standard group suggesting a possible lack of tolerability of lanthanum. Alternatively the relatively low rate of withdrawal among the standard group could be due to access to other forms of drugs to which they switched whereas there was no option for those on lanthanum.
- There was a relatively greater number of patients treated with lanthanum that "resolved with sequelae" within one year (N=12) compared to other phosphate binders (N=3). (Numbers adjusted for discontinuations). These numbers are too small to make any clinically meaningful comments. The nature of the sequelae are not given by the sponsor.

Endocrine System

- There is a higher level of serum parathyroid (PTH) concentration at baseline among patients on lanthanum compared to those on Standard therapy. One of the predictors of bone mineral density in patients on dialysis is parathyroid hormone. Histomorphometric studies suggest that maintenance of PTH levels between two to four times the upper limit of normal is associated with the lowest prevalence of two common forms of renal osteodystrophy namely osteitis fibrosa cystica and adynamic bone disease ***(Zayour et al., Predictors of bone mineral density in patients on hemodialysis. Transplant Proc. 2004 36: 1297-1301).*** Considering that these patients were randomized this reviewer cannot explain why there is such a difference in PTH levels at baseline (Figures 5 and 8). The relatively higher level of PTH in the lanthanum group predisposes this group of patients to a lower prevalence osteodystrophy compared to those on standard therapy. However, the change in PTH levels from baseline is comparable to those on Standard therapy throughout the period of 1 year of study. The reason for these PTH differences at baseline perhaps makes the histological categories of the groups different and suggests that two treatment groups were not balanced at baseline.
- In the bone sub-study, Table 25 in vol. 60 Section 8.7 – 8116 in the sponsor's submission is confusing and is not correct in respect of adverse events in body system - musculoskeletal system experienced in > 2% of patients – Bone Sub–study. This has now been corrected (Table 60).
- The possible association between hyperparathyroidism and breast cancer is discussed on page 167 of this review (Ref. on page 75).

Mortality

- The lanthanum Phase 2-3 studies were not designed to collect longitudinal mortality data from the study participants. However, the sponsor collected mortality data from almost 97% of the study population using an approach of data collection that was tied to a single date of follow-up. The sponsor suggested that continued mortality data collection within the Phase

2-3 program will not yield any better results than those already obtained, due to patient attrition, HIPAA regulations and Investigator cooperation. To resolve this issue, the sponsor [ ] for further mortality data collection and ongoing long-term safety surveillance. The proposed plan has been submitted to the Agency.

- Mortality rates adjusted for discontinuations appear to be higher in the group receiving lanthanum compared to standard group. At 44 months, mortality rate was 23.8% (418/1754) among lanthanum group compared to 20.4 %(202/990) in the standard group (Dr V Friedlin). However the survival curves overlie each other suggesting no difference between the two groups.
- The absence of long term (>3.5 years, mean half life of lanthanum =3.57 years) follow-up of relatively large numbers of patients treated with lanthanum with adverse events affecting bones and GI is worrisome from the mortality point of vies. Considering that only 11% of ESRD patients on dialysis survive for 10 years, any treatment modality that will reduce mortality should be encouraged in this cohort of survivors. It is perhaps justifiable for this 11% who survive for 10 years that steady state levels of lanthanum should be known in humans so that the effect compartment (efficacy and safety) are better characterized.

Cardiovascular System-QT-Underlined areas are from approvable letter

The additional data required from the sponsor are clearly spelt out below.

- Lanthanum appears to prolong the QT interval by a mean of 5-10 milliseconds when compared with the other phosphate binders, as shown in the LAM-IV-307 study. This effect is poorly characterized in the available trial data and additional clinical data are needed on the following:
    - Time-course of the effects of lanthanum on QT interval, including time to resolution following drug discontinuation.(See Appendix 11)
    - Assessment of link between QT prolongation and risk of cardiac death in patients with ESRD. Such an assessment may be done using the available and pending data from the long-term clinical trials. (See Appendix 7-10)

Electrocardiogram analyses were performed in studies 204, 205, 302, 307, 308 and QT prolongation was noted in the interim data reported in study 307. Using the same criteria as the Agency the sponsor has evaluated patients with an overall increase in QT interval from baseline of > 30 msec or > 60msec.In addition the sponsor has evaluated patients with a QT interval > 480 msec. The position of the sponsor is that the risk of cardiac death is not associated with changes within the observed duration of 5-10 msec. By carrying out a number of studies the sponsor has characterized the effect of lanthanum on the QT interval. The data from these studies are graphically represented in Appendices 7 – 11.The sponsor showed that there was no significant difference in the frequency of QT prolongation between the two treatment groups using data from the 15 month safety report. In LAM-IV-307 where a large number of patients were in an open label long term follow up study there is a statistically significant increase of QT prolongation at one time point and that was at week 14 (visit 9) (p=0.019) (See Appendix 11). The magnitude of this prolongation was 6.9 msec (N=457) which is well below the 10 msec threshold for cardiac risk of new chemical entities. For patients discontinued and followed up the same blip of an increased prolongation of 5.9 msec at 14 weeks was observed (p=0.015) (See Appendix 12). This blip in increase was seen again in the time course of the change from baseline and then disappears. The significance of this ephemeral but consistent increase in QT prolongation at week 14 in not known. It would however be correct to infer that lanthanum does not have a consistent effect on QT interval over the 24 month period of

follow up. (Appendices 11-13). This could be a time related peak effect of lanthanum on QT interval as there is an increase of plasma lanthanum level from week 7 (Table 40)..

- In study LAM - IV - 307, a slightly higher proportion of lanthanum patients demonstrated a QT prolongation of ≥30 msec and ≥60msec compared to those on standard therapy at the 24 month drug exposure. However events known to have an association with QT prolongation were reported with comparable frequencies in both treatment groups. On this basis the QT prolongation associated with lanthanum does not seem to have a clinically meaningful adverse event as of the follow up date of June 2003.
- The safety data submitted suggest comparable frequency of cardiac-related SAEs and patient deaths in LAM-IV-307 in the two treatment groups.
- The sponsor has made considerable effort in providing additional data to address the deficiency on QT as stated in the approvable letter.

Bioequivalence for new formulation

- Bioequivalence issue should be resolved. Lanthanum is available as a chewable unflavored tablet in two dosage strengths (250 mg, and 500 mg) for oral administration.

The strength of this product is based on the active moiety, Lanthanum and not the salt Lanthanum Carbonate. Because of the uncertainties of lanthanum toxicity in tissues where it is deposited and accumulate, (See Table 49 for plasma lanthanum conc.), this reviewer recommends that the recognized serious adverse events and the potential for worsening of such adverse events over time, particularly bones and GI should be adequately reflected in the labeling. However, the sponsor's [redacted] described below, appears to go a long way in addressing these concerns.

B. [redacted]

[redacted]

Redacted 1

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

[ ]

Recommendation for .

[ ]

APPEARS THIS WAY
ON ORIGINAL

II. Summary of clinical findings

A. Brief Overview of clinical program

The clinical development of FOSRENOL is focused on its ability to act as a phosphate binder and thus treat hyperphosphatemia associated with end-stage renal disease. Therefore, FOSRENOL is indicated for [redacted]

The demographics of patients in the clinical program are summarized in Table 1 below.

Table 1: Demographics in lanthanum development program

Baseline demographics for patients enrolled in the lanthanum carbonate program							
Devpt.	**Phase 1**		**Phase 2-3**				
Treatment group	**LaC**	**Placebo/ others**	**Short Term**		**Long term**		**All Phases 2/3**
			LaC	**Placebo**	**LaC**	**ACPB**	**LaC**
No. receiving study medication	***179**	**76**	**298**	**95**	**1507**	**941**	**1705**
Age (yrs)							
N	***179**	**76**	**298**	**95**	**1507**	**941**	**1705**
Mean±SD	29.5±9.99	25.7±6.47	57.4±14.42	57.7±14.11	55.9±14.40	56.0±14.23	56.1±14.43
Age Group							
18-50	168(93.9)	76(100)	84(28.2)	28(29.5)	522(34.6)	326(34.6)	580(34.0)
51-64	10(5.6)	0	105(35.2)	29(30.5)	520(34.5)	325(34.5)	587(34.4)
65+	1(0.6)	0	109(36.6)	38(40.0)	465(30.9)	289(30.7)	538(31.6)
Sex							
Male	146(81.6)	76(100.0)	185(62.1)	52(54.7)	935(62.0)	580(61.6)	1056(61.9)
Female	33(18.4)	0	113(37.9)	43(45.3)	572(38.0)	361(38.4)	649(38.1)
Race							
Caucasian	152(84.9)	63(82.9)	142(47.7)	45(47.4)	1029(68.3)	569(60.5)	1142(67.0)
Black	5(2.8)	0	131(44.0)	43(45.3)	378(25.1)	277(29.4)	450(26.4)
Hispanic	6(3.4)	0	15(5.0)	4(4.2)	61(41.0)	56(6.0)	70(4.1)
All others	16(8.9)	13(17.1)	10(3.4)	3(3.2)	39(2.6)	39(4.1)	43(2.5)
Weight (pounds)							
Mean±SD	161.4±25.0	159.0±19.15	172.2±39.34	175.8±44.94	171.7±41.64	173.9±43.9	171.6±41.31
Height							
Mean±SD	68.7±3.01	69.3±2.43	66.9±4.20	66.9±4.23	66.9±4.15	67.0±4.24	66.9±4.16

- 10 patients had ESRD*.

The inclusion and exclusion criteria for the program and the 2 sub-studies of LAM-IV-307 are summarized below.

Inclusion criteria

- Patients of either sex at least 12 years old with chronic renal failure who had undergone hemodialysis for chronic renal failure 3 times a week for at lease the previous two months, and who currently requires phosphate binders for the treatment of hyperphosphatemia (>5.9mg/dL) were eligible for enrollment.
- Patient or legal representative must have ability to give written informed consent
- Patient must be judges by the investigator to have the capacity to be compliant with the protocol
- Patients including those who have undergone renal transplantation in the past must have received 3 times a week hemodialysis for chronic renal failure for at least the previous 2 months.

Exclusion criteria

- Pregnant women
- Women of re[productive potential who did not agree to use effective birth control measures
- Patients with a screening calcium level below 7.9mg/dL.
- Patients with clinically significant uncontrolled concurrent illness that may impair capacity of patient to participate by informed consent.
- Patient with any significant GI surgery of GI disorders such as peptic ulcer, Crohns disease, GI bleed within the past 6 months past or present GI malignancy.
- Patients with elevated liver enzymes more than 3 times the upper limit of normal.
- Patients with life-threatening malignancy or multiple myeloma.
- HIV positive patients.
- Patients who had been exposed to an experimental drug within 30 days prior to screening.

Exclusion criteria for cognitive function sub-study

- Patients unable to complete the training sessions after 2 attempts
- Patients with documented aluminum related bone disease or dementia
- Patients on psychotropic drugs stabilized for less than 1 month
- Patients were not allowed to smoke or drink alcohol within one hour prior to the test.

Exclusion criteria for bone biopsy sub-study

- Patients allergic to tetracycline
- Patients on medication known to affect bone metabolism during 6 months prior to biopsy
- Patients requiring long term therapy with steroids at doses > 5mg prednisolone per day or equivalent
- Patients receiving treatment with cyclosporine within the last 6 months
- Patients having parathyroid surgery within 6 months prior to bone biopsy
- Patients with documented aluminum related bone disease

Clinical Studies

A total of 5 clinical studies composed of 3 short-term placebo-controlled double-blind studies (202,204,302) and 2 long-term, active-controlled, open label studies (301, 307) in both hemodialysis and peritoneal dialysis patients were carried out, reported and reviewed in the original NDA. These studies form the basis of this resubmission. These have been reviewed in the original NDA by Dr Pelayo (See Appendix 3 page 138). The update on the long term safety study, LAM-

IV-307, is additional and will be reviewed in additional to previous review as the sponsor hopes to validate her claim on long term safety from data derived from this study. Additional data are also provided by the sponsor to address the deficiencies in the approvable letter (See copy of approvable letter above).

The clinical pharmacology program consisted of 11 studies with PK and PD data (See Table 45) and the clinical program consisted of 5 studies. Efficacy was evaluated in 3 short term, placebo-controlled, double blind studies and 2 long term active controlled open label studies. Safety was evaluated in all the clinical studies including the long term active controlled study, LAM-IV-307 that was an open label, long term, safety follow up study for 2 years. This study had 3 interim reports of safety. The entire safety data have been submitted in the current resubmitted NDA and additional data including recent safety updates have been received. The double blind placebo controlled studies involved a total of 273 ESRD patients (252 on hemodialysis and 21 on peritoneal dialysis. Lanthanum carbonate was divided and taken with meals, and the dose given ranged from 225-3000 mg/day. The efficacy end point was reduction in serum phosphorous level from baseline to an endpoint of double blind treatment compared to placebo.

The current clinical database of exposure to lanthanum is a total of 1,933 healthy volunteers and patients who received lanthanum throughout the clinical development program. Of these, 1,754 patients participated in phase 2-3 studies, and 1,507 patients have participated in long-term studies, of which 212 patients took lanthanum for approximately 2 years. Of the 1,933 patients and subjects in the program, 169 (8.75%) were healthy volunteers given lanthanum and 76 were healthy volunteers given standard therapy. These healthy volunteers participated in the PK/PD studies and were exposed to single and multiple doses of lanthanum carbonate for very short periods of time, <7 days.

The majority of patients with ESRD, if not all, who are on dialysis are known to have clinically significant bone disease that eventually leads to alterations in bone pathology (ROD or renal osteodystrophy). This is presumed to be the case among those enrolled in this study. The severity and extent of the renal osteodystrophy before randomization were not ascertained for balance between the treatment groups. It is therefore not surprising that the parathyroid hormone levels at baseline in the group randomized to lanthanum were higher than in the group randomized to standard group (Figure 8)... The factors that influence the pathogenesis of bone disease in renal failure patients with ESRD include parathyroid hormone (PTH), vitamin D, calcium, phosphate, acidosis, magnesium abnormalities, uremia, dialysis and even renal transplantation.

The most current and effective mechanistic approach for treating hyperphosphatemia associated with renal insufficiency is reduction of intestinal absorption of phosphates by the administration of phosphate binders, i.e., aluminum- (off- label use) or calcium-based phosphate binding agents (Calcium carbonate or calcium acetate) or more recently with RENAGEL ® (sevelamer hydrochloride). Although highly effective as a phosphate binder, long-term use (off-label) of aluminum salts has been shown to result in serious adverse events such as aluminum-related bone disease, dementia, myopathy, hypoparathyroidism, and death. Lanthanum carbonate has been shown to be a phosphate binder and the current resubmission seeks approval for the indication [ ]. The population at risk for hyperphosphatemia in this clinical program are patients with chronic renal failure whose kidneys show clinico-pathological features of chronic renal failure and end stage renal disease and who are on dialysis.

Renal History

The renal history and pathology, i.e the primary renal diagnoses and histories, of patients at screening in the short placebo controlled study (LAM-IV-303) and in the long open label study (LAM-IV-307) are presented in Table 2: This table shows that the leading causes of ESRD are diabetes (34.4%), hypertension (31%) and glomerulonephritis (12%) in both groups of patients. The summary of the renal history at baseline for the ITT population shows a balance between the groups is in Table 3. Tables

Table 2: Primary renal diagnosis of patients at screening-LAM303/LAM307

Primary Renal Diagnosis	LAM-IV-303*		LAM-IV-307** Bone subset	
	Lanthanum N (%)	Standard N (%)	Lanthanum N (%)	Standard N (%)
Diabetes***	10(20)	15(31)	25(25)	24(24)
Glomerulonephritis	7(14)	2(4)	18(18)	19(20)
Hypertension	7(14)	7(14)	35(35)	30(32)
Cystic kidney disease	6(12)	8(16)	3(3)	1(1)
Urologic disease	6(12)	4(8)	2(2)	2(2)
Other known disease	3(6)	9(18)	7(7)	16(17)
Unknown causes	10(10)	4(8)	10(10)	5(5)

LAM-IV-303 patients had ESR failure plus 12 weeks of dialysis at baseline. LAM-IV-307 patients had been on dialysis for an average of 4 years at the time of randomization.
***This should be considered a special population because of differences relating to impaired parathyroid hormone and race compared to other groups.

Table 3: Summary of Baseline Renal History-ITT population

Patient	Lanthanum	Standard
Primary renal diagnosis N (%)		
Diabetes	229(34.4)	230(34.5)
Hypertension	207(31.1)	191(28.6)
Glomerulonephritis	80(12.0)	90(13.5)
Previous Kidney transplant		
No	581(87.2)	589(88.3)
Yes	8512.8)	78(11.7)
Length of time on hemodialysis (yrs)		
N	666	667
Mean years + SD	3.9±3.4	3.8±3.2
Prior therapy N (%)		
Calcium carbonate	241(36.2)	237(35.5)
Calcium acetate	288(43.2)	290(43.5)
Renagel	102(15.3)	107(16.0)
All other therapy	32(4.8)	31(4.6)
Not listed	2(0.3)	2(0.3)
Current dialysis schedule N		

Patient	Lanthanum	Standard
(%)		
M/W/F/	416(62.5)	413(61.9)
T/Th/S	250(37.5)	254(38.1)
Meal Routine N (%)		
2 meals per day	92(13.8)	118(17.7)
3 meals /day	573(86.2)	547(82.3)

Clinical Trials and Demographics

The list of studies for the lanthanum carbonate clinical program carried out in the US and UK are in Section: "Listing of Tables". (Table 45). The demographics of patients enrolled in this program are balanced between the two treatment groups (Tables 41 and 42) including LAM-IV-307. The open label, long term study, LAM-IV-307 evaluated efficacy and safety for up to 2 years and more (Table 42 and 43) and in addition had two sub-studies that separately evaluated cognitive function tests and bone toxicity for up to two years (See demographics of these 2 sub-studies in Tables 40 and 43). These two sub-studies were carried out to evaluate and compare adverse experiences and events in ESRD treated patients and then to compare with aluminum (off label use/treated patients) for relatively longer periods.

Table 4 summarizes the duration of exposure for more than one year to Lanthanum and Table 9 summarizes the rates of discontinuations and withdrawals in all phases of the clinical program. Compared with standard therapy, there were fewer patients exposed to lanthanum over periods of more than one year compared to standard therapy because those on standard therapy had the opportunity to switch to alternatives if what was being taken was not tolerated. The percentages of discontinuations and withdrawals were much higher in the lanthanum group compared to the standard therapy group (Tables 5 and 6). These differences affected the quality and validity of the data submitted by sponsor because most were not adjusted for drug exposure and discontinuations. Several requests had to be made by the Agency for adjustment of data particularly where the sponsor's conclusions were untenable. In this review some of the data have been adjusted for discontinuations and drug exposure and several others have not been adjusted. For example, in the cognitive function tests there were no adjustments for drug exposure or discontinuation. However, in the bone subset study the sponsor submitted adjusted data for fractures following requests by this reviewer (Appendices 5 and 6).

Table 4: Patients treated with lanthanum for >12 months LAM-IV-307

Months	Lanthanum N=682	Standard Therapy N=676
12 months plus	338(49.6%)	472(69.8%)
18 months plus	240(35.2%)	382(56.5%)
*24 months plus	134/682(19.6%)	227/676(33.6%)

* maximum number of months of exposure not stated by sponsor in June 1 2004 submission

Table 5: Disposition of subjects for cognitive function Sub-study LAM-IV-307

	Lanthanum	Standard	Still in washout	TPR
Total enrolled	178	180	4	46
Number remaining in study	34(19.1)	43(23.9)	4(100)	0

Completers	19(10.7)	54(30.0)	0	0
Number withdrawn Reasons for withdrawal:	125(70.2)	83(46.1)	0	46(100)
Adverse events	22(12.4)	6(3.3)	0	1(2.2)
Protocol violation	3(1.7)	1(0.6)	0(0)	3(6.5)
Withdrew consent	33(18.5)	6(3.3)	0(0)	4(8.7)
Transplanted	12(6.7)	16(8.9)	0(0)	0
Lost to follow up	4(2.2)	0	0(0)	1(2.2)
Death	11(6.2)	28(15.6)	0(0)	1(2.2)
Ineligible for titration	0(0)	0(0)	0(0)	25(54.3)
Others	25(14.0)	20(11.1)	0(0)	11(23.9)
Exceeded safety criteria	15(8.4)	6(3.3)	0(0)	2(1.1)
Two PO4 values >10mg/dL	11(6.2)	5(2.8)	0(0)	0
Two PO4 values <2.0mg/dL	0(0)	2(0.3)	0(0)	0
Two Ca*PO4 >90mg2/dL	2(1.1)	1(0.6)	0(0)	0(0)
Calcium >115 mg /dL	0	0	0(0)	0(0)
Increase in PTH>500pg/mL from screening	2(1.1)	0	0	0

Table 6: Disposition of subjects for bone substudy-LAM-IV-307

	Lanthanum N (%)	Standard N (%)	Still in washout	**TPR**
Total enrolled	100	97	2	10
Number remaining in study	58 (58.0)	59(60.8)	2(100.0)	0(0)
Completers	7(7.0)	10(10.3)	0(0)	0(0)
Number withdrawn Reasons for withdrawal:	35(35.0)	28(28.9)	0(0)	10(100.0)
Adverse events	2(2.0)	1(1.0)	0(0)	0
Protocol violation	1(1.0)	1(1.0)	0(0)	0
Withdrew consent	5(5.0)	1(1.0)	0(0)	0
Transplanted	8(8.0)	6(6.2)	0(0)	0
Lost to follow up	0	3(3.1)	0(0)	0
Death	7(7.0)	9(9.3)	0(0)	1(10.0)
Ineligible for titration	0(0)	0(0)	0(0)	7(70.0)
Others	8(8.0)	4(4.1)	0(0)	1(10.0)
Exceeded safety criteria	4(4.0)	3(3.1)	0(0)	1(10.0)
Two PO4 values >10mg/dL	1(1.0)	1(1.0)	0(0)	0(0.0)
Two PO4 values <2.0mg/dL	0	0(0.0)	0(0)	1(10.0)
Two Ca*PO4	2(2.0)	2(2.0)	0(0)	0(0)

>90mg2/dL				
Calcium >115 mg /dL	0	0(0.0)	0(0)	0(0)
Increase in PTH>500pg/mL from screening	1(1.0)	1(1.0)	0(0)	0(0)

Special populations

A case can be made for diabetics to be considered as a special population because bone changes in diabetics on dialysis show significant differences in renal failure compared to non diabetics on dialysis (Refs page 74).

Four hundred and forty seven diabetics with ESRD out of 1754 patients enrolled in the clinical program constituting the largest proportion of patients with renal history (Table 3); 34.4% and 34.5 % of diabetic patients were recruited into the lanthanum clinical program and of these 25 % and 24 % were in the bone subset study, lanthanum and standard groups, respectively (Table 2). This group should be treated as a special population in terms of their unique bone changes when on dialysis (Ref page 74). These changes are well recognized. There is therefore a need to characterize bone changes in diabetics with ESRD exposed to diabetics, since this information is not evident in any of these studies.

There is evidence in the literature that diabetics on hemodialysis have significantly impaired secretion of parathyroid hormone compared with patients on hemodialysis without diabetes mellitus. As a result diabetic bone disease is characterized by low bone turnover resulting from impaired secretion of parathyroid hormone (Tables 3, 7 and 8). This population needs to be looked at in the light of this difference. About 447/1754 (25%) diabetic patients on dialysis were in lanthanum group and 289 /990 (29%) of diabetics on dialysis were on standard therapy. The significant differences in the some of the biochemical parameters between the two treatment groups, particularly serum osteocalcin and glucose, require further evaluation.

Table 7: Diabetic Patients with ESRD in lanthanum program

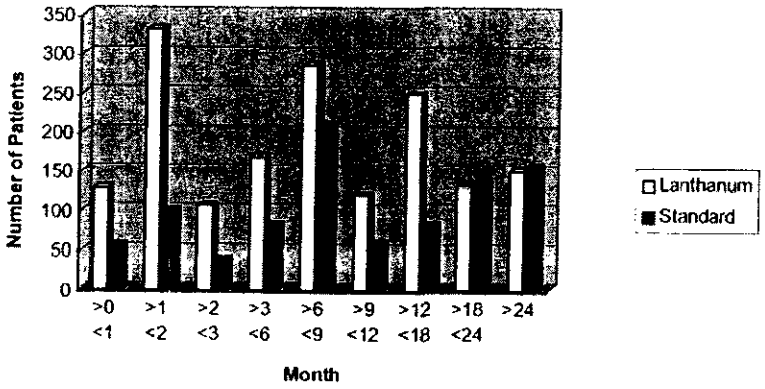
All Phase 2-3 Patients	Lanthanum	Standard
Protocol No.	N=1754	N=990
LAM-202	4 (7%)	na
LAM-204	53 (44%)	na
LAM-301	107 (15%)	41 (15%)
LAM-302	39 (31%)	na
LAM-303	10 (20%)	15 (31%)
LAM-307	234 (34%)	233 (35%)
Total	447 (25%)	289 (29%)

Table 8: Diabetics in bone sub-study with bone biopsies

Phase 2-3 Patients with Bone Biopsies*	Lanthanum	Standard
Protocol No.	N=198	N=174
LAM-301	3 (23%)	na
LAM-303	10 (20%)	15 (31%)
LAM-307	39 (29%)	30 (24%)
Total	52 (26%)	45 (26%)

*Presumed to be Type 2 diabetics. Bone loss is not a problem with younger type 1 diabetics. (Rozadilla A., et al., Bone mineral density in patients with type 1 diabetes mellitus. Joint Bone Spine 2000; 67: 215-218)

Figure 1-ISS. Number of Patients Receiving Multiple Doses of Active Treatment in Phase II and III Studies



[Sponsor's analysis, adapted from NDA 21-468, Four-Month Safety Update. Table 8.8-11.]

Overall there was a greater rate of discontinuation in lanthanum-treated subjects/patients than for those subjects/patients receiving placebo or active control phosphate binders (see below). Because of this imbalance in withdrawal rate, the mean exposure to study drug for all Phase II and III studies was

In all the phases of the clinical program, there were more premature discontinuations and withdrawals in the lanthanum group compared to the comparator. Similarly for adverse events there were more discontinuations for adverse events in the lanthanum group compared to standard therapy (See Table 9)

Table 9: %tages of discontinuations and withdrawals-all phases of lanthanum program

Phase	Lanthanum	Comparator (placebo or active control)
I	15.1	6.6
II	32.2	28.4 (placebo)
III	60.4	41.4

One of the phosphate binders used in this study, RENAGEL, is approved by the FDA for the reduction of phosphorous in ESRD whereas another comparator phosphate binder, Calcium Carbonate, is not approved by the Agency. However, Calcium carbonate is approved in the UK, Netherlands, Sweden, Finland, Switzerland, Germany and Australia. The safety profile of calcium carbonate is not known to the Agency but apparently known in Europe where it is in use for this indication.
The utilization and acceptance of comparative data from studies that used an unapproved drug by the Agency is perhaps exceptional and conclusions reached from such studies may raise regulatory concern and set precedence. Consequently, the application of the term "Standard Therapy" by the sponsor that collectively includes both approved and unapproved phosphate binders may also raise a regulatory issue on validity of data.

This observation, however, should not affect the demonstrated efficacy of lanthanum carbonate because lanthanum was more effective than placebo but both the approved and unapproved

phosphate binders were found to be more effective than lanthanum (See Efficacy conclusion Appendix 3). The comparison of adverse events in this situation where one of the comparator's safety profile is not known may make safety comparisons regulatorily untenable in the Agency. For example, this reviewer shows that in Figures 26 and 27, micrographs derived from a microscopic slide submitted by the sponsor are abnormal and yet these are from a patient's bone at baseline given calcium. This was a bone biopsy obtained at baseline from a patient treated with "calcium". This microscopic slide shows abnormal bone biopsy at baseline from a patient who has been given "Calcium". This exemplifies one of the difficulties that may arise using an unapproved drug such as "Calcium" as a comparator and for which histomorphometric data were used to exclude aluminum-like effects of lanthanum. The frequencies of such baseline data abnormalities in the relatively small, paired, bone biopsy sub-study cannot be verified by this reviewer. This rises in principle some doubt about the validity of conclusions based on histomorphometric data in the bone sub study.

B. Efficacy

The primary efficacy endpoint was the reduction and maintenance of serum phosphate levels in hyperphosphatemic patients with end stage renal disease. A secondary endpoint was the proportion of patients whose phosphorous levels were controlled during the trial to a predefined level of ≤5.9 mg/dL in the US, and ≤5.6 mg/dL in the UK. In the resubmitted NDA, the data presented for efficacy are not different for reduction or maintenance of reduced levels of phosphorous from those described in the original NDA including the LAM- IV -307, that shows similar findings albeit open label (Figure 1). This study showed a progressive decrease in serum phosphorous level in the lanthanum group but not as much as the comparator (Figure 2). The data from the other short term clinical studies are in the review of the original NDA. (See Appendix 3).

In the integrated summary of efficacy of placebo controlled studies in the original NDA, the pre-study serum phosphorous levels (PSPL) for placebo and lanthanum carbonate were similar, 6.186 mg/dL versus 6.251 mg / dL respectively. At the end of washout period, there were no differences (7.39 mg/dL vs 7.69 mg /dL). At the end of dose titration phase the serum phosphorous levels decreased from 7.39mg/dL (end of washout) to 5.62mg /dL and from 7.69mg/dL (end of wash out) to 5.49mg/dL for the placebo and lanthanum groups respectively.($p=0.6942$). The serum phosphorous level at the end of randomization was 7.85±1.96 mg/dL for placebo whereas for patients given lanthanum carbonate serum phosphorous level was 5.94 ±1.65 mg /dL. ($p<0.0001$). Post-randomization levels of phosphorous in the two treatment groups showed significant differences supporting efficacy of lanthanum.

The change from baseline in PSPL during weeks 1 – 7, the titration weeks, shows a decrease in both treatment groups. The mean change was -1.43 for lanthanum and -1.91 for standard showing a statistically significant difference in favor of standard group ($p<0.000$) . Similarly the change during the maintenance phase , weeks 7 – 52 show no significant change at week 52 between the two treatment groups (Table 3 ISE) (Appendix 3).

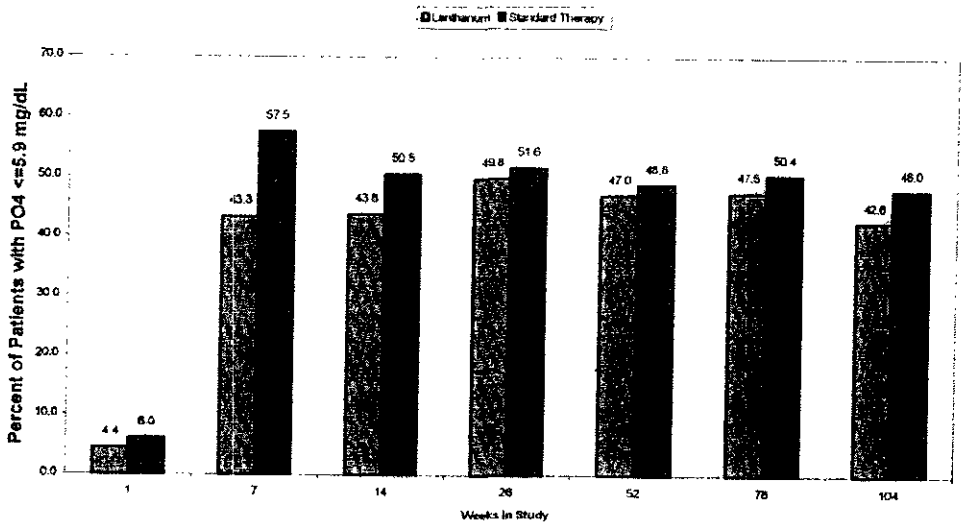
Overall, primary efficacy endpoint was reduction of serum phosphate in end stage renal disease (ESRD) patients with hyperphosphatemia using a temporal decline of pre-dialysis serum Phosphate (PSPL) over time as a basis for comparison of point estimates between lanthanum and other comparators (standard therapy and calcium carbonate). Primary efficacy was determined according

to the level of serum phosphate achieved after 5 weeks in the dose titration phase: serum phosphate levels < 1.80 mmol/L were considered to be the control.

Secondary efficacy was the evaluation of maintenance of control after 25 weeks of treatment including 5 weeks of treatment and 20 weeks of maintenance. Efficacy of lanthanum was demonstrated in the original NDA.

The primary efficacy endpoint in this study was the predialysis serum PO4 levels (PSPL), which were measured at the first dialysis sessions of study visits week 1 to week 7, i. e., titration period (Figure 5SS- In both treatment groups serum PO4 levels declined over time. However, when compared between treatment groups, the change from baseline serum phosphorus level to each follow- up week of dose titration, a greater reduction occurred for patients on standard therapy (p= 0.000). At the end of dose

Figure 1: Percent of patients with PO4 < 5.9mg/dL



Serum phosphorous levels were controlled in 59% and 23% of patients in the lanthanum and placebo groups, respectively, by week 4 (mean difference of 36%; p=0.001). Details of these data are in the original review (See Appendix 3). Overall the efficacy data suggest that lanthanum carbonate when administered orally 3 times a day with meals as compared with placebo is an effective phosphate binder.

Efficacy conclusion - (Page 77)

In summary lanthanum is an effective PO4 binder, controls hyperphosphatemia and maintains the level of serum PO4 at the predefined level for 1 year (Figure 2).

In conclusion, the efficacy data show that lanthanum carbonate reduces serum phosphorous levels and also maintains serum phosphorous levels within normal range in a statistically significant number of subjects. The doses evaluated in all these studies ranged from 225 mg to 3000 mg daily.

Serum Chemistries

The following figures below show the serum levels for phosphorous, total serum calcium, calcium phosphate product, and serum parathyroid levels, serum osteocalcin and bone specific alkaline phosphatase during a period of 1 year of follow up

1) The predialysis phosphorous concentrations are similar at baseline but there is a decrease of the levels over the period of one year (Figure 2).
2) Serum Calcium X Phosphate product levels are similar at baseline but lower in the lanthanum group compared to standard group. (Figure 3)
3) Total serum calcium concentrations are higher at baseline in the lanthanum group compared to standard group but lower in the lanthanum group compared to standard group (Figure 4).
4) Serum parathyroid hormone (PTH) level is higher at baseline in the lanthanum group but comparable levels to standard for the one year. (Figure 5)
5) Serum osteocalcin concentrations(Figure 6)
6) Bone specific alkaline phosphatase(Figure 7)
7) Serum parathyroid hormone levels without the standard deviation bars (Figure 8 and discussion below).

PSPL levels in LAM-IV-307 Over time

Figure 2: Phosphorous levels - LAM-IV-307

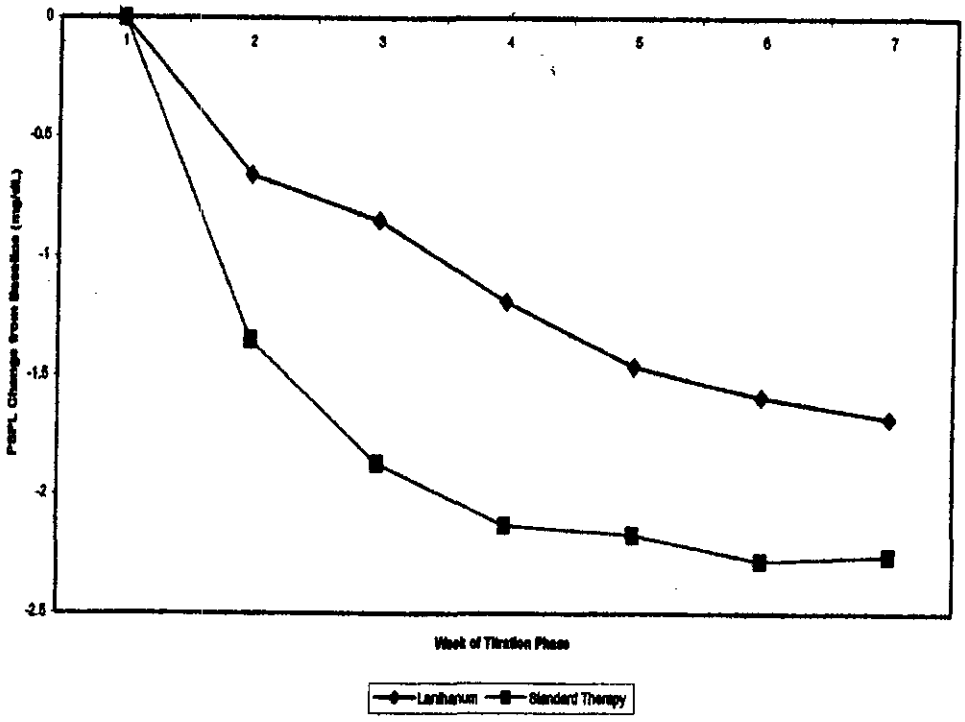


Figure 3: Predialysis phosphate concentrations in patients for 52 weeks

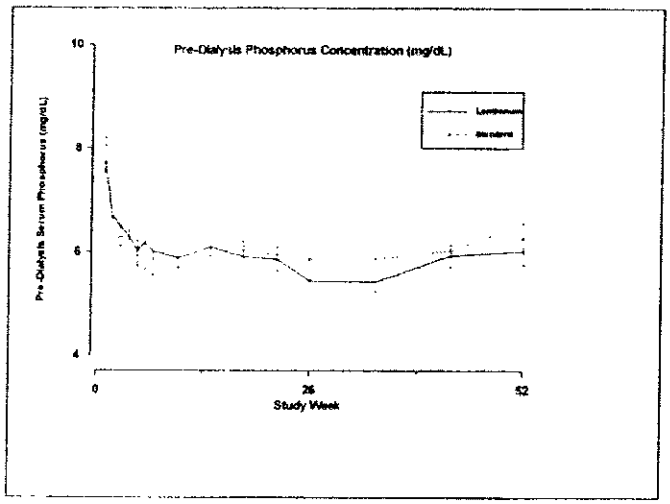


Figure 3: Serum calcium phosphate product in patients for 52 weeks

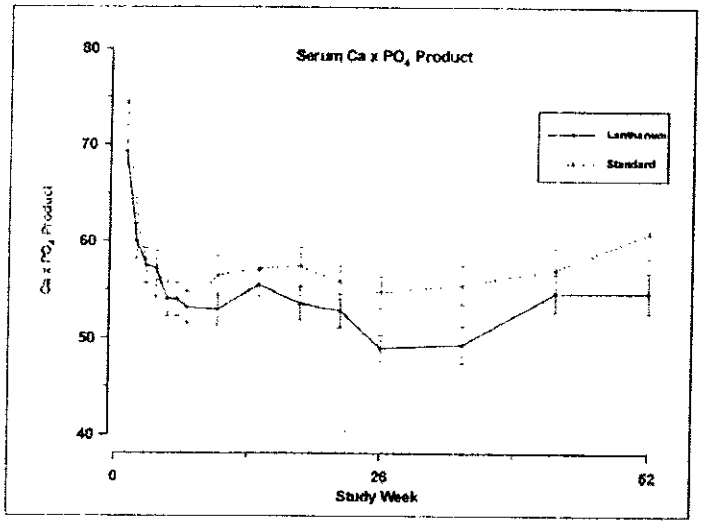


Figure 4: Serum calcium concentration in both treatment groups for one year

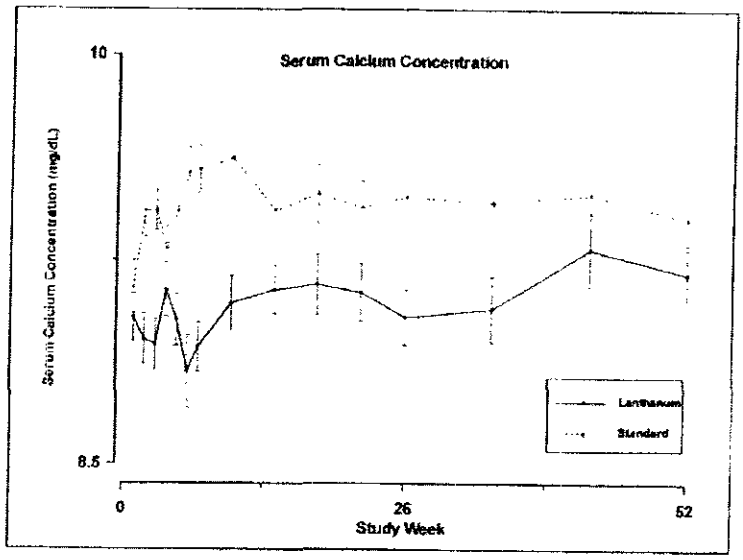
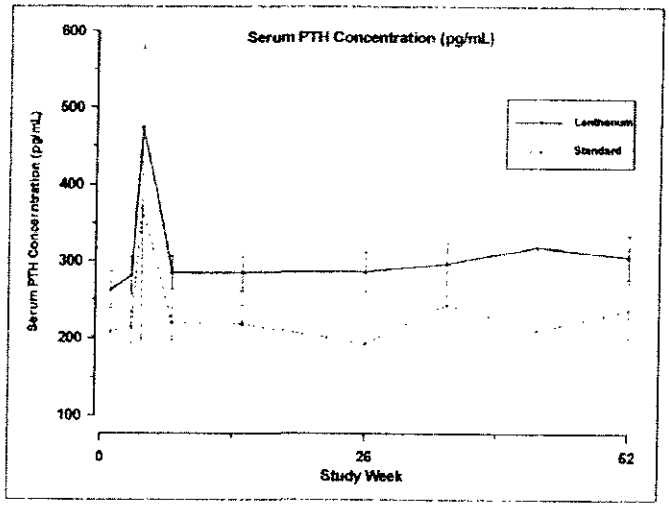


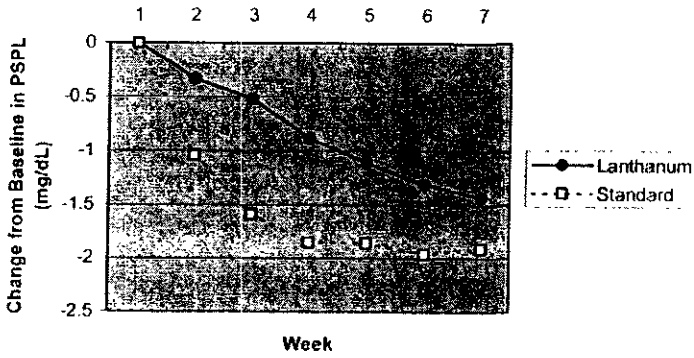
Figure 5: Serum parathyroid concentration in both treatment groups for one year



Lanthanum is available as a chewable unflavored tablet in two dosage strengths (250 mg, and 500 mg) for oral administration.

titration, week 7, the mean (±SD) change from baseline serum phosphorus level was –1.43±2.19 for the lanthanum group versus –1.91±2.20 for the standard therapy group, p<0.000.

Figure 5-ISE. Change from Baseline in PSPL during the Titration Phase (Weeks 1-7) – ITT Population



p-Value	N/A	0.000	0.000	0.000	0.000	0.000	0.000
	599	575	563	536	520	502	493
Std. N=	602	579	580	566	566	548	558

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-307, Vol. 206, Table 14.2.2.1.]

The changes from baseline serum phosphorus level during the maintenance phase, weeks 7 to 52, are summarized in Table 3-ISE. The changes from baseline in PSPL were greater in the standard therapy group at weeks 7, 10, 14 and 26 than in the lanthanum group. At week 52 there were no statistically significant differences between the groups.

Table 3-ISE. Change From Baseline In PSPL During The Maintenance Phase (Weeks 7-52) - ITT Population Of The Safety Update (May 30, 2002).

Week	Baseline (Week 1)	Week 7	Week 10	Week 14	Week 26	Week 52
P-value	N/A	<0.001	<0.0002	0.0042	0.036	1.00
Lanthanum						
Mean Change	N/A	-1.706	-1.672	-1.545	-1.659	-1.682
N	632	531	511	473	364	232
Standard						
Mean Change	N/A	-2.228	-2.170	-1.944	-1.998	-1.685
N	633	588	575	557	495	350

[FDA's Analysis, Dr. Freidlin (HFD-710).]

In the aggregate the data indicate that standard therapy is superior to lanthanum treatment in reducing serum phosphorus levels in patients with end stage renal disease, and thus controlling hyperphosphatemia.

Sub-population Efficacy Analyses: Sub-population efficacy analyses conducted by the sponsor, in placebo-controlled studies (LAM-IV-202, 204 and 302), included the following subgroups: females and males, Caucasians and Blacks and for patients ≤64 and ≥65 years old (Table 4-ISE). Overall, even though the number of patients per subgroup was small, the findings for the sub-populations were consistent with those for the general population, there were no marked differences in the proportion of patients with controlled serum phosphorus based on age, gender or race.

Whole page extracted from original NDA review – Dr Pelayo

C. Safety

The safety update in this review includes case report forms (CRF), and data collected through February 29, 2004. The integrated summary of safety in the original NDA and the 4 month safety update, that was reported separately, has been reviewed in the original NDA. The safety data base consisted of 11 phase I clinical pharmacology studies in 169 healthy volunteers and 10 ESRD patients; 8 phase II and III studies. The total number of healthy volunteers (N = 169) exposed to single and multiple doses of lanthanum was for very short duration of one to 5 days. There were 76 healthy volunteers exposed to standard treatment group. These two groups of patients (169 + 76 = 233) cannot be considered to be at risk for fractures and other serious adverse events including impairment of cognitive function. This cohort has been included in several tables calculated for risk assessments and should be excluded from long term safety analyses. The sponsor has included these healthy volunteers of 233 patients into their database as patients exposed to lanthanum and therefore at risk for fractures and for comparative assessments of other serious adverse events (See Tables 26, 27 and Appendix 5).The validity and accuracy of such unadjusted tables remain either uninterpretable or difficult to make meaningful comments. The reviewer recommends that the sponsor should be requested to submit revised tables to reflect the removal of patients who were only exposed to single or multiple doses lanthanum for less than 7 days in their subsequent submissions. No bone biopsies were obtained from any of these healthy volunteers. Two out of 11 studies involving healthy volunteers were terminated because of unexpected serious adverse events and increased frequencies of adverse events (Studies 101 and 104) (Table 45). The bone changes, if any, in these healthy volunteers were not described or summarized anywhere. The treatment emergent adverse events in these patients are presented in Table 10. There are significant differences between the frequencies of adverse events among those volunteers on lanthanum, particularly GI symptoms, compared to placebo.

Table 10: Phase 1 patients with treatment emergent adverse events - lanthanum program -4 month safety update

Adverse event	**Lanthanum Single dose N=132 n (%)**	**Lanthanum Multiple dose N=111 n (%)**	**Placebo/Others N=76 n (%)**
Nausea	34(25.8)	12(10.8)	2(2.6)
Vomiting	27(20.5)	6(5.4)	1(1.3)
Abdominal pain	13(9.8)	6(5.4)	1(1.3)
Headache	22(16.7)	15(13.5)	2(2.6)
Dizziness	8(6.1)	5(4.5)	2(2.6)
Myalgia	4(3.0)	3(2.7)	0(0.0)
Rash	4(3.0)	3(2.7)	0(0.0)
Constipation	3(3.0)	3(2.7)	0(0.0)

.* Note the significant differences between the frequencies of adverse events among those volunteers on lanthanum, particularly GI symptoms, compared to placebo.

Drug exposure

According to the sponsor 1, 672 patients received lanthanum and 909 patients received standard therapy. Of these, 151 (9%) received lanthanum for > 2 years and 155 (17.1%) received standard therapy for > 2 years. It is evident that these numbers are too few to assess long term safety that will show significant differences between the two groups. The 15-month update on LAM-IV-307 added a further 33 lanthanum patients and 32 standard therapy patients. LAM-IV-303 included 49 patients in both treatment arms. Assuming that these additional patients were treated for > 2 years the total number of patients as of the 15 month safety update will be 151+33+49= 233 for lanthanum and 155+32+49=236 for standard therapy group. According to the sponsor the current clinical database of exposure to lanthanum consists of a total of 1,933 males and females between the ages of 18 and above. These included 169 healthy volunteers (Table 45) and 1,754 patients who received lanthanum throughout the clinical development program. Of the 1,754 patients who participated in phase 2-3 studies, 1,507 patients participated in long-term studies, of which 212/233 patients took lanthanum for approximately 2 years. Of the 212 patients who took lanthanum for more than 2 years only 10 patients (4.7%) had bone biopsies at 2 years and only 3 patients have had bone biopsies between 4 to 5 years (based on sponsor's submission)..

Three interim analyses have been reported to date June 1 2004, for LAM-IV-307. The last interim was in January 2004 and included data collected through May 30 2003. The table below shows the number of patients who have been treated for 12 to 24 months or longer. The average length of drug exposure was 0.98 and 1.33 years respectively for lanthanum and standard therapy.
In addition to the Integrated summary of safety in the original NDA, the additional data presented in the Serious Adverse event analyses are from the LAM-IV-307 Third Interim Clinical Study Report and from updates received up to June 2004. In this open label long term active controlled study, LAM-IV-307, about 68% (461/680) of patients were withdrawn for a variety of reasons in the lanthanum group compared to about 49% (327/674) in the standard group. One hundred and five patients withdrew consent (15.4%) from the lanthanum group compared to 30 (4.5%) who withdrew consent in the standard group suggesting a possible lack of tolerability of lanthanum. Alternatively the relatively low rate of withdrawal among the standard group could be access to other forms of drugs to which they switched whereas there was no option for those on lanthanum. (See Table ....).

There was no histomorphometric evidence of aluminum-like effects observed in bone biopsies in humans exposed to lanthanum. Only 19 patients (10.7%) completed the cognitive function test in the lanthanum group compared to 54 patients (30.0%) in the standard therapy (Table 5).

Other clinical parameters, including ECGs and liver function tests, showed no significant changes between the treatment groups. There was no evidence of an adverse trend in survival against lanthanum compared to standard therapy. However, many factors influenced the validity of making such comparisons. These include patient attrition due to different rates of discontinuation and the high background mortality rate of ESRD. The statistical analyses on mortality will be discussed in the statistical review. Other secondary factors that contributed to mortality included the role of vascular ectopic calcification and consequent atherosclerotic vascular disease (See Table 11).

Deaths

According to the sponsor, no lanthanum-related deaths were observed. Although the survival curves tend to be comparable between the two groups, it is evident that at 44 months, the mortality rate for lanthanum was 23.8 % (418 / 1754); whereas for standard therapy mortality was 20.4% (202/990) (Dr Valeria Friedlin Statistics). This suggests that there is a slight excess of mortality in the lanthanum group after the first half life of lanthanum, 3.5 years. This time point happens to coincide with the mean half life (3.57 years) of lanthanum.

The adverse events that most frequently led to death are in Table 11 below:

Table 11: Adverse events that most frequently led to death in lanthanum program

Adverse event	Lanthanum N 682 (%)	Standard N 676 (%)
Cardiac arrest	12(1.8)	21(3.1)
Myocardial infarction	11(1.6)	13(1.9)
Arrhythmia	5(0.7)	9(1.3)
Sepsis	4(0.6)	9(1.3)

Serious Adverse events

*About 2,696 SAEs were reported throughout the course of the study. Three events were thought to be likely to be drug related: namely: Pancreatitis, GI hemorrhage, and constipation and all were in the lanthanum group (Table 12)

Table 12: Some SAEs with frequencies of 2% or greater adjusted for discontinuations - LAM-IV-307

*Serious Adverse event	Lanthanum N 682 (%)	Standard N 676 (%)
At least one SAe	388(56.9)	481(52.4)
Chest pain and M.I.	30 (4.4)	28(3.0)
Coronary Artery disorder	16(2.3)	31(3.4)
Cardiac arrest	18(2.6)	26(2.8)

Laboratory adverse events:

Laboratory changes that showed consistent significant inter-group differences are in Table 13.
Vital signs that showed consistent significant inter-group differences are in Table 14.

Table 13: Summary of significant inter-group lab. changes from prestudy to month 24 -LAM-IV-307

Laboratory tests	Lanthanum N 682 (%)	Standard N 676 (%)
Cholesterol		Low(p=0.000)
LDL.		Low(p=0.000)
Osteocalcin	High(p=0.000)	
Parathyroid hormone	High(p=0.000)	
Calcium		High(p=0.000
Alkaline Phosphatase	High (p=0.000)	

Table 14: Vital signs with significant inter-group changes from prestudy to month 24LAM307

Vital signs	Lanthanum	Standard

	N 682 (%)	N 676 (%)
Weight (post dialysis)	Higher p=0.019	
SBP	Decrease(p=0.023)	
DBP	Decrease0.034	
Respiratory rate		Increase (p=0.028)

Adverse events

The percentages of the most common adverse events are summarized in Tables 15 and 16 below

Table 15: %tage of patients with most common treatment emergent adverse events in LAM-IV-307 (adjusted for drug exposure)

Adverse Events	Treatment Groups			
	All Adverse Events		*Drug-Related Adverse Events	
	Lanthanum (N=680)	Standard (N=674)	Lanthanum (N=680)	Standard (N=674)
	%	%	%	%
At least one Adverse Event	95	69	22	9
Nausea	35	27	7	0.7
Vomiting	25	20	3	0.3
Diarrhea	22	21	3	0.5
Dialysis graft complication	25	23	0	0
Dyspnea	21	22	0	0
Dizziness	21	19	0	0.1
Headache	21	19	1	0.1
Dialysis graft occlusion	20	19	0	0
Myalgia	20	19	0.4	0
Chest pain	20	17	0.6	0
Coughing	18	19	0.1	0.1
Pain	17	16	0	0
Hypotension	15	16	0	0
Dialysis catheter complication	15	15	0	0
Upper respiratory tract infection	15	12	0	0
Edema peripheral	14	18	0	0
Influenza-like symptoms	14	14	0	0
Fever	14	13	0.3	0
Abdominal pain	16	16	2	0.5
Constipation	13	12	3	1
Pruritus	12	11	0.7	0
Back pain	12	14	0	0
Leg pain	12	11	0	0
Malaise	11	11	0	0
Dyspepsia	10	12	2	1

** As this is an open-label study, these data may be affected by a potential investigator bias.*

Table 16: Summary of treatment emergent adverse events - LAM-IV-307

Category	Treatment Group		
	Total N=1,358 (%)	**Lanthanum N= 682 (%)**	**Standard N= 676 (%)**
No of patients with at least one treatment emergent AE	1,303(95.9)	646(94.7)	657(97.2)
No of patients with at least one likely drug- related treatment emergent AE	237(17.5)	150(22.0)	87(12.9)
No of patients withdrawn for AEs as study outcome	123(9.1)	99(14.5)	24(3.6)
No of patients with at least one SAE	869(64)	388(56.9)	481(71.2)
No of patients with at least one drug related SAE	3(0.22)	3(0.44)	0
No of patients who died during study as study outcome.	128(9.4)	37(5.4)	91(13.5)
No of patients who died during or within 30 days post study.	157(11.6)	52(7.6)	105(15.5)

Lanthanum carbonate safety on Bones - Estimation of half life of lanthanum

The transfer rate of lanthanum into bone is calculated by the sponsor to be 1.125µg/hr and 3.675µg/hr using average and measured highest bioavailability. After 15 years exposure lanthanum concentration accumulation rates in bone would result in 13,922µg/kg and 45,990µg/kg.

Bone biopsies

A total of 105 biopsies and 91 biopsies were provided "on Treatment" population (Table 17). Of these only 63 paired biopsies were suitable for histomorphometric evaluation. This shows the limitation of the data upon which a conclusion on the aluminum like effect is base. In the opinion of this reviewer this is inadequate.

Table 17: Temporal distribution of bone biopsies carried out in bone sub-study of 307

Bone samples provided by the overall "on Treatment " population		
Time of biopsy (months of treatment ±3 months)	**Number of biopsies Lanthanum**	**Number of biopsies Comparator**
Baseline	120	130
6months	3	3
12 months	60	67
18 months	15	8
24 months	14	12
30 months	0	1
48 months	1	0
54 months	11	0
60 months	1	0
Total	**105**	**91**

The table below summarizes all the bone biopsies for evaluation of long term toxicity.

Table 18: Overview of Bone biopsy data from the lanthanum clinical program

Overview of Bone Biopsy Data			
Total number of biopsies	**Biopsies per treatment group**	**Study**	**Submissions**
140	Lac: 34 baseline/one year pairs 2 one year Cac: 35 baseline/one year pairs	**LAM-IV-303**	Original NDA (4/30/2004) LAM-IV-303 Study report
Approvable letter			
142**	Lac: 28 baseline/one year pairs ST: 6 baseline/two year pairs	**LAM-IV-307**	Resubmission LAM-IV-307
21	Lac: 11 off-treatment Cac: 10 off-treatment	**LAM-IV-303**	Resubmission
166	Lac: 91 63 baseline, 5 one year, 19 two year 1 three year, 3 off-treatment ST: 75 58 baseline, 1 one year 12 @ 2 year, 4 off-treatment	**LAM-IV-307**	Resubmission
13	La: 13 1 four year, 11 five yr and one off- treatment	LAM-IV-301	Resubmission
*497 = Total number of biopsies with end stage renal disease in lanthanum studies. LAM – IV- 303 and LAM-IV-307 are controlled studies **(Boldened in table).**			

*** This should be a total of 423; **This should be 68 and not 142.**

From the above table, the bone samples collected include serial bone biopsies from patients on dialysis in two controlled studies (LAM-IV-303 and LAM-IV-307) with one year (LAM – IV-303) or 1 and 2-year (LAM-IV-307) exposure to lanthanum carbonate as a phosphate binder Both studies included a control group treated with standard non-aluminum based phosphate based phosphate binders.

Additional bone samples were obtained as single biopsies from patients with approximately 4 years of lanthanum exposure who continued on open label treatment with lanthanum carbonate in LAM-IV-301. Additional follow-up biopsies were also obtained from patients with one year of exposure to lanthanum carbonate but have been off lanthanum treatment for approximately 2 years (LAM-IV-303), and bone biopsies were also obtained from patients exposed to lanthanum carbonate for 1 or 2 years but had a third biopsy while on treatment or after switching back to standard therapy (LAM-IV-307).

The patient population from which these bone biopsies was clinically heterogenous but they were considered representative and relevant to the ESRD population in the intended clinical setting.

The sponsor prospectively assessed bone accumulation of lanthanum and bone histomorphometry in patients treated with lanthanum carbonate compared to patients treated with standard phosphate binder therapy for periods of one and two years but these data do not reflect steady state for lanthanum... They confirm that lanthanum accumulates in bone of animals and humans. .

The lanthanum exposure profile of patients providing bone biopsies is presented in Tables 19-21. They are categorized into 3 groups:

- An "Overall on treatment "group- any patient who provided at least one bone biopsy sample while receiving either lanthanum or comparator therapy.
- A "Sequential on treatment cohort" (Table 19).
- A "Sequential off treatment cohort"(Table20)

Table 19: Bone biopsies provided by sequential "on treatment cohort in LAM-IV-307

Bone samples provided by the sequential "on treatment" cohort in study LAM-IV-307		
Time of biopsy (months of treatment ± 3 months)	**Number of biopsies Lanthanum**	**Number of biopsies Comparator**
Baseline	10	7
12 months	12	7
18 months	7	3
24 months	5	4

Table 20: Bone biopsies provided by "off treatment" cohort in LAM-IV-307

Bone samples provided by the sequential "off treatment" cohort in study LAM-IV-303		
Time of biopsy (months on/of treatment ± 3 months)	**Number of biopsies Lanthanum**	**Number of biopsies Comparator**
Baseline	10	10
12 months	11	10
24 months	11	10

The total pool of samples included baseline and single time-point biopsies from patients treated with lanthanum carbonate or standard therapy for up to 4 years sequential biopsies from patients similarly treated for up to 2 years, and sequential biopsies from patients treated for 1 year followed by standard therapy for up to a further 2 years. These samples allowed an assessment of lanthanum deposition in bone with time on treatment, as well as an indication of the rate of clearance of lanthanum out of bone. Bone lanthanum concentrations are expressed in ug/G for animal data and ug/kg for human data.

In addition the sponsor investigated bone lanthanum levels and bone histomorphometry in single bone samples in patients who either discontinued treatment with lanthanum carbonate or who

supplied additional bone biopsies while on treatment with lanthanum carbonate for periods of approximately 4 years (Table 18). This reviewer acknowledges the value of histomorphometry as the gold standard for evaluating metabolic bone disease. There is no doubt in the literature that this is the universally accepted method of monitoring and evaluating bone changes over time using iliac bone biopsies. However, it should be pointed out that there are no standardized reference data or universally accepted values for histomorphometric classification and as a result the results and analyses presented here in this NDA are those established in the University of Bone and Mineral Metabolism laboratory. Comparison of data can be made with placebo or with active controls for safety. Unfortunately, the active control used has not been approved by the Agency for safety. Furthermore the Agency has not approved values established by the University of Kentucky, and these values may change over time as we have seen with JNC and NCEP standards that are established by professional bodies. In contrast histopathological diagnosis of osteomalacia and other forms of renal osteodystrophy are standardized but have the limitation of quantification over time. Therefore a combination of histomorphometry and histopathology may be useful in evaluation of bone damage and soft tissue damage surrounding bone. The difficulty here, however, is the lack of enough long term bone biopsies to evaluate. The histological classification of bone disease at baseline is presented in table 21. The histological shifts from baseline are tabulated in Table 22. The reviewer is not comfortable making any comments on the shifts described in Table 22 because one of the slides from the comparator taking an unapproved phosphate binder is abnormal at baseline. According to the sponsor "there were limited data available on which to base the sample size estimates for the bone substudy, therefore numbers were based on practical rather than statistical considerations." Thus the study was not powered to rule out whether lanthanum carbonate has deleterious effect(s) in bone formation as compared with active control.

Table 21: Baseline classification of bone histology LAM-IV-307

Classification	Lanthanum Carbonate Treatment	Standard Treatment
Adynamic bone Disease	43(40.2%)	36(35.3%)
Osteomalacia	0	0
Mixed uremic osteodystrophy	21(19.6%)	21(20.6%)
Hyperparathyroid	26(24.2%)	31(30.4%)
None (inadequate specimen)	17(15.9%)	14(13.7%)
Total	107(100%)	102(100%)

One of the several issues to be resolved in this NDA is therefore lanthanum long term bone toxicity. Lanthanum bone toxicity due to its continuous accumulation is not a primary metabolic disease and should be distinguished from the renal osteodystrophy that has a metabolic complication. Furthermore lanthanum in the bone is slow to clear. The adverse events that may result from continuous lanthanum deposition in bones already affected by renal osteodystrophy are the key issues to be addressed by the review of bone pathology in this resubmission. It may be difficult to separate the two lesions but histomorphometry alone may be inadequate to capture both, hence the need for qualitative assessment of some histological slides that the reviewer will summarize below. The review of bone pathology in rats with ESRD that was carried out by the reviewer on slides provided by the sponsor will be of relevance in evaluating some human materials received from the sponsor on May 7, 2004.

The clinical benefits of lanthanum via the binding of phosphates however appear evident but these are independent of lanthanum accumulation in bones. For example in rats with normal renal function that received lanthanum, this reviewer found histological changes that included severe cortical bone resorption, periosteal thickening, and variable osteoid bands. One animal had an exostosis of the tibia. (Groups C and F).

Table 22: Shift of histological categories at 1 year and 2 yr follow-up LAM-IV-307

	Lanthanum Carbonate Therapy Group											
Baseline		**1 year follow up**						**2 year follow up**				
	N	**ABD**	**HPBD**	**LTOM**	**MUOD**	**None**	**N**	**ABD**	**HPBD**	**LTOM**	**MUOD**	**None**
ABD	16	5	7	0	3	1	8	2	3	0	3	0
MUOD	8	3	3	0	0	1	6	1	2	0	1	2
HPBD	9	1	6	0	2	1	8	0	5	0	1	2
None	3	1	0	0	0	2	3	1	0	1	1	0
Total	36	10	16	0	5	5	25	4	10	1	6	4
Standard therapy												
Baseline		**1 year follow up**						**2 year follow up**				
	N	**ABD**	**HPBD**	**LTOM**	**MUOD**	**None**	**N**	**ABD**	**HPBD**	**LTOM**	**MUOD**	**None**
ABD	12	5	4	0	1	2	5	0	3	0	0	2
MUOD	10	1	5	0	3	1	5	0	4	0	1	0
HPBD	12	3	5	0	2	2	6	3	2	0	1	0
None	5	2	1	0	0	2	3	3	0	0	0	0
Total	39	11	15	0	6	7	19	6	9	0	2	2

ABD=Adynamic bone disease; MUOD=Mixed
HPBD=Hyperparathyroid bone disease

The clearance of lanthanum from tissues was assessed in animals loaded with lanthanum for 4 weeks and maintained off dose for up to 26 weeks. There was differential clearance of lanthanum from the GI of rats. Clearance from bone cartilage and teeth was slow with more than 66% (sternum), 82% (femur, 60% (trachea) and 75 % (teeth) of lanthanum retained in these tissues after 4 weeks off dose in rats.

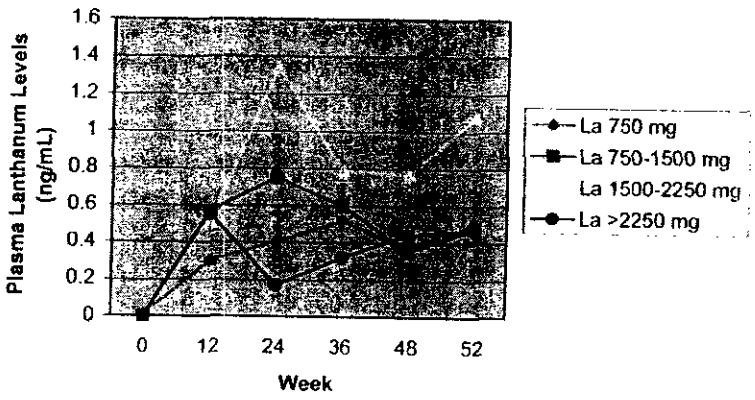
Studies Specifically Conducted to Assess Bone Safety: Study LAM- IV- 303 assessed the effect of lanthanum carbonate compared to calcium carbonate on renal bone disease by comparing bone tissues obtained from paired biopsies. Of the 98 patients randomized into the study, 71 patients received a follow-up biopsy after 52 weeks of treatment, and therefore provided paired biopsy data, however only 63 pairs of biopsies were suitable for histomorphometric measurements.

The significance of the bone biopsy findings is questioned because interpretation of the findings is further confounded by the fact that calcium carbonate, the active control, is not an FDA approved phosphate binder thus its safety profile, as compared with placebo/ standard therapy, is unknown to the Division of Cardio- Renal Drug Products.

Mineralization lag time the primary efficacy endpoint of the study, defined as the mean time interval between deposition and mineralization of any volume of matrix averaged over the entire life span of the osteoid seam is a key variable for the assessment of new bone formation. The median z- scores of mineralization lag time indicate that patients in the lanthanum carbonate group had slower bone formation than those patients receiving the active control, + 0.8 versus + 3.975, respectively.

Specific Findings of Safety Review Plasma and Bone Tissue Levels of Lanthanum: Study LAM-IV- 303 is extracted from original review (Page 41). Plasma lanthanum levels were measured at weeks 0, 12, 24, 36, 48 and 52. In lanthanum- treated patients there were increases in plasma lanthanum for all doses administered compared with baseline levels. The mean plasma levels in the bone substudy are presented in Table 39 from week 7 but not at baseline. There is a dose dependent relationship in plasma lanthanum levels (Figure 2- ISS) (page 43).

Figure 2-ISS. Plasma Lanthanum Levels by Visit and Dose Level in Lanthanum Group – ITT Population

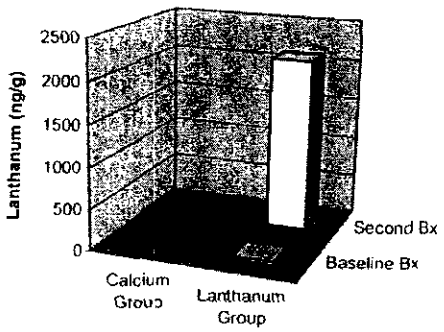


Week	La 750 mg n	La 750-1500 mg n	La 1500-2250 mg n	La >2250 mg n
0	19	6	0	0
12	13	21	3	3
24	12	22	3	2
36	10	19	4	3
48	15	14	4	2
52	11	15	5	3

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-303, Vol. 189, Table 30.]

Figure 3-ISS illustrates bone lanthanum concentrations at baseline and after 52 weeks of treatment. While bone lanthanum concentration remained essentially unchanged in the calcium group, mean±SD 52.2±54.8 ng/g versus. 102.5±165.8 ng/g, in the Lanthanum group there was a marked, over a 50-fold, increase in bone lanthanum concentration, from (mean±SD) 40.4±21.8 to 2104.8±1356.9 ng/g.

Figure 3-ISS. Summary of Bone Lanthanum Concentration by Treatment Group.



[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-303, Vol. 189, Table 17.]

In the aggregate the results on plasma and bone tissue levels indicate that there is a significant gastrointestinal absorption of lanthanum, and that there is accumulation of lanthanum in bone over time. Albeit, the sponsor did not evaluate whether lanthanum accumulates in human tissues other than bone, based on the data from pre-clinical studies one could assume that tissue accumulation of lanthanum in humans is widespread as well. It is also unknown whether there is a "limiting step", in regards to dose

Extracted from original review by Dr Pelayo.- Whole page above.

From a long term perspective, the sponsor acknowledged the need for additional long term safety data that are dependent on the rate at which the absorbed lanthanum is distributed and ultimately cleared from tissues particularly in **bones** of patients receiving lanthanum. The time to steady state of lanthanum in bones is 10 to 15 years.

Table 23: Summary of treatment emergent adverse events in Bone substudy-LAM-IV-307

	Treatment Group		
Category	**Total**	**Lanthanum**	**Standard**
No of patients with at least one treatment emergent AE	190(96.4)	94(94.0)	96(99.0)
No of patients with at least one likely drug related treatment emergent AE	32(16.2)	21(21.0)	11(11.3)
No of patients withdrawn for AEs as study outcome	3(1.5)	2(2.0)	1(1.0)
No of patients with at least one SAE	105(53.3)	53(53.0)	52(53.6)
No of patients with at least one drug related SAE	0	0	0
No of patients who died during study as study outcome.	16(8.1)	7(7.0)	9(9.3)
No of patients who died during or within 30 days post study.	18(9.1)	7(7.0)	11(11.3)

No comments will be made on data that are not adjusted because they are misleading e.g. Table 24.

Table 24: Frequencies of adverse events in musculoskeletal system experienced in >2% of patients in the bone sub-study LAM-307 (unadjusted).

	Bone Sub-study		All Patients	
Body system/ AE	**Lanthanum Group (N = 100)**	**Standard Group (N = 97)**	**Lanthanum Group (N = 680)**	**Standard Group (N = 674)**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Subjects with at least one adverse event	94 (94.0)	96 (99.0)	644 (94.7)	654 (97.0)
Musculoskeletal System Disorders	33 (33.0)	50 (51.5)	259 (38.1)	334 (43.8)
Myalgia	19 (19.0)	21 (21.6)	135 (19.9)	183 (27.2)
Skeletal pain	11 (11.0)	9 (9.3)	50 (7.4)	69 (10.2)
Arthralgia	5 (5.0)	17 (17.5)	61 (9.0)	90 (13.4)
Fracture - NW	4 (4.0)	8 (8.2)	33 (4.9)	47 (7.0)
Muscle weakness	3 (3.0)	6 (6.2)	16 (2.4)	27 (4.0)
Arthritis	1 (1.0)	5 (5.2)	18 (2.6)	26 (3.9)
Back pain	1 (1.0)	3 (3.1)	1 (0.1)	9 (1.3)
Bone disorder	0	2 (2.1)	1 (0.1)	6 (0.9)
Osteochondrosis	0	2 (2.1)	6 (0.9)	5 (0.7)
Osteoporosis	0	2 (2.1)	0	2 (0.3)

Table 25: Lanthanum clearance from bone sequential off treatment patients LAM-IV-303

Time after first dose (months)	Time off treatment (months)	Bone lanthanum concentration	
		Mean value	Median value
0	-	45.3(n=10)	43.0 (n=10)
12	0	2806.27(n=11)	2887.0(n=11)
36	24	1902.94(n=11)	1441.3(n=11)
Slope* (month)		-0.0162	-0.0289
T1/2		42.82 months	23.94 months
		3.57 years	2.00 years

*Assumes constant rate of lanthanum clearance out of bone after cessation of treatment: LAM-303

Table 26: Prevalence rates (unadjusted) of fractures in patients treated with lanthanum and standard therapy s of June 1 2004 - Reviewer

Months	Lanthanum N=682	Standard Therapy N=676
12 months plus	338(49.6%)	472(69.8%)
18 months plus	240(35.2%)	382(56.5%)
Reporting Fractures 12-23 months	15/578(2.7%)*	19/854(4.3%)*
24 months plus	134/682(19.6%)	227/676(33.6%)
Reporting fractures 24 months plus	6/285(2.1%)*	3/227(1.3%)*

Tables 27 and 28 present fracture data from the 15-month and 25 month safety database that includes data for all Phase 2 and Phase 3 studies. The numbers of patients experiencing fractures in both groups is low. In patients exposed to lanthanum carbonate for any time, a total of 63 patients (n=1754, 3.6%) experienced 77 fractures. In patients treated with standard therapy, 50 patients (n=990, 5.1%) experienced 67 fractures at some time during the study. Thus overall in both groups, the overall fracture rate was similar. The fracture rate as a function of treatment duration was also low and remained relatively constant in the Lanthanum and standard therapy groups, ranging from 2% to 3.9% in yearly intervals. These data have now been modified (See appendix 5). The highest yearly interval fracture rate was in the patients exposed to standard therapy during the second year of treatment. While there appears to be a slightly higher rate of fractures in the Lanthanum group exposed for between 24 and 35 months, the numbers of events overall are very low and are similar to the comparable Standard therapy group (5 LaC and 3 Standard therapy). Similar results are observed in the 25-month safety database where an additional 2 patients in each group are included. A total of 238 patients in the Lanthanum groups and 227 patients in comparable standard therapy groups have been followed for at least 24 months.

Table 27:%patients in phase 2-3 studies reporting fractures adjusted for drug exposure-15 month safety update

Length of Drug Exposure	Lanthanum (n=1754)			Standard Therapy (n=990)		
	Patients % (N/n)	Patients discontinued (d)	Adjusted % (N/m)	Patients % (N/n)	Patients discontinued (d)	Adjusted % (N/m)
[0-2] months	0.8 (14/1754)	443	0.9 (14/1532)	1.2 (12/990)	107	1.3 (12/936)
[3-5] months	0.8 (9/1196)	164	0.8 (9/1114)	0.7 (6/811)	56	0.8 (6/783)
[6-11] months	2.1 (22/1027)	249	2.4 (22/902)	1.5 (11/730)	122	1.6 (11/669)
[12-23] months	1.9 (12/636)	176	2.2 (12/548)	3.9 (19/492)	137	4.5 (19/423)
[24-35] months	2.4 (5/212)	20	2.5 (5/202)	1.0 (2/196)	3	1.0 (2/194)
>=36 months	2.1 (1/47)	1	2.2 (1/46)	na (0/0)	Na	na

Adjusted % = rate adjusted for patients discontinuation for the corresponding interval;
N= Number of patients who experienced the event;
n=number of patients who were at risk for the event at the start of the interval;
m= (n-0.5*d), adjusted number of patients who were at risk for the event at the start of the interval, where d is the number of patients who discontinued during the interval.

Table 28:%phase 2-3 patients reporting fractures adjusted by drug exposure-25 month database (data cut-off Feb 2004)

Length of Drug Exposure	Lanthanum (n=1756)			Standard Therapy (n=992)		
	Patients % (N/n)	Patients discontinued (d)	Adjusted % (N/m)	Patients % (N/n)	Patients discontinued (d)	Adjusted % (N/m)
[0-2] months	0.8 (14/1756)	443	0.9 (14/1534)	1.2 (12/992)	107	1.3 (12/938)
[3-5] months	0.8 (9/1200)	164	0.8 (9/1118)	0.9 (7/813)	56	0.9 (7/785)
[6-11] months	2.1 (22/1033)	250	2.4 (22/908)	1.5 (11/742)	122	1.6 (12/681)
[12-23] months	2.3 (15/647)	184	2.7 (15/555)	3.7 (19/511)	147	4.3 (19/437)
[24-35] months	2.1 (5/238)	21	2.2 (5/227)	1.3 (3/227)	4	1.3 (3/225)
>=36 months	2.1 (1/47)	1	2.2 (1/46)	na (0/0)	Na	na

Adjusted % = rate adjusted for patients discontinuation for the corresponding interval;
N= Number of patients who experienced the event;
n=number of patients who were at risk for the event at the start of the interval;
m= (n-0.5*d), adjusted number of patients who were at risk for the event at the start of the interval, where d is the number of patients who discontinued during the interval.

Figure 6: Serum osteocalcin concentration in both treatment groups

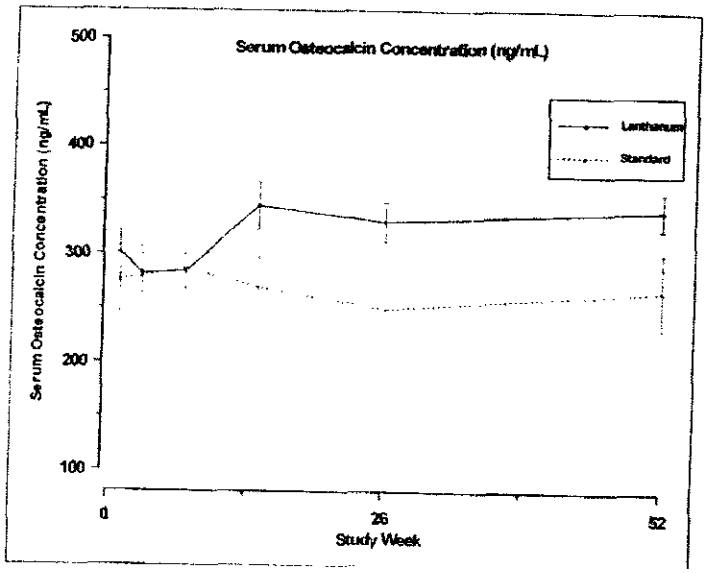


Figure 7: Serum bone specific alkaline phosphatase in both treatment groups for one year

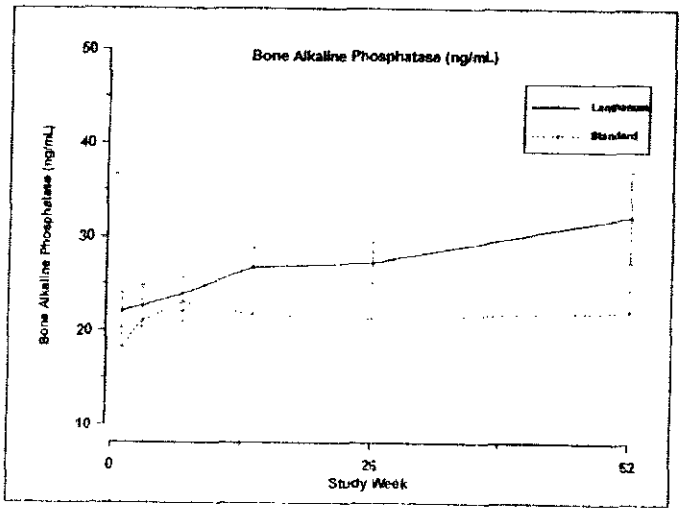
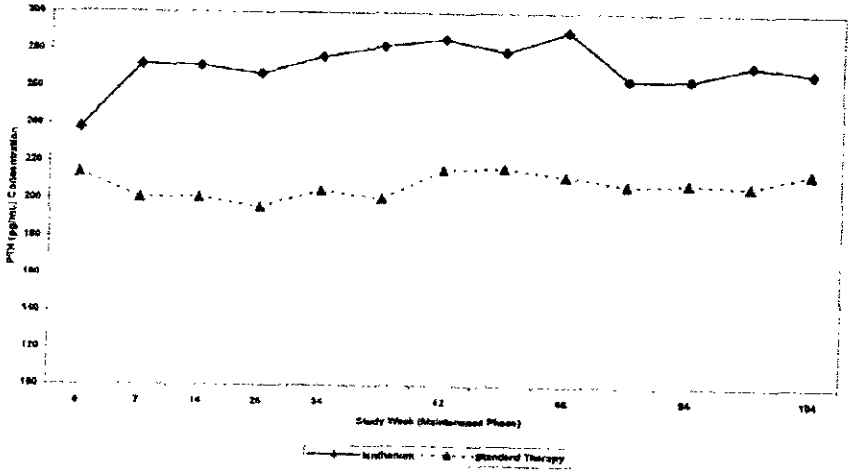


Figure 8: Serum parathyroid hormone in both treatment groups for one year



GI Adverse events

In reviewing the GI deficiencies and the concerns of the Agency in the resubmitted NDA, this reviewer attempts to find out if the sponsor has addressed fully the deficiency as stated in the relevant section of the approvable letter reproduced below.

Excerpt from Approvable letter – re GI deficiency

"It is clear that the rate of discontinuation for adverse events (especially gastrointestinal adverse events) was significantly higher for patients receiving lanthanum compared with standard phosphate binders over all periods of exposure in the clinical trials. Insufficient information is available regarding the resolution of these symptoms following lanthanum discontinuation. While in most cases such symptoms would be expected to resolve when a study drug is discontinued, given the high concentration of lanthanum in the GI tract following oral administration and the uncertainties about the rate of elimination of lanthanum in patients with ESRD, our concern is that these symptoms may not resolve quickly, presenting a real risk of malnutrition and additional injury in this population.

Resolution of this clinical issue will require data regarding the timing and extent of resolution of reported serious adverse events (especially events leading to discontinuation) in patients receiving lanthanum in the long term trials."

The data presented in the GI safety analysis are from the most recent complete dataset available including the 15- month and the 25-month data updates of the integrated summary of safety (ISS Table 5 original review), and also data from LAM-IV-303. The most serious adverse events were in the gastrointestinal tract where there were comparatively high concentrations of lanthanum. The time to onset of an adverse event and time from event to resolution of the GI adverse events among those discontinued from the lanthanum treated patients are important for safety evaluation. The sponsor has been unable to provide this information despite several requests (Table from sponsor: Table 31). The unadjusted rates of GI adverse events are presented in Table 29 and the rates for GI adverse events adjusted for drug exposure are presented in Table 30. The rates for major GI adverse events are comparable between the groups when adjusted but when the rates are not adjusted there are statistically significant differences (Table 30).

Table 29: Integrated review of safety - original review by Dr Pelayo (unadjusted for discontinuation)

Adverse event	Lanthanum N=1474 n (%)	Active control N=909 n (%)
Nausea	50 (3.4)***	3 (0.3)
Vomiting	44 (3.0) ***	3(0.3)
Diarrhea	32 (2.2) ***	3(0.3)
Abdominal Pain	23 (1.6) ***	1 (0.1)
Flatulence	11 (0.7) **	0(0.0)
Constipation	10 (0.7)	3(0.3)
Dyspepsia	10 (0.7) *	0(0.0)
Gastrointestinal Disorder NOS	10 (0.7)	1 (0.1)

***p<0.05; **p<0.01; ***p<0.001 compared to the comparator.

Table 30:Rates of GI adverse events adjusted for drug exposure - Dr Valeria Friedlin Statistics Division

GI Adverse Event	Lanthanum N=1213	Standard Therapy N=941
Abdominal Pain	13 %	12 %
Constipation	10 %	10 %
Diarrhea	18 %	16 %
Dyspepsia	7 %	9 %
Nausea	27 %	20 %
Vomiting	22 %	16 %

Table 31: Distribution of GI adverse events over time to onset of event without stop dates for resolution- adjusted for discontinuation.- Sponsor

Outcome	Time to onset	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
resolved	1-4 wks	277	680	0.41	201	674	0.30
resolved	5-26 wks	544	618	0.88	644	651	0.99
resolved	27-52 wks	328	414	0.79	513	535	0.96
resolved	>1 Year	375	269	1.39	825	396	2.08
resolved w/ sequelae	1-4 wks	0	680	0.00	0	674	0.00
resolved w/ sequelae	5-26 wks	7	618	0.01	1	651	0.00
resolved w/ sequelae	27-52 wks	5	414	0.01	2	535	0.00

Outcome							
resolved w/ sequelae	>1 Year	1	269	0.00	2	396	0.01
unresolved	1-4 wks	39	680	0.06	29	674	0.04
unresolved	5-26 wks	68	618	0.11	77	651	0.12
unresolved	27-52 wks	56	414	0.14	61	535	0.11
unresolved	>1 Year	52	269	0.19	122	396	0.31

On July 9, 2004 the following response was received from the sponsor who had claimed that information on time to resolution of GI adverse events had been sent to the Agency in their resubmission pakage:
" A subsequent request was received on July 8th for this table to present number of patients with an event rather than number of events (which will exclude multiple events with the same outcome in each time category). This table is attached below. For clarification, time to onset is the time from start of study treatments to the time of start of the adverse event and time to resolution is the time between the start of the adverse event and the stop date of the event. Caution should be applied in interpreting these tables as the categories of time to onset are of differing durations."

From tables 31 and 32 submitted by the sponsorand referred to in the above statement, there is no information on the start of adverse events and the stop dates of the events and no time to resolution. However, the sponsor claims that the majority of the events were resolved within 3 weeks. In the absence of data on "stop dates of GI adverse events, there is still no evidence to support this claim despite several requests from the agency and the sponsor's claim that the information had been submitted. (See table32 below).

From table 32 supplied by the sponsor, there is new information on the number of patients with GI adverse events it is evident that no conclusion can be made on time to resolution as there is no information about time of onset of adverse event to stop date of event. In effect, the duration of these GI adverse events to resolution as requested for in the approvable letter has not been provided.

Table32 supplied by sponsor has been modified by reviewer to obtain the frequencies of adverse events per patient over time. This provided crude rates of frequencies of the adverse events (Table 33). The frequencies of adverse events per patient are similar between the groups. The time to onset of the adverse events related to the number of patients at risk are similar between the groups but these cannot be used as surrogates for time to resolution of the adverse events.

The justification for requesting this vital information on time to resolution is to ascertain the duration of GI adverse events in patients on lanthanum that led to discontinuation compared to those on standard therapy. Since the major proportion of lanthanum is known to reside in the GI and since adverse events are very common in lanthanum treated patients it is important to find out how long these adverse events lasted before complete resolution compared to standard therapy particularly in

those patients that the drug has been stopped. From available data, this information is not forthcoming and therefore still constitutes a deficiency.

The most serious adverse events were in the Gastrointestinal tract where there were comparatively high concentrations of lanthanum in the GI compared to other tissues. The time to event and time from event to resolution of the GI adverse events among those discontinued from the lanthanum treated patients are important for safety evaluation

APPEARS THIS WAY
ON ORIGINAL

Table 32Distribution of GI AE outcomes with no stop dates for resolution

Distribution of GI AE Outcomes by Time to Onset, Adjusted for Discontinuations							
		Lanthanum Carbonate			Standard Therapy		
Outcome	Time to onset	#patients with an event	#patients at risk	#patients with an event/ #patients at risk*	#patients with an event	#patients at risk	#patients with an event/ #patients at risk*
resolved	1-4 wks	178	680	0.26	137	674	0.20
resolved	5-26 wks	233	618	0.38	281	651	0.43
resolved	27-52 wks	161	414	0.39	231	535	0.43
resolved	>1 Year	115	269	0.43	222	396	0.56
resolved w/ seq	1-4 wks	0	680	0.00	0	674	0.00
resolved w/ seq	5-26 wks	6	618	0.01	1	651	0.00
resolved w/ seq	27-52 wks	5	414	0.01	2	535	0.00
resolved w/ seq	>1 Year	1	269	0.00	2	396	0.01
unresolved	1-4 wks	33	680	0.05	26	674	0.04
unresolved	5-26 wks	54	618	0.09	55	651	0.08
unresolved	27-52 wks	37	414	0.09	50	535	0.09
unresolved	>1 Year	42	269	0.16	76	396	0.19

Table 33:Distribution of GI AE outcomes adjusted for discontinuations and modified by reviewer

Distribution of GI AE Outcomes by Time to Onset, Adjusted for Discontinuations									
		Lanthanum Carbonate				Standard Therapy			
Outcome	Time to onset	FreqAEs/#patient; #patients with an event		#patients at risk	# patients with an event/ #patients at risk	FreqAEs/#patient; #patients with an event		#patients at risk	# patients with an event/ #patients at risk
resolved	1-4 wks	(1.6)	178(277events)	680	0.26	(1.46)	137/201 events	674	0.20
resolved	5-26 wks	(2.34)	233(544 events)	618	0.38	(2.91)	281/644events	651	0.43
resolved	27-52 wks	(2.04)	161/329(events)	414	0.39	(2.22)	31/513 events	535	0.43
resolved	>1 Year	(3.3)	115/375(events)	269	0.43	(3.7)	222/825 events	396	0.56
resolved w/ seq	1-4 wks		0	680	0.00		0	674	0.00
resolved w/ seq	5-26 wks		6	618	0.01		1	651	0.00
resolved w/ seq	27-52 wks		5	414	0.01		2	535	0.00
resolved w/ seq	>1 Year		1	269	0.00		2	396	0.01
unresolved	1-4 wks	(1.2)	33/39(events)	680	0.05	(1.1)	26/29 events	674	0.04
unresolved	5-26 wks	(1.3)	54/68 (events)	618	0.09	(1.4)	55/77events	651	0.08
unresolved	27-52 wks	(1.5)	37/56(events)	414	0.09	(1.22)	50/61 events	535	0.09
unresolved	>1 Year	(1.24)	42/52(events)	269	0.16	(1.6)	76/122events	396	0.19

* Source Sponsor table submitted to address the time to resolution of GI adverse events.
( ) Reviewer's data on frequencies per patient.

Quoting from the sponsor's letter of July 8, 2004: "In addition, Dr. Williams has inquired whether or not Table 25 (page 98) from the LAM-IV-307 interim study report (included in the resubmission) contained an error in the numbers and/or percentages of patients per treatment group. Upon review, an error in the number of patients was noted and a revised table is attached." The revised table from the sponsor has been included in this review.

According to the sponsor, no lanthanum-related deaths were observed. According to the Agency, at 44 months the mortality rate for lanthanum treated patients was 23.8 % (418 / 1754) whereas for standard therapy patients mortality was 20.4% (202/990). The survival curves for both treatment groups were indistinguishable. The adverse events most frequently leading to death in both treatment groups are comparable but the data in Table 34 below are unadjusted for discontinuations. Similarly the frequencies for serious adverse events are in Table 35 and these are also unadjusted.

Table 34:Adverse events most frequently leading to death

Adverse event	Lanthanum N 682 (%)	Standard N 676 (%)
Cardiac arrest	12(1.8)	21(3.1)
Myocardial infarction	11(1.6)	13(1.9)
Arrhythmia	5(0.7)	9(1.3)
Sepsis	4(0.6)	9(1.3)

Table 35: Some serious adverse events with frequencies of 2% or greated adjusted for discontinuations - LAM-IV-307

*Serious Adverse event	Lanthanum N 682 (%)	Standard N 676 (%)
At least one SAe	388(56.9)	481(52.4)
Chest pain and M.I.	30 (4.4)	28(3.0)
Coronary Artery disorder	16(2.3)	31(3.4)
Cardiac arrest	18(2.6)	26(2.8)

*2,696 SAEs were reported throughout the course of the study. Three were thought to be likely to be drug related: Pancreatitis, GI hemorrhage, and constipation and all were in the lanthanum group.

Laboratory changes that showed consistent significant inter-group differences are tabulated below but these are also unadjusted. Serum osteocalcin parathyroid hormone and bone specific alkaline phosphatase are significantly higher among the lanthanum treated patients compared to the lanthanum treated patients (Table 36).

Table 36: Summary of inter-group lab changes from pre-study to month 24- LAM-IV-307 (visit 21)

Laboratory tests	Lanthanum N 682 (%)	Standard N 676 (%)
Cholesterol		Low (p=0.000)
LDL.		Low (p=0.000)
Osteocalcin	High (p=0.000)	
Parathyroid hormone	High (p=0.000)	
Calcium		High(p=0.000)
Alkaline Phosphatase	High (p=0.000)	

The two major safety concerns that led to this resubmission are in respect of GI adverse events that led to discontinuations and also long term evaluation of bone toxicity.

GI Adverse events

The current data presented in the GI safety analysis are from the most recent complete dataset available including the 15- month and the 25-month data updates of the integrated summary of safety (ISS), and also data from LAM-IV-303. Tables 29 and 30 show that GI adverse events show comparable inter-group rates. Table 38 was submitted by the sponsor in response to the resubmission as data for time to resolution. It is evident that this does not fully respond to the deficiency in the approvable letter.

Table 37 shows the percentages of patients with commonest treatment adverse events in study 307. Note the preponderance of GI adverse events, nausea, vomiting and diarrhea in the tabulated percentages of Patients with Most Common Treatment-Emergent Adverse Events.

Table 37: Commonest treatment-emergent adverse events adjusted by V Friedlin - 307

Adverse Events	Treatment Groups			
	All Adverse Events		*Drug-Related Adverse Events	
	Lanthanum (N=680)	Standard (N=674)	Lanthanum (N=680)	Standard (N=674)
	%	%	%	%
At least one Adverse Event	95	69	22	9
Nausea	35	27	7	0.7
Vomiting	25	20	3	0.3
Diarrhea	22	21	3	0.5
Dialysis graft complication	25	23	0	0
Dyspnea	21	22	0	0
Dizziness	21	19	0	0.1
Headache	21	19	1	0.1
Dialysis graft occlusion	20	19	0	0
Myalgia	20	19	0.4	0
Chest pain	20	17	0.6	0
Coughing	18	19	0.1	0.1
Pain	17	16	0	0
Hypotension	15	16	0	0
Dialysis catheter complication	15	15	0	0
Upper respiratory tract infection	15	12	0	0
Edema peripheral	14	18	0	0
Influenza-like symptoms	14	14	0	0
Fever	14	13	0.3	0
Abdominal pain	16	16	2	0.5
Constipation	13	12	3	1
Pruritus	12	11	0.7	0
Back pain	12	14	0	0
Leg pain	12	11	0	0

Malaise	11	11	0	0
Dyspepsia	10	12	2	1

* *As this is an open-label study, these data may be affected by a potential investigator bias.*

Table 38: Table submitted as time to resolution by sponsor-adjusted by statistician

Time to onset of adverse event	Lanthanum 1752 events (680 patients)	Standard Therapy 2480 events (674 patients)
0-7 days	1158 (66%)	1776 (72%)
8-14 days	112 (6%)	138 (6%)
15-21 days	59 (3%)	54 (2%)
22-28 days	26 (2%)	33 (1%)
>28 days/unresolved	397 (23%)	479 (19%)
Valerie Friedlin - FDA		

The exposure to lanthanum over time is summarized in Table 39.

Table 39: Exposure to lanthanum carbonate LAM-IV-307

	Lanthanum	**Standard Therapy**
Treatment duration	N(%)	N(%)
< 1 month	44(6.5)	18(2.7)
≥1<2	71(10.4)	24(3.6)
≥2<3	34(5.0)	17(2.5)
≥3<6	76(11.1)	44(6.5)
≥6<9	70(10.3)	52(7.7)
≥9<12	49(7.2)	49(7.2)
≥12<18	98(14.4)	90(13.3)
≥18<24	106(15.5)	155(22.9)
≥24	134(19.6)	227(33.6)
Total Patients	682	676
Mean time of exposure	356.6±267.6	484.6±249.6

Only 10 patients had plasma lanthanum evaluation at 24 months in the bone substudy. There is a progressive increase in mean plasma lanthanum levels over time. There is a more than 100% increase between the mean plasma level at 7 weeks and 24 months in the subset of patients followed for bone biopsies. This suggests that the steady state has not been reached at 2 years in the bone substudy (Table 40). This is a significant observation that a 2 year period is inadequate for the followup of bone changes as the peak effect has not become manifested. The histomorphometric and histological studies on bone biopsies in the resubmission are based on a 2-year follow up that appears inadequate. The sponsors claim that the median half life of lanthanum is 2 years and the mean half life is 3.57 years. At 2 years, the mean plasma lanthanum level has not reached a steady state and therefore the peak effect of lanthanum on bone is not known. The relationship between plasma levels of lanthanum and bone changes at this time point is not known. This contributes to some of the uncertainties of lanthanum pharmacokinetics and pharmacodynamics.

Table 40:Mean plasma lanthanum levels in bone sub-study-LAM-IV-307

	Lanthanum group		
Visit	**N**	**Lanthanum levels (ng/mL)**	**Min – Max (ng.mL)**
Screening	96	0.0±0.05	0.0-0.42
Week 7	98	0.3±0.24	0.0-1.78
Week 26	88	0.4±0.55	0.0-4.59
Week 52	66	0.4±0.48	0.0-2.57
Month 24	10	0.7±0.76	0.0-2.53

D. Dosing

The proposed initial dose for adults is 750 mg daily with meals; doses should be divided among meals with more doses for a heavy meal. Doses may be increased or decreased gradually to bring serum phosphate levels below 6 mg/dL. Most patients may require a daily dose of 1,500 mg of lanthanum and the sponsor does not recommend doses greater than 3,000 mg. Fosrenol will be available in 250 mg, 500 mg, [ ] chewable tablets packaged in bottles of [ ]100 tablets, respectively.

E. Special populations

A. [

]

Geriatric population

A total of 538 (31.6%) adults over the age of 65 participated in all phase II /III studies. The efficacy subpopulation study showed no difference between the males and females and between the young and the old. Detailed studies on this geriatric age group are required.

Diabetics

447 diabetic patients enrolled in the clinical program constitute the largest proportion of patients with renal history were recruited into the bone subset study were diabetics. Since bone changes in diabetics show differences in renal failure compared to non diabetics (Refs page 74) This group should be treated as a special population in terms of bone changes to lanthanum. See page

The distribution of diabetics in both treatment groups is shown in Tables 7 and 8.

Clinical review

III. Introduction and Background

Hyperphosphatemia is a disorder of mineral metabolism invariably associated with renal insufficiency and inability to excrete phosphate efficiently.

This is a review of LAM-IV-307. Other studies have been reviewed in Appendix 3. FOSRENOL (Lanthanum Carbonate) is a phosphate binder that acts in the lumen of the gastrointestinal tract to bind dietary phosphorus released from food during digestion. According to the sponsor, " 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 ($P0_4$) groups. In the presence of HCI 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 La3+ in the gastrointestinal tract and the high affinity of La_3+ for $P0_4$ 2- . This binding results in the formation of highly insoluble lanthanum phosphate salt, which cannot be absorbed and therefore is excreted, thus significantly reducing phosphate absorption." This is the basis for the treatment of hyperphosphatemia.

Phosphate balance is maintained during the early stages of chronic renal insufficiency provided glomerular filtration rate (GFR) exceeds 25 to 30 mL/min. The total renal excretion of inorganic phosphate (Pi) is normal because a progressive reduction in tubular Pi transport leads to increased excretion by the remaining functioning nephrons. When glomerular filtration rate falls to less than 25 to 30 mL/mm and dietary phosphate intake remains constant, phosphate balance can no longer be maintained by reduction of tubular transport, and hyperphosphatemia develops. This occurs despite significant increase in the fractional excretion of phosphate (increasing from 60% to 90%) of the filtered load. With hyperphosphatemia, the filtered load of phosphate per nephron increases and phosphate excretion rises. As a result, phosphate balance and renal excretory rate is reestablished but at a higher serum phosphate level,
i. e., hyperphosphatemia.

With decreasing GFR, clinically undetectable phosphate retention develops, which in turn reduces ionized calcium, with consequent stimulation of parathyroid hormone (PTH) secretion. Hyperphosphatemia, caused by chronic renal failure (CRF) and end-stage renal disease (ESRD), plays a critical role in development of soft-tissue calcification, including calcification of blood vessel walls, secondary hyperparathyroidism and renal osteodystrophy. Bone pain, skeletal disease associated with bone deformity and fractures are the most common clinical manifestations of renal osteodystrophy. Hence, control of serum phosphate levels is essential in the management of patients with ESRD due to the obligatory requirement for dietary protein and the inability of dialysis to adequately remove the associated phosphate load.

Fosrenol contains the active ingredient, lanthanum carbonate hydrate. It is an orally active phosphate binder. Fosrenol is indicated for the

Fosrenol binds dietary phosphorus from food and inhibits absorption of phosphorus to the blood by the formation of highly insoluble complexes that cannot easily pass through the wall of the gastrointestinal tract.

Table 41:Demographics in lanthanum carbonate development program

Baseline demographics for patients enrolled in the lanthanum carbonate program							
Devpt.	**Phase 1**		**Phase 2-3**				
Treatment group	**LaC**	**Placebo/ others**	**Short Term**		**Long term**		**All Phase 2/3**
			LaC	**Placebo**	**LaC**	**ACPB**	**LaC**
No. receiving study medication	***179**	**76**	**298**	**95**	**1507**	**941**	**1705**
Age (yrs)							
N	***179**	**76**	**298**	**95**	**1507**	**941**	**1705**
Mean±SD	29.5±9.99	25.7±6.47	57.4±14.42	57.7±14.11	55.9±14.40	56.0±14.23	56.1±14.43
Age Group							
18-50	168(93.9)	76(100)	84(28.2)	28(29.5)	522(34.6)	326(34.6)	580(34.0)
51-64	10(5.6)	0	105(35.2)	29(30.5)	520(34.5)	325(34.5)	587(34.4)
65+	1(0.6)	0	109(36.6)	38(40.0)	465(30.9)	289(30.7)	538(31.6)
Sex							
Male	146(81.6)	76(100.0)	185(62.1)	52(54.7)	935(62.0)	580(61.6)	1056(61.9)
Female	33(18.4)	0	113(37.9)	43(45.3)	572(38.0)	361(38.4)	649(38.1)
Race							
Caucasian	152(84.9)	63(82.9)	142(47.7)	45(47.4)	1029(68.3)	569(60.5)	1142(67.0)
Black	5(2.8)	0	131(44.0)	43(45.3)	378(25.1)	277(29.4)	450(26.4)
Hispanic	6(3.4)	0	15(5.0)	4(4.2)	61(41.0)	56(6.0)	70(4.1)
All others	16(8.9)	13(17.1)	10(3.4)	3(3.2)	39(2.6)	39(4.1)	43(2.5)
Weight (pounds)							
Mean±SD	161.4±25.0	159.0±19.15	172.2±39.34	175.8±44.94	171.7±41.64	173.9±43.9	171.6±41.31
Height							
Mean±SD	68.7±3.01	69.3±2.43	66.9±4.20	66.9±4.23	66.9±4.15	67.0±4.24	66.9±4.16

- 10 patients had ESRD.

The demographics of patients in the double blind, active controlled and open label studies are in Tables below:

Table 42:Demographics LAM-IV-303 I-T-T population

Patient population	LAM-IV-303 ITT Population		
	Lanthanum Group	**Standard Group**	**All enrolled**
N	49	49	98
Age (years) Mean Range	 55.9±13.5 27-80	 54.0±15.2 18-75	 55.0±14.3 18-80
Gender Male Female	 31(63) 18(37)	 28(57) 21(43)	 59(60) 39(40)
Race N (%) Caucasian Black Hispanic Asian Oriental Mixed race Other	 45(92) 0 0 1(2) 0 2(4) 1(2)	 46(94) 0 0 1(2) 0 2(4) 0	 91(93) 0 0 2(2) 0 4(4) 1(1)

Demographics

Table 43: Summary of Demographics - LAM-IV-307

	Randomized Patients		
Patient population	**Lanthanum**	**Standard**	**All enrolled**
N	680	674	1, 552
Age(yrs) N (%)			
18-50	285(41.9)	259(38.5)	605(39.1)
51-64	218(32.1)	226(33.6)	512(33.1)
65+	177(26.0)	188(27.9)	432(27.9)
Mean±SD	53.8±14.5	54.9±14.4	54.9±14.5
Gender N (%)			
Male	389(57.2)	414(61.4)	930(59.9)
Female	291(42.8)	260(38.6)	622(40.1)
Race N(%)			
Caucasian	303(44.6)	313(46.4)	700(45.1)
Black	301(44.3)	274(40.7)	667(43.0)
Hispanic	54(7.9)	55(8.2)	122(7.9)
Asian PI	3(0.4)	13(1.9)	18(1.2)
Native American	6(0.9)	6(0.9)	14(0.9)
Others	13(1.9)	13(1.9)	30(1.9)
Weight (lbs)			
N	676	671	1,540

	Randomized Patients		
Patient population	**Lanthanum**	**Standard**	**All enrolled**
Mean±SD	177.9±48.2	178.5± 46.8	178.2±47.4
Height			
N	669	661	1,518
Mean±SD	66.8±4.4	67.2±4.3	67.0±4.4

Table 44: Demographics - Bone sub-study randomized - LAM-IV-307

	LAM-IV-307 Randomized patients		
	Lanthanum Group	**Standard Group**	**All enrolled**
N	**102**	**99**	**201**
Age (years) Mean±SD	50.0±14.6	51.8±12.8	50.9±13.8
Gender			
Male	68(66.7)	73(73.7)	141(70.2)
Female	34(33.3)	26(26.3)	60(30.0)
Race			
Caucasian	34(33.3)	35(35.3)	69(34.3)
Black	51(50.0)	46(46.5)	97(48.3)
Hispanic	6(5.9)	8(8.1)	14(7.0)
Asian	1(1.0)	3(3.0)	4(2.0)
Mixed race	1(1.0)	0	1(0.5)
Other	9(8.8)	7(7.1)	16(8.0)

Efficacy

Overall, primary efficacy endpoint was reduction of serum phosphate in end stage renal disease (ESRD) patients with hyperphosphatemia using a temporal decline of pre-dialysis serum Phosphate (PSPL) over time as a basis for comparison of point estimates between lanthanum and other comparators (standard therapy and calcium carbonate). Primary efficacy was determined according to the level of serum phosphate achieved after 5 weeks in the dose titration phase: serum phosphate levels < 1.80 mmol/L were considered to be the control.

Secondary efficacy was the evaluation of maintenance of control after 25 weeks of treatment including 5 weeks of treatment and 20 weeks of maintenance. Efficacy of lanthanum had already been demonstrated in the original NDA and also shown in the additional study LAM-IV-307.

Safety

The safety profile of lanthanum in the original review was discussed under short and long term studies regardless of the study phase. In view of the very long period it takes for lanthanum to reach steady stage in organs including bones (10-15 years) and in view of its widespread distribution in tissues all over the body, short term safety assessments are considered inadequate for long term bone / other tissue toxicity. Particularly as there are other approved products that are more effective for the same indication and with less or comparable frequencies of adverse events. Therefore, the relatively long term studies,

though open label, and actively controlled, are acceptable for long term toxicity assessments. The three active controlled, open label studies that would qualify for this would therefore be LAM-IV-301, 303 and 307 and he two prominently affected organs are bones and gastrointestinal tract

Analyses of adverse events in patients who received lanthanum and standard therapy showed statistically significant differences in 24 out of 26 distinct adverse events with p values ranging from <0.05 to <0.001. Critical appraisal of these differences in favor of lanthanum can be attributed to a lack of adjustments for drug exposure. Once this is corrected for there are no significant differences between the two groups. Table 4 – ISS in the original review summarizes all the differences in treatment emergent adverse events in patients with a frequency > 10% in long term studies. In the long term studies, a total of 236 (16%) of patients administered lanthanum carbonate discontinued treatment compared to 46(5.1%) of active control treated patients ($p<0.001$). This suggests a higher rate of discontinuation among patients receiving lanthanum compared to standard therapy.

A total of 190 patients representing about 81% of all discontinuations in the lanthanum group withdrew prematurely from the study because of GI adverse events. These high rates of discontinuations indicate poor tolerability compared to other phosphate binders. The incidence of Gastrointestinal adverse events in the patients treated with Lanthanum is comparable to the incidence of Gastrointestinal adverse events in patients treated with standard therapy.

Discontinuations due to GI adverse events were higher in the Lanthanum treatment group due to the study design rather than to the type or severity of GI adverse event. Patients who had GI adverse events on Lanthanum were required to discontinue from the study when modifications to the phosphate binder treatment were required, while patients in the standard therapy arms could receive and/or change to any approved phosphate binder without being removed from the study. When changes in standard phosphate therapy were treated in a similar fashion to Lanthanum patients, then the projected rate of discontinuations due to GI adverse events was similar in both groups.

The most common GI adverse events leading to discontinuation in the Lanthanum group were nausea, vomiting and diarrhea. These events were most likely to occur early in dosing, and there was no increase in incidence of these events with time on Lanthanum treatment.

Gastrointestinal adverse events in the Lanthanum group were generally of short duration (<14 days) whether patients continued Lanthanum or discontinued from the study. The duration of GI adverse events did not increase with increased exposure to Lanthanum. Only a small number of events in patients in any of the Phase II-III clinical studies with Lanthanum did not resolve within 28 days or led to death. There was no pattern in these patients with prolonged events to identify a specific symptom or syndrome associated with Lanthanum treatment.

In conclusion, adverse events in the GI body system are common in patients treated with Standard phosphate binder therapy as well as Lanthanum. There is no signal of increased GI adverse events in patients treated with Lanthanum in comparative studies of up to 2 years duration.).

Table 45: Percentage of most common adverse events in LAM-IV-307 (adjusted for drug exposure)

Adverse Events	Treatment Groups			
	All Adverse Events		*Drug-Related Adverse Events	
	Lanthanum (N=680)	Standard (N=674)	Lanthanum (N=680)	Standard (N=674)
	%	%	%	%
At least one Adverse Event	95	69	22	9
Nausea	35	27	7	0.7
Vomiting	25	20	3	0.3
Diarrhea	22	21	3	0.5
Dialysis graft complication	25	23	0	0
Dyspnea	21	22	0	0
Dizziness	21	19	0	0.1
Headache	21	19	1	0.1
Dialysis graft occlusion	20	19	0	0
Myalgia	20	19	0.4	0
Chest pain	20	17	0.6	0
Coughing	18	19	0.1	0.1
Pain	17	16	0	0
Hypotension	15	16	0	0
Dialysis catheter complication	15	15	0	0
Upper respiratory tract infection	15	12	0	0
Edema peripheral	14	18	0	0
Influenza-like symptoms	14	14	0	0
Fever	14	13	0.3	0
Abdominal pain	16	16	2	0.5
Constipation	13	12	3	1
Pruritus	12	11	0.7	0
Back pain	12	14	0	0
Leg pain	12	11	0	0
Malaise	11	11	0	0
Dyspepsia	10	12	2	1

** As this is an open-label study, these data may be affected by a potential investigator bias.*

Serious adverse events that led to treatment discontinuation in the long term open label study, LAM IV 307, were reported by 114 (17%) lanthanum patients (with one patient reporting 2 SAEs) and 170 (25%) among standard therapy patients.

Exposure to Lanthanum Carbonate LAM-IV-307 see Table 38.
Only 10 patients had plasma lanthanum evaluation at 24 months. There is a progressive increase in mean plasma lanthanum levels over time. There is a two fold increase between the mean plasma level at 7 weeks and 2 years in this subset of patients followed for bone biopsies.

Mean Plasma Lanthanum levels Bone Sub-study - LAM-IV-307-See table 39.

A. **Drug Established, proposed trade name, Drug class, Dose Regimens age groups, Sponsor's proposed Indication.**

B. **The sponsor's indication of FOSRENOL was for** [

]

Proposed Trade Name: FOSRENOL.
Drug Class: PHOSPHATE BINDER
Sponsor's Proposed Indication(s): [ ]
Chewable unflavored tablets in two dosages for oral administration (250 mg and 500 mg).
Sponsor's proposed indication(s) the sponsor is seeking the following indication " fosrenol . [

]

Age Groups 18 – 67 years, both sexes, Caucasians and other ethnic groups were enrolled in the program.

The strength of this product is based on the active moiety Lanthanum and not the salt Lanthanum Carbonate. The active ingredient in lanthanum carbonate chewable tablets is lanthanum (III) carbonate hydrate, an inorganic salt with the approximate formula of $La_2 (C0_3)_3 .4H_20$. The sponsor's proposed trade name for lanthanum carbonate is FOSRENOL .

Drug class
FOSRENOL (Lanthanum Carbonate) is a phosphate binder that acts in the lumen of the gastrointestinal tract to bind dietary phosphorus released from food during digestion. According to the sponsor, " the chemical basis for this being the ionic binding properties of La3+ , which has an overwhelming preference for oxygen donor atoms of which the most common ligands are carboxyl and phosphate ($P0_4$) groups. In the presence of HCI 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 La3+ . The activity

of lanthanum carbonate as a phosphate binder is dependent on the availability of soluble La3+ in the gastrointestinal tract and the high affinity of La_3+ for $P0_4$ 2- . This binding results in the formation of highly insoluble lanthanum phosphate salt, which cannot be absorbed and therefore is excreted, thus significantly reducing phosphate absorption." This is the basis for the treatment of hyperphosphatemia.

C. State of Armamentarium for Indication(s)

State of armamentarium for indication(s) currently, there are two drug products, phoslo . and renagel, approved by the FDA for the treatment of hyperphosphatemia associated with end- stage renal disease. The active ingredients of phoslo . and Renagel . are calcium acetate and sevelamer hydrochloride (polly [allylamine hydrochloride] cross linked with epichlorohydrin), respectively. Both phosphate binders are approved for oral administration. Calcium carbonate is not approved for this indication by the FDA but the sponsor used this as an active control and comparator.

D. Important Milestones in Product Development –

There is no important milestone with this product development because there are other products that are effective in patients with hyperphosphatemia.

E. Other Relevant Information

Idiopathic hyperphosphatasia is a rare high bone turnover congenital bone disease in which affected children are normal at birth but develop progressive long bone deformities, fractures, vertebral collapse, skull enlargement and deafness. It is an autosomal recessive bone disease. Histologically, there is evidence of extremely rapid bone resorption and formation. There is considerable phenotypic variation from presentation in infancy to late presentation in childhood with minimal deformity. It has been linked to deletion or mutation in the TNFRSF11B gene that encodes for osteoprotegrin (OPG), an important modulator of RANKL-mediated bone resorption and the gene regulates osteoclast development. It is also linked to a locus on the long arm of chromosome 8 (8q24). This is a genetic bone disease whereas hyperphosphatemia is an acquired bone disease.

The photomicrographs obtained by this reviewer from the sponsor's bone slides do not support the sponsor's conclusion that rats with normal renal function show "no", repeat, "no" bone changes. Furthermore the sponsor's claim that the lanthanum concentrations in humans were within the range of lanthanum concentrations in rats with normal renal function given lanthanum carbonate and since there are no bone changes it is unlikely that lanthanum does or will do any harm to bones in humans. The whole basis of this claim cannot be sustained since the abnormal bone changes in the long bones of lanthanum treated rats with normal renal function can also be found in lanthanum treated uremic rats although to a lesser degree.

The sum total of lanthanum toxicity on rat bones with normal renal function is that there is an abnormal cortical metaphyseal lesion consisting of multiple cortical erosions with fibro-proliferative, periosteal thickening overlying the areas of bone damage. Similar

cortical lesions are seen in lanthanum treated uremic rats. In effect lanthanum toxicity on bone may be additive to renal bone disease. In support of this is the elevated alkaline bone specific alkaline phosphatase that is increased in patients receiving lanthanum at 2 year follow up (See Figure 7)

Histologcal examination of bones from rats with normal renal function treated with Lanthanum showed moderate to severe bone resorption predominantly in the metaphysis of long bones and periosteal thickening overlying the areas of bone loss. Demineralization was also seen in these long bones. Histological examination of iliac biopsies from humans with ESRD treated with lanthanum also showed bone changes that became more severe over time (Safety Section Figures 24-25).

IV. Clinically relevant Findings from Chemistry, Animal Pharmacology and Toxicology Biopharm Statistics and others

A. Description of Rat bone histopathology slides and lanthanum effects- Source reviewer

Bone pathology and bone toxicity

Disease manifestations in bones can be regarded as a function of time, place and quantity and they are more readily comprehended when correlated with the evolving and changing cellularity of bone development, structure and function.. However the evaluation of drug induced toxicity can best be detected by a careful examination of structural defects affecting both the osseous and myeloid components of bone. The selective vulnerability of the metaphysis is well recognized particularly in inflammation. It is therefore not surprising that the metaphysis is affected most frequently in lanthanum toxicity in the rats. The architectural disruption of metaphyseal cortical bone and the accompanying reparative fibrosis and periosteal thickening characterize the lanthanum injury to long bones of rats with normal renal function given lanthanum carbonate. A brief descriptive pathology of these observed lesions, not previously reported, is as follows:

The abnormal histological lesions found in slides from 7 rats with normal renal function were predominantly in the metaphyseal and metadiaphyseal areas of the long bones. The lesions are consistent with areas of bone loss that are usually characterized by multiple defects with irregular edges in the cortices of long bones. Periosteal thickening overlying the areas of bone loss was common and the extent of the periosteal abnormality varied with the size of the cortical bone defects. These bone defects may have inflammatory cells in their vicinity or may have large cells that may be osteoclasts. In some areas of severe cortical bone loss resulting in architectural disruption, the defect may be completely replaced by fibrocollagenous tissue. (Figure 9) The cortical bone defects may be surrounded by collagenized desmoplastic fibroblastic cells, and may be relatively vascular suggesting an inflammatory type of granulation tissue. Xanthoma cells were not seen in these vascular granulation tissue.

There are a few host osteoclasts adjacent to the erosions of the cortical surface of the metaphysis.

Similar lesions seen in rats with normal renal function are also seen in uremic rats given lanthanum but the lesions in the uremic rats were more severe. Since the rat with normal renal function differs from the uremic rats in that there is no hypophosphatemia, it is

conceivable that the observed changes in the normal rat represent lanthanum toxicity to bone. No immunohistochemistry was done on these bones. These observed changes are subtle in places and could be easily missed.

B. Description of pathology of human bones exposed to Lanthanum Carbonate-Reviewer

All the bone biopsies from patients exposed to lanthanum carbonate showed abnormalities at baseline and at follow up regardless of follow up. These abnormalities represent renal osteodystrophy and its variants. Of relevance is the fact that the cortical bone defects seen in rats with normal renal function given lanthanum are also seen in ESRD humans given lanthanum. The 3 unpaired slides from patients given lanthanum for 4/5 yrs are too few to make any meaningful comments particularly with the poor technical preparation of the slides submitted for review (See Figures 16-17). Some of the slides submitted had no cortical bone for microscopic examination. However, the temporal differences among the paired biopsies have been captured by histomorphometry and reported in the NDA but the possible confounding effect of lanthanum cannot be dissected from the histomorphometric evaluation even with comparators. There is no compelling evidence that lanthanum does not affect bones in humans. There is evidence that lanthanum accumulates in bones in humans and in animals. For comparative data among treatment groups to be compelling the severity and extent of bone changes in patients with ESRD at baseline should be equal. Since this was not ascertained prior to randomization, the only empirical clinical parameter left is the evaluation of fractures in both treatment groups.

However, with rapid advances in molecular biology, identification of systemic and local biomolecules that are known to regulate bone metabolism can now be achieved. For example, the study of localization and levels of expression and synthesis of these factors in bone and its microenvironment is now feasible through applications of in situ hybridization histochemistry (ISHH) and immunohistochemistry (IHC). Application of ISHH allows study of specific mRNA expression. Combining histomorphometric techniques with ISHH and IHC elevates the study of bone metabolism and pathology to greater heights. In effect, cellular and molecular issues can now be studied to evaluate subclinical and clinical outcomes ***(Langub MC, Faugere MC, Malluche HH. Pediatric Nephrol 14: 629-635, 2000***. This technique was available and in use at the time the sponsors had a meeting with the Agency. This should have been considered and applied to elucidate the role of lanthanum in bone toxicity.

C. Adequacy of Histomorphometry versus histological diagnosis of bone pathology

Mineralized sections of bone can be qualitatively or quantitatively evaluated. Qualitative assessment and interpretation of ESRD bone from rats was carried out during preclinical phase 1 studies by the sponsor. While an extensive bone survey of bones is not feasible in humans the sponsor, in agreement with the agency, agreed to qualitative and quantitative assessment of bone biopsies from the iliac crest of patients exposed to lanthanum and standard treatment. The two separate methods of histology and histomorphometry are required to evaluate bone biopsies in patients exposed to lanthanum for the treatment of

hyperphosphatemia. Histomorphometric evaluation of bone provides objective data on static and dynamic parameters of bone structure, formation and resorption. Therefore this is a classical research tool for studying bone physiology and pathology. Assuming that histomorphometric data of bone acknowledges the variation within the sites used for bone samples by use of proper control groups, and considering that this is a useful tool for evaluating differences in repeat bone biopsies after a treatment regimen it is not clear if a point estimate from a bone biopsy is adequate to predict pathological changes, such as fractures, or even frequencies, severity and extent of fractures, that will take place over time. Of significant relevance is the example that patients with low turnover osteodystrophy had a fracture rate of 0.2 fractures /dialysis year whereas patients with osteitis fibrosa had 0.1 fractures /dialysis year. Patients with low turnover osteodystrophy suffered fractures of mainly axial rather than appendicular bones in contrast to what is seen in patients with osteitis fibrosa. The adequacy of using histomorphometry alone for evaluating lanthanum induced bone toxicity is therefore in question. It does not detract from its use for quantitating dynamic parameters of bone remodeling but does not provide compelling evidence for bone changes and metastatic calcification in soft tissue changes that may be due to hyperparathyroidism and or hyperphosphatemia. In the opinion of the reviewer reports of routine histological examination of all bone biopsies, scheduled and unscheduled, should have been submitted for review. Instead the sponsors submitted categories into which the histomorphometric data fell and used those as basis for pre- and post exposure to lanthanum carbonate. Furthermore, histomorphometry was used as a basis for excluding aluminum-like associated bone toxicity. It has not taken into account the microenvironment of the bone that is also susceptible to lanthanum toxicity. Because of relatively large discontinuations in the Lanthanum group versus standard therapy, the fracture rates should be adjusted for drug exposure as the discontinuation rate (for example in LAM-IV-307) was 65% for lanthanum versus 45% even if histomorphometry were going to be accepted as the sole measure for toxicity. The reviewer does not consider that histomorphometry is adequate for evaluating lanthanum bone toxicity particularly as the steady state concentration of lanthanum in bones is several fold higher compared to standard therapy.Furthermore lanthanum continues to accumulate in bones over time and in other tissues including the microenvironment of bones. Histomorphometry does not evaluate the changes in the soft tissues and marrow of bones making it an inadequate tool for evaluating toxicity of lanthanum in bone and its microenvironment..

V. Human PK and PD

This is in Biopharm review by Dr A. Dorantes.

The clearance of lanthanum from tissues was assessed in animals loaded with lanthanum for 4 weeks and maintained off dose for up to 26 weeks. There was differential clearance of lanthanum from the GI of rats . Clearance from bone cartilage and teeth was slow with more than 66% (sternum), 82% (femur, 60% (trachea) and 75 % (teeth) of lanthanum retained in these tissues after 4 weeks off dose in rats. These data have implications for human PK and PD effects particularly adverse events affecting bones and GI.

VI. Description of clinical data and sources

A. Overall Data

Overview of types of data

The resubmitted NDA included data from the original NDA and additional data that addressed the deficiencies in the approvable letter. After several requests, teleconferences and meetings, the sponsor provided all the data required for this review. The data consisted of reports from the clinical trial program and long term follow up as requested in the approvable letter. Publications on bone pathology were also provided to justify the use of morphometry for evaluation of bone toxicity. The literature review provided by the sponsor is not adequate and the FDA reviewer has identified specific areas of inadequacy in relevant references provided by the sponsor particularly in the following areas: The Agency's efforts to provide these references are on page 70.

- Molecular bone morphometry,
- Bone changes in diabetics on dialysis,
- Cytokines in renal osteodystrophy,
- Hyperparathyroidism and breast cancer,
- Periosteal gene expression and mechanical loading on bone mass. These references have been added by the FDA. See Section on Literature review by Agency

Sources of data

Medical review by Juan Carlos Pelayo dated 12.31.02
Secondary Medical review by Norman Stockbridge dated 2.3.03
Chemistry reviews by Kris Raman dated 12.31.02; 1.16.03
Statistical Review of Clinical data and addendum by Valeria Friedlin dated 11.05.02 and 12.30.02
Pharmacology/Toxicology Review by John Koerner dated 12.4.02
Pharmacology/Toxicology Review by Xavier Joseph dated 12.4.02
Sponsors submissions on EDR, Hard copies of NDA 21468 dated volumes 13- 89??
NDA submissions dated May 21 and 22, June 7, 14, 19 and 28,
July 11, 25 and 30, August 5, 14, 27 (two), 29 and 30 (three), September 10, 13, 16, 18 and 25,October 3, 8, 22, 24 and 28, November 1, 4, 11, 15, 21, 22 (two), 27 (two) and 29, December 13 (two), 16, 18, 20 (two), 23, 2002 and January 23, 27 and 28, and February 12, 2003.
NDA 21468 serial March 2004
NDA 21468 serial April 2004
NDA 21-468 serial 074 of June 1 2004
NDA 21468 serial 075 of June 2 2004
Publications on bone diseases in chronic renal failure
Publications on intestinal absorbtion in renal failure
IND 55054 vol 7.1 of 1999
Protocol Amendments IND 55054 Serial no 035
Case report Forms (crf)

Updated application summary
Additional non-clinical study reports

R007-LAM-111A R00456-LAM-111D R00711-LAM-111D
Additional PK and bioavailability, clinical data and additional analyses of clinical data including Drug disposition Overall bone histomorphometry QT assessment Adverse event Assessment Updated Summary of safety [ ] Mortality Assessment
Additional clinical study reports LAM-IV-307 (interim) LAM-IV-301 LAM-IV-205 LAM-IV-116 LAM-IV-117

B. Tables listing the clinical trials

Table 46 summarizes all the clinical studies evaluated in the primary review of this NDA. It is noteworthy that no studies have been carried out in the pediatric age group (See recommendation on page 98).

Table 46: Overview of clinical studies using healthy volunteers in lanthanum program

Study Ref	Type of Study	Lanthanum Doses	Duration of Treatment	Total No. Subjects on Lanthanum (no subjects per dose)	Study Design
Completed Studies					
Clinical Pharmacology					
LAM-IV-101	Safety and PD profile	52mg	Single dose	**10**	Double blind, randomised, placebo controlled, rising dose
LAM-IV-104	Safety and PD profile	52, 105, 262 and 524mg	Single dose at each dose level (7 days between doses)	**19** 52mg = 7 105mg = 12 262mg = 11 524mg = 9	Double blind, randomised, placebo controlled, rising dose
LAM-IV-105	Safety and PD profile, multiple dose	262, 524, 786, 1315, 2096, 3145 and 4718 mg/day	15 days dosing on alternate days followed by 3 consecutive days at MTD.	**14** 262mg = 14 524mg=14 786mg = 13 1315mg = 13 2096mg = 13 3145mg = 13 4718mg = 13	Double blind, randomised, placebo controlled, rising dose followed by 3 days at MTD.
LAM-IV-108	PK profile, single rising dose	250, 500, 1000 and 2000mg/day	Single dose at each dose level (2 days between doses)	**10**	Double blind, randomised, placebo controlled, ascending dose
LAM-IV-109	PK profile, multiple dose	3000mg/day	5 days	**6**	Double blind, randomised, placebo

Study Ref	Type of Study	Lanthanum Doses	Duration of Treatment	Total No. Subjects on Lanthanum (no subjects per dose)	Study Design
					controlled, multiple dose
LAM-IV-110	PK profile and effects of food, multiple dose	3000mg/day	3 days	36	Open-label, randomised, 3-way cross-over
LAM-IV-111	PK profile in haemodialysis patients and healthy subjects	1000mg (single dose) 3000mg/day (multiple dose)	Two single doses (14 days apart), Multiple dosing – 14 days	**8 healthy subjects 10 ESRD patients**	Open label
LAM-IV 112	PK and interaction with citrate	1000mg	Single dose of lanthanum, or single dose of lanthanum with orange juice, or single dose of lanthanum with effercitrate	25	Open-label, randomised, 3-way cross-over
LAM-IV-113	Interaction with warfarin	3000mg/day	Single dose of warfarin or single dose of warfarin after 4th dose of 1000mg lanthanum	14	Open label, randomised,2-way crossover
Study Ref	Type of Study	Lanthanum Doses	Duration of Treatment	**Total No. Subjects on Lanthanum (no subjects per dose)**	Study Design
Completed Studies					
Clinical Pharmacology (cont'd)					
LAM-IV-114	Interaction with digoxin	3000mg/day	Single dose of digoxin or single dose of digoxin after 4th dose of 1000mg lanthanum	14	Open label, randomised,2-way crossover
LAM-IV-115	Interaction with metoprolol	3000mg/day	Single dose of metoprolol or single dose of metoprolol after 4th dose of 1000mg lanthanum	13	Open label, randomised,2-way crossover
SPD405-117	Bioavailability	120µg (lanthanum chloride) - IV 1000mg (lanthanum carbonate) - oral	A single dose of lanthanum either as a 4-hour constant rate IV infusion or as orally administered chewable tablets	16 IV 120µg = 8 Oral 1000mg = 8	Open label, parallel group

C. Post marketing Experience

This drug has so far not been approved and therefore there has been no post marketing experience of this drug.

D. Literature review by Sponsor

References

List of references provided by sponsor in original NDA plus the following:

Selbert JL et al.,. Bone biopsy studies in the diagnosis and treatment of renal osteodystrophy Contr Nephrol 1988: 64, 49-57 (Karger Basel).

Pei et al., Risk factors for renal osteodystrophy : A multivariant analysis. J Bone Min Res 1995: 10, 149-156

Malluche et al., The role of bone biopsy in the management of patients with renal osteodystrophy: Editorial Review J Am Soc Nephrol 1994: 4, 1631-1642

Hutchison et al.,Histological radiological and biochemical features of the adynamic bone lesion in continuous ambulatory dialysis patients. Am J Nephrol 1994: 14, 19-29

Parfitt et al.,Bone histomorphometry, standardization of nomenclature symbols and units. J Bone Mineral Research 1987: 6, 595-610

Parfitt et al.,Osteomalacia and related Disorders Metabolic Bone Disease 3rd Edition 1998:327-385

Quarles LD et al., J Bone Mineral Research 1998: 4, 671-677

Parfitt et al., Stereological basis of bone histomorphometry: Theory of quantitative microscopy and reconstruction of the third dimension CRC Press 1983: 60-65

Julian et al., Rapid loss of vertebral Mineral density after renal transplantation. New England journal of Medicine 1991: 544-545

Moniere Faugere et al., Trends in renal osteodystrophy: a survey from 1983 to 1995 in a total of 2248 patients. Nephrol Dial transplant 1996: 11, 111-120

Recker RR Bone biopsy and histomorphometry in clinical practice. Rheumatic Disease Clinics of North America 1994 20 609 – 627.

The following references that are deficient in sponsor's references representing Agency's efforts in literature review for this NDA

D. Literature Review by Reviewer / Agency

References

Langub MC, Faugere MC, Malluche HH: Molecular bone morphometry.

Pediatr Nephrol 2000: 14, 629-35

Monier-Faugere MC, Malluche HH. Role of cytokines in renal osteodystrophy.

Curr Opin Nephrol Hypertens 1997: 6, 327-32

Raab-Cullen DM, Thiede MA, Petersen DN, Kimmel DB, Recker RR.

Mechanical loading stimulates rapid changes in periosteal gene expression.

Calcif Tissue Int 1994: 55, 473-478

Inaba M, Okuno S, Nagasue K, Otoshi T, et.al.,

Impaired secretion of parathyroid hormone is coherent to diabetic hemodialyzed patients

Am J Kidney Dis 2001: 38, S139-142

Inaba M, Okuno S, Nagasue K, Ueda M et al.,

Impaired secretion of parathyroid hormone, but not refractoriness of osteoblast is a major mechanism of low bone turnover in hemodialyzed patients with diabetes mellitus

Am J Kid Dis 2002: 39, 1261 -1269

Sawaya BP, Butros R, Naqvi S, Geng Z et al.,Differences in bone turnover and intact PTH levels between African American and Caucasian patients with end-stage renal disease.

Kid Int 2003: 64, 737-742

Kaji H, Hattori S, Sekita K, Sugimoto et al., Factors affecting bone mineral density in hemopdialysis patients with diabetic nephropathy.

Endocr J 2003: 50, 127-133

Michels KB, Fei X, Brandt L, Anders Ekbom: Hyperthyroidism and subsequent incidence of breast Cancer Int J Cancer 2004: 110, 449 – 451

1: Piraino B, Chen T, Cooperstein L, Segre G, Puschett J.
Fractures and vertebral bone mineral density in patients with renal osteodystrophy.
Clin Nephrol. 1988 Aug;30(2):57-62.
PMID: 3180516

2: Piraino B, Chen T, Puschett JB.
Elevated bone aluminum and suppressed parathyroid hormone levels in hypercalcemic dialysis patients.
Am J Nephrol. 1989;9(3):190-7.
PMID: 2757078

3: Atsumi K, Kushida K, Yamazaki K, Shimizu S, Ohmura A, Inoue T.
Risk factors for vertebral fractures in renal osteodystrophy.
Am J Kidney Dis. 1999 Feb;33(2):287-93.
PMID: 10023640

4: Shin SK, Kim DH, Kim HS, Shin KT, Ma KA, Kim SJ, Kwak YS, Ha SK, Sherrard DJ. Renal osteodystrophy in pre-dialysis patients: ethnic difference?
Perit Dial Int. 1999;19 Suppl 2:S402-7.
PMID: 10406554

5: Heaf JG, Nielsen LP, Mogensen NB.
Use of bone mineral content determination in the evaluation of osteodystrophy among hemodialysis patients.
Nephron. 1983;35(2):103-7.
PMID: 6621754

6: Nowak Z, Tlustochowicz W, Wankowicz Z.
[Bone mineral density in patients with irreversible renal failure treated with peritoneal dialysis]
Pol Arch Med Wewn. 2001 Nov;106(5):1035-40. Polish.
PMID: 12026516

7: Piraino BM, Rault R, Dominguez JH, Puschett JB.
Renal osteodystrophy in patients on hemodialysis for more than 10 years.

Miner Electrolyte Metab. 1986;12(5-6):390-6.
PMID: 3807834

8: Salusky IB, Ramirez JA, Oppenheim W, Gales B, Segre GV, Goodman WG. Biochemical markers of renal osteodystrophy in pediatric patients undergoing CAPD/CCPD. Kidney Int. 1994 Jan;45(1):253-8.
PMID: 8127016

9: Rodriguez-Perez JC, Plaza C, Torres A, Vega N, Anabitarte A, Fernandez A, Lorenzo V, Hortal L, Palop L. Low turnover bone disease is the more common form of bone disease in CAPD patients.
Adv Perit Dial. 1992;8:376-80.
PMID: 1361827

10: Andress DL, Endres DB, Maloney NA, Kopp JB, Coburn JW, Sherrard DJ. Comparison of parathyroid hormone assays with bone histomorphometry in renal osteodystrophy. J Clin Endocrinol Metab. 1986 Nov;63(5):1163-9.
PMID: 3760116

11: Kuhlman JE, Fishman EK, Siegelman SS.
Computed tomographic features of renal osteodystrophy.
Orthop Rev. 1989 Dec;18(12):1290-5.
PMID: 2512563

12: Zayour D, Daouk M, Medawar W, Salamoun M, El-Hajj Fuleihan G.
Predictors of bone mineral density in patients on hemodialysis.
Transplant Proc. 2004 Jun;36(5):1297-301.
PMID: 15251316

13: Gerakis A, Hadjidakis D, Kokkinakis E, Apostolou T, Raptis S, Billis A. Correlation of bone mineral density with the histological findings of renal osteodystrophy in patients on hemodialysis.
J Nephrol. 2000 Nov-Dec;13(6):437-43.
PMID: 11132760

14: Meema HE, Rabinovich S, Meema S, Lloyd GJ, Oreopoulos DG.
Improved radiological diagnosis of azotemic osteodystrophy.
Radiology. 1972 Jan;102(1):1-10. No abstract available.
PMID: 5008148

15: Meema HE, Oreopoulos DG, Rabinovich S, Husdan H, Rapoport A.
Periosteal new bone formation (periosteal neostosis) in renal osteodystrophy. Relationship to osteosclerosis, osteitis fibrosa, and osteoid excess.
Radiology. 1974 Mar;110(3):513-22. No abstract available.
PMID: 4204516

16: Mathias R, Salusky I, Harman W, Paredes A, Emans J, Segre G, Goodman W.
Renal bone disease in pediatric and young adult patients on hemodialysis in a children's hospital. J Am Soc Nephrol. 1993 Jun;3(12):1938-46.
PMID: 8338926

17: Coen G, Ballanti P, Bonucci E, Calabria S, Costantini S, Ferrannini M, Giustini M, Giordano R, Nicolai G, Manni M, Sardella D, Taggi F.
Renal osteodystrophy in predialysis and hemodialysis patients: comparison of histologic patterns and diagnostic predictivity of intact PTH.
Nephron. 2002 May;91(1):103-11.
PMID: 12021526

18: Chazan JA, Libbey NP, London MR, Pono L, Abuelo JG.
The clinical spectrum of renal osteodystrophy in 57 chronic hemodialysis patients: a correlation between biochemical parameters and bone pathology findings. Clin Nephrol. 1991 Feb;35(2):78-85. PMID2019018

19: Jarava C, Armas JR, Salgueira M, Palma A.
Bone alkaline phosphatase isoenzyme in renal osteodystrophy.
Nephrol Dial Transplant. 1996;11 Suppl 3:43-6.
PMID: 8840311

**20: Stehman-Breen CO, Sherrard D, Walker A, Sadler R, Alem A, Lindberg J. Racial differences in bone mineral density and bone loss among end-stage renal disease patients. Am J Kidney Dis. 1999 May;33(5):941-6.
PMID: 10213653**

E. Important Issues with Pharmacologically Related Agents

Calcium carbonate was used as a comparator and was found to be more effective initially even though it is not approved by the Agency for this indication.

VII. Clinical Review Methods

A. How the review was conducted

This reviewer focused on the clinical components of safety in the clinical lanthanum program and also on the data from open label long term study (307) for assessment of safety. These included the following:

- The adverse events leading to discontinuation, particularly, overall serious adverse events in long term studies involving the gastrointestinal systems of patients who had discontinued on the drug.
- The adverse events leading to discontinuation, particularly, overall serious adverse events in long term studies involving the musculoskeletal system of patients who had discontinued on the drug.
- The adverse events leading to discontinuation, particularly, overall serious adverse events in long term studies involving the bones of patients who had discontinued on the drug.

- Serious adverse events leading to permanent discontinuation of lanthanum treatment for other reasons.
- The time taken for the serious GI adverse events to resolve chiefly among those discontinued and had been taken off study drug.
- The adequacy of the bone toxicity evaluation using histomorphometry alone and relevance of shifts in histopathology diagnoses to lanthanum toxicity.

B. Overview of materials consulted in Review -

See page 66.

C. Overview of Methods used to evaluate data quality and integrity

The approach used in the delineation of the safety profile of FOSRENOL in hyperphosphatemic patients with end- stage renal disease undergoing dialysis included: examination of the clinical database for deaths, discontinuations, serious adverse events, as well as an analysis of the routinely collected safety data (i. e., treatment emergent adverse events, laboratory findings, and vital signs). ECG data were evaluated specifically to determine whether lanthanum carbonate causes changes in QT/ QTc (Appendices 7-13). To determine whether lanthanum carbonate has an adverse effect on bone formation results from bone biopsies and incidence of fractures were examined.

D. Were trials conducted in accordance with acceptable ethical standards

DSI will report on this aspect.

E. Evaluation of financial disclosure

This was complied with as sponsor submitted a disclosure with the original NDA but not with the resubmission.

F. 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.

Table 47: Drug supply for LAM-IV-307

Dose	Batch
375mg	OH2769 and OH 2770
750 mg	OH2769 and OH 2770
1500 mg	OH2769 and OH 2770
2250 mg	OH2769 and OH 2770
3000 mg	OH2769 and OH 2770

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 vital signs physical examinations and cognitive function assessments.

Secondary

- To assess maintenance of control of serum phosphorous (PO4) with long term use of lanthanum carbonate.
- To assess the long term effect of lanthanum carbonate on the calcium phosphorous product (Ca*P04) 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 Design

This was an open label, randomized, multicenter, Phase III, comparator controlled, parallel group study of the long term-study 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 of study participation. To be eligible to enter the dose titration phase, patient's PO4 levels had to be >5.9mg/dL. Eligible patients were randomized to a 1:1 ratio to receive lanthanum carbonate or their pre-study standard phosphate binder. Weekly assessments of their PO4 were carried out and their phosphate binder dose titrated for a period of 6 weeks. Patients randomized to lanthanum received 750 mg daily unless at the discretion of the investigator the patient required a starting dose of 1500 mg

Doses were titrated as necessary up to a maximum of 3000mg/day, and were adjusted based on the results of the PO4 levels taken at the first dialysis session of the week. If the patients PO4 level dropped below 3.1 mg/dL the patients lanthanum dose could be 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. The washout period was one to 3 weeks for part 1, dose titration was for 6 months Part 2 and 24 months for the maintenance treatment phase (Part 3). Patients were allowed to switch their binders throughout the study or to combine their binders to achiev optimale PO4 control.

Demographics

Table 48:Summary Demographics - open label long term study LAM-IV-307

	Randomized Patients		
Patient population	**Lanthanum**	**Standard**	**All enrolled**
N	680	674	1, 552
Age(yrs) N (%)			
18-50	285(41.9)	259(38.5)	605(39.1)
51-64	218(32.1)	226(33.6)	512(33.1)

	Randomized Patients		
Patient population	**Lanthanum**	**Standard**	**All enrolled**
65+	177(26.0)	188(27.9)	432(27.9)
Mean±SD	53.8±14.5	54.9±14.4	54.9±14.5
Gender N (%)			
Male	389(57.2)	414(61.4)	930(59.9)
Female	291(42.8)	260(38.6)	622(40.1)
Race N(%)			
Caucasian	303(44.6)	313(46.4)	700(45.1)
Black	301(44.3)	274(40.7)	667(43.0)
Hispanic	54(7.9)	55(8.2)	122(7.9)
Asian PI	3(0.4)	13(1.9)	18(1.2)
Native American	6(0.9)	6(0.9)	14(0.9)
Others	13(1.9)	13(1.9)	30(1.9)
Weight (lbs)			
N	676	671	1,540
Mean±SD	177.9±48.2	178.5± 46.8	178.2±47.4
Height			
N	669	661	1,518
Mean±SD	66.8±4.4	67.2±4.3	67.0±4.4

The disposition of patients in this study are in Tables 49-52. The number of patients randomized to the bone substudy is only 100 in the lanthanum group and 97 in the standard therapy group (Table 49).About 68% of patients were withdrawn from the lanthanum group compared to about 49% in the standard therapy group (Table 50). Tables 51 and 52 present the disposition of the two sub-studies on cognitive function tests and the bone substudy. Note the relative higher withdrawal rate of patients from the lanthanum groups in both sub-studies.

Table 49: Disposition of patients for long term safety evaluation - LAM-IV-307

	Lanthanum (N)	**Standard (N)**
Number planned as per protocol	500	500
Total enrolled (1,552)		
Terminated before randomization (198)		
Randomized (1,354)	680	674
Total for safety evaluation	680	674
ITT population	666	667
Sub-study-Cognitive Function (408)		
Randomized (358)	178	180
Sub- study – Bone biopsies (209)		
Randomized (197)	100	97

Table 50: Disposition of subjects for long term safety evaluation-LAM-IV-307

	Lanthanum N(%)	Standard N(%)	Still in washout	TPR
Total enrolled	680	674	10	188
Number remaining in study	86(12.6)	98(14.5)	10(100.0)	0(0)
Completers	133(19.6)	249(36.9)	0(0)	0(0)
Number withdrawn Reasons for withdrawal:	**461(67.8)**	**327(48.5)**	**0(0)**	**188(100.0)**
Adverse events	98(14.4)	24(3.6)	0(0)	6(3.2)
Protocol violation	13(1.9)	5(0.7)	0(0)	7(3.7)
Withdrew consent	105(15.4)	30(4.5)	0(0)	20(10.6)
Transplanted	50(7.4)	69(10.2)	0(0)	2(1.1)
Lost to follow up	9(1.3)	8(1.2)	0(0)	1(0.5)
Death	35(5.1)	87(12.9)	0(0)	4(2.1)
Ineligible for titration	0(0)	0(0)	0(0)	100(53.2)
Others	101(14.9)	72(10.7)	0(0)	46(24..5)
Exceeded safety criteria	50(7.4)	32(4.7)	0(0)	2(1.1)
Two PO4 values >10mg/dL	32(4.7)	22(3.3)	0(0)	1(0.5)
Two PO4 values <2.0mg/dL	0(0)	2(0.3)	0(0)	1(0.5)
Two Ca*PO4 >90mg2/dL	13(1.9)	7(1.0)	0(0)	0(0)
Calcium >115 mg /dL	1(0.1)	1(0.1)	0(0)	0(0)
Increase in PTH>500pg/mL from screening	5(0.7)	1(0.1)	0(0)	0(0)

Table 51: Disposition of subjects for cognitive function tests substudy - LAM-IV-307

	Lanthanum	**Standard**	**Still in washout**	**TPR**
Total enrolled	178	180	4	46
Number remaining in study	34(19.1)	43(23.9)	4(100)	0
Completers	19(10.7)	54(30.0)	0	0
Number withdrawn Reasons for withdrawal:	125(70.2)	83(46.1)	0	46(100)
Adverse events	22(12.4)	6(3.3)	0	1(2.2)
Protocol violation	3(1.7)	1(0.6)	0(0)	3(6.5)
Withdrew consent	33(18.5)	6(3.3)	0(0)	4(8.7)

Transplanted	12(6.7)	16(8.9)	0(0)	0
Lost to follow up	4(2.2)	0	0(0)	1(2.2)
Death	11(6.2)	28(15.6)	0(0)	1(2.2)
Ineligible for titration	0(0)	0(0)	0(0)	25(54.3)
Others	25(14.0)	20(11.1)	0(0)	11(23.9)
Exceeded safety criteria	15(8.4)	6(3.3)	0(0)	2(1.1)
Two PO4 values >10mg/dL	11(6.2)	5(2.8)	0(0)	0
Two PO4 values <2.0mg/dL	0(0)	2(0.3)	0(0)	0
Two Ca*PO4 >90mg2/dL	2(1.1)	1(0.6)	0(0)	0(0)
Calcium >115 mg /dL	0	0	0(0)	0(0)
Increase in PTH>500pg/mL from screening	2(1.1)	0	0	0

Table 52: Disposition of subjects for bone substudy -LAM-IV-307

	Lanthanum N(%)	Standard N(%)	Still in washout	**TPR**
Total enrolled	100	97	2	10
Number remaining in study	58 (58.0)	59(60.8)	2(100.0)	0(0)
Completers	7(7.0)	10(10.3)	0(0)	0(0)
Number of pts. withdrawn Reasons for withdrawal:	**35(35.0)**	**28(28.9)**	**0(0)**	**10(100.0)**
Adverse events	2(2.0)	1(1.0)	0(0)	0
Protocol violation	1(1.0)	1(1.0)	0(0)	0
Withdrew consent	5(5.0)	1(1.0)	0(0)	0
Transplanted	8(8.0)	6(6.2)	0(0)	0
Lost to follow up	0	3(3.1)	0(0)	0
Death	7(7.0)	9(9.3)	0(0)	1(10.0)
Ineligible for titration	0(0)	0(0)	0(0)	7(70.0)
Others	8(8.0)	4(4.1)	0(0)	1(10.0)
Exceeded safety criteria	4(4.0)	3(3.1)	0(0)	1(10.0)
Two PO4 values >10mg/dL	1(1.0)	1(1.0)	0(0)	0(0.0)
Two PO4 values <2.0mg/dL	0	0(0.0)	0(0)	1(10.0)
Two Ca*PO4 >90mg2/dL	2(2.0)	2(2.0)	0(0)	0(0)
Calcium >115 mg /dL	0	0(0.0)	0(0)	0(0)
Increase in PTH>500pg/mL from screening	1(1.0)	1(1.0)	0(0)	0(0)

Inclusion criteria

- Patients of either sex at least 12 years old with chronic renal failure who had undergone hemodialysis for chronic renal failure 3 times a week for at lease the

previous two months, and who currently requires phosphate binders for the treatment of hyperphosphatemia (>5.9mg/dL) were eligible for enrollment.

- Patient or legal representative must have ability to give written informed consent
- Patient must be judges by the investigator to have the capacity to be compliant with the protocol
- Patients including those who have undergone renal transplantation in the past must have received 3 time a week hemodialysis for chronic renal failure for at least the previous 2 months.

Exclusion criteria

- Pregnant women
- Women of re[productive potential who did not agre to use effective birth control measures
- Patients with a screening calcium level below 7.9mg/dL
- Patients with clinically significant uncontrolled concurrent illness that may impair capacity of patient to participate by informed consent.
- Patient with any significant GI surgery of GI disorders such as peptic ulcer. Crohns disease, GI bleed within the past 6 months past or present GI malignancy.
- Patients with elevated liver enzymes more than 3 times the upper limit of normal.
- Patients with life-threatening malignancy or multiple myeloma.
- HIV positive patients.
- Patients who had been exposed to an experimental drug within 30 days prior to screening.

Exclusion criteria for cognitive function sub-study

- Patients unable to complete the training sessions after 2 attempts.
- Patients with documented aluminum related bone disease or dementia.
- Patients on psychotropic drugs stabilized for less than 1 month.
- Patients were not allowed to smoke or drink alcohol within one hour prior to the test.

Exclusion criteria for bone biopsy sub-study

- Patients allergic to tetracycline.
- Patients on medication known to affect bone metabolism during 6 months prior to biopsy.
- Patients requiring long term therapy with steroids at doses > 5mg prednisolone per day or equivalent.
- Patients receiving treatment with cyclosporine within the last 6 months.
- Patients having parathyroid surgery within 6 months prior to bone biopsy.
- Patients with documented aluminum related bone disease.

VIII. Integrated Review of Efficacy

A Brief statement of conclusions

Lanthanum has been shown to be an effective phosphate binder.

B General approach to review of the efficacy of the Drug

The reviewer consulted all the sources of data listed on pages 66-67 of this review.

C Detailed Review of Trials by indication
The detailed review of the trials by indication are in Appendix 3 by Dr Pelayo.

D Efficacy Conclusions- for all trials
The primary efficacy endpoint was the reduction and maintenance of serum phosphate levels in hyperphosphatemic patients with end stage renal disease. A secondary endpoint was the proportion of patients whose phosphorous levels were controlled during the trial to a predefined level of ≤5.9 mg/dL in the US, and ≤5.6 mg/dL in the UK. In the resubmitted NDA, the data presented for efficacy are not different for reduction or maintenance of reduced levels of phosphorous from those described in the original NDA including the LAM- IV -307, that shows similar findings albeit open label (Figure below page 84). This study showed a progressive decrease in serum phosphorous level in the lanthanum group but not as much as the comparator (Figures 1 and 2). The data from the other short term clinical studies are in the review of the original NDA. (See Appendix 3).

In the integrated summary of efficacy of placebo controlled studies in the original NDA, the pre-study serum phosphorous levels (PSPL) for placebo and lanthanum carbonate were similar, 6.186 mg/dL versus 6.251 mg / dL respectively. At the end of washout period, there were no differences (7.39 mg/dL vs 7.69 mg /dL). At the end of dose titration phase the serum phosphorous levels decreased from 7.39mg/dL (end of washout) to 5.62mg /dL and from 7.69mg/dL (end of wash out) to 5.49mg/dL for the placebo and lanthanum groups respectively.($p=0.6942$). The serum phosphorous level at the end of randomization was 7.85±1.96 mg/dL for placebo whereas for patients given lanthanum carbonate serum phosphorous level was 5.94 ±1.65 mg /dL. ($p<0.0001$). Post-randomization levels of phosphorous in the two treatment groups showed significant differences supporting efficacy of lanthanum.

The change from baseline in PSPL during weeks 1 – 7, the titration weeks, shows a decrease in both treatment groups. The mean change was -1.43 for lanthanum and -1.91 for standard showing a statistically significant difference in favor of standard group ($p<0.000$) . Similarly the change during the maintenance phase , weeks 7 – 52 show no significant change at week 52 between the two treatment groups (Table 3 ISE) (Appendix 3).

Overall, primary efficacy endpoint was reduction of serum phosphate in end stage renal disease (ESRD) patients with hyperphosphatemia using a temporal decline of pre-dialysis serum Phosphate (PSPL) over time as a basis for comparison of point estimates between lanthanum and other comparators (standard therapy and calcium carbonate). Primary efficacy was determined according to the level of serum phosphate achieved after 5 weeks in the dose titration phase: serum phosphate levels < 1.80 mmol/L were considered to be the control.

The primary efficacy endpoint in this study was the predialysis serum PO4 levels (PSPL), which were measured at the first dialysis sessions of study visits week 1 to week

7, i. e., titration period. In both treatment groups serum PO4 levels declined over time. However, when compared between treatment groups, the change from baseline serum phosphorus level to each follow- up week of dose titration, a greater reduction occurred for patients on standard therapy (p= 0.000).

Secondary efficacy was the evaluation of maintenance of control after 25 weeks of treatment including 5 weeks of treatment and 20 weeks of maintenance. Efficacy of lanthanum was demonstrated in the original NDA. The open label study was not placebo controlled but the efficacy data are in figure below and Table 61 below. The results of phosphate levels in the maintenance period did not meet the prespecified level of < 5.9mg/dL in the lanthanum group and in most of the time points for the standard group (Table 61). Since this is not the primary endpoint and this is not the pivotal study for efficacy, these data provide additional information.

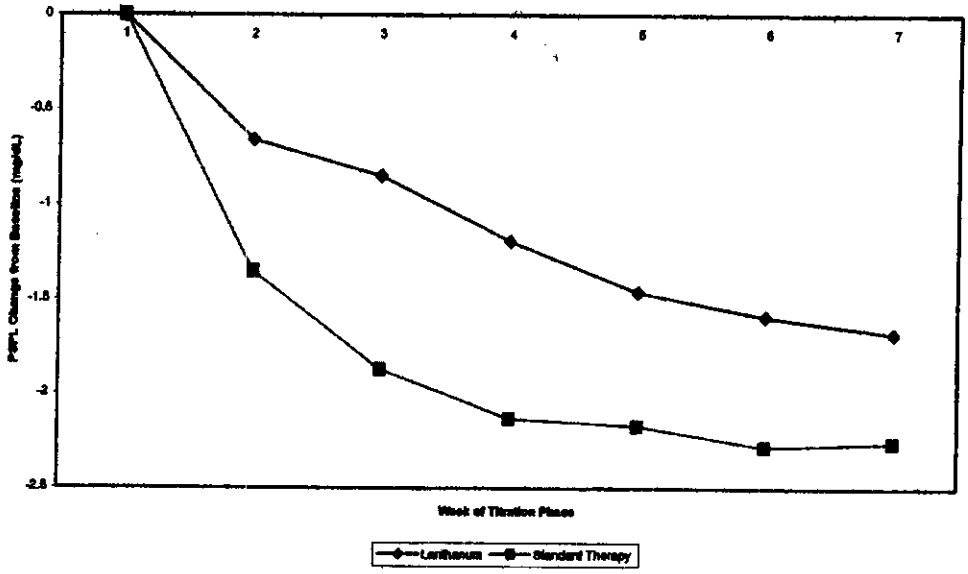
Efficacy

The efficacy endpoint was the control of PO4 levels (measured at the first dialysis session of the week) defined as maintaining PO4 <5.9mg/dL. Other endpoints included predialysis calcium levels calcium phosphorous product and serum PTH levels.

The primary efficacy evaluation during this study was measurement of the PSPL to ensure that the serum phosphorous level was maintained within predefined acceptable limits.

Pre-dialysis serum phosphorous level (PSPL) values were measured at the first dialysis session of each study visit and were assigned "controlled" or "non controlled" groups for individual patients. The data were examined separately at the end of the titration phase and at study weeks 14, 26, 52, and months 18 and 24 for differences in the proportion of controlled patients among lanthanum doses versus standard therapy. The analysis was performed for I-T-T and Per protocol (PP) populations.

Serum calcium levels, PTH levels, and Ca*PO4 product were also examined.



APPEARS THIS WAY
ON ORIGINAL

Table 53:Serum phosphorous levels by visit and treatment group ITT population during the maintenance phase - LAM-IV-307

Table 9 Summary of Serum Phosphorous Levels by Visit and Treatment Group (ITT population) During the Maintenance Phase

Visit No.	Week / Month	Serum Phosphorous Levels (mg/dL) by Treatment Group							
		Lanthanum n=666				Standard Therapy n=667			
		Mean	SD	N	Range (min-max)	Mean	SD	N	Range (min-max)
7	Week 7	6.4	1.7	559		5.8	1.7	619	
9	Week 14	6.5	1.7	509		6.0	1.8	594	
12	Week 26	6.3	1.9	414		6.0	1.8	550	
15	Week 52	6.3	1.8	315		6.2	2.0	445	
16	Month 14	6.3	1.7	267		6.1	1.9	407	
17	Month 16	6.4	1.9	230		6.1	1.9	365	
18	Month 18	6.2	1.8	202		6.1	1.9	335	
19	Month 20	6.2	1.8	174		6.1	2.0	299	
20	Month 22	6.2	1.9	150		5.9	1.8	262	
21	Month 24	6.3	1.7	136		6.1	1.9	252	

Data Source: Section 14, Table 14.2.2.2

IX. Integrated review of safety

A. Brief Statement of conclusions

B. Description of patient exposure (See tables 53 and 54)

Table 54: Lanthanum exposure during titration phase only- LAM-IV-307

Daily dose	Tablet strength (mg)	No of tablets per day	No ot tablets per meal
375	250	1.5	0.5
750	250	3	1
1500	250	6	2
2250	250	9	3
3000	250	12	4
Starting dose at investigator's discretion			

Table 55: Duration of lanthanum carbonate exposure -LAM-IV-307

	Lanthanum	Standard Therapy
Treatment duration	N(%)	N(%)
< 1 month	44(6.5)	18(2.7)
≥1<2	71(10.4)	24(3.6)
≥2<3	34(5.0)	17(2.5)
≥3<6	76(11.1)	44(6.5)
≥6<9	70(10.3)	52(7.7)
≥9<12	49(7.2)	49(7.2)
≥12<18	98(14.4)	90(13.3)
≥18<24	106(15.5)	155(22.9)
≥24	134(19.6)	227(33.6)
Total Patients	682	676
Mean time of exposure	356.6±267.6	484.6±249.6

C. Methods and specific findings of safety review

For methods of safety review the reviewer has consulted sources of data listed on pages 66-67. This reviewer finds that the sponsor has been unable to provide the essential data requested in the approvable letter in respect of GI and bone changes. The sponsor has provided adequate information on the time course of the QT interval and the relationship of prolonged QT intervals and adverse events including death. The deficiencies that remain are as follows: The time to resolution after drug withdrawal has not been provided. Additional information on bone biopsies since the approvable is not forthcoming. Only 3 slides of bone biopsies have been provided in patients with 4-5 year follow up. Analyses of fractures, however, have been provided covering a period of 3 years but the percentages calculated for persons at risk included healthy volunteers and patients on placebo who were exposed to the drug for about 7 days. These patients should have been excluded thus making the sponsor's data uninterpretable. Assuming that these data are acceptable because the proportion of healthy volunteers may not impact the conclusion that there are no differences between the risk of fracture at two/three years between the two groups, the risk of fracture varies with the histological category of renal bone disease and the number of years on dialysis. The conclusion that there is no difference between the risk of fracture between the two treatment groups require further analyses. This reviewer has maintained the position that histomorphometry alone is inadequate for assessment of lanthanum bone toxicity.

The sponsor refers to the use of histological characterization of the bone lesions but has not provided detailed histological reports on each of the bones evaluated. The histological shifts presented in Table 22 may be used for adjustment of the fracture rates between the 2 groups based on the rates published in the literature. **Patients with low turnover osteodystrophy have been shown to have a fracture rate of 0.2 fractures /dialysis year whereas patients with osteitis fibrosa had 0.1 fractures /dialysis year (Piraino B et al Fractures and vertebvral bone mineral density in patients with renal osteodystrophy. Clin Nephrol 1988: 30 57-62)** **See page 71.**

Cardiovascular system

Normal ECG at baseline:

A total of 468 patients in study 307 had normal ECGs at baseline, pretreatment. Of these 251 and 217 were in the lanthanum and standard therapy groups, respectively. Out of 251 patients on lanthanum, 26 (10.4%) patients had died whereas 19 (8.8%) out of 217 on standard therapy had died. The Log rank test showed that the two survival curves were almost superimposed (p=0.5226). However at 44 months, there was a slightly higher mortality in the lanthanum group. The hazard ratio shows that old patients were more likely to die than young patients (HR=1.068; p<0.0001); patients with longer treatment durations were less likely to die compared to those with shoerter durations (HR0.938; p<0.0005)

Abnormal ECG at baseline

A total of 886 patients in study 307 had normal ECGs at baseline, pretreatment. Of these 429 and 457 were in the lanthanum and standard therapy groups, respectively. Out of 429 patients on lanthanum, 109 (25.4%) patients had died whereas 138 (30.2%) out of 457 patients on standard therapy had died. The Log rank test showed that the two survival curves were separated but not statistically significant (p=0.1545). These curves have not been adjusted for discontinuations (68%) that occurred more in the lanthanum group compared to the standard group (49%). However, at 44 months, there was a slightly higher mortality (but not significant)in the lanthanum group. The hazard ratio estimates show that old patients were more likely to die than young patients (HR=1.037; p<0.0001); patients with longer treatment durations were less likely to die compared to those with shorter durations (HR 0.914; p<0.0001). Adjustments were not made for discontinuations in this cohort therefore the data on mortality are uninterpretable. As to be expected, patients with abnormal cardiac pathologies at baseline were more likely to die compared to those with normal ECG at baseline.

Neoplasms

There appears to be a slight excess of colon cancers in the lanthanum group and also more benign breast masses in the lanthanum group compared to standard therapy (Table 64).

D. Adequacy of safety testing

The issue of adequacy is whether the 2 year follow up is adequate knowing what we know about lanthanum accumulation in bones and knowing that there is evidence that lanthanum damages long bones in rats with normal renal function, albeit at high lanthanum doses. Therefore, the unresolved issue that has to be determined is whether chronic administration of lanthanum that damages bone structure in rats with normal renal function will do the same in humans with already damaged bones and if lanthanum does damage bones in rats do you expect the rats to develop fractures within the short period of observation.

While an extensive long term follow up of bone changes may not be feasible in clinical trials, the sponsor, in agreement with the agency, agreed to qualitative and quantitative assessment of bone biopsies from the iliac crest of patients exposed to lanthanum and standard treatment. The two separate methods of histology and histomorphometry were required to evaluate bone biopsies in patients exposed to both lanthanum and standard

therapy for the treatment of hyperphosphatemia. Histomorphometric evaluation of bone provides objective data on static and dynamic parameters of bone structure, formation and resorption. Therefore this is an accepted classical research tool for studying bone physiology and pathology. However there is a limitation that histomorphometry does not evaluate the microenvironment of bones such as marrow, blood vessels, periosteum and endosteum. Assuming that histomorphometric data of bone acknowledges the variation within the sites used for bone samples by use of proper control groups, and considering that this is a useful tool for evaluating differences in repeat bone biopsies after a treatment regimen it is not clear if a point estimate from a bone biopsy is adequate to predict pathological changes, such as fractures, or even frequencies, severity and extent of fractures, that will take place over time. Of significant relevance is the example that patients with low turnover osteodystrophy had a fracture rate of 0.2 fractures /dialysis year whereas patients with osteitis fibrosa had 0.1 fractures /dialysis year.

The photomicrographs derived from the sponsor's slides do not support the sponsor's conclusion that these rats with normal renal function show "no", repeat, "no" bone changes. Furthermore the sponsor's claim that the lanthanum concentrations in humans were within the range of lanthanum concentrations in rats with normal renal function and since they showed no changes it is unlikely that lanthanum will do any harm to bones in humans. Based on this assumption, the basis of this assertion therefore falls flat on its face based on this assumption. It is my opinion that the changes in the long bones of rats with normal renal function are also present in bones of uremic rats treated with lanthanum and these changes are additional to renal bone changes.
The sum total of the effect of lanthanum on rat bones with normal renal function is that there is a metaphyseal lesion consisting of multiple cortical bone defects due to resorption with fibro-proliferative periosteal thickening overlying the bone lesions and repairing the cortical defects in places. Similar lesions are seen in uremic rats given lanthanum.

The sponsor claimed that in the open label long term study (307) the majority of the GI adverse events resolved within the first week and others resolved within the following two weeks. This has not been substantiated as there no data on stop dates in the data base for resolution of GI adverse events.

E. Summary of Critical Safety findings and limitations of data

Bones:
Studies Specifically Conducted to Assess Bone Safety: Study LAM- IV- 303 assessed the effect of lanthanum carbonate compared to calcium carbonate on renal bone disease by comparing bone tissues obtained from paired biopsies. Of the 98 patients randomized into the study, 71 patients received a follow-up biopsy after 52 weeks of treatment, and therefore provided paired biopsy data, however only 63 pairs of biopsies were suitable for histomorphometric measurements.

The two separate methods of histology and histomorphometry were required to evaluate bone biopsies in patients exposed to both lanthanum and standard therapy for the treatment of hyperphosphatemia. Histomorphometric evaluation of bone provides

objective data on static and dynamic parameters of bone structure, formation and resorption. Therefore this is an accepted classical research tool for studying bone physiology and pathology. However there is a limitation that histomorphometry does not evaluate the microenvironment of bones such as marrow, blood vessels, periosteum and endosteum.

The validity of the bone biopsy findings is questioned because according to the sponsor's acknowledgement that " there were limited data available on which to base the sample size estimates, therefore numbers were based on practical rather than statistical considerations." Thus the study was not powered to rule out whether lanthanum carbonate has deleterious effect(s) in bone formation as compared with active control. The interpretation of the findings is further confounded by the fact that calcium carbonate, the active control, is not an FDA approved phosphate binder thus its safety profile, as compared with placebo/ standard therapy, is unknown to the Division of Cardio- Renal Drug Products.

G.I.:
There are no studies specifically conducted to assess time to resolution of GI adverse events after the drug had been stopped in patients discontinued for GI adverse events. The sponsor has been unable to provide this information from their database. This is a limitation of data as the sponsor could provide data on the time to onset of the adverse events but not provide the stop dates on these events to ascertain if these events resolved within a reasonable time compared with the comparator.

X. Dosing Regimen and Administration Issues

This has been discussed elsewhere in this review (Page 55).

Safety

Primary objective of this study was to assess drug safety. Other objectives included assessing the maintenance of control of serum phosphorous with long term use of lanthanum compared to standard therapy.
Safety assessments included the following:

- Adverse events
- Vital signs
- Laboratory tests
- Pregnancy tests
- ECGs
- Physical examination
- Questionnaire of palatability
- Mini-mental state examination
- Plasma lanthanum levels: A predialysis blood sample was taken at screening and at study visits 3,7,9,12,18,21 (End of study) and at screening and visit 21 only for those on standard therapy.
- Medical History at screening.

Subset of 100 patients as part of full blood profile

- Vitamin A
- Vitamin D
- Vitamin E
- Vitamin K
- Serum folate
- and Vitamin B12

Subset for bone evaluation and or cognitive function test.

- Bone biopsies for mineralization
- Cognitive function

Adverse events

Adverse events were assessed for differences between treatment groups (lanthanum versus standard therapy) for the number of AEs and the number and percent of patients reporting AEs.

Clinical laboratory Tests

Changes from baseline in the clinical laboratory tests were compare between the treatment groups throughout the titration and maintenance phases of the study using analysis of variance. Comparisons between the two treatment groups at baseline were carried out using 2 sample t-test. The number of clinically significant abnormal laboratory tests observed during the study was reported.

Vital signs

Vital signs were analyzed for changes from the beginning of the maintenance to a followup maintenance visit for lanthanum versus standard treatment during the maintenance period using analysis of variance. For patients on lanthanum treatment plasma lanthanum concentrations were plotted and analyzed for changes from pre-dosing.

Cognitive function sub-study

Summary statistics were calculated for each measure and each time point by treatment. For each measure, baseline data were subtracted from the data at each post-baseline assessment to derive differences from baseline scores in ITT patients.

Bone biopsy sub-study - ITT population

Study plan for bone substudy:

A subset of 58 patients per treatment group (29 patients per group randomized to a 1 year biopsy and 29 patients per group randomized to a 2 year biopsy who agreed to participate in the primary study.

The goal of the proposed substudy was to determine whether treatment with lanthanum carbonate induces mineralization defect. It is important to note that the sponsors did not plan to study lanthanum toxicity on bone and its microenvironment.

With the sample size chosen, the study will have a power of 80% to yield a statistically significant result. This effect was selected as the smallest effect that would be important to detect in the sense that any smaller effect would not be of clinical or substantive significance. This was based on an assumption but there are no data to support this

assumption. The sponsors claim that the effect size of this magnitude is reasonable and could be anticipated in this field of research. This reviewer is concerned about the validity of this assumption because it has no basis and because of the relatively long half life of lanthanum. The mean plasma lanthanum level in the bone substudy is in Table 55 below and the drug exposure including doses administered during the titration phase are in Tables 56-58.
The distribution of patients with mineralization defect and activation frequency categories among the two groups were tested by logistic regression adjusted for baseline category. Summary statistics of the mean and SE of mean, were provided for the lanthanum carbonate and standard therapy groups at baseline and follow up biopsy visits and also the change between baseline and follow up.

The frequency distributions at baseline and follow up visits and shift tables of mineralization defect, activation frequency mineralization lag time and osteoid thickness categories from baseline to the second biopsy were also presented by treatment group.
Key Parameters used for histomorphometric assessments

- Primary response variables relating to mineralization are Mineralization lag time and osteoid thickness.
- MLt >100 days and O.th >20μm; worsening of MLt was defined as a 20% increase in either parameter.
- Primary response variables relating to bone turn over are activation frequency, number of osteoclasts and osteoblasts erosion depth and osteoid surface bone surface (%).

None of the above evaluations was carried out in the uremic rats and in rats with normal renal function tests.

Table 56: Mean plasma lanthanum levels in the bone substudy LAM-IV-307

	Lanthanum group		
Visit	**N**	**Lanthanum levels (ng/mL)**	**Min – Max (ng.mL)**
Screening	96	0.0±0.05	
Week 7	98	0.3±0.24	
Week 26	88	0.4±0.55	
Week 52	66	0.4±0.48	
Month 24	10	0.7±0.76	

Drug exposure

Table 57: Drug Exposure during titration phase LAM-IV- 307

Daily dose	Tablet strength (mg)	No of tablets per day	No ot tablets per meal
375	250	1.5	0.5
750	250	3	1
1500	250	6	2
2250	250	9	3
3000	250	12	4

Starting dose at investigator's discretion

Table 58:Exposure to lanthanum carbonate LAM-IV-307

	Lanthanum	Standard Therapy
Treatment duration	N(%)	N(%)
< 1 month	44(6.5)	18(2.7)
≥1<2	71(10.4)	24(3.6)
≥2<3	34(5.0)	17(2.5)
≥3<6	76(11.1)	44(6.5)
≥6<9	70(10.3)	52(7.7)
≥9<12	49(7.2)	49(7.2)
≥12<18	98(14.4)	90(13.3)
≥18<24	106(15.5)	155(22.9)
≥24	134(19.6)	227(33.6)
Total Patients	682	676
Mean time of exposure	356.6±267.6	484.6±249.6

Table 59:Summary of lanthanum doses administered in Bone sub-study- LAM-IV-307

	Daily dose of lanthanum administered				
	375	750	1500	2250	3000
Visit	**N(%)**	**N(%)**	**N(%)**	**N(%)**	**N(%)**
Week 7(94)	0	22	21	21	20
Week 26(80)	0	16	18	17	23
Week52(70)	0	17	10	15	21
Month 24(10)	0	0	1	4	4

Safety-Adverse events

Table 60: Summary of treatment emergent adverse events in bone sub-study - LAM-IV-307

	Treatment Group		
Category	**Total**	**Lanthanum**	**Standard**
No of patients with at least one treatment emergent AE	190(96.4)	94(94.0)	96(99.0)
No of patients with at least one likely drug related treatment emergent AE	32(16.2)	21(21.0)	11(11.3)
No of patients withdrawn for AEs as study outcome	3(1.5)	2(2.0)	1(1.0)
No of patients with at least one SAE	105(53.3)	53(53.0)	52(53.6)
No of patients with at least one drug related SAE	0	0	0
No of patients who died during study	16(8.1)	7(7.0)	9(9.3)

	Treatment Group		
Category	Total	Lanthanum	Standard
as study outcome.			
No of patients who died during or within 30 days post study.	18(9.1)	7(7.0)	11(11.3)

Table 61: Frequencies of adverse events in musculoskeletal system experienced in >2% of patients in bone sub-study LAM-IV-307 (unadjusted)

	Bone Sub-study		All Patients	
Body system/ AE	**Lanthanum Group (N = 100)**	**Standard Group (N = 97)**	**Lanthanum Group (N = 680)**	**Standard Group (N = 674)**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Subjects with at least one adverse event	94 (94.0)	96 (99.0)	644 (94.7)	654 (97.0)
Musculoskeletal System Disorders	33 (33.0)	50 (51.5)	259 (38.1)	334 (43.8)
Myalgia	19 (19.0)	21 (21.6)	135 (19.9)	183 (27.2)
Skeletal pain	11 (11.0)	9 (9.3)	50 (7.4)	69 (10.2)
Arthralgia	5 (5.0)	17 (17.5)	61 (9.0)	90 (13.4)
Fracture - NW	4 (4.0)	8 (8.2)	33 (4.9)	47 (7.0)
Muscle weakness	3 (3.0)	6 (6.2)	16 (2.4)	27 (4.0)
Arthritis	1 (1.0)	5 (5.2)	18 (2.6)	26 (3.9)
Back pain	1 (1.0)	3 (3.1)	1 (0.1)	9 (1.3)
Bone disorder	0	2 (2.1)	1 (0.1)	6 (0.9)
Osteochondrosis	0	2 (2.1)	6 (0.9)	5 (0.7)
Osteoporosis	0	2 (2.1)	0	2 (0.3)

Data Source: Section 14, Table 14.3.1.2B

Table 62:% of patients with phosphate <5.9mg/dL

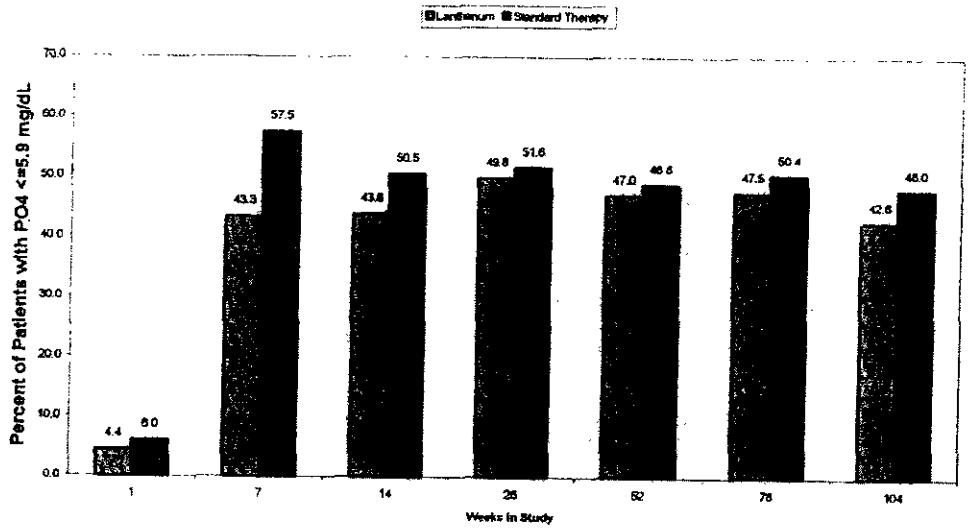


Figure 9:Serum calcium concentration- 2 yr follow up -LAM-IV-307

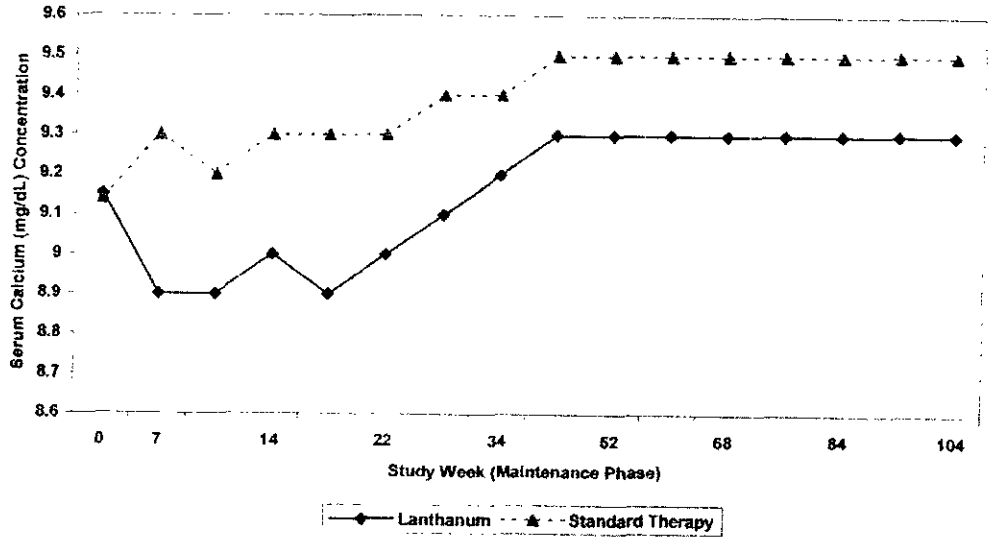


Figure 10:Serum calcium phosphate product levels in both treatment groups -2 years-307

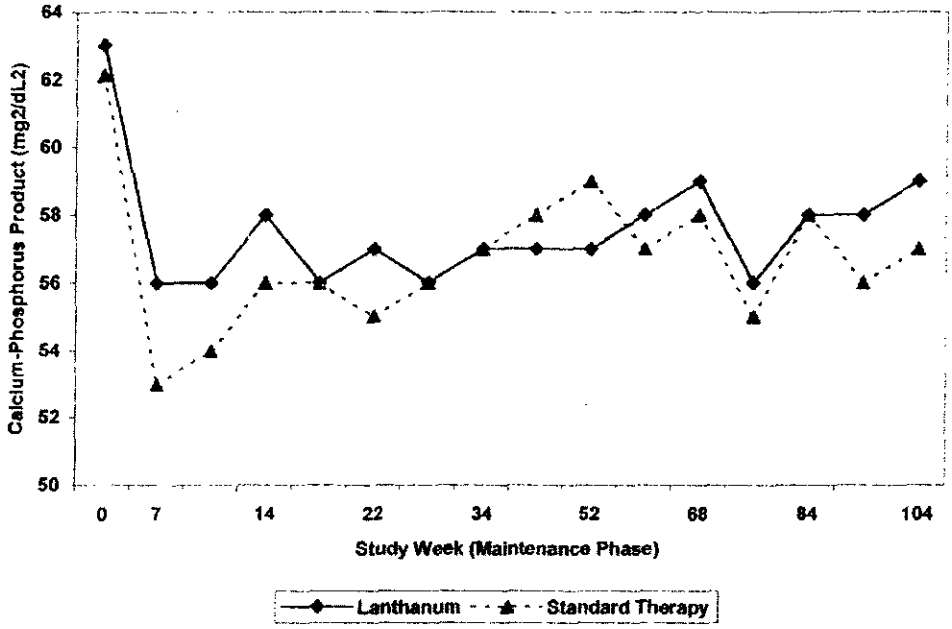
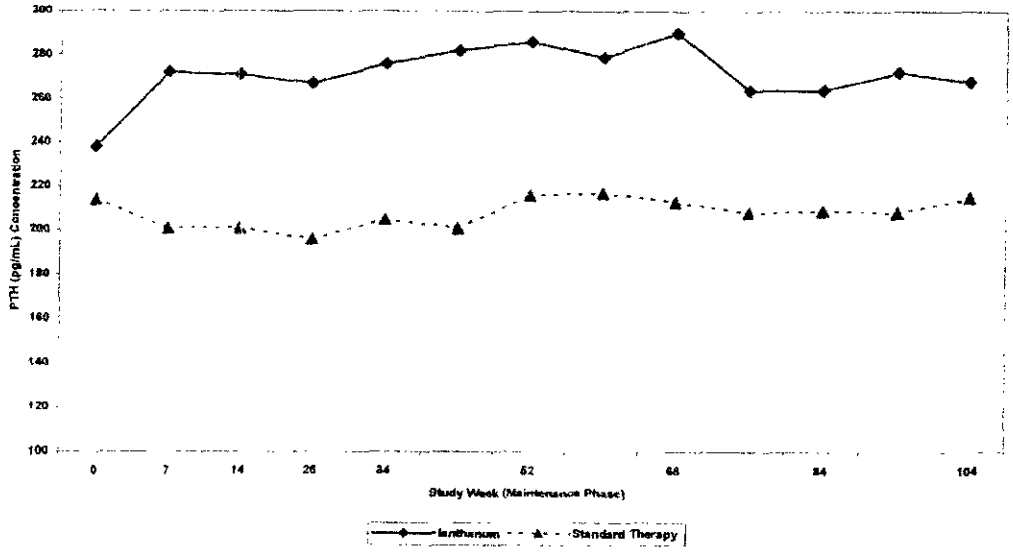


Figure 11: Serum parathyroid levels for 2 years - LAM-IV-307



Safety results and frequencies of neoplasms in long term studies

A total of 129 patients were reported to have neoplasms - 77 in lanthanum and 52 in standard therapy.

According to the sponsor the distribution of neoplasms, both benign and malignant, are similar to what would be expected for this population of patients on chronic dialysis. While there were more neoplasms diagnosed in the group of patients exposed to Lanthanum, the sponsor claimed that there was a longer observation period in the Lanthanum group compared to standard treatment. The nature of the malignant neoplasms are such that most should have been detected at the time of enrollment into the clinical trial but the sponsor has been unable to document the absence of these neoplasms that became manifest during follow up (Table 64). There is no excess of neoplasms among the lanthanum patients compared to standard group

Table 63: Neoplasms observed in LAM-IV Phase II and III clinical studies

	Lanthanum	**Standard Therapy**
	N=1754	N=990
Malignant Lesions		
Bladder Ca	2	0
Breast Ca	2	2
Chronic Myelogenous Leukemia	1	0
Colon Ca	4	1
Esophageal Ca	1	1
Gall Bladder Ca	0	1
Leukemia (AML)	1	0
Lung Ca	6	3
Melanoma	2	0
Prostate Ca	1	2
Renal Ca	1	2
Sarcoma	0	1
Skin Cancers (BCC, SCC, other)	9 (0.5%)	8 (0.8%)
Thyroid Ca	1	1
Unknown Primary	4	0
Benign Lesions		
Breast mass, nodule or lump	10 (0.6%)	4 (0.4%)
Hemangioma	1	0
Lipoma	3	2
Meningioma	0	1
Nevus	1	0
Ovarian Mass NOS	1	
Parathyroid Adenoma	3	3
Polyps GI tract Various Locations	10 (0.6%)	11 (1.1%)
Uterine Fibroids	3	1
Unknown Tumors or NOS	**10 (0.6%)**	**8 (0.8%)**
Total	**77 (4.3%)**	**52 (5.3%)**

NOS: Not otherwise specified. There appears to be a slight excess of colon cancers in the lanthanum group and also more benign breast masses in the lanthanum group compared to standard therapy.

Hypercalcemia, hyperparathyroidism and breast cancer

In a case control study conducted in Italy an elevated prevalence of primary parathyroid adenoma was observed among breast cancer patients. Hypercalcemia which has been found in 30-40% of breast cancer patients is the most frequent metabolic complication of breast cancer, and hyperparathyroidism which regulates serum calcium levels is the other most important disorder that induces hypercalcemia. A recent publication on the record linkage study in Sweden analyzed a total number of 9, 835 women who underwent surgery for primary parathyroid adenoma were followed to evaluate the hypothesis of the association between hyperparathyroidism and breast cancer. Preliminary data are available on the coexistence of primary hyperparathyroidism and breast cancer. Secondary hyperthyroidism that occurs in patients with hyperphosphatemia has not been investigated. In this study there were 4 cases of breast cancer and 14 cases of breast lump (Table 46). The parathyroid status of these patients is not known. There are more breast lumps in the patients on lanthanum compared to standard therapy and this is unadjusted but there are equal numbers of breast cancer between both groups. The significance of this reported trend is that patients with breast lumps and cancer should probably be excluded from therapy that has hypercalcemia as an adverse event as seen in this lanthanum program.(FDA Reference list page ////)

Bone

"The effect of lanthanum on bone was assessed in Study LAM-IV-303 by evaluating paired bone biopsies from ESRD patients on lanthanum and calcium carbonate. Of the 98 patients randomized into the study, 72 patients had a follow-up biopsy after 52 weeks. Histomorphometric measurements were carried out on only 63 pairs of biopsies. This small number of biopsies was not powered enough to detect a difference when compared with active control. Assuming that histomorphometry alone is adequate for sequential evaluation the comparator, calcium carbonate, is not an approved phosphate binder by the FDA. The safety profile of calcium carbonate is not known. Furthermore there is no qualitative evaluation of the bone biopsies particularly bone components that are not conducive to histomorphometric measurements. These inadequacies in the evaluation of bone changes constitute a basis for the approvable letter sent to the sponsor.

Suffice it to say that lanthanum continues to accumulate in bones and a steady state is yet to be determined in human bones. However, a steady state of lanthanum in the bone may take more than 10 years and this raises the adequacy of 2/3 year exposure for assessment of toxicity.

In a small number of lanthanum treated patients, plasma lanthanum levels appear to show a dose-dependent trend. While bone lanthanum concentration was unchanged in patients in the calcium group, there was a 50 fold increase in bone lanthanum concentration among patients administered lanthanum. This suggests that there is considerable accumulation of lanthanum in bone over a 52 week period.

One of the clinically meaningful features of lanthanum deposition in bones is the frequency of fractures. The data in the table of fractures supplied by the sponsor in the original NDA cannot be evaluated because there were so many discontinuations among

the lanthanum group (N=619; 65.1%) compared to the comparator (N=605; 45.6%). The reduced frequency of fractures in the lanthanum group (4.33%) compared to the comparator group (5.76%) is therefore untenable without adjustment for drug exposure (10.2 vs 14.1 months exposure for lanthanum and comparator, respectively)." Adjusted data shows no difference between the two groups (Dr V Friedlin).

The fracture rates that have been compared between the two groups without reference to the histological categories of renal bone disease assume a homogenous distribution histological types of fracture in both groups and therefore comparable rates of fracture. It has been shown that rates of fractures/dialysis year differ with histological categories of bone disease in patients on dialysis. Patients with low turnover osteodystrophy had a fracture rate of 0.2 fractures /dialysis year whereas patients with osteitis fibrosa had 0.1 fractures /dialysis year. Based on this information the conclusion derived from data analyzed by the sponsor in Appendix 5 and Appendix 6 become untenable. This will need to be adjusted for the histological categories. The shifts in histological categories of bone disease from baseline to end of 2 years differ between the two groups (Table 22).

Tables showing fracture analyses

Table 64: Time to event analysis of physician identified potential fracture-LAM-IV-307

Adverse Events Analyzed	Number (%) of patients reporting at least one fracture-potential AEs and survival analysis			Estimated Mean (Month) of survival	
	Lanthanum N=1754	Standard N=990	Pvalue Log rank	Lanthanum	Standard
AEs of 1st occurence	403 (23.0%)	304 (30.7%)	0.0126	23.2	16.5

Table 65: Time to event of key words searched for fractures LAM-IV-307

Adverse Events Analyzed	Number (%) of patients reporting at least one fracture-potential AEs and survival analysis			Estimated Mean (Month) of survival	
	Lanthanum N=1754	Standard N=990	p-value (log rank)	Lanthanum	Standard
AEs of 1st occurence	72(4.1%)	59(6.0%)	0.3573	34.2	23.0

Table 66: Summary of time to event analysis of key words searched fractures-LAM-IV-307

Adverse Events Analyzed	Number (%) of patients reporting at least one fracture-potential AEs and survival analysis			Estimated Mean (Month) of survival
				Lanthanum
	Lanthanum	Standard	Pvalue	Standard

	(n=1754)	(n=990)	(log-rank)		
AEs of 1st occurence	63(3.6%)	50(5.1%)	0.4612	34.5	23.2

Table 67: Summary of SAEs > 1% by body system for studies 307, 405-309 and 405-315.

	Lanthanum Group N (%)	Standard Therapy N (%)	Total N (%)
Number of SAEs reported	185	126	311
Application Site disorders	3(1.6)	1(0.8)	4(1.3)
Cellulitis	3(1.6)	1(0.8)	4(1.3)
Body as a whole-General disorders	15 (8.1)	11 (8.7)	26 (8.4)
Chest Pain	3(1.6)	4(3.2)	7(2.3)
Fever	3(1.6)	1(0.8)	4(1.3)
Syncope	2(1.1)	1(0.8)	3(1.0)
Cardiovascular Disorders General	18(9.7)	12(9.5)	30(9.6)
Cardiac Failure	10(5.4)	8(6.3)	18(5.8)
Hypertension aggravated	5(2.7)	1(0.8)	6(1.9)
Hypotension	0	2(1.6)	2(0.6)
CNS and PNS	7(3.8)	4(3.2)	11(3.5)
Convulsions	2(1.1)	1(0.8)	3(1.0)
Encephalopathy	2(1.1)	0	2(0.6)
Dialysis complication	13(7.0)	6(4.8)	19(6.1)
Dialysis Graft complication	4(2.2)	0	4(1.3)
Dialysis Graft Creation	0	2(1.6)	2(0.6)
Dialysis Graft Occlusion	7(3.8)	1(0.8)	8(2.6)
Endocrine Disorders	5(2.7)	1(0.8)	6(1.9)
Hyperparathyroidism	5(2.7)	1(0.8)	6(1.9)
Gastrointestinal System Disorders	13(7.0)	10(7.9)	23(7.4)
Abdominal Pain	2(1.1)	0	2(0.6)
Gastric Dilatation	0	4(3.2)	4(1.3)
GI Hemorrhage	3(1.6)	3(2.4)	6(1.9)
Hemorrhage Rectum	2(1.1)	1(0.8)	3(1.0)
Heart Rate and Rhythm Disorders	10(5.4)	14(11.1)	24(7.7)
AV Block complete	2(1.1)	0	2(0.6)
Cardiac Arrest	3(1.6)	4(3.2)	7(2.3)
Atrial fibrillation	2(1.1)	5(4.0)	7(2.3)
Metabolic and Nutritional disorders	8(4.3)	4(3.2)	12(3.9)
Fluid overload	3(1.6)	1(0.8)	4(1.3)
Hyperkalemia	2(1.1)	0	2(0.6)
Musculoskeletal System Disorders	7(3.8)	3(2.4)	10(3.2)
Osteomyelitis	3(1.6)	1(0.8)	4(1.3)
Myo, Endo, Pericardial and Valve disorders	15(8.1)	12(9.5)	27(8.7)

	Lanthanum Group N (%)	Standard Therapy N (%)	Total N (%)
Angina	5(2.7)	2(1.6)	7(2.3)
Coronary Artery Disorder	4(2.2)	3(2.4)	7(2.3)
Endocarditis	2(1.1)	0	2(0.6)
Myocardial Infarction	3(1.6)	4(3.2)	7(2.3)
Neoplasm	3(1.6)	1(0.8)	4(1.3)
Genital neoplasm malignant, male	2(1.1)	0	2(0.6)
Platelet, Bleeding and clotting disorders	3(1.6)	1(0.8)	4(1.3)
Psychiatric Disorders	0	2(1.6)	2(0.6)
Resistance Mechanism disorders	15(8.1)	10(7.9)	25(8.0)
Infection	4(2.2)	1(0.8)	5(1.6)
Infection Bacterial	4(2.2)	4(3.2)	8(2.6)
Sepsis	7(3.8)	3(2.4)	10(3.2)
Respiratory System Disorders	18(9.7)	16(12.7)	34(10.9)
Chronic obstructive Airways Disease	0	2(1.6)	2(0.6)
Dyspnea	1(0.5)	2(1.6)	3(1.0)
Pneumonia	7(3.8)	7(5.6)	14(4.5)
Pulmonary Edema	4(2.2)	0	4(1.3)
Respiratory insufficiency	4(2.2)	0	4(1.3)
Secondary Terms	4(2.2)	5(4.0)	9(2.9)
Transplant rejection	0	2(1.6)	2(0.6)
Urinary System Disorders	10(5.4)	4(3.2)	14(4.5)
Renal Transplant	6(3.2)	4(3.2)	10(3.2)
Vascular (Extracardiac) Disorders	15(8.1)	7(5.6)	22(7.1)
Cerebrovascular Disorder	1(0.5)	3(2.4)	4(1.3)
Peripheral ischemia	7(3.8)	1(1.6)	9(2.9)
Thrombophlebitis Deep	2(1.1)	0	2(0.6)
Vein disorder	2(1.1)	0	2(0.6)

Table 68: Deaths reported in studies 301EE, 307,405-309 and 405-315

Study	Drug	Cause of death	Related to Treatment
LAM-IV-301 EE	Lanthanum	Endocarditis	?not related
LAM-IV-301 EE	Lanthanum	Cardiac arrest	?not related
LAM-IV-301 EE	Lanthanum	Sepsis	?not related
LAM-IV-301 EE	Lanthanum	Sepsis	?not related
LAM-IV-307	ST	Pneumonia	?not related
LAM-IV-307	Lanthanum	Pneumonia	?not related
LAM-IV-307	Lanthanum	Renal Failure	?not related

LAM-IV-307	ST	Cardiac arrest	?not related
LAM-IV-307	ST	Sepsis	?not related
LAM-IV-307	Lanthanum	Thrombophlebitis Deep	unlikely
LAM-IV-307	ST	Arrhythmia ventricular	?not related
LAM-IV-307	ST	Hepatic failure	?not related
LAM-IV-307	ST	Chronic Obstructive airways dis.	Not related
LAM-IV-307	ST	Unknown	?not related
LAM-IV-307	Lanthanum	Cardiac arrest	?not related
LAM-IV-307	Lanthanum	Cardiac failure	?not related
LAM-IV-307	ST	Cardiac arrest	?not related
LAM-IV-307	ST	Inflicted Injury	?not related
LAM-IV-307	ST	MI	?not related
LAM-IV-307	Lanthanum	Sepsis	?not related
LAM-IV-307	ST	Cerebrovascular disorder	?not related
LAM-IV-307	Lanthanum	Cardiac failure	?not related
LAM-IV-309	Lanthanum	Renal failure	unknown
LAM-IV-309	Lanthanum	MI	?not related
LAM-IV-309	Lanthanum	Cardiac arrest	Unlikely
LAM-IV-309	Lanthanum	Cerebral hemorrhage	Unlikely
LAM-IV-309	Lanthanum	Fever	unlikely
LAM-IV-315	Lanthanum	Respiratory insufficiency	?not related

XI. Conclusions and Recommendations

A. Conclusions

1)**GI adverse events:** The first concern of the Agency about GI adverse events was clearly spelt out in the following paragraph in quote is reproduced.

"While in most cases such symptoms would be expected to resolve when a study drug is discontinued, given the high concentration of lanthanum in the GI tract following oral administration and the uncertainties about the rate of elimination of lanthanum in patients with ESRD, our concern is that these symptoms may not resolve quickly, presenting a real risk of malnutrition and additional injury in this population. Resolution of this clinical issue will require data regarding the timing and extent of resolution of reported serious adverse events (especially events leading to discontinuation) in patients receiving lanthanum in the long term trials".
This reviewer has not received and been unable to find summary data in the resubmission that addresses this concern satisfactorily and completely.

On July 9, 2004, this reviewer received from the sponsor an email statement accompanied by Table 31 that is in quote below:
"A subsequent request was received on July 8th for this table to present number of patients with an event rather than number of events (which will exclude multiple events with the same outcome in each time category). This table is attached below. For clarification, time to onset is the time from start of study treatments to the time of start of the adverse event and time to resolution is the time between the start of the adverse event and the stop date of the event. Caution should be applied in interpreting these tables as the categories of time to onset are of differing durations."

It is evident that the sponsor has been unable to resolve this clinical issue after one year of the approvable letter. In one of the teleconferences held with the sponsor and one of the meetings held with the sponsor, the Agency's requirements were made very clear and during the internal meeting held recently on July 8 2004, the Acting Director of the Division expressed what will be required to satisfy this deficiency. This concern therefore remains unresolved. The sponsor's [redacted] does not address this deficiency in particular. This remains an outstanding issue.

2) **Bones:** The second concern is about the safety of lanthanum in bones of patients exposed to the drug.
It is evident that the sponsor has provided some evidence that the bone changes in patients exposed to lanthanum are not similar to those seen in aluminum toxicity based on histomorphometry of 2/3 year follow up of the patients. While this reviewer agrees with this position it is important to be on record that this conclusion, in the opinion of the reviewer, is based on relatively little data.

According to the sponsor, the bone sub-study "was not powered to rule out whether lanthanum carbonate has deleterious effect(s) in bone formation as compared with active control".

Based on the table submitted by the sponsor (Table 18), it should be on record that the total number of bone biopsies obtained from lanthanum patients is only about 125 /497 (25%) at baseline and the percentage of paired bone biopsies at 1 year is 67 while at 2 years it is 19 out of the total of 497 biopsies (13.5%.). The histomorphometric analyses upon which the conclusion that lanthanum does not produce an aluminum-like effect is based on paired biopsies over a period of 1 to 2 years. The reviewer is not aware of any paired biopsies at 3 – 5 years. There was only one 3 off-treatment biopsy in LAM-IV-307. In the opinion of this reviewer this conclusion is based very little data over a relatively short time. Furthermore the sponsor has provided a total of 3 microscopic slides of bone biopsies, and these uninterpretable, from 3 patients on the drug for 4 – 5 years.

The appropriate paragraphs (2) from the approvable letter is in quote below:

"It is clear from the bone histological examination that lanthanum is absorbed following oral administration and is then deposited in tissues. It is deposited widely in animals, including the GI tract, bone and cardiac tissues in patients with ESRD. There is less information available, but bone deposition has been clearly demonstrated. As we do not yet know if (or when) a steady-state tissue concentration of lanthanum should be expected following chronic use, it is difficult to use the present database to assess the possibility of significant long-term toxicities resulting from tissue deposition of lanthanum. Given the history of significant, but unpredicted, long-term bone toxicity following the use of aluminum containing antacids, where toxicity was not manifest clinically for several years after initial exposure, the current database is inadequate with respect to long-term follow-up to exclude significant toxicity, including bone toxicity.

Additional long-term data will therefore be needed. Deciding on the extent and duration of long-term safety data will require additional data on the rate at which lanthanum continues to be deposited during chronic administration of lanthanum to patients with ESRD. These data will provide a basis for discussions of how to assess the long term safety of lanthanum."

It is evident from the resubmitted NDA that the sponsor has not provided data in the resubmission to address the uncertainties expressed in the approvable letter after one year. The Agency stated that it is difficult to use the present database to assess the possibility of significant long term toxicities resulting from tissue deposition of lanthanum.

In response, the sponsor has provided a table with 497 biopsies (Table 18 in clinical review) from patients exposed to lanthanum with bone biopsies and titled " Overview of bone biopsy data" from 3 studies LAM 303, 301 and 307". A critical analysis of this data shows that some of these biopsies were paired but the majority (>80.5%) were unpaired biopsies.

Studies Specifically Conducted to Assess Bone Safety is the double blind placebo-controlled study: Study LAM- IV- 303. This study assessed the effect of lanthanum carbonate and compared it to calcium carbonate on renal bone disease by comparing bone tissues obtained from paired biopsies. Of the 98 patients randomized into the study, 71 patients received a follow-up biopsy after 52 weeks of treatment, and therefore provided paired biopsy data, however only 63 pairs of biopsies were suitable for histomorphometric measurements at one year. This rate of achievement was not achieved during year 2, 3 4 or 5 as some patients have been on drug for 5 years. Therefore it cannot be categorically stated that no aluminum effects have been found but it will be more accurate to say that within the 2 year period of follow up no aluminum-like effects have been found.

The significance of the bone biopsy findings is questioned because according to the sponsor "there were limited data available on which to base the sample size estimates, therefore numbers were based on practical rather than statistical considerations." Thus the study was not powered to rule out whether lanthanum carbonate has deleterious effect(s) in bone formation as compared with active control. The interpretation of the findings is further confounded by the fact that calcium carbonate, the active control, is not an FDA approved phosphate binder thus its safety profile, as compared with placebo/ standard therapy, is unknown to the Division of Cardio- Renal Drug Products.

A total of 105 biopsies and 91 biopsies were provided "on Treatment" population (Table 17).Of these only 63 paired biopsies were suitable for histomorphometric evaluation. This shows the limitation of the data upon which a conclusion on the aluminum like effect is base. In the opinion of this reviewer this is inadequate.

The sponsor claims that 212 patients on lanthanum had been followed up for >2 years but not all these 212 patients have paired biopsies for evaluation. Very few have paired biopsies over 2 years. Based on table 18 submitted by the sponsor , there were 67/497 (13.5%)e paired biopsies for one year, 19(3.8%) for 2 years, 1 patient has paired biopsies on 3 year treatment, and neither do the 2 patients on 4 year study drug have paired biopsies nor the only patient on study drug for 5 years. In fact, there were only 34 paired biopsies at one year in the lanthanum group and 35 biopsies in the standard group at one year before the approvable letter. Since then there have been 19 unpaired bone biopsies at 2 years and 1 unpaired biopsy at 3 years off - treatment. It is therefore evident that additional data from paired biopsies from both treatment groups will be required to assess the possibility of significant long term toxicities. The total number of 497 biopsies claimed by the sponsor in table 18 appears to be incorrect. In that table the total number of biopsies, 142, that is derived from LAM-IV-307 totalled 68. The total number of biopsies should therefore be 423 and not 497. The sponsor also claimed that studies LAM-IV-303 and LAM-IV-307 were controlled studies. Study 307 is an open label study with comparator control, and one of the comparators is not approved by the Agency (Table 18)

However if fractures are used to surrogate for long term lanthanum toxicity on bones then question arises whether the small numbers of fractures reported over a 3 year period are adequate and represent the peak effect of lanthanum in bones. Since the steady state for lanthanum has not been reached in bones and also in plasma at 2 years one cannot be certain whether this period of 3 years is adequate or not. Based on the sponsors tables were 66 patients with 80 fractures in the lanthanum group compared to 52 patients with 69 fractures in the standard group over a 3 year period. The sponsor claims that there were 1756 patients and 992 patients in the lanthanum and standard therapy groups, respectively at risk but this reviewer notes that these figures included healthy volunteers who received drug for a few days and had no underlying renal bone disease.

The most recent tables on fracture incidence per 100 patient years received today July 14 from the sponsor and inserted as Appendix 5 and Appendix 6 reflect data at 15- and 25-month data cut off points. The overall fracture rate appears lower in the lanthanum group compared to the standard group (4.16% (66/1585) and 5.6% (52/914). These are comparable rates between the two treatment groups. While this suggests that the risks of fractures in both groups are the same, fracture rates differ with histological categories of fractures in patients on dialysis. There is no evidence to show that the histological categories are the same in both treatment groups (Table 22). The shifts in histological categories of bone disease from baseline to end of 2 years differ between the two groups (Table 22).

The fracture rates that have been compared between the two groups without reference to the histological categories of renal bone disease assume a homogenous distribution of histological types of fracture in both groups and therefore compared fracture rates. It has been shown in the literature that rates of fractures/dialysis year differ with histological categories of bone disease in patients on dialysis. For example, patients with low turnover osteodystrophy had a fracture rate of 0.2 fractures /dialysis year whereas patients with osteitis fibrosa had 0.1 fractures /dialysis year. Based on this information the conclusion derived from data analyzed by the sponsor in Appendix 5 and Appendix 6 become untenable. The data will therefore need to be verified for histological categories of those followed up for 2 years and the rates adjusted for the histological categories.

If bone specific alkaline phosphatase level are used as surrogate for bone activity there is a statistically significant difference in the change from baseline at visit 12 between the two treatment groups (5.69ng/mL) for lanthanum vs 2.04ng /mL for standard therapy (p=0.000). There is no information on this parameter at month 24 (i.e. visit 21). This suggests that bone activity or remodeling is greater in the bones of patient on lanthanum compared to standard therapy.

Another issue is whether a drug that accumulates in the bone and has a very long half life unlike standard therapy drugs that does not accumulate in the bones is comparable in terms of bone behavior to toxic chemicals.

This reviewer is concerned about the length of follow up and the paucity of bone biopsies available for review. This can be answered from pharmacovigilance and risk management program.

The limitation of histomorphometry, as the sole tool, for evaluating lanthanum bone toxicity was that changes in the soft tissues, namely periosteum and bone marrow, were excluded from this assessment. Other routine means of assessing soft tissues that are part of bones, for example histology, should be reported in future evaluations of bone toxicity.

This reviewer does not have compelling evidence that the sponsor has addressed this deficiency fully [ ] does not specifically address this issue of bone toxicity.

3) The issue of the QT interval has been addressed satisfactorily (Appendices 7-13).

4) At 44 months the mortality rate is higher in the group on lanthanum (23.8%) compared to standard therapy (20.4%) according to the statistician.

5) Financial disclosure was submitted with the original NDA and was sighted by this reviewer but there was no financial disclosure with the resubmitted NDA.

In conclusion, this reviewer does not have sufficient evidence to show that the sponsor has addressed the two safety issues fully as stated in the approvable letter. Since the approvable letter the sponsors should have been able to produce more data and evidence on bone safety as they have claimed that they have the largest cohort of bone biopsies in their program.

The [ ] do not seem to make provision to address these deficiencies after approval. In the event that this NDA is approved, it is recommended that these deficiencies be addressed [ ]

B. Recommendations

- This reviewer recommends an approvable status with caution. This recommendation is based on clinical research experience that bone biopsies in humans are not readily and easily obtainable.

- The sponsor must assure the Agency about the uncertainties surrounding lanthanum's safety that still remain about lanthanum carbonate's safety by providing the information in the approvable letter of Feb 28, 2003.

These include :

- Additional data from paired biopsies from both treatment groups to assess the possibility of significant long term toxicities are still required because out of a total of 105 biopsies from lanthanum group and 91 biopsies from standard "on Treatment" population (Table 17). The total number (497) of bone biopsies in the

sponsor's table 18 is not correct. The total should be about 423 of which there are only 69 paired biopsies obtained from a double blind controlled trial (303).

- Additional data on time to stop dates for patients with serious GI adverse events, particularly those discontinued and drug stopped are still outstanding and are still required.

- Unless [ ] can be used to these outstanding deficiencies the sponsor should be issued an approvable letter as there is ample evidence on record asking the sponsor for these data.

- The [ ] do not seem to make provision to address these deficiencies after approval. In the event that this NDA is approved, it is recommended that these deficiencies be addressed [ ]

- This reviewer does not recommend a waiver for pediatric studies because the potential for lanthanum toxicity is real in bones of young people whose epiphyses have not united. The pathological changes in the bones of young rats with normal renal function administered lanthanum show some changes in the metaphysis and to a less extent in the epiphysis. There is slight hyperplasia of the epiphyseal cells of the young rats which may be within normal limits and the majority of the young rats show changes in the metaphyseal side of the epiphyseal plates.

- This reviewer will therefore recommend a deferral. Since the sponsors enrolled patients from the age of 12, a 10-year follow up of these patients may provide some useful information about bone growth and other bone abnormalities.

- There is evidence in the literature that diabetics on dialysis have significantly impaired secretion of parathyroid hormone compared with patients on hemodialysis without diabetes mellitus. As a result diabetic bone disease is characterized by low bone turnover resulting from impaired secretion of parathyroid hormone. This population needs to be looked at in the light of this difference. About 447/1754 (25%) diabetic patients on dialysis were in lanthanum group and 289 /990 (29%) of diabetics on dialysis war on standard therapy. The significant differences in the biochemical parameters between the two groups, particularly serum osteocalcin and glucose, may be explained by this cohort.

Appendix

Appendix 1: Adverse events coded as fracture in Phase 2-3 studies

15 month safety Database: Adverse Events coded as Fractures in Phase 2-3 studies

No.	Treatment Received	Protocol No.	Site No.	Subject ID	Onset Date	Time to Event (week)	WHOART Preferred Term	Adverse Event Reported Term
1	Lanthanum	LAMIV204	14	SA004		78	FRACTURE-NW	FX LT HIP
2	Lanthanum	LAMIV204	14	SA006		1	FRACTURE-NW	TRANSCONDULAR FX RT HUMRS
3	Lanthanum	LAMIV204	14	SA006		64	FRACTURE-NW	TRANSCONDYLAR FX RT HUMERS
4	Lanthanum	LAMIV204	18	SA004		18	FRACTURE-NW	FRACTURE R GREAT TOE
5	Lanthanum	LAMIV204	18	SA006		53	FRACTURE-NW	FRACTURE R FEMUR
6	Lanthanum	LAMIV301	11	0015		7	FRACTURE PATHOLOGICAL	SPONTANEOUS HIP FRACTURE SUBCAPITAL LEFT HIP
7	Lanthanum	LAMIV301	11	0563		43	FRACTURE PATHOLOGICAL	FRACTURE OF LEFT OS PUBIS RAMUS SUPERIOR AND INFERIOR
8	Lanthanum	LAMIV301	12	0120		17	FRACTURE PATHOLOGICAL	FRACTURE OF RIGHT FEMUR
9	Lanthanum	LAMIV301	13	0168		8	FRACTURE PATHOLOGICAL	VERTEBRAL FRACTURE LUMBAL 1
10	Lanthanum	LAMIV301	13	0168		73	FRACTURE	RIB FRACTURE
11	Lanthanum	LAMIV301	15	0104		113	FRACTURE	FRACTURE OF HUMERUS IN RIGHT ARM
12	Lanthanum	LAMIV301	15	0158		92	FRACTURE	RIB FRACTURE
13	Lanthanum	LAMIV301	15	0493		21	FRACTURE PATHOLOGICAL	FRACTURE LEFT WRIST
14	Lanthanum	LAMIV301	15	0495		78	FRACTURE	FRACTURE RIGHT ARM
15	Lanthanum	LAMIV301	18	0271		33	FRACTURE PATHOLOGICAL	COLLAPSED VERTEBRA
16	Lanthanum	LAMIV301	18	0272		6	FRACTURE PATHOLOGICAL	HIP FRACTURE LEFT
17	Lanthanum	LAMIV301	37	0704		7	FRACTURE PATHOLOGICAL	PELVIC FRACTURE (CAUSED BY BICYCLE ACCIDENT 23/05/99)
18	Lanthanum	LAMIV301	37	0704		19	FRACTURE PATHOLOGICAL	REHABILITATION AS AN INPATIENT (RENA DUE TO PRIOR ACETABULUM FRACTURE)
19	Lanthanum	LAMIV301	41	0051		120	FRACTURE	PELVIS FRACTURE CAUSED BY TUMBLING
20	Lanthanum	LAMIV301	41	0051		154	FRACTURE	PELVIC FRACTURE AFTER CAR ACCIDENT
21	Lanthanum	LAMIV301	41	0054		109	FRACTURE	OPEN FRACTURE LEFT THUMB
22	Lanthanum	LAMIV301	42	0525		21	FRACTURE PATHOLOGICAL	FRACTURE OF LEFT CLAVICULA
23	Lanthanum	LAMIV301	56	1238		29	FRACTURE PATHOLOGICAL	FRACTURE OF LEFT PATELLA
24	Lanthanum	LAMIV301	59	1110		32	FRACTURE PATHOLOGICAL	FRACTURE OF RIGHT HIP

25	Lanthanum	LAMIV301	75	0354	1 FRACTURE PATHOLOGICAL
BROKEN AREA ON LOWER LEFT LEG					
26	Lanthanum	LAMIV301	93	0794	110 FRACTURE
FRACTURE OF RADIUS (TRAUMATIC)					
27	Lanthanum	LAMIV301	93	0797	160 FRACTURE
ANCLE FRACTURE WEBER B LEFT					
28	Lanthanum	LAMIV301	93	0805	127 FRACTURE
ANKLE FRACTURE					
29	Lanthanum	LAMIV301	93	0813	5 FRACTURE PATHOLOGICAL
FRACTURE OF THE UPPER ARM					
30	Lanthanum	LAMIV301	94	1172	11 FRACTURE PATHOLOGICAL
SUBCAPITAL HUMERUS FRACTURE					
31	Lanthanum	LAMIV301	94	1174	3 FRACTURE PATHOLOGICAL
FRACTURE OF LEFT FOREARM, SUPERFICIAL SKIN LESION					
32	Lanthanum	LAMIV301	94	1174	139 FRACTURE
RADIUS FRACTURE					
33	Lanthanum	LAMIV302	307	010	20 FRACTURE-NW
FRACTURE R WRIST					
34	Lanthanum	LAMIV302	316	010	27 FRACTURE-NW
R FRACTURED WRIST					
35	Lanthanum	LAMIV302	316	010	27 FRACTURE-NW
FRACTURED R ANKLE					
36	Lanthanum	LAMIV302	316	015	33 FRACTURE-NW
OCCULT PELVIC FRACTURED R HIP					
37	Lanthanum	LAMIV307	105	01008	24 FRACTURE-NW
LEFT HIP FRACTURE					
38	Lanthanum	LAMIV307	111	11102	32 FRACTURE-NW
LEFT - FRACTURE PELVIC RAMUS					

Appendix 1, Table 1
15-Month Safety Database: Adverse Events Coded As Fracture in Phase 2-3 Studies

No.	Treatment Received	Protocol No.	Site No.	Subject ID	Onset Date	Time to Event (week)	WHOART Preferred Term	Adverse Event Reported Term
39	Lanthanum	LAMIV307	117	03002		97	FRACTURE-NW	3 PART IMPACTED RT PROX1MAL HUMERUS FRAC
40	Lanthanum	LAMIV307	117	03002		98	FRACTURE-NW	ANT. DISPLACEMENT RT PROXL HUMERUS SHAFT
41	Lanthanum	LAMIV307	120	01002		36	FRACTURE-NW	FRACTURE L CLAVICLE
42	Lanthanum	LAMIV307	120	01010		22	FRACTURE-NW	COMPRESSION FX OF T12
43	Lanthanum	LAMIV307	129	01001		25	FRACTURE-NW	BROKEN RIB L
44	Lanthanum	LAMIV307	129	01011		77	FRACTURE-NW	R - LEG FRACTURED TIBIA WITH CRUTCHES
45	Lanthanum	LAMIV307	130	01021		69	FRACTURE-NW	R HEEL FRACTURE
46	Lanthanum	LAMIV307	144	01011		36	FRACTURE-NW	RIGHT INFERIOR PUBIC RAMI FRACTURE PAIN
47	Lanthanum	LAMIV307	149	01007		35	FRACTURE-NW	DISPLACED FRACTURE OF PATELLA R
48	Lanthanum	LAMIV307	150	01008		9	FRACTURE-NW	FRACTURED R LEG
49	Lanthanum	LAMIV307	150	03004		30	FRACTURE-NW	L RIB FRACTURE
50	Lanthanum	LAMIV307	155	01002		66	FRACTURE-NW	FRACTURED HUMERUS
51	Lanthanum	LAMIV307	155	01002		66	FRACTURE-NW	SUPRA CONDYLOR R ELBOW FRACTURE
52	Lanthanum	LAMIV307	155	02009		85	FRACTURE-NW	BROKEN TOE
53	Lanthanum	LAMIV307	165	01004		43	FRACTURE-NW	FX R ZYGOMATIC ARCH
54	Lanthanum	LAMIV307	167	01016		21	FRACTURE-NW	FRACTURE RIGHT FOOT
55	Lanthanum	LAMIV307	167	01027		56	FRACTURE-NW	FRACTURE, RT. HAND
56	Lanthanum	LAMIV307	167	01034		47	FRACTURE-NW	COMPRESSION FRACTURE OF VERTEBRAE
57	Lanthanum	LAMIV307	167	01034		47	FRACTURE-NW	COMPRESSION FRACTURE OF VERTEBRAE
58	Lanthanum	LAMIV307	170	01008		18	FRACTURE-NW	FRACTURED BACK
59	Lanthanum	LAMIV307	170	02001		24	FRACTURE-NW	L FOOT BONE - LITTLE TOE BROKEN 3 PLACES
60	Lanthanum	LAMIV307	170	03001		14	FRACTURE-NW	FRACTURE RIGHT TIBIA
61	Lanthanum	LAMIV307	177	01008		93	FRACTURE-NW	HAIRLINE FX ELBOW
62	Lanthanum	LAMIV307	182	01002		40	FRACTURE-NW	BROKEN RING AND MIDDLE FINGER RIGHT HAND
63	Lanthanum	LAMIV307	182	01018		48	FRACTURE-NW	(R) BROKEN COLLAR BONE
64	Lanthanum	LAMIV307	186	01012		11	FRACTURE-NW	(L) FOOT FRACTURE
65	Lanthanum	LAMIV307	188	01003		45	FRACTURE-NW	FRACTURED ANKLE
66	Lanthanum	LAMIV307	200	01002		1	FRACTURE-NW	L ARM FRACTURE
67	Lanthanum	LAMIV307	200	01002		1	FRACTURE-NW	L CLAVICLE FRACTURE
68	Lanthanum	LAMIV307	200	01002		22	FRACTURE-NW	LEFT ARM FRACTURE
69	Lanthanum	LAMIV307	206	01004		6	FRACTURE-NW	BROKE L FINGER

70	Lanthanum	LAMIV307	206	01012	24 FRACTURE-NW
FRACTURED (R) HIP					
71	Lanthanum	LAMIV307	206	01012	56 FRACTURE-NW
FRACTURED FEMUR LEFT					
72	Lanthanum	LAMIV307	206	01020	40 FRACTURE-NW
BROKEN L FOOT					
73	Lanthanum	LAMIV307	210	02002	5 FRACTURE-NW
(R) FEMUR FX					
74	Lanthanum	LAMIV307	213	01013	51 FRACTURE-NW
FALL WITH FRACTURE OF RIGHT METATARSALS					
75	Lanthanum	LAMIV307	213	01013	52 FRACTURE-NW
FRACTURE OF RIGHT 3 RD METATORSAL					
76	Lanthanum	LAMIV307	213	01013	52 FRACTURE-NW
FRACTURE OF RIGHT 3RD AND 4TH METATARSAL					
77	Lanthanum	LAMIV307	219	01002	34 FRACTURE-NW
LEFT ARM FRACTURE					
78	Standard	LAMIV301	15	0158	15 FRACTURE PATHOLOGICAL
FRACTURE ISCHIOPUBIC RAMUS LEFT					
79	Standard	LAMIV303	7	701	3 FRACTURE-NW
TRAUMATIC FRACTURE OF RADIUS					

Appendix 1, Table 1
15-Month Safety Database: Adverse Events Coded As Fracture in Phase 2-3 Studies

No.	Treatment Received	Protocol No.	Site No.	Subject ID	Onset Date	Time to Event (week)	WHOART Preferred Term	Adverse Event Reported Term
80	Standard	LAMIV303	13	1301		41	FRACTURE-NW	FRACTURA MANDIBULAE (CAR ACCIDENT)
81	Standard	LAMIV303	13	1301		42	FRACTURE-NW	HOSPITALIZATION DUE TO FRACTURA MANDIBULAE
82	Standard	LAMIV307	103	01010		94	FRACTURE-NW	AVULSION TIP (R) FEM GREATER TROCHANTER
83	Standard	LAMIV307	103	02002		12	FRACTURE-NW	R FOOT FX
84	Standard	LAMIV307	112	01011		30	FRACTURE-NW	FX L 5TH METATARSAL
85	Standard	LAMIV307	117	01006		48	FRACTURE-NW	FRACTURE RT FIFTH METACARPAL
86	Standard	LAMIV307	117	01010		101	FRACTURE-NW	CLOSED FRACTURE LEFT HUMERUS
87	Standard	LAMIV307	120	01001		27	FRACTURE-NW	FRACTURED L TOES
88	Standard	LAMIV307	120	01001		50	FRACTURE-NW	L WRIST HAIRLINE FX
89	Standard	LAMIV307	120	01001		83	FRACTURE-NW	FX LEFT HAND
90	Standard	LAMIV307	120	01001		83	FRACTURE-NW	FX L HAND
91	Standard	LAMIV307	120	02004		1	FRACTURE-NW	FX HUMERUS
92	Standard	LAMIV307	121	01010		86	FRACTURE-NW	L MALLEOUS FRACTURE
93	Standard	LAMIV307	122	01009		77	FRACTURE-NW	CRACKED RIBS 5-9
94	Standard	LAMIV307	122	01009		77	FRACTURE-NW	BROKEN 4TH TOE L FOOT
95	Standard	LAMIV307	122	02001		30	FRACTURE-NW	RIGHT FRACTURED COLLARBONE
96	Standard	LAMIV307	124	01006		10	FRACTURE-NW	LT BROKEN ARM
97	Standard	LAMIV307	126	01020		27	FRACTURE-NW	FRACTURED R ANKLE
98	Standard	LAMIV307	126	01020		28	FRACTURE-NW	FRACTURED RIGHT ANKLE
99	Standard	LAMIV307	130	01004		69	FRACTURE-NW	R RIB FRACTURE
100	Standard	LAMIV307	140	01010		1	FRACTURE-NW	FRACTURE FOOT
101	Standard	LAMIV307	141	01011		47	FRACTURE-NW	FRACTURED R RIB
102	Standard	LAMIV307	149	01039		9	FRACTURE-NW	FRACTURED (L) HIP
103	Standard	LAMIV307	151	01005		57	FRACTURE-NW	FRACTURE R FOOT
104	Standard	LAMIV307	156	01027		62	FRACTURE-NW	INSUFFICIENCY FRACTURE RIGHT FOOT
105	Standard	LAMIV307	163	01001		49	FRACTURE-NW	WORSENING L1 COMPRESSION FX
106	Standard	LAMIV307	163	01016		38	FRACTURE-NW	(L) HIP FRACTURE
107	Standard	LAMIV307	165	01001		34	FRACTURE-NW	UNDISPLACED FRACTURE L ILIAC BONE
108	Standard	LAMIV307	165	01001		34	FRACTURE-NW	UNDISPLACED FRACTURE OF (L) ILIAC BONE
109	Standard	LAMIV307	165	01001		57	FRACTURE-NW	COMPRESSION FX L4
110	Standard	LAMIV307	167	01015		105	FRACTURE-NW	LEFT PUBIC RAMI FRACTURE

111 Standard LAMIV307 167 01042 1 FRACTURE-NW
R FOOT FRACTURE
112 Standard LAMIV307 167 01042 57 FRACTURE-NW
FRACTURE R FOOT
113 Standard LAMIV307 168 01002 14 FRACTURE-NW
FRACTURED (R) SHOULDER/WRIST
114 Standard LAMIV307 168 01002 15 FRACTURE-NW
FRACTURED R SHOULDER / WRIST
115 Standard LAMIV307 168 02006 34 FRACTURE-NW
FRACTURED THORACIC VERTEBRAE
116 Standard LAMIV307 168 02006 41 FRACTURE-NW
FRACTURED THORACIC VERTEBRAE
117 Standard LAMIV307 176 01012 76 FRACTURE-NW
COMMINUTED FRACTURE OF LEFT SCAPULA
118 Standard LAMIV307 176 01012 84 FRACTURE-NW
FRACTURE DISTAL PHALANX LT. 4TH FINGER
119 Standard LAMIV307 181 01007 7 FRACTURE-NW
(L) GREAT TOE STRESS FRACTURE
120 Standard LAMIV307 182 01015 78 FRACTURE-NW
FRACTURED (L) HIP

Appendix 1, Table 1
15-Month Safety Database: Adverse Events Coded As Fracture in Phase 2-3 Studies

Treatment No. Received	Protocol No.	Site No.	Subject ID	Onset Date	Time to Event (week)	WHOART Preferred Term	Adverse Event Reported Term
121 Standard	LAMIV307	182	01023		21	FRACTURE-NW	BROKEN TOE 4TH ON L FOOT
122 Standard	LAMIV307	182	01029		63	FRACTURE-NW	BROKEN NOSE
123 Standard	LAMIV307	184	01007		47	FRACTURE-NW	VERTEBRAL COMPRESSION FRACTURES
124 Standard	LAMIV307	184	01009		54	FRACTURE-NW	COMPRESSION FX L4, L5
125 Standard	LAMIV307	185	01011		9	FRACTURE-NW	(L) FRACTURE FEMUR
126 Standard	LAMIV307	185	01011		9	FRACTURE-NW	L FRACTURE FEMUR
127 Standard	LAMIV307	185	01026		85	FRACTURE-NW	BROKEN JAW
128 Standard	LAMIV307	185	01032		8	FRACTURE-NW	EXACERBATION OF VERTEBRAL COMPRESSION FX
129 Standard	LAMIV307	185	01032		15	FRACTURE-NW	EXACERBATION OF COMPRESSION FRACTURE
130 Standard	LAMIV307	190	01005		94	FRACTURE-NW	FRACTURE OF HIP
131 Standard	LAMIV307	192	01002		100	FRACTURE-NW	FRACTURED R HAND
132 Standard	LAMIV307	193	19302		85	FRACTURE-NW	ANKLE FRACTURE
133 Standard	LAMIV307	194	02010		3	FRACTURE-NW	FRACTURE OF RIGHT RIBS
134 Standard	LAMIV307	199	01002		45	FRACTURE-NW	NON-DISPLACED FRACTURE L 1ST METATARSAL
135 Standard	LAMIV307	199	01002		45	FRACTURE-NW	TRANSVERSE FRACTURES 2ND-4TH METATARSALS
136 Standard	LAMIV307	199	01002		45	FRACTURE-NW	STRESS FRACTURE L DISTAL TIBIA
137 Standard	LAMIV307	200	01010		41	FRACTURE-NW	HAIRLINE L LEG FRACTURE
138 Standard	LAMIV307	206	01001		85	FRACTURE-NW	FRACTURED R WRIST
139 Standard	LAMIV307	206	01003		58	FRACTURE-NW	BROKEN/LACERATED L THUMB
140 Standard	LAMIV307	206	01008		19	FRACTURE-NW	FRACTURED HIP (L)
141 Standard	LAMIV307	206	01008		20	FRACTURE-NW	DISLOCATED/REFRACTURED HIP L
142 Standard	LAMIV307	208	02001		2	FRACTURE-NW	MULTIPLE FRACTURES
143 Standard	LAMIV307	210	01011		12	FRACTURE-NW	BROKEN (R) GREAT TOE
144 Standard	LAMIV307	219	01007		3	FRACTURE-NW	R HIP FRACTURE

Fracture in Phase 2-3 Studies

No.	Treatment Received	Protocol No.	Site No.	Subject ID	Onset Date	Time to Event (week)	WHOART Preferred Term	Adverse Event Reported Term
1	Lanthanum	LAMIV204	14	SA004		78	FRACTURE-NW	FX LT HIP
2	Lanthanum	LAMIV204	14	SA006		1	FRACTURE-NW	TRANSCONDULAR FX RT HUMRS
3	Lanthanum	LAMIV204	14	SA006		64	FRACTURE-NW	TRANSCONDYLAR FX RT HUMERS
4	Lanthanum	LAMIV204	18	SA004		18	FRACTURE-NW	FRACTURE R GREAT TOE
5	Lanthanum	LAMIV204	18	SA006		53	FRACTURE-NW	FRACTURE R FEMUR
6	Lanthanum	LAMIV301	11	0015		7	FRACTURE PATHOLOGICAL	SPONTANEOUS HIP FRACTURE SUBCAPITAL LEFT HIP
7	Lanthanum	LAMIV301	11	0563		43	FRACTURE PATHOLOGICAL	FRACTURE OF LEFT OS PUBIS RAMUS SUPERIOR AND INFERIOR
8	Lanthanum	LAMIV301	12	0120		17	FRACTURE PATHOLOGICAL	FRACTURE OF RIGHT FEMUR
9	Lanthanum	LAMIV301	13	0168		8	FRACTURE PATHOLOGICAL	VERTEBRAL FRACTURE LUMBAL 1
10	Lanthanum	LAMIV301	13	0168		73	FRACTURE	RIB FRACTURE
11	Lanthanum	LAMIV301	15	0104		113	FRACTURE	FRACTURE OF HUMERUS IN RIGHT ARM
12	Lanthanum	LAMIV301	15	0158		92	FRACTURE	RIB FRACTURE
13	Lanthanum	LAMIV301	15	0493		21	FRACTURE PATHOLOGICAL	FRACTURE LEFT WRIST
14	Lanthanum	LAMIV301	15	0495		78	FRACTURE	FRACTURE RIGHT ARM
15	Lanthanum	LAMIV301	18	0271		33	FRACTURE PATHOLOGICAL	COLLAPSED VERTEBRA
16	Lanthanum	LAMIV301	18	0272		6	FRACTURE PATHOLOGICAL	HIP FRACTURE LEFT
17	Lanthanum	LAMIV301	37	0704		7	FRACTURE PATHOLOGICAL	PELVIC FRACTURE (CAUSED BY BICYCLE ACCIDENT 23/05/99)
18	Lanthanum	LAMIV301	37	0704		-9	FRACTURE PATHOLOGICAL	REHABILITATION AS AN INPATIENT (RENA DUE TO PRIOR ACETABULUM FRACTURE)
19	Lanthanum	LAMIV301	41	0051		170	FRACTURE	PELVIS FRACTURE CAUSED BY TUMBLING
20	Lanthanum	LAMIV301	41	0051		154	FRACTURE	PELVIC FRACTURE AFTER CAR ACCIDENT
21	Lanthanum	LAMIV301	41	0054		109	FRACTURE	OPEN FRACTURE LEFT THUMB
22	Lanthanum	LAMIV301	42	0525		21	FRACTURE PATHOLOGICAL	FRACTURE OF LEFT CLAVICULA
23	Lanthanum	LAMIV301	56	1238		29	FRACTURE PATHOLOGICAL	FRACTURE OF LEFT PATELLA
24	Lanthanum	LAMIV301	59	1110		32	FRACTURE PATHOLOGICAL	FRACTURE OF RIGHT HIP
25	Lanthanum	LAMIV301	75	0354		1	FRACTURE PATHOLOGICAL	BROKEN AREA ON LOWER LEFT LEG
26	Lanthanum	LAMIV301	93	0794		110	FRACTURE	FRACTURE OF RADIUS (TRAUMATIC)
27	Lanthanum	LAMIV301	93	0797		160	FRACTURE	ANCLE FRACTURE WEBER B LEFT
28	Lanthanum	LAMIV301	93	0805		127	FRACTURE	ANKLE FRACTURE

Appendix 1, Table 2
25-Month Safety Database: Adverse Events Coded As

29	Lanthanum	LAMIV301	93	0813	5 FRACTURE PATHOLOGICAL FRACTURE OF THE UPPER ARM
30	Lanthanum	LAMIV301	94	1172	11 FRACTURE PATHOLOGICAL SUBCAPITAL HUMERUS FRACTURE
31	Lanthanum	LAMIV301	94	1174	3 FRACTURE PATHOLOGICAL FRACTURE OF LEFT FOREARM, SUPERFICIAL SKIN LESION
32	Lanthanum	LAMIV301	94	1174	139 FRACTURE RADIUS FRACTURE
33	Lanthanum	LAMIV302	307	010	20 FRACTURE-NW FRACTURE R WRIST
34	Lanthanum	LAMIV302	316	010	27 FRACTURE-NW R FRACTURED WRIST
35	Lanthanum	LAMIV302	316	010	27 FRACTURE-NW FRACTURED R ANKLE
36	Lanthanum	LAMIV302	316	015	33 FRACTURE-NW OCCULT PELVIC FRACTURED R HIP
37	Lanthanum	LAMIV307	105	01008	24 FRACTURE-NW LEFT HIP FRACTURE
38	Lanthanum	LAMIV307	111	11102	32 FRACTURE-NW LEFT - FRACTURE PELVIC RAMUS

Appendix 1, Table 2
25-Month Safety Database: Adverse Events Coded As Fracture in Phase 2-3 Studies

Treatment No. Received	Protocol No.	Site No.	Subject ID	Onset Date	Time to Event (week)	WHOART Preferred Term	Adverse Event Reported Term
39 Lanthanum	LAMIV307	117	03002		97	FRACTURE-NW	3 PART IMPACTED RT PROXIMAL HUMERUS FRAC
40 Lanthanum	LAMIV307	117	03002		98	FRACTURE-NW	ANT. DISPLACEMENT RT PROXL HUMERUS SHAFT
41 Lanthanum	LAMIV307	120	01002		36	FRACTURE-NW	FRACTURE L CLAVICLE
42 Lanthanum	LAMIV307	120	01010		22	FRACTURE-NW	COMPRESSION FX OF T12
43 Lanthanum	LAMIV307	129	01001		25	FRACTURE-NW	BROKEN RIB L
44 Lanthanum	LAMIV307	129	01011		77	FRACTURE-NW	R - LEG FRACTURED TIBIA WITH CRUTCHES
45 Lanthanum	LAMIV307	130	01021		69	FRACTURE-NW	R HEEL FRACTURE
46 Lanthanum	LAMIV307	144	01011		36	FRACTURE-NW	RIGHT INFERIOR PUBIC RAMI FRACTURE PAIN
47 Lanthanum	LAMIV307	149	01007		35	FRACTURE-NW	DISPLACED FRACTURE OF PATELLA R
48 Lanthanum	LAMIV307	150	01008		9	FRACTURE-NW	FRACTURED R LEG
49 Lanthanum	LAMIV307	150	03004		30	FRACTURE-NW	L RIB FRACTURE
50 Lanthanum	LAMIV307	155	01002		66	FRACTURE-NW	FRACTURED HUMERUS
51 Lanthanum	LAMIV307	155	01002		66	FRACTURE-NW	SUPRA CONDYLOR R ELBOW FRACTURE
52 Lanthanum	LAMIV307	155	02009		85	FRACTURE-NW	BROKEN TOE
53 Lanthanum	LAMIV307	165	01004		43	FRACTURE-NW	FX R ZYGOMATIC ARCH
54 Lanthanum	LAMIV307	167	01016		21	FRACTURE-NW	FRACTURE RIGHT FOOT
55 Lanthanum	LAMIV307	167	01027		56	FRACTURE-NW	FRACTURE, RT. HAND
56 Lanthanum	LAMIV307	167	01034		47	FRACTURE-NW	COMPRESSION FRACTURE OF VERTEBRAE
57 Lanthanum	LAMIV307	167	01034		17	FRACTURE-NW	COMPRESSION FRACTURE OF VERTEBRAE
58 Lanthanum	LAMIV307	170	01008		18	FRACTURE-NW	FRACTURED BACK
59 Lanthanum	LAMIV307	170	02001		24	FRACTURE-NW	L FOOT BONE - LITTLE TOE BROKEN 3 PLACES
60 Lanthanum	LAMIV307	170	03001		14	FRACTURE-NW	FRACTURE RIGHT TIBIA
61 Lanthanum	LAMIV307	177	01008		93	FRACTURE-NW	HAIRLINE FX ELBOW
62 Lanthanum	LAMIV307	182	01002		40	FRACTURE-NW	BROKEN RING AND MIDDLE FINGER RIGHT HAND
63 Lanthanum	LAMIV307	182	01018		48	FRACTURE-NW	(R) BROKEN COLLAR BONE
64 Lanthanum	LAMIV307	182	01045		94	FRACTURE-NW	RIGHT HIP FRACTURE
65 Lanthanum	LAMIV307	186	01012		11	FRACTURE-NW	(L) FOOT FRACTURE
66 Lanthanum	LAMIV307	188	01003		45	FRACTURE-NW	FRACTURED ANKLE
67 Lanthanum	LAMIV307	196	01005		67	FRACTURE-NW	L ACETABULAR FRACTURE
68 Lanthanum	LAMIV307	200	01002		1	FRACTURE-NW	L ARM FRACTURE
69 Lanthanum	LAMIV307	200	01002		1	FRACTURE-NW	L CLAVICULE FRACTURE

70	Lanthanum	LAMIV307	200	01002	22 FRACTURE-NW
LEFT ARM FRACTURE					
71	Lanthanum	LAMIV307	206	01004	16 FRACTURE-NW
BROKE L FINGER					
72	Lanthanum	LAMIV307	206	01012	24 FRACTURE-NW
FRACTURED (R) HIP					
73	Lanthanum	LAMIV307	206	01012	56 FRACTURE-NW
FRACTURED FEMUR LEFT					
74	Lanthanum	LAMIV307	206	01020	40 FRACTURE-NW
BROKEN L FOOT					
75	Lanthanum	LAMIV307	210	01006	72 FRACTURE-NW
BROKEN TOE R FOOT LRG. TOE					
76	Lanthanum	LAMIV307	210	02002	5 FRACTURE-NW
(R) FEMUR FX					
77	Lanthanum	LAMIV307	213	01013	51 FRACTURE-NW
FALL WITH FRACTURE OF RIGHT METATARSALS					
78	Lanthanum	LAMIV307	213	01013	51 FRACTURE-NW
FRACTURE OF RIGHT METATARSAL					
79	Lanthanum	LAMIV307	213	01013	52 FRACTURE-NW
FRACTURE OF RIGHT 3RD AND 4TH METATARSAL					

Appendix 1, Table 2
25-Month Safety Database: Adverse Events Coded As Fracture in Phase 2-3 Studies

No.	Treatment Received	Protocol No.	Site No.	Subject ID	Onset Date	Time to Event (week)	WHOART Preferred Term	Adverse Event Reported Term
80	Lanthanum	LAMIV307	219	01002		34	FRACTURE-NW	LEFT ARM FRACTURE
81	Standard	LAMIV301	15	0158		15	FRACTURE PATHOLOGICAL	FRACTURE ISCHIOPUBIC RAMUS LEFT
82	Standard	LAMIV303	7	701		3	FRACTURE-NW	TRAUMATIC FRACTURE OF RADIUS
83	Standard	LAMIV303	13	1301		41	FRACTURE-NW	FRACTURA MANDIBULAE (CAR ACCIDENT)
84	Standard	LAMIV303	13	1301		42	FRACTURE-NW	HOSPITALIZATION DUE TO FRACTURA MANDIBULAE
85	Standard	LAMIV307	103	01010		94	FRACTURE-NW	AVULSION TIP (R) FEM GREATER TROCHANTER
86	Standard	LAMIV307	103	02002		12	FRACTURE-NW	R FOOT FX
87	Standard	LAMIV307	112	01011		30	FRACTURE-NW	FX L 5TH METATARSAL
88	Standard	LAMIV307	117	01006		48	FRACTURE-NW	FRACTURE RT FIFTH METACARPAL
89	Standard	LAMIV307	117	01010		101	FRACTURE-NW	CLOSED FRACTURE LEFT HUMERUS
90	Standard	LAMIV307	120	01001		27	FRACTURE-NW	FRACTURED L TOES
91	Standard	LAMIV307	120	01001		50	FRACTURE-NW	L WRIST HAIRLINE FX
92	Standard	LAMIV307	120	01001		83	FRACTURE-NW	FX LEFT HAND
93	Standard	LAMIV307	120	01001		83	FRACTURE-NW	FX L HAND
94	Standard	LAMIV307	120	02004		1	FRACTURE-NW	FX HUMERUS
95	Standard	LAMIV307	121	01010		86	FRACTURE-NW	L MALLEOUS FRACTURE
96	Standard	LAMIV307	122	01009		77	FRACTURE-NW	CRACKED RIBS 5-9
97	Standard	LAMIV307	122	01009		77	FRACTURE-NW	BROKEN 4TH TOE L FOOT
98	Standard	LAMIV307	122	02001		30	FRACTURE-NW	RIGHT FRACTURED COLLARBONE
99	Standard	LAMIV307	124	01006		10	FRACTURE-NW	LT BROKEN ARM
100	Standard	LAMIV307	126	01020		27	FRACTURE-NW	FRACTURED R ANKLE
101	Standard	LAMIV307	126	01020		28	FRACTURE-NW	FRACTURED RIGHT ANKLE
102	Standard	LAMIV307	130	01004		69	FRACTURE-NW	R RIB FRACTURE
103	Standard	LAMIV307	140	01010		1	FRACTURE-NW	FRACTURE FOOT
104	Standard	LAMIV307	141	01011		47	FRACTURE-NW	FRACTURED R RIB
105	Standard	LAMIV307	149	01039		9	FRACTURE-NW	INTERTROCHANTERIC LEFT HIP FRACTURE
106	Standard	LAMIV307	149	01048		12	FRACTURE-NW	R BROKEN WRIST
107	Standard	LAMIV307	151	01005		57	FRACTURE-NW	FRACTURE R FOOT
108	Standard	LAMIV307	156	01027		62	FRACTURE-NW	INSUFFICIENCY FRACTURE RIGHT FOOT
109	Standard	LAMIV307	163	01001		49	FRACTURE-NW	WORSENING L1 COMPRESSION FX
110	Standard	LAMIV307	163	01015		98	FRACTURE-NW	(L) HIP FRACTURE

111	Standard	LAMIV307	165	01001	34 FRACTURE-NW
UNDISPLACED FRACTURE L ILIAC BONE					
112	Standard	LAMIV307	165	01001	34 FRACTURE-NW
UNDISPLACED FRACTURE OF (L) ILIAC BONE					
113	Standard	LAMIV307	165	01001	57 FRACTURE-NW
COMPRESSION FX L4					
114	Standard	LAMIV307	167	01015	105 FRACTURE-NW
LEFT PUBIC RAMI FRACTURE					
115	Standard	LAMIV307	167	01042	1 FRACTURE-NW
R FOOT FRACTURE					
116	Standard	LAMIV307	167	01042	57 FRACTURE-NW
FRACTURE R FOOT					
117	Standard	LAMIV307	167	01042	83 FRACTURE-NW
BROKEN BONE L FOOT					
118	Standard	LAMIV307	168	01002	14 FRACTURE-NW
FRACTURED (R) SHOULDER/WRIST					
119	Standard	LAMIV307	168	01002	15 FRACTURE-NW
FRACTURED R SHOULDER / WRIST					
120	Standard	LAMIV307	168	02006	34 FRACTURE-NW
FRACTURED THORACIC VERTEBRAE					

Appendix 1, Table 2
25-Month Safety Database: Adverse Events Coded As Fracture in Phase 2-3 Studies

Treatment No.	Received	Protocol No.	Site No.	Subject ID	Onset Date	Time to Event (week)	WHOART Preferred Term	Adverse Event Reported Term
121	Standard	LAMIV307	168	02006		41	FRACTURE-NW	FRACTURED THORACIC VERTEBRAE
122	Standard	LAMIV307	176	01012		76	FRACTURE-NW	COMMINUTED FRACTURE OF LEFT SCAPULA
123	Standard	LAMIV307	176	01012		84	FRACTURE-NW	FRACTURE DISTAL PHALANX LT. 4TH FINGER
124	Standard	LAMIV307	181	01007		7	FRACTURE-NW	(L) GREAT TOE STRESS FRACTURE
125	Standard	LAMIV307	182	01015		78	FRACTURE-NW	FRACTURED (L) HIP
126	Standard	LAMIV307	182	01023		21	FRACTURE-NW	BROKEN TOE 4TH ON L FOOT
127	Standard	LAMIV307	182	01029		63	FRACTURE-NW	BROKEN NOSE
128	Standard	LAMIV307	184	01007		47	FRACTURE-NW	VERTEBRAL COMPRESSION FRACTURES
129	Standard	LAMIV307	184	01009		54	FRACTURE-NW	COMPRESSION FX L4, L5
130	Standard	LAMIV307	185	01011		9	FRACTURE-NW	L FRACTURE FEMUR
131	Standard	LAMIV307	185	01026		85	FRACTURE-NW	BROKEN JAW
132	Standard	LAMIV307	185	01032		8	FRACTURE-NW	EXACERBATION OF VERTEBRAL COMPRESSION FX
133	Standard	LAMIV307	185	01032		15	FRACTURE-NW	EXACERBATION OF COMPRESSION FRACTURE
134	Standard	LAMIV307	190	01005		94	FRACTURE-NW	FRACTURE OF HIP
135	Standard	LAMIV307	192	01002		100	FRACTURE-NW	FRACTURED R HAND
136	Standard	LAMIV307	193	19302		85	FRACTURE-NW	ANKLE FRACTURE
137	Standard	LAMIV307	194	02010		3	FRACTURE-NW	FRACTURE OF RIGHT RIBS
138	Standard	LAMIV307	199	01002		45	FRACTURE-NW	NON-DISPLACED FRACTURE L 1ST METATARSAL
139	Standard	LAMIV307	199	01002		45	FRACTURE-NW	TRANSVERSE FRACTURES 2ND-4TH METATARSALS
140	Standard	LAMIV307	199	01002		45	FRACTURE-NW	STRESS FRACTURE L DISTAL TIBIA
141	Standard	LAMIV307	200	01010		41	FRACTURE-NW	HAIRLINE L LEG FRACTURE
142	Standard	LAMIV307	206	01001		85	FRACTURE-NW	FRACTURED R WRIST
143	Standard	LAMIV307	206	01003		58	FRACTURE-NW	BROKEN/LACERATED L THUMB
144	Standard	LAMIV307	206	01008		19	FRACTURE-NW	FRACTURED HIP (L)
145	Standard	LAMIV307	206	01008		23	FRACTURE-NW	DISLOCATED/REFRACTURED HIP L
146	Standard	LAMIV307	208	02001		2	FRACTURE-NW	MULTIPLE FRACTURES
147	Standard	LAMIV307	210	01011		12	FRACTURE-NW	BROKEN (R) GREAT TOE
148	Standard	LAMIV307	213	01012		104	FRACTURE-NW	R ANKLE FRACTURE
149	Standard	LAMIV307	219	01007		3	FRACTURE-NW	R HIP FRACTURE

By Preferred Term

WHOART preferred label	Lanthanum # of events in WHO-ART	Lanthanum # (%) of pts (n=680)	Standard # of events in WHO-ART	Standard Adjusted % of pts	Standard # (%) of pts (n=674)
AAA ANY EVENTS	1752	444 (65.3)	2480	51.9	486 (72.1)
ABDOMEN ENLARGED	3	3 (0.4)	13	0.9	8 (1.2)
ABDOMINAL ADHESIONS	1	1 (0.1)	2	0.2	2 (0.3)
ABDOMINAL PAIN	160	110 (16.2)	256	15.5	145 (21.5)
ANAL FISSURE	1	1 (0.1)	0	.	0
ANOREXIA	40	36 (5.3)	67	6.2	58 (8.6)
APPENDICITIS	2	2 (0.3)	2	0.1	1 (0.1)
APPETITE INCREASED	1	1 (0.1)	3	0.3	3 (0.4)
BOWEL MOTILITY DISORDER	1	1 (0.1)	1	0.1	1 (0.1)
CHANGE IN BOWEL HABITS	1	1 (0.1)	9	0.5	5 (0.7)
COLITIS	5	5 (0.7)	1	0.1	1 (0.1)
COLITIS PSEUDOMEMBRANOUS	0	0	1	0.1	1 (0.1)
CONSTIPATION	124	93 (13.7)	160	12.6	118 (17.5)
DIARRHOEA	248	154 (22.6)	376	21.9	205 (30.4)
DIARRHOEA, CLOSTRIDIUM DIFFICILE	4	4 (0.6)	2	0.2	2 (0.3)
DISEASES OF OESOPHAGUS	0	0	3	0.3	3 (0.4)
DIVERTICULITIS	9	7 (1.0)	11	1.2	11 (1.6)
DIVERTICULOSIS	5	5 (0.7)	6	0.6	6 (0.9)
DUODENAL ULCER	3	3 (0.4)	6	0.6	6 (0.9)
DUODENAL ULCER HAEMORRHAGIC	1	1 (0.1)	0	.	0
DUODENAL ULCER REACTIVATED	1	1 (0.1)	0	.	0
DUODENITIS	0	0	4	0.4	4 (0.6)
DYSPEPSIA	99	70 (10.3)	171	12.5	117 (17.4)

WHOART preferred label	Lanthanum # of events in WHO-ART	Lanthanum # (%) of pts (n=680)	Standard # of events in WHO-ART	Standard Adjusted % of pts	Standard # (%) of pts (n=674)
DYSPHAGIA	11	10 (1.5)	7	0.7	7 (1.0)
ENTERITIS	1	1 (0.1)	0	.	0
ERUCTATION	3	2 (0.3)	2	0.2	2 (0.3)
FAECAL INCONTINENCE	4	2 (0.3)	2	0.2	2 (0.3)
FAECES DISCOLOURED	0	0	1	0.1	1 (0.1)
FLATULENCE	31	26 (3.8)	38	3.2	30 (4.5)
GASTRIC DILATATION	9	8 (1.2)	31	2.0	19 (2.8)
GASTRIC ULCER	5	5 (0.7)	6	0.6	6 (0.9)
GASTRIC ULCER HAEMORRHAGIC	2	2 (0.3)	2	0.2	2 (0.3)
GASTRITIS	27	24 (3.5)	38	3.7	35 (5.2)
GASTRO-INTESTINAL DISORDER NOS	12	9 (1.3)	13	1.1	10 (1.5)
GASTROENTERITIS	18	17 (2.5)	15	1.5	14 (2.1)
GASTROESOPHAGEAL REFLUX	19	17 (2.5)	25	2.5	23 (3.4)
GI HAEMORRHAGE	29	18 (2.6)	33	2.9	27 (4.0)
GI MUCOSAL NECROSIS GENERAL	0	0	1	0.1	1 (0.1)
GI NEOPLASM BENIGN	4	4 (0.6)	8	0.9	8 (1.2)
GINGIVAL RECESSION	0	0	1	0.1	1 (0.1)
GINGIVITIS	3	3 (0.4)	0	.	0
GUM HYPERPLASIA	0	0	1	0.1	1 (0.1)
HAEMATEMESIS	2	2 (0.3)	6	0.6	6 (0.9)
HAEMORRHAGE RECTUM	4	4 (0.6)	18	1.6	15 (2.2)
HAEMORRHOIDS	11	11 (1.6)	18	1.8	17 (2.5)
HICCUP	3	3 (0.4)	4	0.4	4 (0.6)

WHOART-preferred label	Lanthanum # of events in WHO-ART	Lanthanum #(%) of pts (n=680)	Standard # of events in WHO-ART	Standard Adjusted % of pts	Standard #(%) of pts (n=674)
ILEUS	4	3 (0.4)	2	0.2	2 (0.3)
INCREASED STOOL FREQUENCY	0	0	1	0.1	1 (0.1)
INCREASED STOOL URGENCY	0	0	1	0.1	1 (0.1)
INTESTINAL FISTULA	0	0	2	0.1	1 (0.1)
INTESTINAL ISCHAEMIA	1	1 (0.1)	4	0.4	4 (0.6)
INTESTINAL NECROSIS	0	0	1	0.1	1 (0.1)
INTESTINAL OBSTRUCTION	2	2 (0.3)	7	0.7	7 (1.0)
INTESTINAL ULCERATION	2	2 (0.3)	1	0.1	1 (0.1)
MELAENA	10	10 (1.5)	23	2.5	23 (3.4)
MOUTH DRY	3	3 (0.4)	12	1.3	12 (1.8)
MUCOSITIS NOS	0	0	1	0.1	1 (0.1)
NAUSEA	444	239 (35.1)	604	27.2	255 (37.8)
OESOPHAGEAL ULCERATION	2	2 (0.3)	2	0.2	2 (0.3)
OESOPHAGEAL VARICES	1	1 (0.1)	1	0.1	1 (0.1)
OESOPHAGITIS	11	11 (1.6)	11	1.1	10 (1.5)
OESOPHAGOSPASM	0	0	2	0.2	2 (0.3)
ORAL HAEMORRHAGE	1	1 (0.1)	1	0.1	1 (0.1)
PANCREATITIS	9	8 (1.2)	8	0.6	6 (0.9)
PEPTIC ULCER	3	3 (0.4)	2	0.1	1 (0.1)
PEPTIC ULCER AGGRAVATED	0	0	1	0.1	1 (0.1)
PERIODONTAL DESTRUCTION	1	1 (0.1)	3	0.3	3 (0.4)
PERITONITIS	1	1 (0.1)	3	0.3	3 (0.4)
PROCTITIS	0	0	1	0.1	1 (0.1)

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

WHOART preferred label	Lanthanum # of events in WHO-ART	Lanthanum # (%) of pts (n=680)	Standard # of events in WHO-ART	Standard Adjusted % of pts	Standard # (%) of pts (n=674)
RECTAL DISORDER	2	2 (0.3)	1	0.1	1 (0.1)
RECTAL PROLAPSE	1	1 (0.1)	0	.	0
SALIVARY GLAND ENLARGEMENT	1	1 (0.1)	2	0.2	2 (0.3)
STOMATITIS	0	0	1	0.1	1 (0.1)
STOMATITIS ULCERATIVE	2	2 (0.3)	1	0.1	1 (0.1)
TENESMUS	1	1 (0.1)	2	0.2	2 (0.3)
TONGUE OEDEMA	0	0	1	0.1	1 (0.1)
TOOTH ACHE	32	21 (3.1)	16	1.6	15 (2.2)
TOOTH CARIES	4	4 (0.6)	7	0.6	6 (0.9)
TOOTH CARIES AGGRAVATED	0	0	1	0.1	1 (0.1)
TOOTH DISORDER	10	9 (1.3)	17	1.7	16 (2.4)
VOMITING	297	172 (25.3)	373	20.8	195 (28.9)

Appendix 3: Extract from original NDA review-Dr Pelayo

The sponsor alsoAppendix evaluated the number and percentage of patients whose serum phosphate was controlled, i. e., between 1.3 mmol/ L to 1.8 mmol/ L, in part 2 of the study (Table 1- ISE). Lanthanum treatment was statistically significantly better than placebo in controlling serum phosphate levels.

Table 1- ISE. Number (%) of Patients with Controlled Serum Phosphates – ITT Population Lanthanum N= 17 n(%) Placebo N= 19 n(%) p- Value Week 5 13(76.5) 14(73.7) 1.0 End of Treatment 11(64.7) 4(21.1) 0.008 [FDA's Analysis, Dr. Freidlin (HFD- 710)]

Protocol LAM- IV- 204 (US): This was a randomized, double blind, placebo controlled, parallel group, dose ranging study of lanthanum carbonate in subjects with ESRD receiving hemodialysis. Patients were randomly allocated, in a 1: 1: 1: 1: 1 ratio, to daily doses of lanthanum carbonate 225 mg, 675 mg, 1350 mg, 2250 mg or placebo. Study drug (chewable tablets) was taken three times a day with meals. The study had three phases: 1) 1 to 3- week single blind placebo run in4 , 2) followed by randomization of eligible subjects into a six week double blind treatment phase, and a 2 week, single blind placebo run out phase. The primary endpoint was the reduction of pre- dialysis serum phosphate levels from washout levels following six weeks of treatment.

A total of 145 subjects were randomized to double blind treatment, placebo n= 32, lanthanum 225 mg/ day n= 28, 675 mg/ day n= 29, 1350 mg/ day n= 30, and 2250 mg/ day n= 26. Eighty patients (55%) were male, 102 (71%) black, 36 (25%) whites, and 6 (4%) other races. The average age was 56.4 years. The mean duration of dialysis range from 2.5 to 4.3 years.

Active- Controlled Studies LAM- IV- 301, and - 307 Protocol LAM- IV- 301 (EU): This was an open- label, randomized8 (2: 1 ratio to either lanthanum carbonate or calcium carbonate9), active comparator controlled, parallel group study of lanthanum carbonate in patients with ESRD receiving hemodialysis. Lanthanum carbonate and calcium carbonate were taken (chew) after meals and titrated as needed from 375 mg to 3000 mg (elemental lanthanum) and 1500 mg to 9000 mg (elemental calcium), respectively, to achieve a phosphate level of = 1.8 mmol/ L. The study had the following periods: 1) 1 to 3- week screening and washout period, 2) randomization followed by 5- week dose titration period, 3) 20- week treatment phase, 4) a 24- week extension phase during which all patients received lanthanum carbonate, and 5) an optional 2- year extension phase. 10

A total of 800 patients received at least one dose of study drug, 533 received lanthanum carbonate and 267 received calcium carbonate. 11 The patient population was primarily male (65.3%), white (96.2%) with a mean age of 57.7 years.

Protocol LAM- IV- 307 (US): This was an open- label, randomized, multicenter, Phase III, comparator controlled, parallel group study of the long tern safety of lanthanum carbonate for controlling hyperphosphatemia in chronic renal failure patients undergoing hemodialysis three times per week. The study had the following periods: 1) screening and 1 to 3- week washout period, 2) randomization by 6- week dose titration period (phosphate binders to be titrated to achieve a phosphate level of = 5.9 mg/ dl), and 3) a 24 months maintenance phase.

Eligible patients were randomized 1: 1 (500 patients per arm) to either lanthanum carbonate up to a maximum of 3000 mg/ day or their pre- study standard therapy, which was one or more of the available phosphate binders, i. e., Renagel . (17%), Phoslo . (34.5%) or Tums . (calcium carbonate, 44.%). 12 The primary efficacy endpoint in this study was the predialysis PO4 levels (PSPL), which were measured at the first dialysis sessions of study visits, including pre- study and washout.

Fifty- nine percent of the study population was male with an average age of 55.3 years, race was evenly distributed between Caucasian and Black, 46.2% versus 43.0%, respectively

The primary efficacy endpoint in this study was the predialysis serum PO4 levels (PSPL), which were measured at the first dialysis sessions of study visits week 1 to week 7, i. e., titration period (Figure 5- In both treatment groups serum PO4 levels declined over time. However, when compared between treatment groups, the change from baseline serum phosphorus level to each follow- up week of dose titration, a greater reduction occurred for patients on standard therapy (p= 0.000).

Efficacy Conclusions: The sponsor is seeking the following indication: " FOSRENOL . is indicated for C

J

A conclusion as to the effectiveness of FOSRENOL . (lanthanum carbonate) to control hyperphosphatemia, i. e., to reduce and maintain serum phosphorus levels within normal level, in patients with end- stage renal disease undergoing dialysis could be arrived at from the results of the double- blind, placebo- controlled studies LAM- IV- 202 (UK), - 204 (US), and - 302 (US). In the aggregate, the data indicate that lanthanum carbonate when administered orally three times a day with meals as compared with placebo is an effective phosphate binder in that reduces (LAM- IV- 202, - 204, and - 302) and maintains (LAM- IV- 202 and - 302) serum phosphorus levels within normal range in a statistically significant number of subjects. The doses tested in those studies ranged from 225 mg to 3000 mg daily.

The effectiveness of lanthanum carbonate to control hyperphosphatemia in patients with end- stage renal disease undergoing dialysis was also compared in open- label studies to calcium carbonate (LAM- IV- 301) and to standard therapy (LAM- IV- 307).

Of note, the FDA has not approved calcium carbonate13 for use as a phosphate binder. Notwithstanding, after 5 weeks of treatment, lanthanum carbonate was significantly less effective than calcium carbonate in controlling hyperphosphatemia in patients with end stage renal disease (LAM- IV- 301). This disparity in effectiveness between the drugs was not longer present by week 25.

The results from study LAM- IV- 307 data indicate that lanthanum carbonate, when compared with standard therapy, is significantly inferior in reducing/ maintaining serum phosphorus levels in patients with end stage renal disease, and thus controlling hyperphosphatemia.

In summary, the data from the clinical development program of FOSRENOL . (lanthanum carbonate) supports the notion that this drug product is a phosphate binder, however its ability to bind phosphate is inferior to currently approved phosphate binders.

INTEGRATED SUMMARY OF SAFETY

The primary focus of this section is on the adequacy of safety testing and assessments carried out in the clinical development program with the main objective of delineating the safety profile of FOSRENOL . (lanthanum carbonate). To this end the medical reviewer utilized NDA desk copies and the electronic version provided with the original submission, SAS datafiles14 and as well as material provided by the sponsor in response to special requests, i. e., ECG15 , overall mortality16 data and incidence of bone fractures. The safety information provided by the sponsor in the four- month safety update was also reviewed and the results were incorporated in this integrated review of safety.

The approach used in the delineation of the safety profile of FOSRENOL . in hyperphosphatemic patients with end- stage renal disease undergoing dialysis included: examination of the clinical database for deaths, discontinuations, serious adverse events, as well as an analysis of the routinely collected safety data (i. e., treatment emergent adverse events, laboratory findings, and vital signs). ECG data were evaluated specifically to determine whether lanthanum carbonate causes changes in QT/ QTc. To determine whether lanthanum carbonate has an adverse effect on bone formation results from bone biopsies and incidence of fractures were examined.

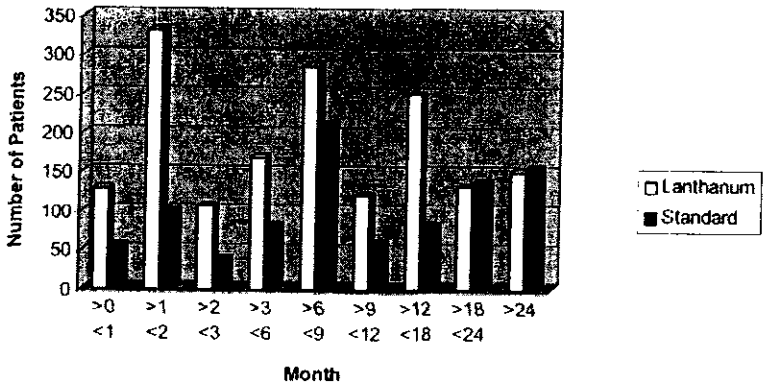
Clinical Safety Data: Safety data from the following studies were examined: 11 clinical pharmacology Phase I studies in healthy volunteers and patients with ESRD (LAM- IV- 101, 104, 105, 108, 109, 110, 111, 112, 113, 114, and 115) 17 and 8 Phase II- III studies (LAM- IV- 202, 204, 205, 301, 302, 303, 307, and 308).

The safety information derived from the pharmacology Phase I studies is limited given the short- term exposure and that few subjects were evaluated, lanthanum carbonate n= 179 and placebo/ other n= 76.

Studies LAM- IV- 202, 204, and 302 were placebo- controlled trials of short duration, randomized treatment ranged from 4 to 6 weeks, and enrolled few patients each; lanthanum carbonate 17 and placebo 19, lanthanum carbonate 113 and placebo 32, and lanthanum carbonate 50 and placebo 44, respectively.

Study LAM- IV- 303 evaluated a small number of patients, 49 in each lanthanum carbonate and calcium carbonate18 groups, approximately two- thirds of these patients had bone biopsy data collected and were

Figure 1-ISS. Number of Patients Receiving Multiple Doses of Active Treatment in Phase II and III Studies



[Sponsor's analysis, adapted from NDA 21-468, Four-Month Safety Update, Table 8.8-11.]

Overall there was a greater rate of discontinuation in lanthanum-treated subjects/patients than for those subjects/patients receiving placebo or active control phosphate binders (see below). Because of this imbalance in withdrawal rate, the mean exposure to study drug for all Phase II and III studies was

significantly less for lanthanum carbonate than for placebo or active control phosphate binders, 246.2 days versus 330.2 days, respectively. 20 Noteworthy, most of the long-term exposure to lanthanum and thus long- term safety data come from open- label and more importantly uncontrolled studies (LAM- IV- 205, 308, and 301).

Subjects/ Patients Discontinuations: In the Phase I studies 15.1% (n= 27) of the subjects discontinued prematurely in the lanthanum group versus 6.6% (n= 5) of the subjects receiving placebo/ other. In the Phase II- III short- term studies21 the rate of withdrawal was higher for those patients receiving lanthanum carbonate than for the placebo- treated patients, 32.2% (n= 96) versus 28.4% (n= 27). Similarly, in the Phase III long- term

studies22 the percentage of patients discontinuing lanthanum carbonate therapy was greater than for active control phosphate binders, 60.4% versus 41.4%.

In the majority of the studies the described discrepancy in discontinuation rates between treatment groups was in part due to the fact that subjects/ patients receiving lanthanum carbonate discontinued prematurely because of adverse events or consent withdrawal at a greater rate than those receiving placebo or active control phosphate binders. In all Phase II and II studies, more lanthanum- treated patients than those subjects receiving placebo or standard therapy were discontinued because of adverse events (15.6% versus 5.1%), consent withdrawal (10.7% versus 5.3%), protocol violations (4.5% versus 1.2%), and safety related criteria (4.7% versus 3.1%).

Deaths: The analysis of deaths performed by the sponsor and reported in the original NDA submission and four- month safety update was based on the deaths that occurred while patients were on a study.

According to the report in the four- month safety update, no subjects died during the Phase I studies, during the short- term Phase II- III studies, 2 patients (0.7%) treated with lanthanum carbonate died and no patients treated with placebo died. In the long- term studies, 66 patients (4.5%) treated with lanthanum carbonate died and 83 patients (9.1%) treated with active control phosphate binders died while on study, according to the sponsor this difference was statistically significant ($p< 0.001$).

Because patients who were withdrawn prematurely from any of the clinical trials were not followed up to study's completion and the marked difference in withdrawal rates among groups, the sponsor was asked by the Division of CardioRenal Drug Products to collect up to date mortality data from all the patients who participated in the clinical development program of FOSRENOL . . In response to that request the sponsor mailed a one- page contact form to each study site for each individual patient who participated in any Phase II- III studies. According to the sponsor a total of 2519 patients received at least one active treatment in Phase II- III studies since 162 patients died while on study the contact form was sent out to the remaining 2357 patients during September 2002. As of October 31, 2002, 1974 forms were returned and the information entered into the database. In addition " four known deaths that occurred during the 30 days follow- up period post study were [also] entered into the database." According to the sponsor, " the present mortality data represents a follow- up rate of 85% [(162+ 1974+ 4)/ 2519]."

Table 1- ISS summarizes number and percentage of deaths according to the four- month safety update cut- off date of May 30, 2002, and the updated mortality data cut- off date of October 30, 2002. The updated mortality data underscores the misleading effect that missing data could have in the interpretation of any study, in that the statistically significant difference in mortality rates in favor of lanthanum documented in the four-month safety update vanishes when a follow- up rate of 85% was achieved. The updated mortality data indicate that mortality rates were slightly higher in the lanthanum group as compared with the standard therapy group, 21.9% versus 19.4%.

In a meeting held with the sponsor on December 3, 2002, the Division of CardioRenal Drug Products reiterated to the sponsor the need to collect mortality data in 100% of the patients. In response to the Division's request the sponsor submitted on December 20, 2002, an updated version of the mortality data,

Albeit, the safety data resulting from Phase I studies and short- term phase II- III placebo-controlled studies contribute to delineate the safety profile of short- term exposure to lanthanum carbonate, the long- term safety of lanthanum carbonate can not be inferred from such studies. In this regard, the long- term safety of lanthanum carbonate must be surmised from the active- controlled and open- label long- term studies LAM- IV- 301, - 303, and - 307.24 However, there are significant inadequacies with the design of the studies as well as a significant imbalance in drug exposure that together prevents the characterization of the long- term safety profile of lanthanum carbonate in this population with any degree of confidence. 25 Notwithstanding the marked deficiencies already mentioned, Table 4- ISS summarizes adverse events occurring with an incidence = 10% by treatment group. Noteworthy, each adverse event, regardless of body system, with an incidence = 10% invariably occurred at a greater rate in active control than in lanthanum carbonate, and the noted differences were statistically significant in 24 out of a total of 26 distinct adverse events, with p- values ranging from < 0.05 to < 0.001.

This outcome represents both a medical as well as a statistical anomaly and in all likelihood the result of: 1) a significantly higher rate of discontinuation and thus shorter exposure to lanthanum carbonate, and 2) the long- term studies' open- label design that could have led to significant underreporting of adverse events due to investigators' biases. These deficiencies made safety comparisons significantly biased unquestionably in favor of lanthanum carbonate treatment preventing an accurate delineation of the long-term safety profile of the drug. Unfortunately, hitherto, there is not a statistical analysis that could accurately either remedy deficiencies in study design and investigators' biases or substitute for missing data.

Discontinuations Due to Adverse Events: In the short- term studies 26 (8.7%) patients receiving lanthanum carbonate and 5 (5.3%) patients treated with placebo discontinued due to adverse events. Overall, 236 (16.0%) of patients treated with lanthanum carbonate discontinued treatment during the long- term Phase II- III studies while 46 (5.1%) of patients treated with active control discontinued ($p< 0.001$). 26 A total of 190 patients representing 80.5% of all the discontinuations in the lanthanum carbonate group withdrew prematurely from the study because of adverse events related to the gastrointestinal system; nausea, vomiting, diarrhea and abdominal pain were the major causes leading to discontinuation in this group (Table 5- ISS). The results indicate that lanthanum carbonate is significantly less well tolerated than other phosphate binders.

Studies Specifically Conducted to Assess Safety: Study LAM- IV- 303 assessed the effect of lanthanum carbonated compared with calcium carbonate on renal bone disease by comparing bone tissue obtained from paired biopsies. Of the 98 patients randomized

into the study, 71 patients received a follow- up biopsy after 52 weeks of treatment, and therefore provided paired biopsy data, however only 63 pairs of biopsies were suitable for histomorphometric measurements.

The significance of the bone biopsy findings is questioned because according to the sponsor " there was limited data available on which to base the sample size estimates, therefore numbers were based on practical rather than statistical considerations." Thus the study was not powered to rule out whether lanthanum carbonate has deleterious effect(s) in bone formation as compared with active control. The interpretation of the findings is further confounded by the fact that calcium carbonate, the active control, is not an FDA approved phosphate binder thus its safety profile, as compared with placebo/ standard therapy, is unknown to the Division of Cardio- Renal Drug Products.

Mineralization lag time the primary efficacy endpoint of the study, defined as the mean time interval between deposition and mineralization of any volume of matrix averaged over the entire life span of the osteoid seam, is a key variable for the assessment of new bone formation. The median z- scores of mineralization lag time indicate that patients in the lanthanum carbonate group had slower bone formation than those patients receiving the active control, + 0.8 versus + 3.975, respectively.

Specific Findings of Safety Review Plasma and Bone Tissue Levels of Lanthanum: Data on plasma and bone tissue levels of lanthanum from Study LAM- IV- 303 is next presented. Plasma lanthanum levels were measured at weeks 0, 12, 24, 36, 48 and 52.27 In lanthanum- treated patients there were increases in plasma lanthanum for all doses administered compared with baseline levels- in baseline plasma samples lanthanum was not detectable. Albeit the small sample size prevents one to be conclusive as to whether there is a dose relationship, plasma lanthanum levels appear to be dose- dependent (Figure 2- ISS).

and/ or plasma and tissue levels, for the absorption and accumulation of lanthanum. Simply said the sponsor failed to properly study the absorption, distribution, and extent of accumulation and elimination of lanthanum either in a healthy or ESRD populations.

Bone fractures:
The interpretation of the incidence rates for bone fractures is significantly confounded, among others, by 1) the observation of very few events during the comparative period of the phase II- III studies, 2) the fact that except for study LAM- IV- 307 the other studies comparative phases were very short in duration, and 3) that there was a marked imbalance in patient discontinuation rates in study LAM- IV- 307, 65.1% versus 45.6% respectively for lanthanum and comparator. 28 Therefore, it cannot be concluded whether lanthanum carbonate, as compare with standard therapy, is associated with a greater rate of bone fractures.

2. The results from pre- clinical studies submitted in NDA 21- 468 indicate that lanthanum when administered orally undergoes gastrointestinal absorption, which results

in tissue (bone, heart, kidney, liver, etc.) accumulation in healthy animals with normal renal function. The latter is relevant in that one of the routes for lanthanum excretion is the kidney. 33 Review of the pre- clinical data also suggests that lanthanum plasma levels have no predictive value as far as tissue levels and by and large lanthanum levels in tissues are significantly greater, by many order of magnitude, than plasma levels. Furthermore, the extent of tissue accumulation of lanthanum appears to be both dose and time dependent.

3. Pre- clinical studies performed by the sponsor34 and by other investigators35 in a chronic renal failure rat model indicate that lanthanum carbonate results in a dose-dependent decrease in bone formation and osteomalacia. In this regard, in study LAM-IV- 303 the median z- scores of mineralization lag time obtained from bone biopsies indicate that patients in the lanthanum carbonate group had slower bone formation than those patients receiving the active control.

4. As was the case in animals, data from clinical trials indicate that lanthanum also undergoes gastrointestinal absorption in humans, in that lanthanum can be detected in plasma of patients exposed to it (oral administration). Plasma levels of lanthanum appear to be influenced by dose and length of exposure. Analysis of bone biopsy material from study LAM- IV- 303 provides irrefutable evidence that there is tissue, i. e., bone, accumulation of lanthanum in humans, thus one could infer that the tissue accumulation of lanthanum is widespread. Because of the compromised ability to eliminate any administered lanthanum, due to renal impairment, the population for which the use of lanthanum is intended might experience over time significant accumulation of lanthanum in vital tissues. The results from study Lam- IV- 111 indicate that lanthanum is not dialyzable to any significant extent through hemodialysis. 36 Albeit, the available data clearly indicate that lanthanum is absorbed in the gastrointestinal tract, the sponsor failed to assess how much is absorbed and to describe its fate. Based on the pre- clinical data is reasonable to conclude that tissue accumulation of lanthanum in humans will significantly increase not only with dose but also with time of exposure. It could be argued that the morbidity associated with lanthanum administration may change significantly over time. The latter is relevant because the patient population for whom lanthanum is intended requires treatment with a phosphate binder for many years, that is up until the time of either kidney transplant or death occurs.

5. Of note, patients who were withdrawn prematurely from any of the clinical trials were not followed up to study's termination date. In the long- term study LAM- IV- 307, the largest of all the clinical trials 647 patients received lanthanum and 642 received standard therapy, lanthanum- treated patients had a significantly higher rate of discontinuation than those patients treated with standard therapy, 62.7% versus 42.3%. The latter resulted in patients in the lanthanum group having a significantly shorter drug exposure to study drug than those subjects in standard therapy. Mean exposure was 284.3 days for the lanthanum group versus 397.0 days for the standard therapy group (p= 0.001). 37 In the study LAM- IV- 301 the safety of lanthanum carbonate (n= 533) is compared with that of calcium carbonate (n= 267) for only 25 weeks, i. e., five weeks during the titration phase and 20 weeks during the maintenance phase, thereafter subjects were switched to

lanthanum carbonate. Noteworthy, calcium carbonate is not an FDA approved phosphate binderthus its safety profile, as compared with placebo or standard therapy, is unknown to the Division of Cardio- Renal Drug Products. Finally, studies LAM- IV- 301 and 307, in which the safety of lanthanum carbonate versus that of calcium carbonate or standard therapy is compared, had an open- label design, which could have led to significant underreporting of adverse events due to investigators' biases. Thus, because of the lack of adequate follow- up coupled with shorter drug exposure for the lanthanum group in study LAM- IV- 307 in addition to the long- term studies' open- label design, safety comparisons are significantly biased unquestionably in favor of lanthanum carbonate treatment.

6. Patients receiving lanthanum carbonate as compared with those subjects receiving placebo or standard therapy had greater discontinuation rates, primarily because of a greater incidence of adverse events and consent withdrawal; indicating that lanthanum is significantly less well tolerated than either placebo or standard therapy.

7. Noteworthy, a large portion of the log- term exposure to lanthanum and thus the long-term safety data are derived not only from open- label but also uncontrolled studies (LAM- IV- 205, 308, and 301). 38

8. ECG data obtained from patients randomized into study LAM- IV- 307 suggest that long- term exposure to lanthanum causes prolongation of the QT interval, which in turn could be associated with significant morbid and mortal events.

9. The updated mortality data, in which mortality data are available for 94.5% of the patients 39 , indicate that mortality rates were higher in patients receiving lanthanum as compared with those patients treated with active controls, with a difference between treatment groups of 4.4% against lanthanum carbonate.

10. Finally, statistical analyses can accurately neither substitute for missing data nor rectify for deficiencies in study design, investigators' biases, and differences in drug exposure.

Safety Conclusions: The short- term exposure to lanthanum carbonate is mostly characterized by adverse events related to the gastrointestinal system such as nausea, vomiting, diarrhea, and abdominal pain. Of note, these gastrointestinal manifestations were the major cause leading to discontinuation in this group, indicating that lanthanum carbonate is significantly less well tolerated than placebo or standard therapy.

Conversely, the safety of long- term exposure to lanthanum carbonate, for the reasons discussed in detail above, cannot be defined with any degree of confidence. Notwithstanding, it is of major concern 1) the detrimental effect that lanthanum has on bone mineralization lag time, 2) that long- term exposure to lanthanum may cause prolongation of the QT interval, and 3) higher mortality rates in patients receiving lanthanum as compared with those patients treated with active controls, with an absolute difference of ~ 4.4%.

Fosrenol is available as a chewable unflavored tablet in two dosage strengths (250 mg, and 500 mg) for oral administration.
Demographics and other characteristics of study population in phase i studies, the majority of subjects were male (81.6% of subjects who received lanthanum carbonate, 100% of subjects who received placebo) and caucasian (84.9% and 82.9%, respectively). the mean age was similar for the two treatment groups: 29.5 years for subjects who received lanthanum carbonate, and 25.7 years for subjects who received placebo; ages ranged from 18 to 67 years.

of the 1672 patients who received lanthanum carbonate treatment in the phase ii- iii studies, the majority were male (61.8%), caucasian (67.5%), and the mean age was 56.3 years (range: 19 to 87 years). patients were evenly distributed among the 3 age groups of 18 to 50 years, 51 to 64 years, and 65 years and older, with 32.0% to 34.8% of patients in each.

patients' demographics remain unchanged for the short- term phase ii- iii studies. in the short- term phase ii- iii studies, 298 patients were treated with lanthanum carbonate and 95 patients were treated with placebo.

there were more male than female patients in each treatment group (62.1% of patients treated with lanthanum carbonate were male, 54.7% of patients treated with placebo were male). race was fairly evenly divided between caucasian and black in both treatment groups (range of 44.0% to 47.7% for each race). patients were almost equally divided among the 3 age groups of 18 to 50 years, 51 to 64 years, and 65 years and older (28.2%, 35.2%, and 36.6% respectively, for the lanthanum carbonate treatment group and 29.5%, 30.5%, and 40.0%, respectively, for the placebo treatment group).

in the long- term phase ii- iii studies, 1474 patients were treated with lanthanum carbonate and 909 patients were treated with active control. patients' demographics were either identical to or consistent with those previously reported in the nda. there were more male than female patients in each treatment group (61.9% of patients treated with lanthanum carbonate were male, 61.3% of patients treated with active control were male). race was predominantly caucasian (68.9% of patients treated with lanthanum carbonate, 61.5% of patients treated with active control). patients were almost equally divided among the 3 age groups of 18 to 50 years, 51 to 64 years, and 65 years and older (33.7%, 34.9%, and 3 1.3%, respectively, for patients treated with lanthanum carbonate and 3 3.8%, 34.9%, and 31.2%, respectively, for patients treated with active control).

use in special populations the studies submitted in support of this NDA did not evaluate patients within the pediatric age groups. the reader is referred to the integrated summary of efficacy where the effectiveness of lanthanum carbonate in sub- populations based on age, race, and gender is presented.

integrated summary of efficacy the effectiveness of lanthanum carbonate in reducing and maintaining serum phosphate levels in hyperphosphatemic patients, male or female aged

18 or older, with end-stage renal disease (ESRD) undergoing hemo- or peritoneal-dialysis has been evaluated in five placebo- or active- controlled phase ii (LAM – IV - 202 and 204) and iii (LAM - IV - 301, 302 and 307) clinical studies conducted in the us and europe. the efficacy of lanthanum carbonate was assessed by examining the change from baseline in serum phosphate levels and the proportion of patients whose serum phosphate levels were controlled, i. e., serum phosphate = 5.6 mg/ dl for european studies (lam- iv- 202, and - 301) and = 5.9 mg/ dl for the us studies (lam- iv- 204, - 302, and - 307), an intent to treat approach was used to evaluate efficacy.

studies LAM - IV- 202, - 204, and - 302 had a randomized, double blind, placebo-controlled and parallel group design; while lam- iv- 301 and - 307 were randomized, open- label, active- controlled and parallel group studies. in total the studies randomized 2303 patients, 1329 received lanthanum carbonate and 974 received either placebo (n= 95) or other phosphate binders (n= 879). in studies lam- iv- 202, - 204, and - 302 180 patients received lanthanum carbonate and 95 received placebo. in study LAM- IV - 301 the comparator was calcium carbonate (n= 267) and 533 patients were treated with lanthanum carbonate. study LAM – IV - 307 compared the effects of lanthanum carbonate in 616 subjects versus the effects of standard therapy on 612 patients. standard therapy in that study comprised the used of the following commercially available phosphate binders: renagel . , phoslo . and tums . .3 treatment duration in the aforementioned studies ranged from 4 weeks to 23 months.

placebo- controlled studies lam- iv- 202, - 204, and - 302 protocol lam- iv- 202 (uk): this was a randomized, double blind, placebo controlled, parallel group, dose ranging study of lanthanum carbonate in subjects receiving hemodialysis or capd. the study had two parts: 1) 2- week washout period, followed by a four- week titration (lanthanum carbonate 375 mg to 2250 mg) until the serum phosphate reached and was maintained at a level between 1.3 mmol/ l to 1.8 mmol/ l, and 2) a four- week double blind, parallel group phase where patients were randomized to receive either their maintenance dose of lanthanum or placebo.

3 renagel . (sevelamer hydrochloride), and phoslo . (calcium acetate) are fda- approved phosphate binders, however tums . an over the counter formulation of calcium carbonate has not been approved by

Safety Conclusions

No lanthanum-related deaths were observed. There was no evidence of aluminum-like effects observed in bone or impaired cognitive function. Other clinical parameters, including ECGs and liver function tests, showed no significant changes. There was no evidence of an adverse trend in survival against lanthanum compared to standard therapy. However, many factors influenced making such comparisons, including patient attrition due to different rates of discontinuation and the high background mortality rate of ESRD. Other secondary factors contributing to mortality included the role of vascular ectopic calcification and consequent atherosclerotic vascular disease.

A synopsis of the efficacy and safety review is described briefly below:

The results from study LAM- IV- 307 data indicate that lanthanum carbonate, when compared with standard therapy, is significantly inferior in reducing/ maintaining serum phosphorus levels in patients with end stage renal disease, and thus controlling hyperphosphatemia.

Efficacy Conclusions
In summary, the data from the clinical development program of FOSRENOL (lanthanum carbonate) supports the notion that this drug product is a phosphate binder, however its ability to bind phosphate is inferior to currently approved phosphate binders.

The reviewer of the original NDA concluded that orally administered lanthanum three times a day with meals is an effective phosphate binder compared with placebo. Furthermore lanthanum maintains serum phosphorous levels within normal range in a statistically significant number of subjects using doses ranging from 225 mg to 3000 mg daily.

The reviewer noted that the Agency had not approved calcium carbonate for the indication of phosphate binding. Notwithstanding this observation, calcium carbonate appeared to be more effective in controlling hyperphosphatemia in patients with ESRD, albeit ephemeral, as the superiority of calcium carbonate over lanthanum was no longer evident after 25 weeks of administration (Study 301).

The current reviewer of this NDA notes that lanthanum carbonate is equally effective in the treatment of hyperphosphatemia but it would appear that it takes a longer time to do so than the comparators used in the standard treatment. There is compelling evidence that it is more effective than placebo in ESRD. On this basis it can be concluded that there is clinical benefit. For approval, safety of lanthanum carbonate should be established.

Safety The primary focus of this section is on the adequacy of safety testing and assessments carried out in the clinical development program with the main objective of delineating the safety profile of FOSRENOL . (lanthanum carbonate). To this end the medical reviewer utilized NDA desk copies and the electronic version provided with the original submission, SAS datafiles14 and as well as material provided by the sponsor in response to special requests, i. e., ECG15 , overall mortality16 data and incidence of bone fractures. The safety information provided by the sponsor in the four- month safety update was also reviewed and the results were incorporated in this integrated review of safety.

The approach used in the delineation of the safety profile of FOSRENOL. in hyperphosphatemic patients with end- stage renal disease undergoing dialysis included: examination of the clinical database for deaths, discontinuations, serious adverse events, as well as an analysis of the routinely collected safety data (i. e., treatment emergent adverse events, laboratory findings, and vital signs). ECG data were evaluated specifically to determine whether lanthanum carbonate causes changes in QT/ QTc. To

determine whether lanthanum carbonate has an adverse effect on bone formation results from bone biopsies and incidence of fractures were examined.

Clinical Safety Data: Safety data from the following studies were examined: 11 clinical pharmacology Phase I studies in healthy volunteers and patients with ESRD (LAM- IV- 10l, 104, 105, 108, 109, 110, 111, 112, 113, 114, and 115) 17 and 8 Phase II- III studies (LAM- IV- 202, 204, 205, 301, 302, 303, 307, and 308).

The safety information derived from the pharmacology Phase I studies is limited given the short- term exposure and that few subjects were evaluated, lanthanum carbonate n= 179 and placebo/ other n= 76.

Studies LAM- IV- 202, 204, and 302 were placebo- controlled trials of short duration, randomized treatment ranged from 4 to 6 weeks, and enrolled few patients each; lanthanum carbonate 17 and placebo 19, lanthanum carbonate 113 and placebo 32, and lanthanum carbonate 50 and placebo 44, respectively.

Study LAM- IV- 303 evaluated a small number of patients, 49 in each lanthanum carbonate and calcium carbonate18 groups, approximately two- thirds of these patients had bone biopsy data collected and were

significantly less for lanthanum carbonate than for placebo or active control phosphate binders, 246.2 days versus 330.2 days, respectively. 20 Noteworthy, most of the long-term exposure to lanthanum and thus long- term safety data come from open- label and more importantly uncontrolled studies (LAM- IV- 205, 308, and 301).

Subjects/ Patients Discontinuations: In the Phase I studies 15.1% (n= 27) of the subjects discontinued prematurely in the lanthanum group versus 6.6% (n= 5) of the subjects receiving placebo/ other. In the Phase II- III short- term studies21 the rate of withdrawal was higher for those patients receiving lanthanum carbonate than for the placebo- treated patients, 32.2% (n= 96) versus 28.4% (n= 27). Similarly, in the Phase III long- term studies22 the percentage of patients discontinuing lanthanum carbonate therapy was greater than for active control phosphate binders, 60.4% versus 41.4%.

In the majority of the studies the described discrepancy in discontinuation rates between treatment groups was in part due to the fact that subjects/ patients receiving lanthanum carbonate discontinued prematurely because of adverse events or consent withdrawal at a greater rate than those receiving placebo or active control phosphate binders. In all Phase II and II studies, more lanthanum- treated patients than those subjects receiving placebo or standard therapy were discontinued because of adverse events (15.6% versus 5.1%),

consent withdrawal (10.7% versus 5.3%), protocol violations (4.5% versus 1.2%), and safety related criteria (4.7% versus 3.1%).

Deaths: The analysis of deaths performed by the sponsor and reported in the original NDA submission and four- month safety update was based on the deaths that occurred while patients were on a study.

According to the report in the four- month safety update, no subjects died during the Phase I studies, during the short- term Phase II- III studies, 2 patients (0.7%) treated with lanthanum carbonate died and no patients treated with placebo died. In the long- term studies, 66 patients (4.5%) treated with lanthanum carbonate died and 83 patients (9.1%) treated with active control phosphate binders died while on study, according to the sponsor this difference was statistically significant ($p< 0.001$).

Because patients who were withdrawn prematurely from any of the clinical trials were not followed up to study's completion and the marked difference in withdrawal rates among groups, the sponsor was asked by the Division of CardioRenal Drug Products to collect up to date mortality data from all the patients who participated in the clinical development program of FOSRENOL . . In response to that request the sponsor mailed a one- page contact form to each study site for each individual patient who participated in any Phase II- III studies. According to the sponsor a total of 2519 patients received at least one active treatment in Phase II- III studies since 162 patients died while on study the contact form was sent out to the remaining 2357 patients during September 2002. As of October 31, 2002, 1974 forms were returned and the information entered into the database. In addition " four known deaths that occurred during the 30 days follow- up period post study were [also] entered into the database." According to the sponsor, " the present mortality data represents a follow- up rate of 85% [(162+ 1974+ 4)/ 2519]."

Table 1- ISS summarizes number and percentage of deaths according to the four- month safety update cut- off date of May 30, 2002, and the updated mortality data cut- off date of October 30, 2002. The updated mortality data underscores the misleading effect that missing data could have in the interpretation of any study, in that the statistically significant difference in mortality rates in favor of lanthanum documented in the four-month safety update vanishes when a follow- up rate of 85% was achieved. The updated mortality data indicate that mortality rates were slightly higher in the lanthanum group as compared with the standard therapy group, 21.9% versus 19.4%.

In a meeting held with the sponsor on December 3, 2002, the Division of CardioRenal Drug Products reiterated to the sponsor the need to collect mortality data in 100% of the patients. In response to the Division's request the sponsor submitted on December 20, 2002, an updated version of the mortality data,

Albeit, the safety data resulting from Phase I studies and short- term phase II- III placebo-controlled studies contribute to delineate the safety profile of short- term exposure to lanthanum carbonate, the long- term safety of lanthanum carbonate can not be inferred

from such studies. In this regard, the long- term safety of lanthanum carbonate must be surmised from the active- controlled and open- label long- term studies LAM- IV- 301, - 303, and - 307.24 However, there are significant inadequacies with the design of the studies as well as a significant imbalance in drug exposure that together prevents the characterization of the long- term safety profile of lanthanum carbonate in this population with any degree of confidence. 25 Notwithstanding the marked deficiencies already mentioned, Table 4- ISS summarizes adverse events occurring with an incidence = 10% by treatment group. Noteworthy, each adverse event, regardless of body system, with an incidence = 10% invariably occurred at a greater rate in active control than in lanthanum carbonate, and the noted differences were statistically significant in 24 out of a total of 26 distinct adverse events, with p- values ranging from < 0.05 to < 0.001.

This outcome represents both a medical as well as a statistical anomaly and in all likelihood the result of: 1) a significantly higher rate of discontinuation and thus shorter exposure to lanthanum carbonate, and 2) the long- term studies' open- label design that could have led to significant underreporting of adverse events due to investigators' biases. These deficiencies made safety comparisons significantly biased unquestionably in favor of lanthanum carbonate treatment preventing an accurate delineation of the long-term safety profile of the drug. Unfortunately, hitherto, there is not a statistical analysis that could accurately either remedy deficiencies in study design and investigators' biases or substitute for missing data.

Discontinuations Due to Adverse Events: In the short- term studies 26 (8.7%) patients receiving lanthanum carbonate and 5 (5.3%) patients treated with placebo discontinued due to adverse events. Overall, 236 (16.0%) of patients treated with lanthanum carbonate discontinued treatment during the long- term Phase II- III studies while 46 (5.1%) of patients treated with active control discontinued ($p< 0.001$). 26 A total of 190 patients representing 80.5% of all the discontinuations in the lanthanum carbonate group withdrew prematurely from the study because of adverse events related to the gastrointestinal system; nausea, vomiting, diarrhea and abdominal pain were the major causes leading to discontinuation in this group (Table 5- ISS). The results indicate that lanthanum carbonate is significantly less well tolerated than other phosphate binders.

Studies Specifically Conducted to Assess Safety: Study LAM- IV- 303 assessed the effect of lanthanum carbonated compared with calcium carbonate on renal bone disease by comparing bone tissue obtained from paired biopsies. Of the 98 patients randomized into the study, 71 patients received a follow- up biopsy after 52 weeks of treatment, and therefore provided paired biopsy data, however only 63 pairs of biopsies were suitable for histomorphometric measurements.

The significance of the bone biopsy findings is questioned because according to the sponsor " there was limited data available on which to base the sample size estimates, therefore numbers were based on practical rather than statistical considerations." Thus the study was not powered to rule out whether lanthanum carbonate has deleterious effect(s)

in bone formation as compared with active control. The interpretation of the findings is further confounded by the fact that calcium carbonate, the active control, is not an FDA approved phosphate binder thus its safety profile, as compared with placebo/ standard therapy, is unknown to the Division of Cardio- Renal Drug Products.

Mineralization lag time the primary efficacy endpoint of the study, defined as the mean time interval between deposition and mineralization of any volume of matrix averaged over the entire life span of the osteoid seam, is a key variable for the assessment of new bone formation. The median z- scores of mineralization lag time indicate that patients in the lanthanum carbonate group had slower bone formation than those patients receiving the active control, + 0.8 versus + 3.975, respectively.

Specific Findings of Safety Review Plasma and Bone Tissue Levels of Lanthanum: Data on plasma and bone tissue levels of lanthanum from Study LAM- IV- 303 is next presented. Plasma lanthanum levels were measured at weeks 0, 12, 24, 36, 48 and 52.27 In lanthanum- treated patients there were increases in plasma lanthanum for all doses administered compared with baseline levels- in baseline plasma samples lanthanum was not detectable. Albeit the small sample size prevents one to be conclusive as to whether there is a dose relationship, plasma lanthanum levels appear to be dose- dependent (Figure 2- ISS).

and/ or plasma and tissue levels, for the absorption and accumulation of lanthanum. Simply said the sponsor failed to properly study the absorption, distribution, and extent of accumulation and elimination of lanthanum either in a healthy or ESRD populations.

Bone fractures: The interpretation of the incidence rates for bone fractures is significantly confounded, among others, by 1) the observation of very few events during the comparative period of the phase II- III studies, 2) the fact that except for study LAM- IV- 307 the other studies comparative phases were very short in duration, and 3) that there was a marked imbalance in patient discontinuation rates in study LAM- IV- 307, 65.1% versus 45.6% respectively for lanthanum and comparator. 28 Therefore, it cannot be concluded whether lanthanum carbonate, as compare with standard therapy, is associated with a greater rate of bone fractures.

2. The results from pre- clinical studies submitted in NDA 21- 468 indicate that lanthanum when administered orally undergoes gastrointestinal absorption, which results in tissue (bone, heart, kidney, liver, etc.) accumulation in healthy animals with normal renal function. The latter is relevant in that one of the routes for lanthanum excretion is the kidney. 33 Review of the pre- clinical data also suggests that lanthanum plasma levels have no predictive value as far as tissue levels and by and large lanthanum levels in tissues are significantly greater, by many order of magnitude, than plasma levels. Furthermore, the extent of tissue accumulation of lanthanum appears to be both dose and time dependent.

3. Pre- clinical studies performed by the sponsor34 and by other investigators35 in a chronic renal failure rat model indicate that lanthanum carbonate results in a dose-dependent decrease in bone formation and osteomalacia. In this regard, in study LAM-IV- 303 the median z- scores of mineralization lag time obtained from bone biopsies indicate that patients in the lanthanum carbonate group had slower bone formation than those patients receiving the active control.

4. As was the case in animals, data from clinical trials indicate that lanthanum also undergoes gastrointestinal absorption in humans, in that lanthanum can be detected in plasma of patients exposed to it (oral administration). Plasma levels of lanthanum appear to be influenced by dose and length of exposure. Analysis of bone biopsy material from study LAM- IV- 303 provides irrefutable evidence that there is tissue, i. e., bone, accumulation of lanthanum in humans, thus one could infer that the tissue accumulation of lanthanum is widespread. Because of the compromised ability to eliminate any administered lanthanum, due to renal impairment, the population for which the use of lanthanum is intended might experience over time significant accumulation of lanthanum in vital tissues. The results from study Lam- IV- 111 indicate that lanthanum is not dialyzable to any significant extent through hemodialysis. 36 Albeit, the available data clearly indicate that lanthanum is absorbed in the gastrointestinal tract, the sponsor failed to assess how much is absorbed and to describe its fate. Based on the pre- clinical data is reasonable to conclude that tissue accumulation of lanthanum in humans will significantly increase not only with dose but also with time of exposure. It could be argued that the morbidity associated with lanthanum administration may change significantly over time. The latter is relevant because the patient population for whom lanthanum is intended requires treatment with a phosphate binder for many years, that is up until the time of either kidney transplant or death occurs.

5. Of note, patients who were withdrawn prematurely from any of the clinical trials were not followed up to study's termination date. In the long- term study LAM- IV- 307, the largest of all the clinical trials 647 patients received lanthanum and 642 received standard therapy, lanthanum- treated patients had a significantly higher rate of discontinuation than those patients treated with standard therapy, 62.7% versus 42.3%. The latter resulted in patients in the lanthanum group having a significantly shorter drug exposure to study drug than those subjects in standard therapy. Mean exposure was 284.3 days for the lanthanum group versus 397.0 days for the standard therapy group ($p= 0.001$). 37 In the study LAM- IV- 301 the safety of lanthanum carbonate ($n= 533$) is compared with that of calcium carbonate ($n= 267$) for only 25 weeks, i. e., five weeks during the titration phase and 20 weeks during the maintenance phase, thereafter subjects were switched to lanthanum carbonate. Noteworthy, calcium carbonate is not an FDA approved phosphate binderthus its safety profile, as compared with placebo or standard therapy, is unknown to the Division of Cardio- Renal Drug Products. Finally, studies LAM- IV- 301 and 307, in which the safety of lanthanum carbonate versus that of calcium carbonate or standard therapy is compared, had an open- label design, which could have led to significant underreporting of adverse events due to investigators' biases. Thus, because of the lack of adequate follow- up coupled with shorter drug exposure for the lanthanum group in study LAM- IV- 307 in addition to the long- term studies' open- label design, safety

comparisons are significantly biased unquestionably in favor of lanthanum carbonate treatment.

6. Patients receiving lanthanum carbonate as compared with those subjects receiving placebo or standard therapy had greater discontinuation rates, primarily because of a greater incidence of adverse events and consent withdrawal; indicating that lanthanum is significantly less well tolerated than either placebo or standard therapy.

7. Noteworthy, a large portion of the log- term exposure to lanthanum and thus the long-term safety data are derived not only from open- label but also uncontrolled studies (LAM- IV- 205, 308, and 301). 38

8. ECG data obtained from patients randomized into study LAM- IV- 307 suggest that long- term exposure to lanthanum causes prolongation of the QT interval, which in turn could be associated with significant morbid and mortal events.

9. The updated mortality data, in which mortality data are available for 94.5% of the patients 39 , indicate that mortality rates were higher in patients receiving lanthanum as compared with those patients treated with active controls, with a difference between treatment groups of 4.4% against lanthanum carbonate.

10. Finally, statistical analyses can accurately neither substitute for missing data nor rectify for deficiencies in study design, investigators' biases, and differences in drug exposure.

Safety

The summary of the review of the original NDA is as follows:

The safety profile of lanthanum was discussed in the original review under short and long term studies regardless of the study phase. In view of the very long period it takes for lanthanum to reach steady stage in organs including bones (10-15 years) and in view of its widespread distribution in tissues all over the body, short term safety assessments are most likely inadequate for long term tissue toxicity. Therefore, the relatively long term studies, though open label, and actively controlled, are considered to be more suitable for long term toxicity assessments. The three active controlled, open label studies that would qualify would therefore be LAM-IV-301, 303 and 307. The two prominently affected organs are bones and gastrointestinal tract

Analyses of adverse events in patients who received lanthanum and standard therapy showed statistically significant differences in 24 out of 26 distinct adverse events with p values ranging from <0.05 to <0.001. Critical appraisal of these differences in favor of lanthanum can be attributed to a number of factors, namely 1) significantly higher rate of discontinuations and shorter exposure to lanthanum carbonate, and the lack of placebo control in these studies. Adjustment to drug exposure and subsequent analyses may shed better light on these differences. Table 4 – ISS in the original review summarizes all the differences in treatment emergent adverse events in patients with a frequency > 10% in long term studies. In the long term studies, a total of 236 (16%) of patients administered

lanthanum carbonate discontinued treatment compared to 46(5.1%) of active control treated patients ($p<0.001$).

A total of 190 patients representing about 81% of all discontinuations in the lanthanum group withdrew prematurely from the study because of GI adverse events. These high rates of discontinuations indicate poor tolerability compared to other phosphate binders. Table 5-ISS in the original review is reproduced below:

Adverse event	Lanthanum N=1474 n (%)	Active control N=909 n (%)
Nausea	50 (3.4)***	3 (0.3)
Vomiting	44 (3.0) ***	3(0.3)
Diarrhea	32 (2.2) ***	3(0.3)
Abdominal Pain	23 (1.6) ***	1 (0.1)
Flatulence	11 (0.7) **	0(0.0)
Constipation	10 (0.7)	3(0.3)
Dyspepsia	10 (0.7) *	0(0.0)
Gastrointestinal Disorder NOS	10 (0.7)	1 (0.1)

***p<0.05; **p<0.01; ***p<0.001 compared to the comparator

RECOMMENDATIONS

The recommendation is that FOSRENOL . (Lanthanum Carbonate) Chewable Tablets should not be approved ; C

I

FOSRENOL . is judged not approvable mainly because the drug's safety is not adequately evaluated, and the current safety evaluation shows that long- term exposure to lanthanum carbonate may be unacceptably toxic. In addition, albeit the data from the clinical development program of FOSRENOL . supports the notion that this drug product is a phosphate binder, its ability to bind phosphate is inferior to currently approved phosphate binders.

Appendix 4: Microscopic appearances of bone damage in normal and uremic rats given lanthanum and also in humans exposed to lanthanum (Figures 9-27).

Microscopic Slides from Rats submitted to the Agency by the sponsor -
Rats with Normal renal function given lanthanum -- C14, C13, CO4, FO1, FO2, C16, C15, Uremic rats receiving vehicle --G12, ;Uremic rats given lanthanum carbonate --- H13, HO2, XO6 and BO4 under letter from sponsor dated October 12, 1999.
Human slides -submitted as per letter dated May 5, 2004 under NDA 21468-serial 072.
Rat with normal renal function administered lanthanum in Figure 10..
Figure 12: Irregular cortical bone with periosteal thickening in metaphyseal area of tibia in a normal rat given lanthanum.

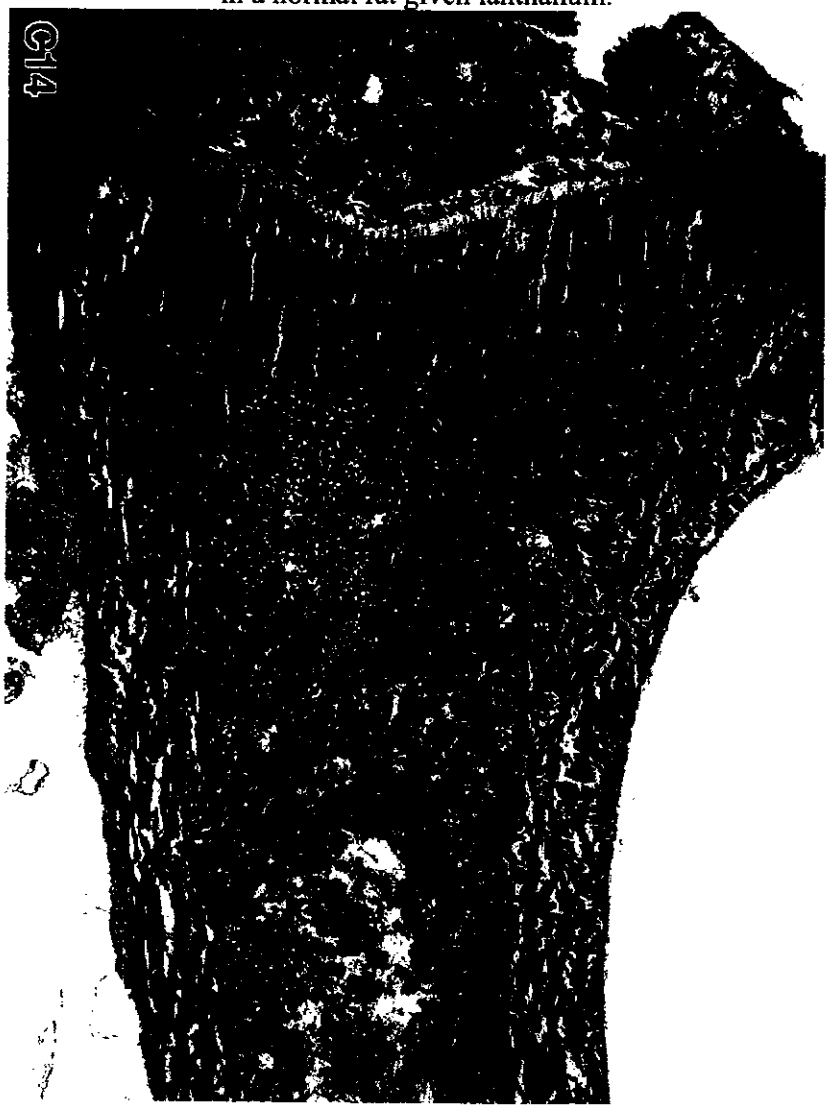
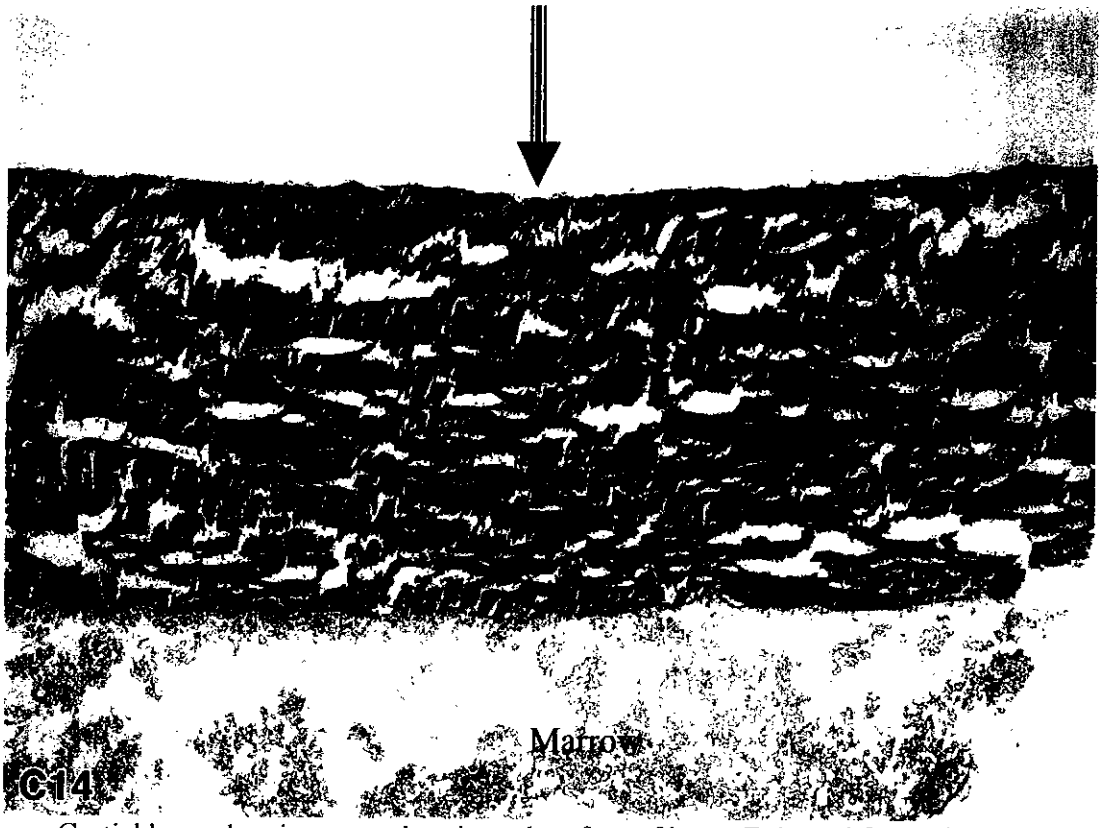


Figure 1 shows irregular cortical bone surface with periosteal thickening in the metaphyseal area of rat tibia- left of photograph (** Enlarged in Figures 3 and 4)

Note the relatively normal cortical surface-right side of photo (Enlarged in Figure 2).

Rat with normal renal function administered lanthanum

Figure 13: Rat with normal renal function showing normal periosteal surface of cortical bone in a normal rat given lanthanum



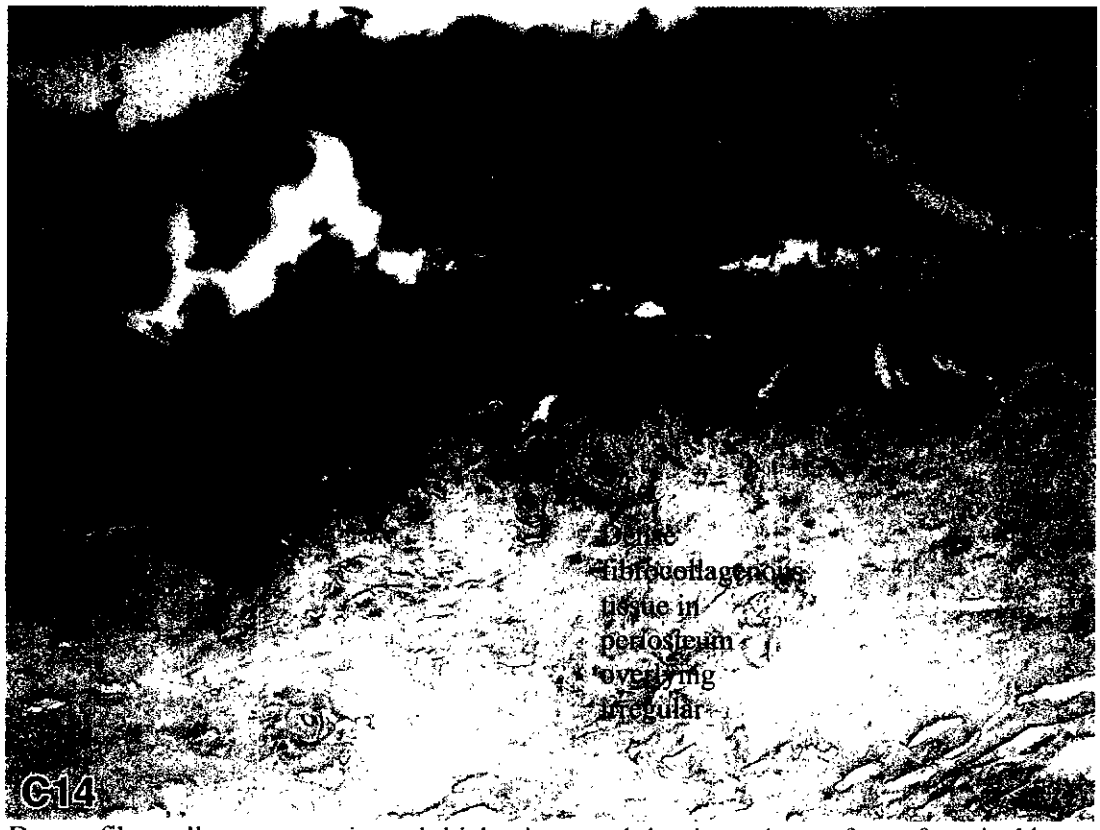
Cortial bone showing normal periosteal surface of bone. Enlarged from Figure 1.

Figure 14: Normal rat given lanthanum showing focal area of demineralization in the endosteal surface of bone where there is no tendon or muscle insertion

Long Arrow traverses periosteal thickening overlying irregular surface of cortical bone of rat with normal renal function given lanthanum ((See ** in Figure 1) Short arrow points to a focal demineralized area of bone.

Rat with normal renal function administered lanthanum

Figure 15: Normal rat with dense fibrocollagenous periosteal thickening and irregular convex surface of cortical bone



Dense fibrocollagenous periosteal thickening overlying irregular surface of cortical bone of rat with normal renal function given lanthanum ((See ** in Figure 1). Note some large cells, that may be osteoclasts, adjacent to the irregular cortical surface.

Rat with chronic renal failure administered lanthanum carbonate

Figure 16:Bone from Uremic rat given lanthanum carbonate showing renal osteodystrophy and periosteal thickening.

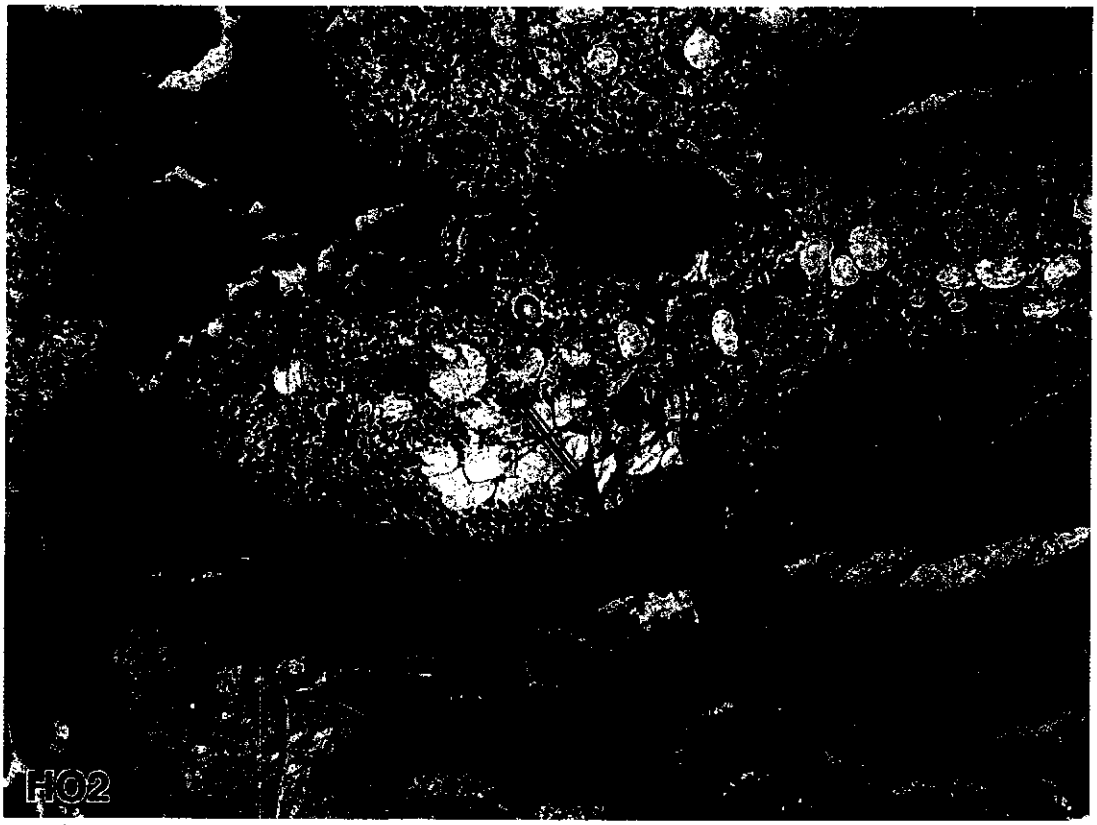
Micrograph of long bone from rat with chronic renal failure administered lanthanum carbonate showing periosteal thickening and irregular cortical bone surface (short arrow) . Note similarity with figures 3 and 4 that show periosteal thickening and irregular cortical surface in rat with normal renal function given lanthanum.

Rat with chronic renal failure administered lanthanum carbonate

Figure 17: Bone from Uremic rat given lanthanum showing renal osteodystrophy and dense fibroproliferative cells and thickened periosteum.

Micrograph of long bone from rat with chronic renal failure administered lanthanum carbonate showing periosteal thickening and irregular cortical bone surface (short arrow and bar) . Note similarity with figures 3 and 4 that show periosteal thickening and irregular cortical surface in rat with normal renal function given lanthanum carbonate.

Figure 18: Bone from uremic rat given lanthanum showing collagen deposition adjacent to bone.showing rena

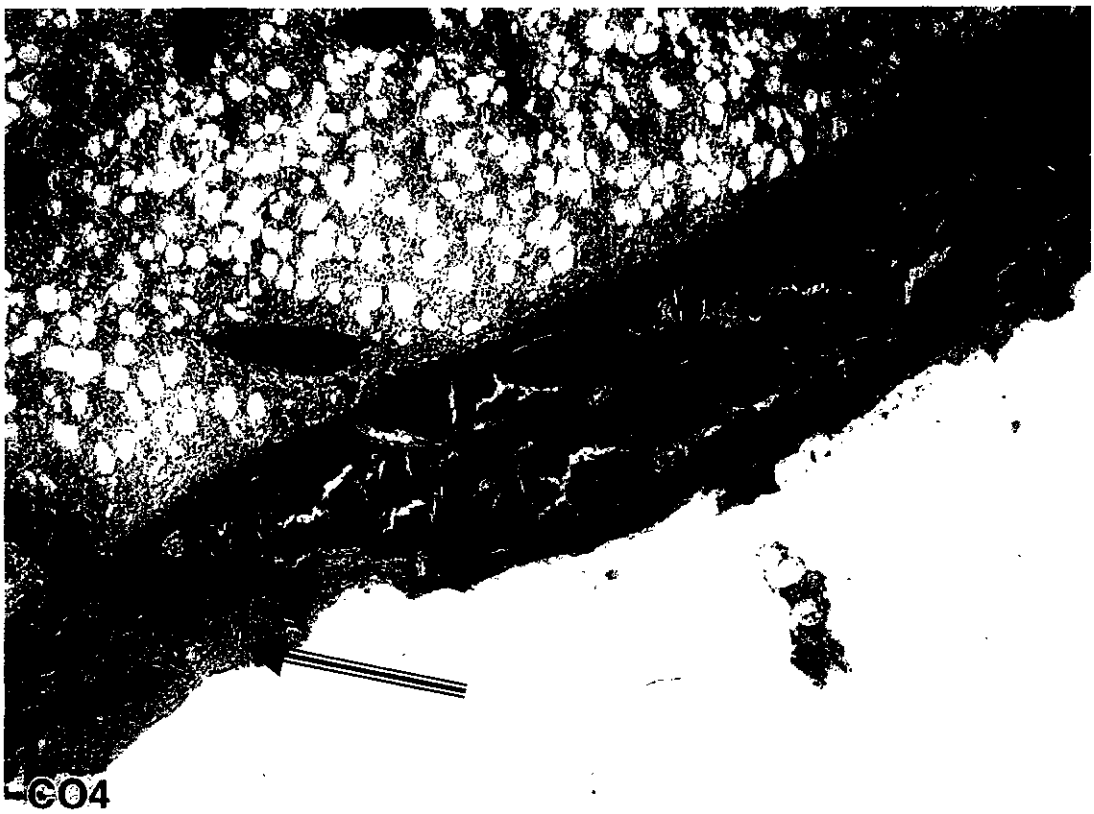


Micrograph of long bone from rat with chronic renal failure administered lanthanum carbonate showing evidence of collagen deposition adjacent to bone (Arrows).

Figure 19: Bone from normal rat with normal renal function showing thickened periosteum.

Dense collagenous periosteal thickening overlying irregular surface of cortical bone of rat with normal renal function given lanthanum . TP= Thickened periosteum.

Figure 20: Bone from normal rat given lanthanum showing destruction of cortical bone with dense fibrocollagenous replacement of bone loss



Dense fibrous tissue replacing areas of bone resorption (arrow) in a rat with normal renal function given lanthanum. The amount of bone resorption and the irregularity of the cortical bone surface is extensive. There is no periosteal or endosteal thickening. This suggests bone damage by lanthanum with replacement fibrosis.

Figure 21: Dense fibrocollagenous periosteal thickening overlying areas of bone loss in a normal rat given lanthanum

Dense fibrocollagenous periosteal thickening overlying irregular surface of cortical bone of rat with normal renal function given lanthanum carbonate.

Figure 22: Vascular fibrocollagenous thickening of periosteum overlying areas of bone loss in a normal rat given lanthanum

Dense fibrocollagenous periosteal thickening overlying irregular surface of cortical bone of rat with normal renal function given lanthanum carbonate. Arrows are in the bone defects resulting from bone loss. Note increased vascularization of periosteum.

Figure 23: Highly vascular thickened periosteum overlying areas of bone loss in a normal rat given lanthanum

: Dense fibrocollagenous periosteal thickening overlying areas of bone loss (arrow) in rat with normal renal function given lanthanum carbonate. The thickened periosteum is highly vascular and has fat cells with granulation tissue suggesting a reparative process to tissue injury.

Figure 24: Exostosis attached to tibia of normal rat given lanthanum

Micrograph of an exostosis (arrow) attached by a muscular pedicle to the metaphysis of a rat with normal renal function given lanthanum carbonate. The "exostosis" is composed of dense hyalinized collagenous tissue and foci of calcification consistent with dystrophic calcification. The etiology of this lesion is not clear.

Figure 25: Uremic rat given lanthanum showing renal osteodystrophy

: Micrograph of rat with chronic renal failure given lanthanum carbonate showing demineralization of the cortex (Long arrow) and irregular cortical surface with bone defects (short arrow) consistent with bone loss.

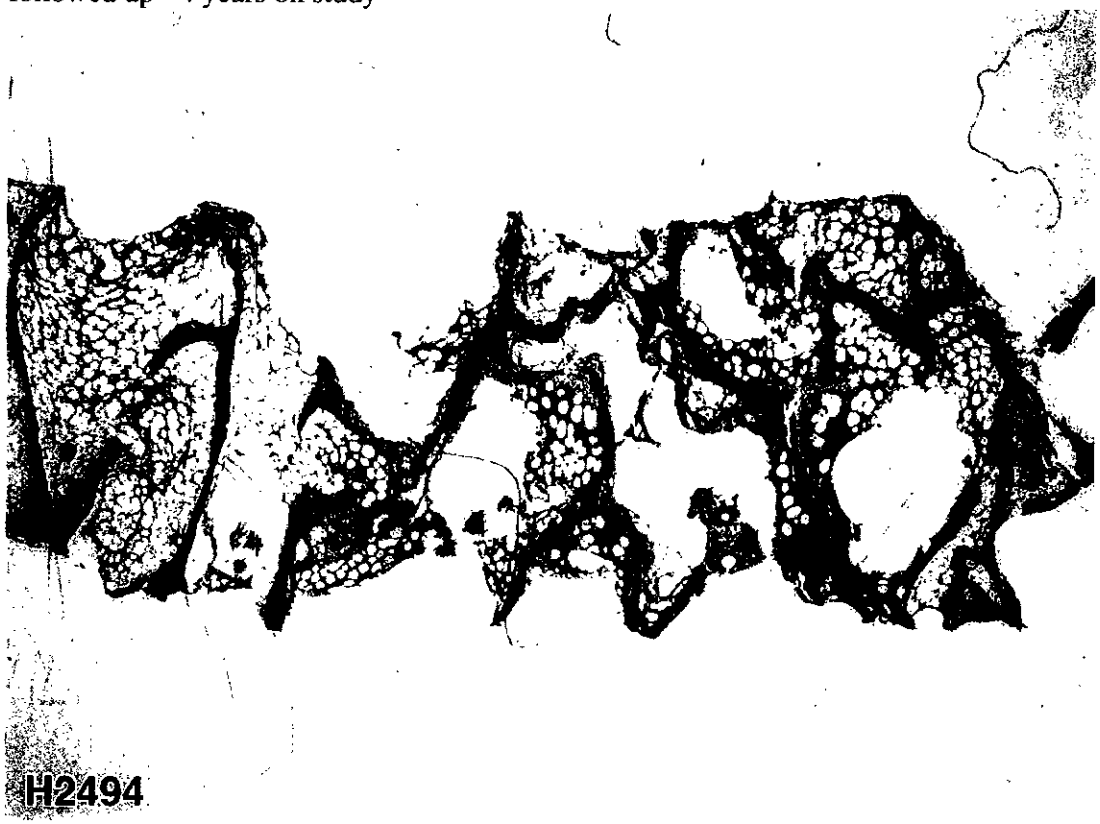
Figure 26: Uremic rat given lanthanum showing renal osteodystrophy

: Micrograph of rat with chronic renal failure given lanthanum carbonate showing demineralization of the cortex (long arrow) and irregular cortical surface with little pits (short arrow) consistent with bone loss.

Figure 27:Microscopic appearance of iliac bone biopsy from a patient after receiving lanthanum for 2 years

Iliac bone biopsy from patient on lanthanum after 2 year follow up. Micrograph shows preparative artifact that is difficult to interpret to the left of field.

Figure 28:Microscopic appearance of iliac bone biopsy from a patient given lanthanum followed up - 4 years on study

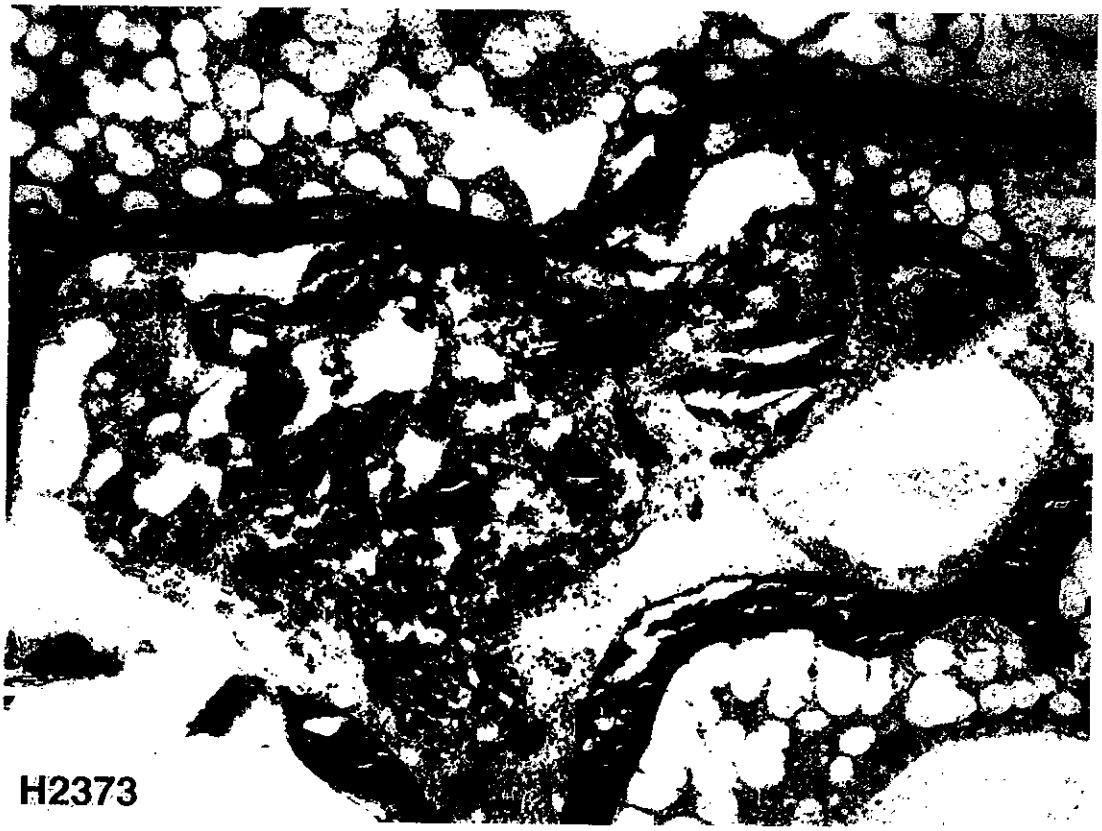


Iliac bone biopsy from patient on lanthanum after 4 years on drug. Micrograph shows extensive thining of bone trabeculae with patchy bone loss. Cellular architecture of marrow is poorly preserved and uninterpretable.

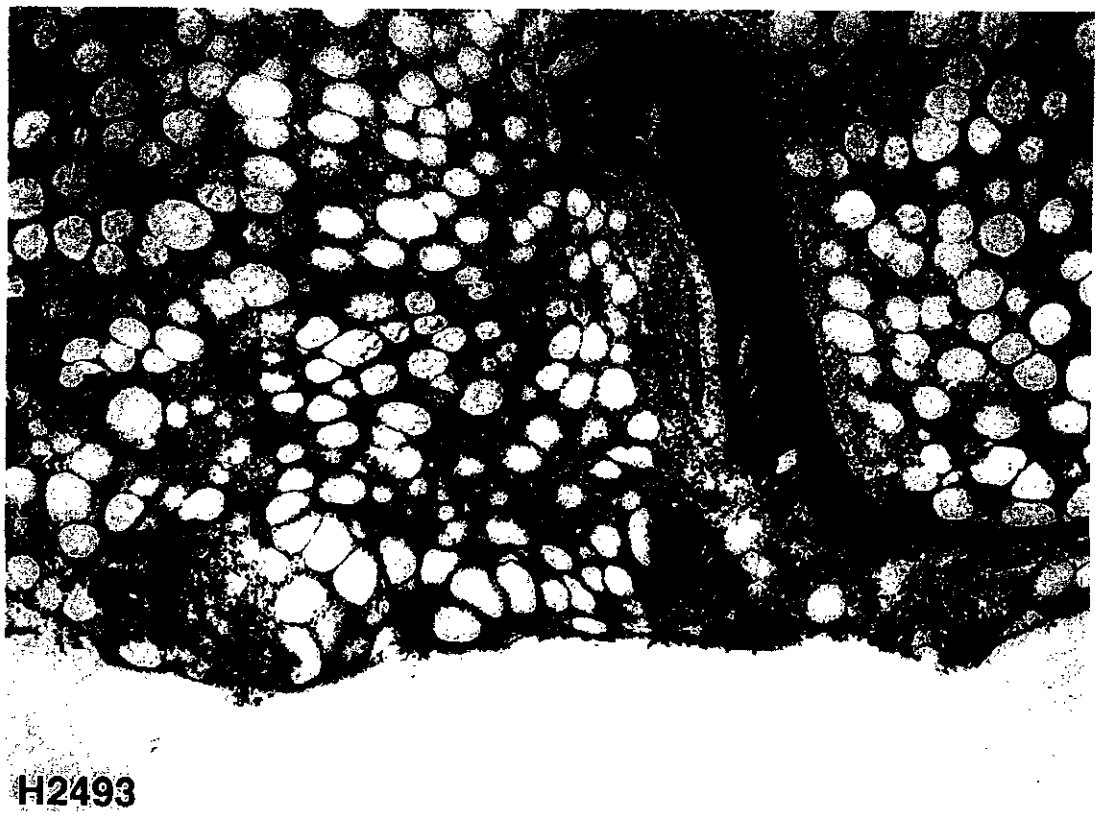
Figure 29:Microscopic appearance of iliac bone biopsy from a patient at baseline given "Calcium" during lanthanum clinical program

Iliac bone biopsy from patient on calcium at baseline. Micrograph shows foci of calcification within marrow that is abnormal. There is also periosteal thickening (arrow). These changes at baseline in a patient treated with Calcium, an unapproved drug, raises the question of using these bone biopsies for comparative purposes in this clinical program. Figure 19 shows a higher power view of one of these foci of calcification in the marrow of this patient.

Figure 30: Higher power view of microscopic appearance of bone at baseline from patient (in Figure 29) given "Calcium" during the lanthanum clinical program.



Iliac bone biopsy from patient on Calcium at baseline. Higher power view of multiple foci of dystrophic calcification in the marrow of patient (arrow) in Figure 26.



Micrograph from a patient on lanthanum for 5 yr on study showing bone loss and dystrophic calcification in the marrow (lower left field).

Appendix Received July 14 2004 : These rates include healthy volunteers exposed to the drug for a few days.

Appendix 5:Fracture rates between treatment groups - 15 month safety update

Type of Analysis	Lanthanum	Standard Therapy
	Patients % (N/n)	Patients % (N/n)
Fracture incidence per 100 patient-years*	4.6 (63/13.68 100 pt years)	5.1 (50/9.77 100 pt years)
Overall fracture rate*	3.6 (63/1754)	5.1 (50/990)
Fracture rate for those with at least 3 months exposure*	5.2 (62/1196)	5.8 (47/811)
Fracture rate for those with at least 6 months exposure*	5.8 (60/1027)	6.2 (45/730)
Overall fracture rate for 301/303/307 combined	3.9 (56/1448)	5.1 (50/990)
Overall fracture rate for 307 only	4.9 (33/680)	7.0 (47/674)

Adjusted % = rate adjusted for patients discontinuation for the corresponding interval;

N= Number of patients who experienced the event;

n=number of patients who were at risk for the event at the start of the interval;

Appendix 6: Fracture rates between treatment groups-25 month safety update

Type of Analysis	Lanthanum	Standard Therapy
	Patients % (N/n)	Patients % (N/n)
Fracture incidence per 100 patient-years*	4.7 (66/14.13 100 pt years)	5.0 (52/10.32 100 pt years)
Overall fracture rate*	3.8 (66/1756)	5.2 (52/992)
Fracture rate for those with at least 3 months exposure*	5.4 (65/1200)	6.0 (49/813)
Fracture rate for those with at least 6 months exposure*	6.1 (63/1033)	6.3 (47/742)
Overall fracture rate for 301/303/307 combined	4.1 (59/1450)	5.2 (52/992)
Overall fracture rate for 307 only	5.3 (36/682)	7.2 (49/676)

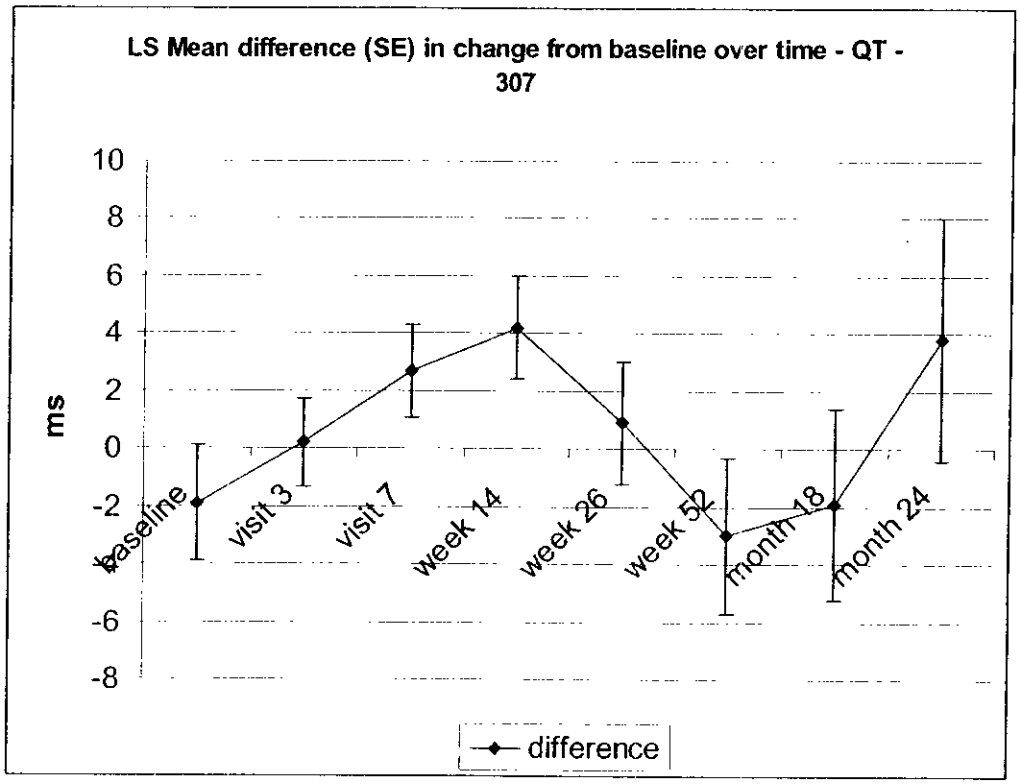
Adjusted % = rate adjusted for patients discontinuation for the corresponding interval;
N= Number of patients who experienced the event;
n=number of patients who were at risk for the event at the start of the interval; * Phase 2-3 studies
Reviewer's comment: Overall fracture rate includes healthy volunteers exposed to the drug for a few days.

Hypercalcemia, hyperparathyroidism and breast cancer

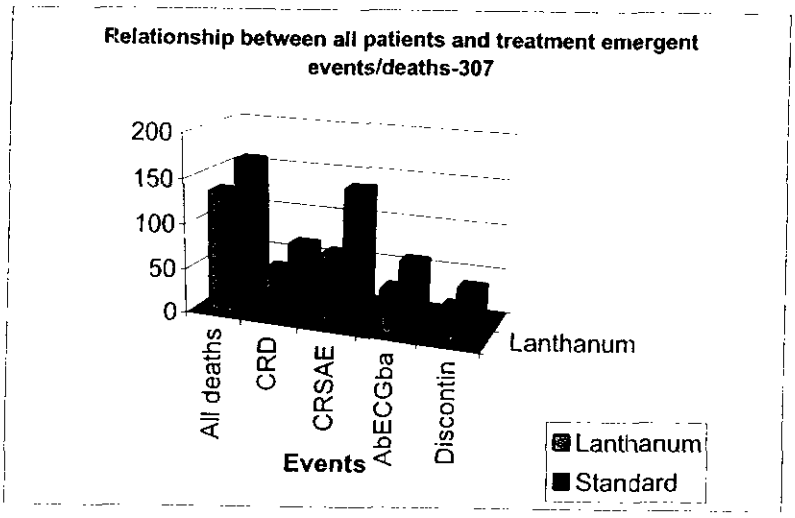
In a case control study conducted in Italy an elevated prevalence of primary parathyroid adenoma was observed among breast cancer patients. Hypercalcemia which has been found in 30-40% of breast cancer patients is the most frequent metabolic complication of breast cancer, and hyperparathyroidism which regulates serum calcium levels is the other most important disorder that induces hypercalcemia. A recent publication on the record linkage study in Sweden analyzed a total number of 9, 835 women who underwent surgery for primary parathyroid adenoma were followed to evaluate the hypothesis of the association between hyperparathyroidism and breast cancer. Preliminary data are available on the coexistence of primary hyperparathyroidism and breast cancer. Secondary hyperthyroidism that occurs in patients with hyperphosphatemia has not been investigated. In this study there were 4 cases of breast cancer and 14 cases of breast lump (Table 46). The parathyroid status of these patients is not known. There are more breast lumps in the patients on lanthanum compared to standard therapy and this is unadjusted but there are equal numbers of breast cancer between both groups. The significance of this reported trend is that patients with breast lumps and cancer should probably be

excluded from therapy that has hypercalcemia as an adverse event as seen in this lanthanum program.(FDA Reference list page 69)

Appendix 7: LS mean diff. change from baseline to 24 months in QT -LAM-IV-307-Reviewer

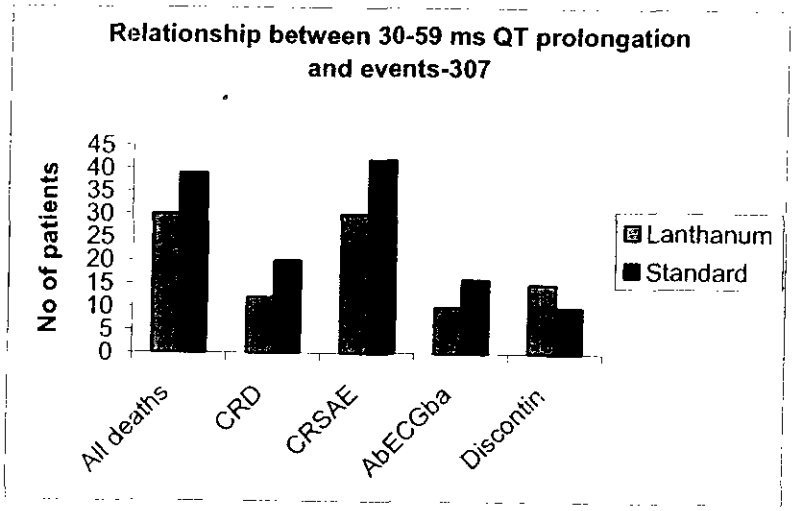


Appendix 8:Relationship between all patients with treatment-emergent QT prolongation and serious adverse events (unadjusted) -307-Reviewer

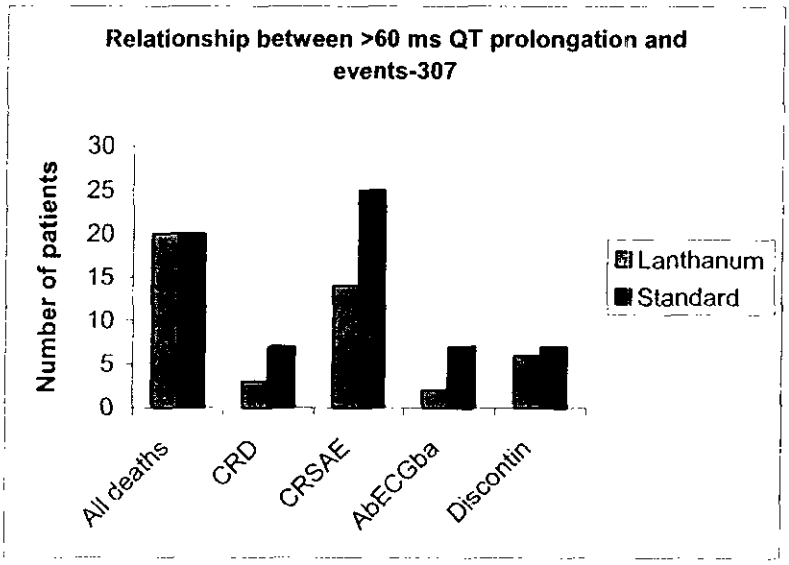


CRD=Cardiac related deaths; CRSAE = Cardiac–related SAE; AbECGba=Abnormal ECG at baseline; Discontin.=Discontinuation. Yaxis=N of patients. Lanthanum front row

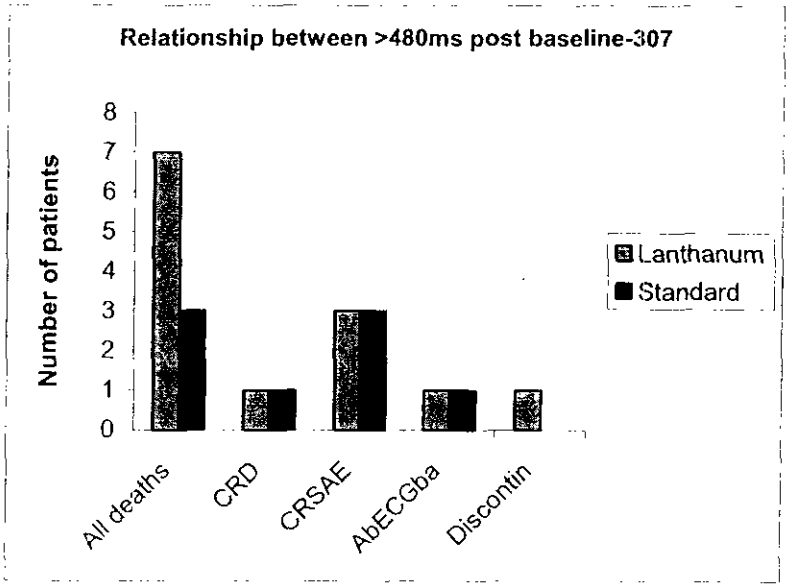
Appendix 9: Relationship between all patients with 30-59ms QT prolongation and events/deaths (unadjusted)-307-Reviewer



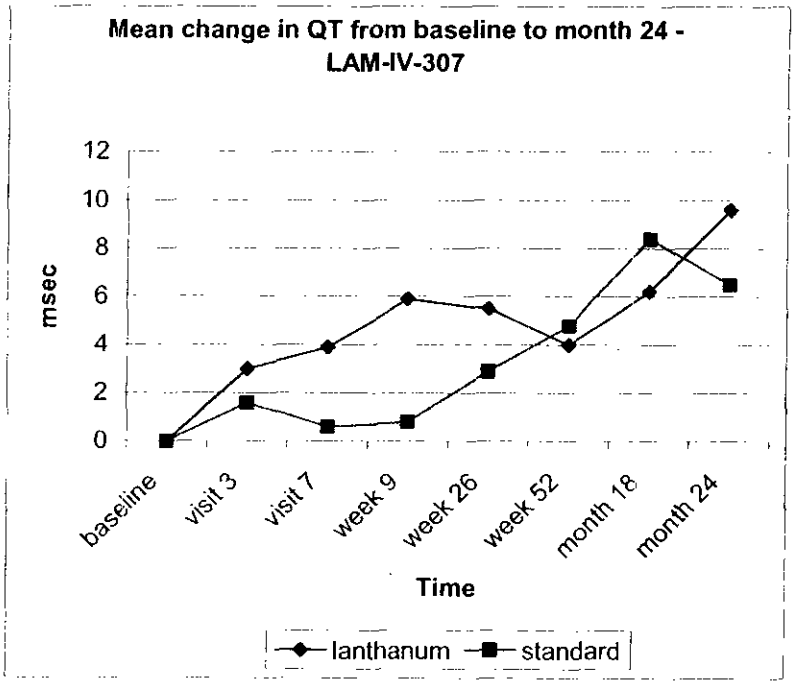
Appendix 10:Relationship between all patients with >60ms QT prolongation and events(unadjusted)-LAM-IV-307-Reviewer



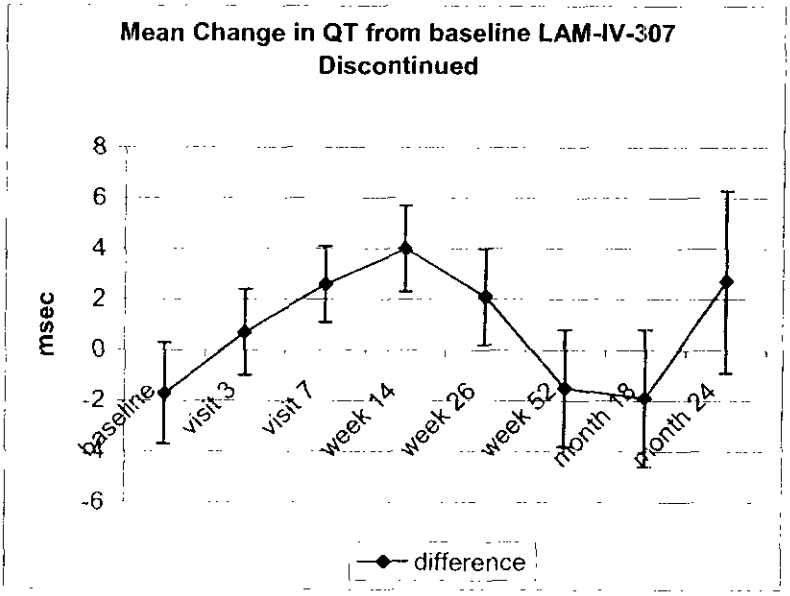
Appendix 11:Relationship between all patients with >480 ms QT post baseline and events(unadjusted)-307-Reviewer



Appendix 12: Time course of Mean QT change from baseline for both treatment groups - LAM-IV-307-Reviewer



Appendix 13: Time course of mean difference in QT change from baseline among discontinued patients -LAM-IV-307-Reviewer



See Appendix 7

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

/s/

Akinwole Williams
7/19/04 08:09:22 PM
MEDICAL OFFICER
Lanthanum review of NDA resubmission

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Secondary Review

NDA: 21-468 (lanthanum carbonate tablets to control hyperphosphatemia in renal failure.

Sponsor: Shire Pharmaceuticals

Review date: 3 February 2003

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Table of contents

List of Tables

List of Figures

1 Source materials

This review is based upon the primary Clinical Pharmacology review (Dr. Dorantes) dated 10 January 2003, the primary Chemistry reviews (Dr. Raman) dated 31 December 2002 and 16 January 2003, the primary Medical review (Dr. Pelayo) dated 31 December 2002, the primary review of Canine Toxicology and Pharmacokinetics (Dr. Koerner) dated 4 December 2002, two primary Statistical Reviews (Dr. Friedlin) dated 5 November 2002 and 6 January 2003, the primary review of Pharmacology and Toxicology (Dr. Joseph) dated 14 January 2003, and the primary Statistical Review of Carcinogenicity (Ms. Choi) dated 15 October 2002.

For completeness, certain studies of pharmacokinetics and pharmacodynamics are briefly reviewed in the appendix, but these studies contribute little to overall understanding of risks and benefits.

APPEARS THIS WAY
ON ORIGINAL

2 Administrative matters

Pediatrics. The sponsor has performed no pediatric studies and requests a waiver of requirements to do so. Since the Pediatric Rule is not in effect, no action is needed.

Financial disclosure. The sponsor categorically denies inappropriate financial arrangements with clinical investigators, as defined under 21 CFR 54.2(a), (b), and (f).

APPEARS THIS WAY
ON ORIGINAL

3 Clinical effectiveness and safety

Dr. Pelayo's review gives a good description of the rationale for treatment. Hemodialysis and dietary restriction are incompletely effective at controlling serum phosphate levels in patients with advanced chronic renal insufficiency. Hyperphosphatemia resulting from reduced excretion of phosphate leads to soft tissue calcification and renal osteodystrophy associated with bone pain, deformities, and fractures. The linkage of these sequelae to hyperphosphatemia is sufficiently strong that serum phosphate level is an acceptable surrogate basis for the approval of agents that control serum phosphate by binding dietary phosphate within the gut.

There is little doubt that lanthanum carbonate (Fosrenol), at doses of 1350 or 2250 mg/day given two or three times per day[1], (doses distinguished from placebo used in one fixed-dose study) is effective in binding phosphate and in controlling levels of serum phosphate. This is shown with statistically significant results (for at least some doses) in three placebo-controlled studies—LAM-IV-302, -202, and -204.

Although the interpretation of long-term studies is difficult because of differential withdrawal, the data suggest that lanthanum carbonate remains effective for many months.

It is also quite likely that lanthanum carbonate is less effective than are other approved (Renagel[2], Phoslo[3]) or unapproved (Tums[4]) drugs employed for phosphate binding[5].

Safety data for lanthanum carbonate come from 1672 subjects with >1 dose at 225 to 3000 mg/day and 909 on other active controls. Of these, 151 subjects received treatment with lanthanum carbonate for >2 years and 155 subjects received treatment with other active drugs for >2 years. Greatly confounding the comparison of safety data from active controls is the higher rate of discontinuation from lanthanum carbonate—15% vs. 7% in phase I studies and 60% vs. 41% in phase III. Adverse events (16% vs. 5%), withdrawal of consent (11% vs. 5%), protocol violations (4% vs. 1%), and "safety criteria" (5% vs. 3%) all contributed to the discrepancy in withdrawal rates on lanthanum carbonate and active controls in phase II-III studies.

Through the end of controlled experience, there were fewer deaths on lanthanum (4.5% in phase III studies) than on controls (9.1%), a difference that was nominally highly statistically significant. In response to a request by DCRDP, a reasonable effort has been made to obtain vital status on all subjects who received at least one dose of study drug or control. As of 20 December 2002, vital status was reported for about 97% of subjects, and the crude mortality rate was 25% on lanthanum carbonate and 21% on active controls, for a crude relative risk of 1.2 (p-value >0.9 by the sponsor's Kaplan-Meier analysis. Figure 1 shows survival data for subjects who participated in Study LAM-IV-307; these data trend in favor of lanthanum carbonate.

---

[1] *This is the dose range distinguished from placebo in one fixed-dose study, LAM_IV-204. Titration studies -302 and -202 used regimens somewhat wider –a few hundred mg to 3 g/day.*

[2] *Sevelamer hydrochloride*

[3] *Calcium acetate*

[4] *Calcium carbonate*

[5] *See figure 15 on page 54 of Dr. Pelayo's review. Control subjects in study LAM-IV-307 were on calcium carbonate (44%), calcium acetate (34%), and sevelamer (17%), but the serum phosphate data are not broken out by treatment. Other calcium carbonate-controlled studies show similar phosphate reduction to lanthanum carbonate*

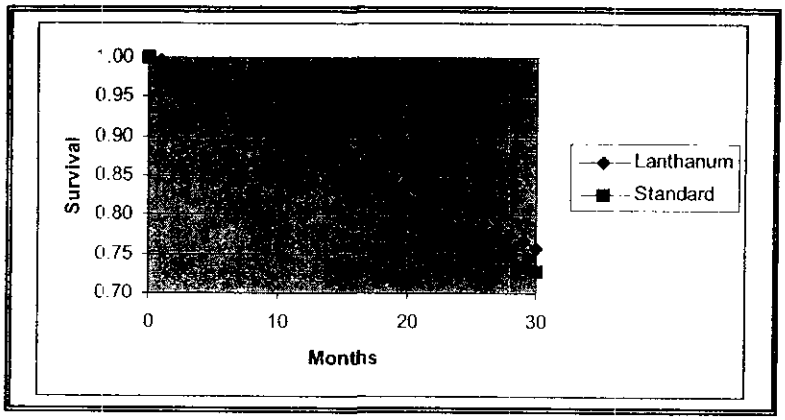


Figure 1. Survival data from Study LAM-IV-307

Reviewer's replot of sponsor's analysis, including contact follow-up for mortality.

How this breaks down for by length of exposure is not given, but the number 1.2 makes no adjustment for the longer exposure on comparators.

A comparison of causes of death for participants in study 307 is shown in Table 1.

Table 1. Causes of death from study LAM-IV-307

	Standard N=642	Lanthanum N=647
Any	24.0%	20.6%
Cardiovascular[6]	11.1%	9.9%
Unknown[7]	3.7%	5.9%
Urinary system	1.7%	1.5%

In short-term, placebo-controlled studies, common adverse events were all more common on lanthanum carbonate. The most common events were nausea (11% vs. 5%), vomiting (9% vs. 4%), graft occlusion (8% vs. 1%), myalgia (7% vs. 4%), abdominal pain (5% vs. 0%), and hypertension, skeletal pain, and anemia (all 3% vs. 0%). These are also crude incidence rates, unadjusted for the lower exposure on lanthanum carbonate[8].

In long-term, active-controlled studies—again without correction for exposure—the most common adverse events were less frequently reported on lanthanum carbonate, as shown in Table 2.

[6] *Includes "CARDIOVASCULAR DISORDERS, GENERAL", "HEART RATE AND RHYTHM DOSORDERS", "MYO ENDO PERICARDIAL & VALVE DISORDERS"*

[7] *Includes "NOT AVAILABLE/ UNKNOWN", "BODY AS A WHOLE - GENERAL DISORDERS"*

[8] *Aside from aforementioned retrospective analysis of mortality, little safety information is available for subjects who withdrew.*

Table 2. Most common adverse events in active control studies[9].

	Control N=909	$La_2(CO_3)_2$ N=1180
Nausea	29%	25%
Vomiting	23%	22%
Diarrhea	22%	17%
Myalgia	20%	14%
Graft complications	23%	13%
Headache	18%	13%
Dyspnea	22%	13%
Graft occlusion	20%	12%
Abdominal pain	17%	12%
Dizziness	19%	12%
Hypotension	18%	12%
Chest pain	16%	11%
Cough	18%	10%

Although there is no formal analysis adjusting for differences in exposure, if one assumes some event is really unrelated to treatment, say, chest pain, then adjusting all the other rates will make nausea and vomiting clearly more common on lanthanum carbonate and most of the other differences will disappear[10].

In contrast, treatment-emergent adverse events leading to withdrawal were more common on lanthanum carbonate than on controls—nausea, vomiting, diarrhea, abdominal pain, etc.

In addition to manifest safety issues, there are other safety issues for which inadequate data exist. Although the intent is to bind phosphate within the gut, in fact some lanthanum carbonate is absorbed and appears in the plasma. How much lanthanum carbonate is bioavailable is not known, and this constitutes a serious deficiency. Absorbed lanthanum does not appear to be dialyzable.

In animals, circulating lanthanum deposits in a wide variety of soft tissues and bone, even with normal renal function. In rats with chronic renal failure, lanthanum carbonate results in decreased bone formation and osteomalacia. Bone biopsies were performed during a 1-year clinical study with lanthanum carbonate ≥750 mg/day, and this study clearly shows the deposition of lanthanum in bone and an increase in bone mineralization lag time, indicating slowed bone formation. Bone fractures were rare in studies, but relatively few subjects underwent long-term treatment, so these data are of limited comfort.

Circulating levels of lanthanum are transiently a few nanomolar, several log-units lower than concentrations known to affect electrophysiological properties of excitable tissues. Gram-per-kilogram oral doses produce nanomolar levels of lanthanum in plasma of dogs[11]; such doses had no effect on QT or RR intervals in dogs. For the most part, this expectation appears to be fulfilled in clinical studies. However, the primary clinical and statistical reviews do note a higher incidence of increases in QTc >60 ms after 2 years.

---

[9] *Adapted from table 4-ISS in the medical officer's review.*

[10] *Dr. Friedlin's original statistical review explains the difficulty of interpreting time-to-event analyses in this setting. Such analyses depend upon censoring being a random event with similar distribution in the different treatment groups. In this case, censoring occurs earlier on lanthanum carbonate, and, without follow-up after withdrawal, earlier censoring protects this group from having later events observed.*

[11] *Dogs with normal renal function exhibited plasma levels of lanthanum only a few-fold higher than did patients with renal failure, so these doses are not as reassuring as they might appear.*

The mean effect in open-label study LAM-IV-307 was between 5 and 10 ms increase compared with active agents, the difference appearing early and not apparently widening over time.

APPEARS THIS WAY
ON ORIGINAL

4 Chemistry

The sponsor seeks approval for 250- and 500-mg chewable tablets.

The proposed proprietary name has been found acceptable by DMETS. Categorical exclusion of the environmental assessment was acceptable. EES review is pending.

Many deficiencies listed in the original chemistry review have now been adequately addressed by the sponsor. The following issues remain open.

- A request to clarify the methods for assay of [ ]
- A request to explain [ ] differences in drug substance manufactured by [ ]
- A request for recent references on the toxicology and biological monitoring of trace metals in humans.
- A request for justification for omitting some testing of drug product used in the manufacture of 500-mg tablets by [ ]
- A request for stability data on 250- and 500-mg tablets manufactured from drug product from [ ]
- A request to name the [ ] in the package insert.

5 Pharmacology

Oral bioavailability of lanthanum carbonate was estimated to be about $5x10^{-7}$ in dogs, but in one animal 2% of a 1 g/kg oral dose was recovered in urine.

During 1-year oral toxicology studies in rats, lanthanum was deposited all along the GI tract, and in liver, lung, heart, bones, and teeth. In dogs, a 4-week oral administration followed by 6 months washout resulted in significant retention of lanthanum in the GI tract (up to 54%), bone (>50%), teeth (29%), liver (82%), and lungs (34%). Lanthanum levels in tissue are much higher than they are in plasma--greater than 10^5 times higher in parts of the gastrointestinal track.

Although single oral (carbonate) and IV (chloride) doses of lanthanum had no effect on canine cardiac hemodynamic and electrophysiological parameters, this study was not considered adequate because of the progressive accumulation of lanthanum in the heart during repeated administration. Studies of repeated administration in the dog were not considered adequate because they lacked a positive control to establish assay sensitivity.

Gene toxicology studies were negative. Two-year carcinogenicity studies in the rat were clean. Non-malignant stomach tumors were seen in the mouse.

Some impaired fertility and embryonic development in the rabbit (but not the rat) was associated with some maternal toxicity in former.

In a chronic renal failure model of the rat, lanthanum carbonate or Renagel were associated with osteomalacia. This was not seen in animals with normal renal function, although levels of lanthanum were similar in bones of normal rats and rats with renal failure. The finding of similar osteomalacia in rats with renal failure treated with either lanthanum carbonate or Renagel suggests that the effect is the result of phosphate binding.

Despite shortcomings of some of the methodology, the Drs. Koerner and Joseph concluded that available safety data supported approval.

6 Biopharmaceutics

As noted previously, orally administered lanthanum carbonate results in unquantified (but small) bioavailability (of lanthanum). Plasma levels rise less than proportionally to dose. Circulating lanthanum is highly protein-bound. Tissue levels of lanthanum can far exceed plasma levels; lanthanum in tissue, particularly bone, persists a very long time.

Elemental lanthanum is obviously not a candidate for any form of metabolism. Neither does it appear to affect activity by various P450 enzymes. Lanthanum is neither a substrate nor an inhibitor of p-glycoprotein transport.

Lanthanum carbonate had no physicochemical interaction with warfarin, digoxin, frusemide, phenytoin, metoprolol, or enalapril.

The following deficiencies are described:

- The proposed dissolution method is acceptable only on an interim basis. The proposed specification for dissolution is not acceptable; the reviewer would like to see — % at — minutes.
- Since clinical studies were performed with the 250-mg tablet, acceptance of the 500-mg tablet will require a demonstration of bioequivalence, or, since the tablets are proportionally similar for each ingredient, a case can be made for a waiver.
- A mass balance study is required.

APPEARS THIS WAY
ON ORIGINAL

7 Summary and recommendations

The biopharmaceutics deficiencies are clearly an adequate basis for considering this application as, at best, "approvable". All of the those deficiencies appear to be remediable, so they are probably not a basis to declare the application "not approvable".

Lanthanum carbonate is effective at binding inorganic phosphate within the gut and thereby controlling plasma phosphate levels in patients with end stage renal disease on dialysis.

Lanthanum carbonate is not particularly well tolerated compared with other treatments for the intended use. However, tolerance is not so poor as to make this an unreasonable product to try, and the marketplace can sort out the appropriate place for a poorly tolerated therapy.

Of more serious safety issues, lanthanum carbonate is associated with slightly higher mortality and slightly increased QT interval.

The mortality effect is particularly difficult to interpret. The estimate has been unstable as the sponsor collected more follow-up data. Few subjects have received lanthanum carbonate for long times, so the effects of lanthanum accumulation are not characterized. And how does one interpret mortality information in subjects who are no longer receiving drug?

The QT prolonging effect of lanthanum carbonate is probably real, but it has not been well characterized, either. Apparently, only the ongoing, open-label study LAM-IV-307 has pertinent data. They show effects developing early in treatment and probably not increasing markedly among subjects exposed for many months. The absolute level of QT prolongation compared with placebo is not known, only that it appears to be 5-10 ms longer than with some other phosphate binders. It is unclear when ECGs were collected relative to peak plasma levels of lanthanum, or if plasma levels of lanthanum relate to QT.

Unlike sevelamer hydrochloride, lanthanum is absorbed and builds up in various tissues, remaining in residence there for a long time. In this respect, it is reminiscent of aluminum salts, now discouraged in patients with renal failure because of effects attributed to tissue accumulation. If lanthanum were as toxic as aluminum, would one know it from the safety data currently available?

We are left, then, with a drug that is effective in controlling hyperphosphatemia associated with advanced renal failure. It is not particularly well tolerated, but this is of no consequence, other than its impact on the quality of long-term safety data. An unknown fraction—perhaps tens or hundreds of milligrams per day—of administered lanthanum is absorbed; its disposition is unknown, but it likely binds to soft tissues, bone, and teeth, because that is what happens in animals. Wherever lanthanum deposits, it likely stays. The clinical consequences of lanthanum absorption, in so far as the data inform us, are none—no compelling increase in mortality, some degree of QT prolongation but no proarrhythmia, no aluminum-like neurotoxicity, no increased incidence of bone fractures.

There are two reasons that the safety data do not provide adequate reassurance.

The first reason is the low power of the safety program, the small number of subjects exposed and the low number of events. If the incidence of mortality or proarrhythmia or neurotoxicity or bone fracture were increased by 50 or 100%, one would have been unlikely to detect them from these data.

The second problem is the progressive deposition of lanthanum makes one expect risk to increase over time, but, because the drug is not well tolerated, long-term safety data are particularly sparse. This problem means that lanthanum carbonate can, at best,

ever be approvable for use for only some fixed time, however far the available safety data support. One can never extrapolate these data to support unlimited, chronic use.

Pending resolution of cited deficiencies in biopharmaceutics, available data support safe and effective use of lanthanum carbonate for the treatment of hyperphosphatemia for a period up to a few weeks. Longer term use should be discouraged because the risk of accumulating lanthanum is not well characterized. Even at that, use in children should be actively discouraged with language more directive than the usual agnosticism.

APPEARS THIS WAY
ON ORIGINAL

Appendix A Studies referenced in primary medical review

The following studies are mentioned, but not reviewed, in the primary medical review.

APPEARS THIS WAY
ON ORIGINAL

A.1 Study LAM-IV-105: A double-blind dose tolerance study to evaluate the safety, pharmacokinetics and pharmacodynamics of a rare earth salt vs. placebo when administered with food in healthy volunteers.

A.1.1 Sites and investigators

LAM-IV-105 was conducted at 1 site in Northern Ireland. The investigator is shown in Table 3.

Table 3. Investigators (Study 105).

Investigator	Location
Johnston Stewart, MB	Belfast, N. Ireland

A.1.2 Background

Protocol amendments: None

Subject enrollment: 4-27 February 1997

A.1.3 Study design

This review is based on the final study report dated 7 March 2001 (vol 1.62).

Subjects were to be healthy males age 18 to 55. In the first part of the study, 14 subjects received placebo or ascending single doses of lanthanum carbonate 0.5 to 9 g[12] every 48 hours. When the highest tolerated dose was identified, placebo or 1/3 of this dose was administered to 12 subjects for 3 days. Dietary phosphate was controlled at <1200 mg/day.

Safety monitoring was conventional. In addition, plasma parathyroid hormone levels were assessed at screening, prior to dosing, and 24 hours after dosing. Plasma levels of lanthanum were measured at baseline and 2, 4, 6, and 24 hours after dosing.

A.1.4 Results

A.1.4.1 Subject demographics & baseline characteristics

All subjects were Caucasian males. The mean age was 31 years.

A.1.4.2 Disposition of subjects

Fourteen subjects enrolled in and completed the ascending dose phase. Twelve of these 14 continued in the 3-day dosing phase; the other two had not received placebo during the ascending dose phase and therefore were not eligible to continue. Of the 12 subjects in part 2, one discontinued early for "personal reasons"

Protocol violations & deviations. Only minor protocol violations were reported.

Concomitant therapies. Given the short duration of the trial no concomitant medications were used during the administration of the study drug.

A.1.4.3 Pharmacokinetics analyses

The highest plasma level recorded for any subject was [redacted] /mL, about 4 times the limit of detection, about 12 hours after the 9-g dose. Population mean plasma levels were never more than about 2 times the limit of detection. In the second part, plasma levels of lanthanum remained about 2 times the limit of detection 6 days after dosing.

---

[12] *These refer to the nominal amount of lanthanum.*

A.1.4.4 Pharmacodynamic effects

Serum sodium and calcium were unaffected by treatment in study part 2. Serum creatinine levels were 98 to 100 μM on placebo and 107 to 110 μM on lanthanum carbonate, a difference that was not, by the sponsor's analysis, statistically significant. Creatinine clearance was about 15% higher on placebo at about 24 hours, but not different by 48 hours. Mean phosphate levels were about 10% lower for about 72 hours after dosing with lanthanum carbonate. Parathyroid hormone levels were about 10% higher after lanthanum administration, for the full 6 days of follow-up. Differences in creatinine clearance, serum phosphate, and parathyroid hormone levels were not statistically significantly different between groups, according to the sponsor's analyses.

Urinary excretion of inorganic phosphate was decreased by two-thirds in the 3 days after administration of lanthanum carbonate, statistically significant by the sponsor's analysis.

A.1.4.5 Safety

Thirteen of 14 subjects reported a total of 125 treatment-emergent adverse events. The most common events were headache, nausea, diarrhea, and abdominal pain, but there was little relationship to dose for any of these.

There were numerous minor abnormalities reported for clinical chemistry, hematology, and urinalysis parameters, none of which appeared to show any relationship to dose.

No safety concerns were manifested in vital signs or physical exams.

A.1.5 Summary

Normal volunteers received ascending single doses of lanthanum carbonate up to 9 g and then 3 g/day for 3 days. The most dramatic effect was a reduction in phosphate excretion, perhaps a result of phosphate binding in the gut, although this is not proven. Lanthanum clearly was absorbed, but the pharmacokinetic analysis was inadequate to assess how much is absorbed or to describe its fate.

A.2 Study LAM-IV-108: A phase I, single centre, randomised, double-blind, placebo controlled, ascending dose study to assess the safety, tolerability, and pharmacokinetics of lanthanum carbonate chewable tablets in healthy male Japanese volunteers.

A.2.1 Sites and investigators

LAM-IV-108 was conducted at 1 site in Japan. The investigator is shown in Table 3.

Table 4. Investigators (Study 108).

Investigator	Location
Takanori Tanaka, MD	Tokyo, Japan

A.2.2 Background

Protocol amendments: Minor changes were made in sampling times.

Subject enrollment: 24 August 1998 to 1 October 1998

A.2.3 Study design

This review is based on the final study report dated 13 February 2001 (vol 1.66).

Subjects were to be healthy males age 20 to 35. Subjects were to receive, at 48-hour intervals, placebo or ascending single oral doses of lanthanum carbonate 250 to 2000 mg[13]. On any given study day, 20% of subjects received placebo. When a subject received placebo on one study day, he received the next highest dose on the next study day. There was no clearly defined primary end point.

Conventional safety monitoring was performed. Pharmacokinetic data were obtained to 12 hours after dosing.

A.2.4 Results

A.2.4.1 Subject demographics & baseline characteristics

All 10 subjects were Japanese males. The mean age was 24 years.

A.2.4.2 Disposition of subjects

All 10 subjects completed all phases of study.

Protocol violations & deviations. No protocol violations were reported.

Concomitant therapies. No concomitant medications were allowed.

A.2.4.3 Pharmacokinetics analyses

Plasma lanthanum pharmacokinetic parameters are shown in Table 5.

Table 5. Pharmacokinetic data (Study 108)

	Placebo	250 mg	500 mg	1000 mg	2000 mg
AUC(0-12h) ng-h/mL	1.1	2.4	3.0	4.0	5.5
Cmax ng/mL					
Tmax h					

Clearly, AUC and Cmax rose less than proportionally with dose. Plasma half-life is not described, but for higher doses, there was substantial carryover at 48 hours.

---

[13] *These refer to the nominal amount of lanthanum*

Twenty-four hour urinary excretion of lanthanum rose with dose, from [redacted] µg at 250 mg to [redacted] µg at 2000 mg, accounting for no more than one part per million of administered dose in the first 24 hours after dosing.

A.2.4.4 Pharmacodynamic effects

Blood levels of inorganic phosphate and calcium were not significantly different among doses. There was a trend for reduced urinary excretion of inorganic phosphate.

A.2.4.5 Safety

Four subjects reported 11 adverse events, 4 after placebo and 4 after the 2-g dose. Nausea and diarrhea were each reported 3 times (once each on placebo). Neither total events nor any individual event appeared to be dose-related.

Various minor laboratory abnormalities were reported.

Vital signs were not much affected. There were no reported abnormalities on physical exam.

A.2.5 Summary

Ten normal volunteers received ascending single doses of lanthanum carbonate up to 2 g. The study did not show an effect on binding of phosphate. Lanthanum clearly was absorbed, but the pharmacokinetic analysis was inadequate to assess how much is absorbed or to describe its fate.

A.3 Study LAM-IV-109: 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.

A.3.1 Sites and investigators

LAM-IV-109 was conducted at 1 site in Japan. The investigator is shown in Table 3.

Table 6. Investigators (Study 109).

Investigator	Location
Takanori Tanaka, MD	Tokyo, Japan

A.3.2 Background

Protocol amendments: None after the start of enrollment

Subject enrollment: 22 June 1999 to 27 July 1999

A.3.3 Study design

This review is based on the final study report dated 19 February 2001 (vol 1.68).

Subjects were to be healthy males age 20 to 35. Subjects were to receive placebo (n=3) or lanthanum carbonate 1 g[14] three times per day for 5 days. Each dose was to be taken after a meal. Subjects remained in clinic for 8 days. Plasma samples for lanthanum levels were obtained at 2, 4, 6, 8, 12, 24, 32, 48, 54, and 78 hours after the last dose. Twenty-four hour pooled urine samples were collected from the day before dosing through day 8. No primary end point was clearly identified

Conventional safety monitoring was performed.

A.3.4 Results

A.3.4.1 Subject demographics & baseline characteristics

All 9 subjects were Japanese males. The mean age was 23 years.

A.3.4.2 Disposition of subjects

All 9 subjects completed the study.

Protocol violations & deviations. No significant protocol violations were reported.

Concomitant therapies. No concomitant medications were allowed.

A.3.4.3 Pharmacokinetics analyses

Plasma levels of lanthanum are shown in Figure 2.

[1] *This dose refers to the amount of elemental lanthanum.*

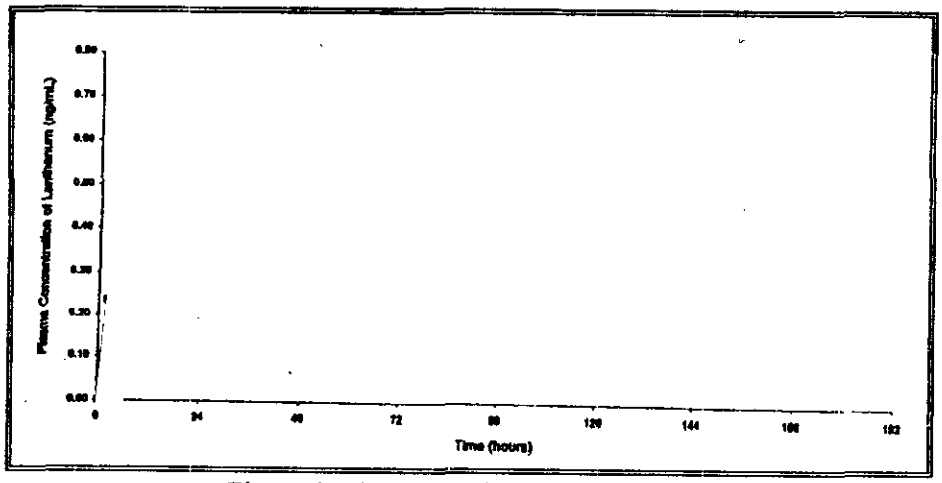


Figure 2. Plasma lanthanum (Study 109)

Figure from sponsor's vol 1.68, page 6-106.

The sampling was inappropriate for tid dosing; peak plasma levels are not likely to be represented in these data. Plasma levels of lanthanum continue to rise throughout 5 days of dosing. The initial half-life is described as about 7 hours, but the terminal half-life is >1 day.

Urinary excretion of lanthanum climbed during administration and generally mirrored plasma levels of lanthanum. Total urinary recovery of lanthanum amounted to <1 part per million of the administered dose, but this study does not establish that this represents all of the absorbed lanthanum.

A.3.4.4 Pharmacodynamic effects

Urinary excretion of phosphate and creatinine clearance are described in Table 7.

Table 7. Urinary phosphate excretion, creatinine clearance (Study 109)

	Phosphate excretion		Creatinine clearance	
	Placebo N=3	Lanthanum N=6	Placebo N=3	Lanthanum N=6
Baseline	0.72	0.68	143	121
Day 2	0.56	0.34	145	132
Day 3	0.62	0.24	143	133
Day 4	0.63	0.20	153	126
Day 5	0.60	0.22	154	135
Day 6	0.63	0.21	147	132

Phosphate excretion was reduced by about two-thirds in the lanthanum group, highly statistically significant by the sponsor's analysis, while creatinine clearance was not much affected.

A.3.4.5 Safety

No adverse events were reported.

Various minor laboratory abnormalities were reported, similar on active drug and placebo.

Vital signs were not much affected. There were no reported abnormalities on physical exam.

A.3.5 Summary

Six normal male volunteers received lanthanum carbonate 1 g tid, with no apparent safety issues. The study showed a substantial effect on urinary excretion of phosphate. Lanthanum clearly was absorbed, but the pharmacokinetic analysis was inadequate to assess how much is absorbed or to describe its fate.

A.4 Study LAM-IV-110: A phase I, single centre, open-label, randomised, three-way crossover study comparing the phosphate ion binding of lanthanum carbonate chewable tablets when administered before, during, or after food in healthy subjects.

A.4.1 Sites and investigators

LAM-IV-110 was conducted at 1 site in Northern Ireland. The investigator is shown in Table 3.

Table 8. Investigators (Study 110).

Investigator	Location
AJ Stewart, MB	Belfast, Northern Ireland

A.4.2 Background

Protocol amendments: The "before food" treatment period was dropped.

Subject enrollment: 19 August 1999 to 2 September 1999

A.4.3 Study design

This review is based on the final study report dated 24 January 2001 (vol 1.70).

Subjects were to be healthy males age 18 to 55. On the first study day, subjects received lanthanum carbonate 1 g[15] 30 minutes before a meal. Because this was poorly tolerated, the "before food" treatment period was dropped. Subjects received, in random order, thrice daily doses of lanthanum carbonate 1 g either with food or 30 minutes after food, for 3 days beginning on days 4 and 10. Subjects were maintained in clinic on a diet with <1200 mg phosphate. Alcohol, caffeine, and fruit juices were prohibited.

Daily urinary phosphate and creatinine excretion was measured for 4 days in each period. Serum creatinine was assessed at baseline and 12 and 24 hours after each dose. Plasma levels of lanthanum were measured frequently on the first day of dosing, and once each on days 2 and 3.

Conventional safety monitoring was performed.

A.4.4 Results

A.4.4.1 Subject demographics & baseline characteristics

Thirty-six subjects enrolled. Twenty-three were males. All were Caucasian. The mean age was 25 years; the range was 18 to 44 years.

A.4.4.2 Disposition of subjects

All but 1 subject completed the study. One subject withdrew after the first dose because of difficulties with phlebotomy.

Protocol violations & deviations. A variety of minor protocol violations were reported, most commonly relating to timing of blood sampling.

Concomitant therapies. No concomitant medications were allowed.

A.4.4.3 Pharmacokinetics analyses

Plasma levels of lanthanum are shown in Figure 3.

---

[15] *The dose refers to the amount of elemental lanthanum*

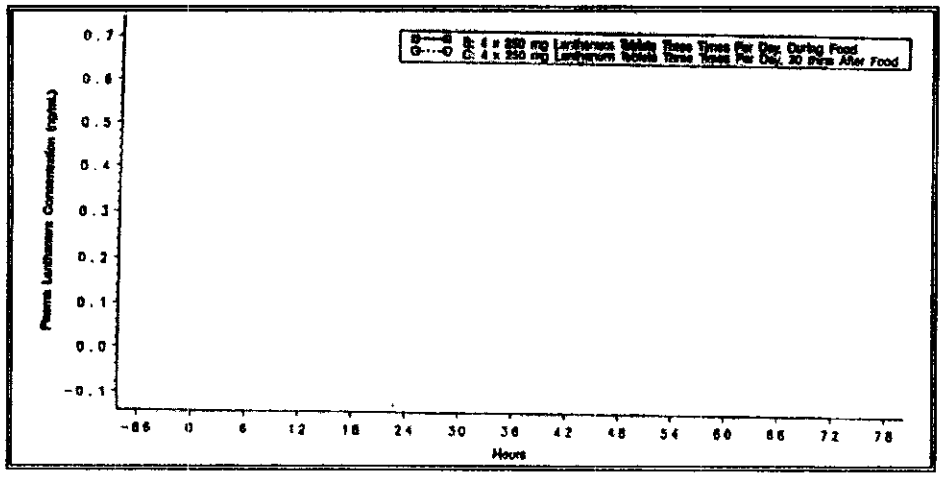


Figure 3. Plasma lanthanum levels (Study 110)

Plasma levels were only measured at time points where data are shown. Peak levels were likely missed.

Plasma levels were slightly higher when lanthanum carbonate was administered 30 minutes after food.

A.4.4.4 Pharmacodynamic effects

Average daily urinary excretion of phosphate was reduced by about 9% when lanthanum was administered with food, compared with administration 30 minutes after food. This difference was statistically significant by the sponsor's analysis.

Creatinine clearance values were generally unchanged from baseline throughout both study periods.

A.4.4.5 Safety

Adverse events, mostly headache, were reported by 50% of subjects after the test dose taken before food. One-third of subjects reported adverse events when lanthanum was administered with or after food. The most common events were headache (19%) and nausea (17%), other events being reported by 3 or fewer subjects. No events were rated as serious.

Various minor laboratory, ECG, physical exam abnormalities were reported.

A.4.5 Summary

Thirty-six normal male and female volunteers received lanthanum carbonate 1 g tid for 3 days, during or after meals, with no apparent safety issues. The study showed a substantial effect on urinary excretion of phosphate. Higher plasma levels of lanthanum and less of a reduction in phosphate excretion were associated with administration after food. Lanthanum clearly was absorbed, but the pharmacokinetic analysis was inadequate to assess how much is absorbed or to describe its fate.

A.5 Study LAM-IV-111: A pharmacokinetic study in healthy volunteers and dialysis patients following single and multiple doses of lanthanum.

A.5.1 Sites and investigators

LAM-IV-111 was conducted at 1 site in the US. The investigator is shown in Table 3.

Table 9. Investigators (Study 111).

Investigator	Location
Marshall Sack, MD	Austin, TX

A.5.2 Background

Protocol amendments: There was one amendment after the start of enrollment, intended to get lanthanum levels assessed in dialysis membranes. However, these data were not obtained

Subject enrollment: 21 December 2000 to 24 July 2001

A.5.3 Study design

This review is based on the final study report dated 11 January 2002 (vol 1.73).

Eight subjects were to be healthy males or females age 18 or older. Eight subjects were to be receiving chronic hemodialysis at least 3 times per week. Dialysis subjects were restricted from use of phosphate binders or calcium supplements (unless hypocalcemic, and then calcium was to be administered at bedtime). All subjects were to receive a single dose of lanthanum carbonate 1 g[16] and blood and urine samples were obtained during the following 48 hours. Two weeks later, subjects received a single dose of lanthanum carbonate 1 g, with dialysis subjects getting hemodialysis 4-8 hours after dosing, and only dialysis subjects getting blood and urine sampling over 48 hours. All subjects then received lanthanum carbonate 1 g tid for 11 days with the final dose 4 to 8 hours prior to hemodialysis. Blood and urine samples were collected for 72 hours after the last dose.

Conventional safety monitoring was performed.

A.5.4 Results

A.5.4.1 Subject demographics & baseline characteristics

Eight control subjects and ten dialysis subjects enrolled. Two dialysis subjects were withdrawn and replaced, so reported analyses are based on 8 subjects per cohort. The mean age was 49 in the control group and 48 in the dialysis group. Six of 8 control group subjects were Caucasian, while only 1 of 10 was Caucasian in the dialysis group. Sixty-one percent were males, not much different between groups.

A.5.4.2 Disposition of subjects

Sixteen of 18 subjects completed the study. One dialysis subject was withdrawn from the multiple-dose phase because of itching and nausea. One dialysis subject was withdrawn from the multiple-dose phase to undergo renal transplant.

Protocol violations & deviations. Compliance was good. Other than the two withdrawals, no significant protocol violations were reported.

Concomitant therapies. Concomitant medications were not discussed.

---

[16] *This dose refers to the amount of elemental lanthanum.*

A.5.4.3 Pharmacokinetics analyses

The sponsor's analyses of pharmacokinetic parameters are summarized in Table 10.

Table 10. Pharmacokinetic parameters (Study 111)

	Single dose without dialysis		Single dose with dialysis	Multiple dose	
	Normal	Renal failure	Renal failure	Normal	Renal failure
AUC ng-h/mL	1.1	3.1	6.4	11.0	31.0
Cmax ng/mL	0.18	0.30	0.56	0.42	1.1
Tmax h	4.1	4.9	5.6	5.5	9.5

Accumulation (Cmax) over 10 days was about 2-fold in normal subjects and 3- to 4-fold in subjects on dialysis. The 2-fold increase in Cmax when dosing in renal failure subjects was followed by dialysis defies explanation[17].

Four subjects in the dialysis group produced urine, one of whom was a high outlier for urinary lanthanum (about 10 times the mean for control subjects, but still only about 10^{-7} of administered dose).

Although some lanthanum appeared in dialysis fluid, the large volume and low concentration probably did not yield a reliable estimate of the amount of lanthanum removed in that manner.

A.5.4.4 Pharmacodynamic effects

No data were collected.

A.5.4.5 Safety

Fourteen out of 18 subjects reported a total of 59 adverse events. The most common were headache (n=10), vomiting (n=6), and nausea (n=4). Events in general were only marginally more common among dialysis subjects than normal controls. The two events leading to withdrawal (transplant and nausea plus itching) were the only events described as serious.

Various minor laboratory abnormalities were reported. The most intriguing are hepatic enzyme elevations in two normal subjects, shown in Table 11.

Table 11. Hepatic enzyme elevations (Study 111)

	Subject 07 58 y old obese Cauc male			Subject 17 39 y old Hispanic male		
	AlkP	ALT	AST	AlkP	ALT	AST
Screen	104	29	14	82	14	18
Day 1	111	25	23	76	10	15
End multi-dose	120	77	51	161	56	40
+ 2 days	109	60	32	—	—	—
+ 3 days	—	—	—	130	50	33
+ 5 days	—	—	—	133	72	59

No further follow-up or explanation is available.

---

[17] *In normal subjects, accumulation was about 2-fold. For renal failure subjects, it is also about 2-fold compared with the "single dose with dialysis" value. So perhaps it is the single-dose, renal failure without dialysis data that are anomalous*

Vital signs were not much affected. There were no reported abnormalities on physical exam.

A.5.5 Summary

Eight normal volunteers and 10 subjects on chronic renal dialysis received lanthanum carbonate 1 g tid for up to 11 days. Two dialysis subjects discontinued for adverse events, one of which was plausibly treatment related. Two normal volunteers experienced poorly characterized minor elevations in hepatic enzymes. Lanthanum clearly was absorbed, but the pharmacokinetic analysis was inadequate to assess how much is absorbed or to describe its fate. Lanthanum also appears in dialysate, but plasma levels of lanthanum are several-fold higher in subjects on hemodialysis.

APPEARS THIS WAY
ON ORIGINAL

A.6 Study LAM-IV-112: A phase I, single-centre, open-label, randomised, three way crossover study to assess the effects of co-administration of citrate on the systemic absorption of lanthanum following a single oral dose.

A.6.1 Sites and investigators

LAM-IV-112 was conducted at 1 site in the UK. The investigator is shown in Table 3.

Table 12. Investigators (Study 112).

Investigator	Location
S Febbraro, MD	Merthyr Tydfil, UK

A.6.2 Background

Protocol amendments: Changes were made in the analytical methods to deal with lanthanum contamination of plasma samples. For unclear reasons, planned analyses of urinary lanthanum levels were not conducted.

Subject enrollment: October to December 2000

A.6.3 Study design

This review is based on the final study report dated 4 December 2001 (vol 1.75).

Subjects were to be healthy males or females age 18 to 55. In random order on study days separated by 2 weeks, subjects received single dose of lanthanum carbonate 1 g[18], alone, with orange juice 200 mL, or with Effercitrate (3 g potassium citrate plus 0.5 g citric acid), in each administered 5 minutes after a low-phosphate breakfast. Blood samples for lanthanum were obtained frequently during the first 24 hours, then less frequently to day 6.

Conventional safety monitoring was performed.

A.6.4 Results

A.6.4.1 Subject demographics & baseline characteristics

Twenty-five subjects, 12 males, mean age of 34, enrolled.

A.6.4.2 Disposition of subjects

One subject withdrew after the first dose, with no reason provided.

Protocol violations & deviations. No significant protocol violations were reported.

Concomitant therapies. Seven subjects received paracetamol for headache.

A.6.4.3 Pharmacokinetics analyses

Plasma levels of lanthanum are shown in Figure 4.

[18] *This dose refers to the amount of elemental lanthanum*

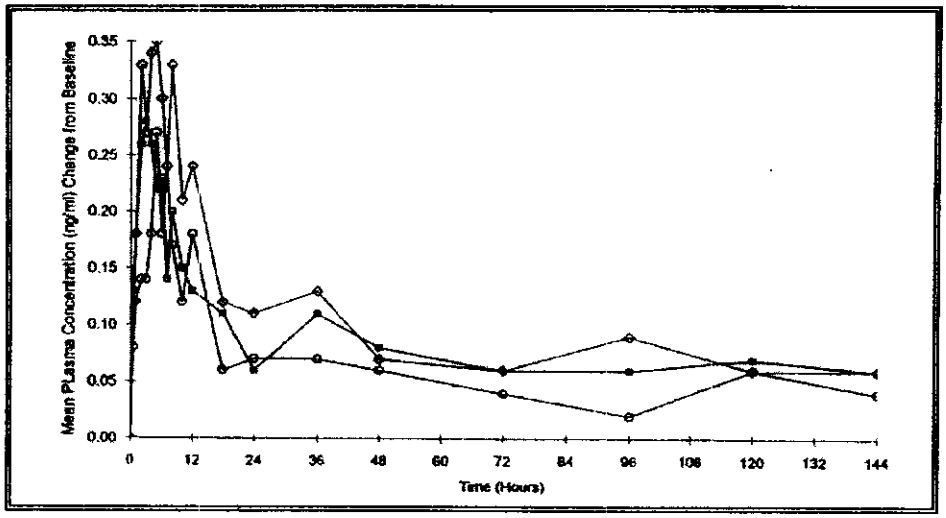


Figure 4. Plasma levels of lanthanum (Study 112)

Lanthanum carbonate alone is shown as circles. Treatment with orange juice is shown as squares. Treatment with potassium citrate is shown as diamonds.

Peak plasma levels ranged from 0.38 (alone) to 0.52 ng/mL (with potassium citrate). The AUC_{0-72} ranged from 6 (alone) to 9 ng-h/mL (with potassium citrate). By the sponsor's analyses, both AUC and Cmax met criteria for bioequivalence of the 3 regimens.

A.6.4.4 Pharmacodynamic effects

No data were collected.

A.6.4.5 Safety

Fifteen out of 25 subjects (60%) reported a total of 40 adverse events, 8 subjects receiving lanthanum alone, 12 subjects with orange juice, and 3 subjects with potassium citrate. The most common were headache (14 events), nausea (9 events) and vomiting (4 events). One episode of vomiting was considered severe.

Subject 121 was a 48-year old female with an unremarkable history and physical exam. She contributed a total of 12 adverse events. She reported headache 3 hours after dosing with lanthanum carbonate alone, headache, nausea, and vomiting after lanthanum plus orange juice, and headache, nausea, and vomiting after lanthanum plus potassium citrate. She was reported to have anemia and thrombocytosis (already high at 495 /nL at baseline, as high as 560 /nL during study), for which she was referred to her physician for further follow-up.

Vital signs were not much affected. There were few reported abnormalities on physical exam. There were no clinically significant effects on laboratory parameters.

A.6.5 Summary

Twenty-five subjects received single oral doses of lanthanum carbonate, alone, with orange juice, and with potassium citrate. Plasma levels of lanthanum carbonate were not much different in the three cases. However, this does not establish the effect of dietary citrate on the ability of lanthanum carbonate to bind phosphate in the gut.

A.7 Study LAM-IV-113: 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.

A.7.1 Sites and investigators

LAM-IV-113 was conducted at 1 site in the UK. The investigator is shown in Table 3.

Table 13. Investigators (Study 113).

Investigator	Location
Jörg Täubel, MD	London, UK

A.7.2 Background

Protocol amendments: There were no amendments after the start of enrollment.

Subject enrollment: February to March 2001

A.7.3 Study design

This review is based on the final study report dated 9 August 2001 (vol 1.113).

Subjects were to be healthy *Caucasian* males age 18 to 35. In random order, subjects received a single oral dose of warfarin 10 mg alone or 30 minutes after the fourth of 4 doses of lanthanum carbonate 1 g[19] tid. Blood samples for warfarin were obtained during the following 7 days. Two weeks were scheduled between crossover periods. During 4 days in clinic, subjects were maintained on a low-phosphate diet.

Conventional safety monitoring was performed.

A.7.4 Results

A.7.4.1 Subject demographics & baseline characteristics

Fourteen male subjects were enrolled. The mean age was 24.

A.7.4.2 Disposition of subjects

All 14 subjects completed the study.

Protocol violations & deviations. No significant protocol violations were reported.

Concomitant therapies. Concomitant medications were not discussed.

A.7.4.3 Pharmacokinetics analyses

The sponsor's analyses of pharmacokinetic parameters are summarized in Table 14.

Table 14. Pharmacokinetic parameters for warfarin (Study 113)

	R-warfarin		S-warfarin	
	Warfarin alone	Warfarin + lanthanum	Warfarin alone	Warfarin + lanthanum
AUC µg-h/mL	31	30	19	18
Cmax ng/mL	558	557	538	541
$T_{1/2}$ h	45	45	32	31
Tmax h	3.0	3.3	2.7	2.8

[19] *This dose refers to the amount of elemental lanthanum.*

The pharmacokinetic properties of warfarin were not materially affected by the administration of lanthanum carbonate 1g tid.

There are no pharmacokinetic data for lanthanum.

A.7.4.4 Pharmacodynamic effects

No data were collected.

A.7.4.5 Safety

Two subjects reported 5 adverse events (4 by one subject), the most serious of which was one episode of vasovagal syncope.

Vital signs were not much affected. There were no reported abnormalities on physical exam.

A.7.5 Summary

Fourteen normal volunteers received warfarin 10 mg alone and after the fourth dose of lanthanum carbonate 1 g tid. Pharmacokinetic properties of warfarin were not much affected by co-administration of lanthanum carbonate.

A.8 Study LAM-IV-114: A phase I, single centre, open label, randomised, crossover study to assess the effects of lanthanum carbonate on the pharmacokinetic parameters of digoxin, following a single oral dose.

A.8.1 Sites and investigators

LAM-IV-114 was conducted at 1 site in the UK. The investigator is shown in Table 3.

Table 15. Investigators (Study 114).

Investigator	Location
Jörg Täubel, MD	London, UK

A.8.2 Background

Protocol amendments: There were no important amendments after the start of enrollment.

Subject enrollment: 13 to 31 March 2001

A.8.3 Study design

This review is based on the final study report dated 21 September 2001 (vol 1.116).

Subjects were to be healthy *Caucasian* males age 18 to 35. In random order, subjects received a single oral dose of digoxin 0.5 mg alone or 30 minutes after the fourth of 4 doses of lanthanum carbonate 1 g[20] tid. Blood samples for digoxin were obtained during the following 4 days. Two weeks were scheduled between crossover periods. During 4 days in clinic, subjects were maintained on a low-phosphate diet.

Conventional safety monitoring was performed.

A.8.4 Results

A.8.4.1 Subject demographics & baseline characteristics

Fourteen male subjects were enrolled. The mean age was 23.

A.8.4.2 Disposition of subjects

All 14 subjects completed the study.

Protocol violations & deviations. No significant protocol violations were reported.

Concomitant therapies. Concomitant medications were not discussed.

A.8.4.3 Pharmacokinetics analyses

The sponsor's analyses of pharmacokinetic parameters are summarized in Table 14.

[20] *This dose refers to the amount of elemental lanthanum.*

Table 16. Pharmacokinetic parameters for digoxin (Study 114)

	Digoxin alone	Digoxin + lanthanum
AUC[21] ng-h/mL	7.7	9.1
Cmax ng/mL	2.0	2.2
$T_{1/2}$ h	11	15
Tmax h	1.5	1.5
B	0.20	0.16

The pharmacokinetic properties of digoxin were not materially affected by the administration of lanthanum carbonate 1g tid.

There are no pharmacokinetic data for lanthanum.

A.8.4.4 Pharmacodynamic effects

No data were collected.

A.8.4.5 Safety

Four subjects reported 4 adverse events, none of which was serious, and only one of which was described as severe (headache).

Vital signs were not much affected. There were no reported abnormalities on physical exam.

A.8.5 Summary

Fourteen normal volunteers received digoxin 0.5 mg alone and after the fourth dose of lanthanum carbonate 1 g tid. Pharmacokinetic properties of digoxin were not much affected by co-administration of lanthanum carbonate.

[21] *This value is AUC_{last}. The extrapolated tails of the $AUC_{0-\infty}$ comprised >20% in some subjects, making these estimates unreliable.*

A.9 Study LAM-IV-115: A phase I, single centre, open label, randomised, crossover study to assess the effects of lanthanum carbonate on the pharmacokinetic parameters of metoprolol, following a single oral dose.

A.9.1 Sites and investigators

LAM-IV-115 was conducted at 1 site in the UK. The investigator is shown in Table 3.

Table 17. Investigators (Study 115).

Investigator	Location
Jörg Täubel, MD	London, UK

A.9.2 Background

Protocol amendments: There were no important amendments after the start of enrollment.

Subject enrollment: 3 to 12 April 2001

A.9.3 Study design

This review is based on the final study report dated 14 September 2001 (vol 1.118).

Subjects were to be healthy *Caucasian* males age 18 to 35. In random order, subjects received a single oral dose of metoprolol 100 mg alone or 30 minutes after the fourth of 4 doses of lanthanum carbonate 1 g[22] tid. Blood samples for metoprolol were obtained during the following 2 days. Three days were scheduled between crossover periods.

Conventional safety monitoring was performed.

A.9.4 Results

A.9.4.1 Subject demographics & baseline characteristics

Fourteen male subjects were enrolled. The mean age was 24.

A.9.4.2 Disposition of subjects

Twelve of 14 subjects completed the study. Two subjects failed to return to clinic on the correct day for the second crossover period; they were dropped from pharmacokinetic analyses.

Protocol violations & deviations. No significant protocol violations were reported.

Concomitant therapies. Concomitant medications were not discussed.

A.9.4.3 Pharmacokinetics analyses

The sponsor's analyses of pharmacokinetic parameters are summarized in Table 14.

Table 18. Pharmacokinetic parameters for metoprolol (Study 115)

	Metoprolol alone	Metoprolol + lanthanum
AUC ng-h/mL	1732	1547
Cmax ng/mL	270	235
$T_{1/2}$ h	4.7	4.5
Tmax h	1.9	2.1
B	0.17	0.17

[22] *This dose refers to the amount of elemental lanthanum.*

The pharmacokinetic properties of metoprolol were not materially affected by the administration of lanthanum carbonate 1g tid.

There are no pharmacokinetic data for lanthanum.

A.9.4.4 Pharmacodynamic effects

No data were collected.

A.9.4.5 Safety

One subject reported headache.

Vital signs were not much affected. There were no reported abnormalities on physical exam.

A.9.5 Summary

Twelve normal volunteers received metoprolol 100 mg alone and after the fourth dose of lanthanum carbonate 1 g tid. Pharmacokinetic properties of metoprolol were not much affected by co-administration of lanthanum carbonate.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Norman Stockbridge
2/3/03 10:24:44 AM
MEDICAL OFFICER