



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Pharmacoepidemiology and Statistical Science  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

**NDA/Serial Number:** 21-468, SN 066

**Drug Name:** Fosrenol (Lanthanum Carbonate Hydrate)

**Indication(s):**  $\square$  1

**Applicant:** Shire Pharmaceutical Inc.

**Date(s):** Resubmission, Volumes 1-39 of 89 dated 1/26/2004

**Review Priority:** Standard

**Biometrics Division:** DB1

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**Keywords:** Confidence interval, labeling, log-rank test, longitudinal data analysis, missing data, open-label, drop-outs, informative censoring, Kaplan-Meier product limit, retrieved dropouts, retrospective, survival analysis.

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## **1. EXECUTIVE SUMMARY**

### **1.1 CONCLUSIONS AND RECOMMENDATIONS**

**Adverse events.** In the 15-month Safety Update of the Phase 2-3 studies, lanthanum was not as well tolerated as standard therapy. Statistically significantly ( $p < 0.001$ ) more lanthanum patients (63 %) discontinued from the studies as compared to standard therapy patients (44 %). Statistically significantly ( $p < 0.001$ ) more lanthanum patients (16 %) discontinued due to adverse events as compared to standard therapy patients (5 %). More of GI events in lanthanum patients (23 %) had duration greater than 28 days or were not resolved as compared to standard therapy (19 %). Because of the statistically significantly shorter drug exposure among lanthanum patients and no follow-up of discontinued patients, comparisons of the rates of adverse events may be biased in favor of lanthanum. Therefore, reported rates of adverse events need to be adjusted for duration of exposure instead of presenting unadjusted rates as in the sponsor's ISS (Integrated Summary of Safety) and proposed labeling.

**Mortality.** In the Phase 2-3 studies, survival analysis including mortality follow up through December 2002 found no statistically significant difference between lanthanum and standard therapy ( $p = 0.89$  by the log-rank test). The Kaplan-Meier curves cross with lanthanum having a higher mortality at the end of study. Mortality rates at 44 months: Lanthanum: 23.8 %; Standard Therapy: 20.4 %. The 95% confidence interval for the difference between lanthanum and standard therapy does not include zero: (0.2 %, 6.6 %). However, using the Kaplan-Meier estimates, the 95% CI for the difference in mortality at 44 months includes zero: (-3.5 %, +9.5 %). Because of the high discontinuation rates and statistically significantly shorter drug exposure among lanthanum patients, reported mortality rates should incorporate mortality follow up of discontinued patients instead of presenting mortality while on treatment (as in the sponsor's ISS and proposed labeling).

### **1.2 BRIEF OVERVIEW OF CLINICAL STUDIES**

Evaluation of long-term safety in this review consists of evaluation of safety in Study LAM-IV-307 and ISS based on Phase 2-3 Studies LAM-IV-202, LAM-IV-204, LAM-IV-205, LAM-IV-301, LAM-IV-302, LAM-IV-307, and LAM-IV-308. Long-term Study LAM-IV-307 was the largest and most important study.

### **1.3 STATISTICAL ISSUES AND FINDINGS**

Because of the statistically significantly shorter drug exposure among lanthanum patients and no follow-up of discontinued patients, comparisons of the rates of adverse events may be biased in favor of lanthanum. Therefore, the sponsor's reported rates of adverse events need to be adjusted for duration of exposure instead of presenting unadjusted rates.

Because of the high discontinuation rates (63 % on lanthanum and 44 % on standard therapy) and statistically significantly shorter drug exposure among lanthanum patients, the sponsor's

mortality assessment should incorporate mortality follow up of discontinued patients instead of reporting mortality while on treatment.

## **2. INTRODUCTION**

The original NDA 20-846 filing date was April 30, 2002, with the data cut off date **October 31, 2001**. Statistical Review of the original NDA 21-468 was entered into DFS in November 2002.

A four-month Safety Update was submitted to the FDA on August 27, 2002. The update presented the interim safety data as of **May 30, 2002**. Statistical Review of the 4-month Safety Update was entered into DFS in December 2002.

A 15-month Safety Update was submitted on January 26, 2004. This update presents the interim safety data as of **May 30, 2003**. This review will focus on the 15-month Safety Update.

### **2.1 OVERVIEW**

Evaluation of safety in this review consists of evaluation of safety in Study LAM-IV-307 and ISS based on Phase 2-3 Studies LAM-IV-202, LAM -IV-204, LAM -IV-205, LAM-IV-301, LAM-IV-302, LAM-IV-307, and LAM-IV-308. Long-term Study LAM-IV-307 was the largest and most important study.

### **2.2 DATA SOURCES**

ISS includes safety data from Phase 2-3 studies LAM-IV-202, LAM -IV-204, LAM -IV-205, LAM-IV-301, LAM-IV-302, LAM-IV-307, and LAM-IV-308. Mortality data in this resubmission consists of the 15-month safety update plus the follow up contact information through December 2002 collected at the October 2002 request of this reviewer. Adverse event data consists of the 15-month update (no follow up of discontinued patients).

## **3. STATISTICAL EVALUATION**

### **3.1 EVALUATION OF EFFICACY**

This review does not include any efficacy evaluation because this resubmission was only for long-term safety.

### **3.2 EVALUATION OF SAFETY**

Evaluation of safety in this review consists of evaluation of safety in Study LAM-IV-307 and ISS based on all Phase 2-3 Studies. Long-term Study LAM-IV-307 was the largest and most important study.

**3.2.1 Safety in the 15-Month Safety Update of Study LAM-IV-307 (Cut off day: May 30, 2003)****Design of Study LAM-IV-307**

This is a USA, Phase 3, ongoing, open label, randomized, multicenter, comparator controlled, parallel group study of the long-term safety of lanthanum carbonate for controlling hyperphosphatemia in chronic renal failure patients undergoing hemodialysis three times per week. The study consisted of three phases: a screening and one- to three-week washout phase (Part 1), followed by a six-week dose-titration phase (Part 2), and finally, a long-term maintenance phase (Part 3), for a total of 24 months. To be eligible to enter the dose-titration phase, patients' PO<sub>4</sub> levels had to be >5.9 mg/dL. Eligible patients were randomized at a 1:1 ratio to receive either lanthanum carbonate or their pre-study standard phosphate binder. Five daily doses of lanthanum were used: 375 mg, 750 mg, 1500 mg, 2250 mg, and 3000 mg. All patients received phosphate binder for up to 24 months.

All patients had PO<sub>4</sub> levels assessed weekly and their phosphate binder dose titrated for a period of six weeks. Patients randomized to the lanthanum arm received a starting dose of 750 mg daily unless, at the discretion of the Investigator, the patient required a starting daily dose of 1500 mg lanthanum. Doses were titrated as necessary up to a maximum of 3000 mg/day, and were adjusted based on the results of the PO<sub>4</sub> levels taken at the first dialysis session of the week. If the patient's PO<sub>4</sub> level dropped below 3.1 mg/dL the patient's lanthanum dose could have been reduced to 375 mg per day. Patients randomized to standard therapy had their dose of phosphate binder titrated according to the drug's label and current clinical practice.

**Inclusion Criteria:** Patients of either sex, at least 12 years of age, with chronic renal failure, who had undergone hemodialysis for chronic renal failure three times per week for at least the previous two months, and who currently required phosphate binders for the treatment of hyperphosphatemia (PO<sub>4</sub> >5.9 mg/dL).

**Duration of Treatment:** The washout phase was one to three weeks (Part 1), dose titration lasted for six weeks (Part 2), and maintenance treatment lasted for 24 months (Part 3).

**The primary objective of this open label study** is to evaluate the **long-term safety** of lanthanum carbonate in chronic renal failure patients with hyperphosphatemia receiving hemodialysis.

**Number of Patients**

A. The original NDA filing date was April 30, 2002, with the data cut off date **October 31, 2001**. The protocol called for a total of at least 500 patients randomized to each arm. As of October 31, 2001, a total of 1,345 patients enrolled with 1,228 patients being randomized to treatment (616 on lanthanum versus 612 on standard therapy). A total of 110 patients were terminated prior to randomization, and 7 patients were still in the washout phase.

**B.** A four-month Safety Update was submitted on August 27, 2002. The update presented the interim safety data as of **May 30, 2002**. The update included additional 61 patients whose data were not available in the original NDA. As of May 30, 2002, a total of 1289 patients were randomized (647 lanthanum versus 642 on standard therapy).

**C.** A 15-month Safety Update was submitted on January 26, 2004. This update presents the interim safety data as of **May 30, 2003**. Compared with the 4-month safety update, this update includes additional 65 patients. As of May 30, 2003, a total of 1,354 patients were randomized (680 on lanthanum versus 674 on standard therapy). This review will focus on the 15-month Safety Update.

#### **Sponsor's Results on 15-Month Safety Update of Study LAM-IV-307 (May 30, 2003)**

The 15-Month Safety Update includes cumulative safety data from additional 65 patients whose data were not available in the 4-Month Safety Update. This update reflects data collected as of May 30, 2003, the cut-off date for the interim report of Study LAM-IV-307, and the safety update. The total number of patients in Study LAM-IV-307 on May 30, 2003, was 1354 (680 in the lanthanum group and 674 in the standard group).

**Mortality.** The sponsor's mortality conclusions on the 15-month Safety Update of Study LAM-IV-307 were based on the mortality rates during treatment period or within 30 days of the final dose of study drug and did not take into account contact mortality follow up of discontinued patients through December 2002. The sponsor concluded that, during treatment period, mortality rate in the lanthanum group (5 %) was smaller than mortality rate the standard therapy group (13 %). During the study or within 30 days of their final dose of study drug, 50 (7 %) of lanthanum patients died as compared to 100 (15 %) of the standard therapy patients.

**Adverse Events.** The sponsor concluded that lanthanum is safe and well tolerated in the study population as compared to the currently used phosphate binders.

#### **Reviewer's Results on 15-month Safety Update (May 30, 2003)**

##### **Extent of Exposure in Study LAM-IV-307 (May 30, 2003)**

Exposure to study drug by time interval is presented in Table 307.1. Table 307.1 shows that patients in the lanthanum group had statistically significantly shorter exposure to the study drug as compared to the patients in the standard therapy group.

**Table 307.1 Duration of Exposure in Study LAM-IV-307 (May 30, 2003)**

Treatment Duration	Treatment Group		P-value*
	Lanthanum Group N(%)	Standard Group N (%)	
	680	674	
< 1 month	44 (6.5)	18 (2.7)	< 0.001
≥ 1 to < 2 months	72 (10.6)	24 (3.6)	< 0.001
> 2 to < 3 months	35 (5.1)	17 (2.5)	0.011
≥ 3 to < 6 months	78 (11.5)	54 (8.0)	0.031
≥ 6 to < 9 months	71 (10.4)	55 (8.2)	0.15
≥ 9 to < 12 months	53 (7.8)	53 (7.9)	0.96
> 12 to < 18 months	129 (19.0)	118 (17.5)	0.49
≥ 18 to < 24 months	90 (13.2)	139 (20.6)	< 0.001
≥ 24 months	108 (15.9)	196 (29.1)	< 0.001
≥ 18 months	198 (29.1)	335 (49.7)	< 0.001
≥ 12 months	327 (48.1)	453 (67.2)	< 0.001

\* Likelihood Ratio Chi-Square in Reviewer's Analysis.

The average length of drug exposure in the lanthanum group was statistically significantly shorter as compared to the standard therapy: Lanthanum: 0.91 (333.3 / 365) year; Standard Therapy: 1.25 (456.7 / 365) year.

#### Discontinuation due to Adverse Events

Statistically significantly ( $p < 0.001$ ) greater percentage of patients in the lanthanum group (14.4 %, 98 patients) were withdrawn because of adverse events as compared to the standard therapy group (3.6 %, 24 patients).

#### Incidence of Adverse Events Adjusted for Mean Drug Exposure

Because of the shorter duration of the drug exposure in the lanthanum group and no follow up of terminated patients, comparisons of adverse event rates without adjustment for drug exposure may be biased in favor of lanthanum. For this reason, this review presents adjusted event rates. To be consistent with the sponsor's Table 23 (8.7 – 8113), the adjustment is performed by multiplying the reported AE rates in the standard therapy group by the factor of 0.71, which is the calculated ratio of lanthanum versus standard therapy mean drug exposure in Study LAM-IV-307. Table 307.2 shows the incidence of adverse events in Study 307 adjusted for drug exposure.

**Table 307.2 The Incidence of Most Common Adverse Events in the 15-Month Safety Update of Study LAM-IV-307 (May 30,2003), 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	18	19	0.1	0.1
Myalgia	20	19	0.4	0
Chest pain	20	17	0.6	0
Coughing	18	19	0.1	0.1
Abdominal pain	16	16	2	0.5
Constipation	13	12	3	1

GI adverse events were among the most common adverse events. Table 307.3 shows duration of GI adverse events in the 15-month Safety Update of Study LAM-IV-307. Note that patients in the lanthanum group had fewer events because they had statistically significantly shorter duration of drug exposure. In the lanthanum group, numerically more GI events had duration greater than two weeks. In the lanthanum group, 23 % of GI events had duration greater than 28 days or were not resolved as compared with 19 % of GI events in the standard therapy group. In the lanthanum group, 27 % of patients had at least one GI event with "duration greater than 28 days/unresolved" as compared with 20 % of patients the standard therapy group.

**Table 307.3 Duration of GI Adverse Events in the 15-Month Safety Update of Study LAM-IV-307**

Duration	Lanthanum (680 patients)	Standard Therapy (674 patients)
	1752 Events	2480 Events
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 %)

**Mortality**

In the 4-Month Safety Update of Study LAM-IV 307, the sponsor's conclusions were based on mortality rates during the treatment period: 3 % in the lanthanum group and 6 % in the standard therapy group. As termination rate in the lanthanum group was very high and statistically significantly greater than in the standard therapy group, comparison of mortality rates during treatment period could be biased in favor of lanthanum. For this reason, in October 2002, this reviewer requested the sponsor to provide up-to-date mortality follow up of all randomized patients (including those who terminated from the study). In response, the sponsor provided mortality follow up of 95 % of all randomized patients through December 2002. In the follow up, mortality rates were much higher than the rates in the original NDA submission and 4-month Safety Update. At 34 months, mortality rates in the follow up were: Lanthanum: 19.9% (135/680); Standard therapy: 23.3 % (157/674) with the 95% confidence interval for the difference in mortality rates between lanthanum and standard therapy including zero: (-7.8 %, +0.9 %). The Kaplan-Meier curves are very close to each other, with lanthanum having numerically lower mortality (p=0.18 by the log-rank test).

**Statistical reviewer conclusions on Study LAM-IV-307**

**Adverse events.** In Study LAM-IV-307, lanthanum was not as well tolerated as standard therapy. Termination rate due to adverse events in the lanthanum group was statistically significantly greater than in the standard therapy group (14.4 % vs. 3.6 %, p<0.001). The percentage of GI events that had duration greater than 28 days or were not resolved was greater in the lanthanum group: Lanthanum: 23 %; Standard therapy: 19 %. Because of the shorter drug exposure in the lanthanum group and no follow-up of the terminated patients, comparisons of the rates of AEs in this open-label study may be biased in favor of lanthanum. Therefore, for comparison of toxicity in this study, adverse event rates should be adjusted for duration of exposure. After adjustment for duration of exposure, statistically significantly (p<0.001) greater percentage of lanthanum patients (94.7 %) had at least one adverse event as compared to the standard therapy patients (68.7 %).

**Mortality.** Because of the shorter duration of drug exposure in the lanthanum group, mortality rates should be based on the mortality follow up including terminated patients instead of mortality during treatment as presented in the sponsor's study synopsis. Mortality rates in the mortality follow up through December 2002 were: Lanthanum: 19.9%; Standard therapy: 23.3 % with the 95% confidence interval for the difference between lanthanum and standard therapy being (-7.8 %, +0.9 %). The log-rank test for the difference in mortality showed p=0.18.

**3.2.2 ISS in the 15-Month Safety Update of Phase 2-3 Studies (Cut off day: May 30, 2003)**

ISS includes safety data from Phase 2-3 studies LAM-IV-202, LAM-IV-204, LAM-IV-205, LAM-IV-301, LAM-IV-302, LAM-IV-307, and LAM-IV-308. **The primary objective of the long-term Phase 2-3 studies** is to evaluate the **long-term safety** of lanthanum carbonate in chronic renal failure patients with hyperphosphatemia receiving hemodialysis.

**Sponsor's Conclusions on the 15-Month Safety Update of Long-Term Phase 2-3 Studies (cut off: May 30, 2003)**

**Mortality.** The sponsor's conclusions on mortality in the 15-month Safety Update were based on the mortality rates during treatment period. In the sponsor's proposed labeling,  $\zeta$

**Adverse Events.** The sponsor's comparisons of adverse event rates were not adjusted for exposure. The sponsor concluded that lanthanum was safe and well tolerated in the study population as compared to the currently used phosphate binders.

**Reviewer's Results on the 15-Month Safety Update of Phase 2-3 Studies (cut off: May 30, 2003)****Duration of Exposure in the 15-Month safety Update of Phase 2-3 Studies (cut off: May 30, 2003)**

Number of patients, discontinuations, and exposure to study drug in Phase 2-3 studies are shown in Table ISS.1.

**Table ISS.1. Duration of exposure and discontinuations in long-term Phase 2-3 Studies**

<b>Duration</b>	<b>Lanthanum N=1705</b>	<b>Standard N=941</b>	<b>P-value</b>
18 < duration < 24 months	109 (6 %)	139 (15 %)	< 0.001
> 24 months	212 (12 %)	196 (21 %)	< 0.001
Mean number of days of exposure (SD)	280 (277)	358 (265)	< 0.001
Number of subjects discontinued	951 (63 %)	410 (44 %)	< 0.001
Number of subjects discontinued to AEs	244 (16 %)	48 (5 %)	< 0.001

Table ISS.1 shows that patients in the lanthanum group had statistically significantly ( $p < 0.001$ ) shorter exposure to the study drug than the patients in the lanthanum group. The average length of drug exposure was 280 day and 358 days, respectively, for lanthanum and standard therapy ( $p < 0.001$ ). Statistically significantly ( $p < 0.001$ ) more lanthanum patients discontinued from the study as compared to standard therapy patients. Statistically significantly ( $p < 0.001$ ) more

lanthanum patients (16 %) discontinued due to adverse events as compared to standard therapy patients (5 %).

### Incidence of Adverse Events Adjusted for Mean Drug Exposure

Because of the shorter duration of the drug exposure in the lanthanum group and no follow up of terminated patients, comparisons of adverse event rates without adjustment for drug exposure may be biased in favor of lanthanum. For this reason, this review presents adjusted adverse event rates. The adjustment is performed by multiplying reported AE rates in the standard therapy group by the factor of 0.66, which is the calculated ratio of lanthanum versus standard therapy mean drug exposure in the post-randomization part of Phase 2-3 studies. GI adverse events were among the most common adverse events. Table ISS.2 shows the incidence of GI adverse events in Phase 2-3 studies adjusted for drug exposure.

**Table ISS.2 Rates of GI Adverse Events in the 15-Month Safety Update of Phase 2-3 Studies (May 30,2003), Adjusted for Drug Exposure**

GI Adverse Event	Lanthanum	Standard Therapy
Abdominal Pain	13.3	11.5
Constipation	10.3	9.6
Diarrhea	18.1	16.2
Nausea	26.7	20.1
Vomiting	22.4	15.9

### Mortality

In the 4-month Safety Update of Phase 2-3 studies, the sponsor reported mortality rates during the treatment period: 4 % in the lanthanum group and 9 % in the standard therapy group. As termination rate in the lanthanum group was very high and statistically significantly greater than in the standard therapy group, comparison of mortality rates during treatment period could be biased in favor of lanthanum. For this reason, in October 2002, this reviewer requested the sponsor to follow up of all randomized patients (including those who terminated from the study) regarding mortality status. In response, the sponsor provided follow up of mortality data on 95 % of all randomized patients through December 2002. In the follow up data, mortality rates were much higher: Namely, mortality at 44 months: Lanthanum: 23.8 % (418/1754); Standard therapy: 20.4 % (202/990). The 95% confidence interval for the difference between lanthanum and standard therapy does not include zero: (0.2 %, 6.6 %). However, using the Kaplan-Meier estimates, the 95% CI for the difference in mortality at 44 months includes zero: (-3.5 %, +9.5 %). The Kaplan-Meier curves cross later in the study, with lanthanum having higher mortality at the end of study (p=0.89 by the log-rank test). Table ISS.3 compares survival in the two treatment groups at 44 months using raw survival frequencies and Kaplan-Meier estimates.

**Table ISS.3 Comparison of Survival at 44 Months in Phase 2-3 Studies**

Method of analysis	Treatment Group		Difference: Lanthanum – Standard Therapy (95 % Confidence Interval )
	Lanthanum N=1754	Standard Therapy N=990	
Survival rate at 44 months	76.2 % (1336/1754)	79.6 % (788/990)	Difference: -3.4 % 95 % CI: (-6.6 %, -0.2 %) (significant difference)
Kaplan-Meier probability of survival at 44 months	69.1 %	72.2 %	Difference: -3.1 % 95 % CI: (-9.5 %, +3.5 %) (non-significant difference)

**Statistical Reviewer's Conclusions:**

**Adverse events.** In the 15-month Safety Update of the Phase 2-3 studies, lanthanum was not as well tolerated as standard therapy. Statistically significantly ( $p < 0.001$ ) more lanthanum patients (63 %) discontinued from the studies as compared to standard therapy patients (44 %). Statistically significantly ( $p < 0.001$ ) more lanthanum patients (16 %) discontinued due to adverse events as compared to standard therapy patients (5 %). More of GI events in lanthanum patients (23 %) had duration greater than 28 days or were not resolved as compared to standard therapy (19 %). Because of the statistically significantly shorter drug exposure among lanthanum patients and no follow up of discontinued patients, comparisons of the rates of adverse events may be biased in favor of lanthanum. Therefore, reported rates of adverse events need to be adjusted for duration of exposure instead of presenting unadjusted rates as in the sponsor's ISS and labeling.

**Mortality.** In the Phase 2-3 studies, survival analysis including mortality follow up through December 2002 found no statistically significant difference ( $p = 0.89$  by the log-rank test) between lanthanum and standard therapy. The Kaplan-Meier curves cross with lanthanum having a higher mortality at the end of study. Mortality rates at 44 months: Lanthanum: 23.8 %; Standard therapy: 20.4 %. The 95% confidence interval for the difference between lanthanum and standard therapy does not include zero: (0.2 %, 6.6 %). However, the 95% CI for the difference in mortality at 44 months using the Kaplan-Meier estimates includes zero: (-3.5 %, +9.5 %). Because of the high discontinuation rates and statistically significantly shorter drug exposure among lanthanum patients, mortality assessment should incorporate mortality follow up of discontinued patients instead of reporting mortality while on treatment (as in the sponsor's ISS and labeling).

**4. FINDINGS IN SPECIAL SUBGROUPS/POPULATIONS**

The long-term safety did not include any special subgroups or populations

## 5. SUMMARY AND CONCLUSIONS

**Adverse events.** In the 15-month Safety Update of the Phase 2-3 studies, lanthanum was not as well tolerated as standard therapy. Statistically significantly ( $p < 0.001$ ) more lanthanum patients (63 %) discontinued from the studies as compared to standard therapy patients (44 %). Statistically significantly ( $p < 0.001$ ) more lanthanum patients (16 %) discontinued due to adverse events as compared to standard therapy patients (5 %). More of GI events in lanthanum patients (23 %) had duration greater than 28 days or were not resolved as compared to standard therapy (19 %). Because of the statistically significantly shorter drug exposure among lanthanum patients and no follow up of discontinued patients, comparisons of the rates of adverse events may be biased in favor of lanthanum. Therefore, reported rates of adverse events need to be adjusted for duration of exposure instead of presenting unadjusted rates as in the sponsor's ISS and labeling.

**Mortality.** In the Phase 2-3 studies, survival analysis including mortality follow up through December 2002 found no statistically significant difference ( $p = 0.89$  by the log-rank test) between lanthanum and standard therapy. The Kaplan-Meier curves cross with lanthanum having a higher mortality at the end of study. Mortality rates at 44 months: Lanthanum: 23.8 %; Standard therapy: 20.4 %. The 95% confidence interval for the difference between lanthanum and standard therapy does not include zero: (0.2 %, 6.6 %). However, the 95% CI for the difference in mortality at 44 months using the Kaplan-Meier estimates includes zero: (-3.5 %, +9.5 %). Because of the high discontinuation rates and statistically significantly shorter drug exposure among lanthanum patients, mortality assessment should incorporate mortality follow up of discontinued patients instead of reporting mortality while on treatment (as in the sponsor's ISS and labeling).

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Kooros Mahjoob

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**STATISTICAL REVIEW AND EVALUATION**

**NDA #:** 21-468

**DRUG NAME:** Fosrenol (Lanthanum Carbonate Hydrate)

**INDICATION:** □

**APPLICANT:** Shire Pharmaceutical Inc.

**DOCUMENTS REVIEWED:** Volumes 1.1-1.2, 1.284-1.490 dated 04/30/02;  
Safety updates dated 8/27/2002, 10/3/02 and 10/8/02

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**STATISTICAL KEY WORDS:** ANCOVA, ANOVA, logistic regression model, multiple comparisons, Dunnett's t-test, co-primary efficacy variables, chi-square test, time-to-event analysis, log rank test, non-random censoring.

**Distribution:** NDA 21-468  
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## **2. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS**

### **2.1 Reviewer's Conclusions**

Primary efficacy analysis of **Study LAM-IV-302** showed that lanthanum was statistically significantly better than placebo relative to change in serum phosphorus at the end of randomized treatment ( $p < 0.0001$ ) and proportion of patients with serum phosphorus level controlled ( $p = 0.0011$ ). Safety analysis found no statistically significant difference between lanthanum and placebo relative to the incidence of adverse events except possibly for the statistically significant difference ( $p = 0.034$ ) in favor of placebo for musculo-skeletal system.

Primary efficacy analysis of **Study LAM-IV-202** showed that lanthanum was statistically significantly better than placebo ( $p = 0.008$ ) relative to the proportion of patients with serum phosphate control at the end of treatment. There was no statistically significant difference between lanthanum and placebo relative to the proportion of patients with adverse events.

Primary efficacy analysis of **Study LAM-IV-204** showed that lanthanum 1350 mg/day and lanthanum 2250 mg/day were statistically significantly better than placebo ( $p < 0.001$ ) relative to the decrease in the serum phosphate level from baseline to the end of treatment. The two lower lanthanum doses (675 mg/day and 225 mg/day) were not statistically different from placebo. Safety analysis found no statistically significant difference between lanthanum and placebo relative to the incidence of adverse events.

The reviewer's analysis of the open label **Study LAM-IV-307** found that patients in the lanthanum group had a statistically significantly shorter drug exposure time and greater termination rate as compared to the standard therapy group ( $p < 0.001$ ). Lanthanum was statistically significantly worse than standard therapy relative to the proportion of patients who withdrew due to: adverse events (80 vs. 17,  $p < 0.0001$ ), protocol violations ( $p = 0.003$ ), consent withdrawal ( $p < 0.001$ ), exceeding safety criteria ( $p = 0.024$ ), and other ( $p = 0.005$ ). Statistically significantly more lanthanum patients experienced at least one drug-related adverse event compared with the standard therapy group: 124 (20.1%) versus 77 (12.6%),  $p < 0.001$ . Lanthanum was statistically significantly worse than standard therapy relative to the following drug related treatment emergent adverse events: nausea ( $p < 0.001$ ), vomiting ( $p < 0.001$ ), diarrhea ( $p = 0.007$ ), abdominal pain ( $p = 0.009$ ) and headache ( $p = 0.031$ ).

This reviewer does not agree with the sponsor's conclusions in study LAM-IV-307 that lanthanum is safer than the standard therapy relative to mortality and adverse events. In this study, termination rate in the lanthanum group was statistically significantly greater than in the standard therapy group (63% vs. 42%,  $p < 0.001$ ) and terminated patients were not followed regarding survival or adverse events. The log-rank tests in the sponsor's time-to-event analysis may give misleading results because they are based on the invalid assumption that censoring is

random and the censoring distributions are the same in the two treatment groups. Because of the significantly shorter drug exposure time and greater termination rate in the lanthanum group and no follow-up of the terminated patients, safety comparisons in this open-label study may be biased in favor of lanthanum. For this reason, in this study, the safety results that are in favor of lanthanum, can be very misleading. On the other hand, the safety results that are in favor of the standard treatment can be considered as conservative and robust. To be conservative, this review mostly presents the safety results of Study LAM-IV-307 that are in favor of standard therapy.

## **2.2 Overview of Clinical Program and Studies Reviewed**

This review examined four lanthanum studies: US double-blind, Phase 3 Study LAM-IV-302, UK double-blind, Phase 2 Study LAM-IV-202, US double-blind, Phase 2 Study LAM-IV-204, and a US open label, long-term safety Study LAM-IV-307.

### **Reviewer's Findings in Studies LAM-IV-302, 202 and 204**

Primary efficacy analysis of the dose titration **Study LAM-IV-302** showed that lanthanum was statistically significantly better than placebo relative to both co-primary efficacy endpoints, change in serum phosphorus at the end of randomized treatment ( $p < 0.0001$ ), and proportion of patients with serum phosphorus level controlled ( $p = 0.0011$ ). Safety analysis found no statistically significant difference between lanthanum and placebo relative to the incidence of adverse events except for the statistically significant difference ( $p = 0.034$ ) in favor of placebo for musculo-skeletal system.

Primary efficacy analysis of the dose titration **Study LAM-IV-202** showed that lanthanum was statistically significantly better than placebo ( $p = 0.008$ ) relative to the proportion of patients with serum phosphate control at the end of treatment. There was no statistically significant difference between lanthanum and placebo relative to the proportion of patients with adverse events.

Primary efficacy analysis of **Study LAM-IV-204** showed that lanthanum 1350 mg/day and lanthanum 2250 mg/day were statistically significantly better than placebo ( $p < 0.001$ ) relative to the decrease in the serum phosphate level from baseline to the end of treatment. The two lower lanthanum doses (675 mg/day and 225 mg/day) were not statistically different from placebo. Safety analysis found no statistically significant difference between lanthanum and placebo relative to the incidence of adverse events.

### **Reviewer's and Sponsor's Findings in Study LAM-IV-307**

The reviewer found that lanthanum is statistically significantly worse than standard therapy relative to the proportion of patients who completed the study ( $p < 0.001$ ). Statistically significantly more lanthanum patients terminated as compared to patients on standard therapy: 386 (63%) vs. 259 (42%),  $p < 0.001$ . Patients in the lanthanum group have a statistically significantly shorter exposure to the study drug compared to the standard therapy group ( $p < 0.001$ ). The reviewer found that lanthanum is statistically significantly worse than standard therapy relative to the proportion of patients who withdrew due to: adverse events (80 vs. 17,

$p < 0.0001$ ), protocol violations ( $p = 0.003$ ), consent withdrawal ( $p < 0.001$ ), exceeding safety criteria ( $p = 0.024$ ), and other ( $p < 0.001$ ). Statistically significantly more lanthanum patients experienced at least one drug-related AE compared with the standard therapy group: 124 (20%) vs. 77 (13%),  $p < 0.001$ . Lanthanum is statistically significantly worse than standard therapy relative to the following drug related treatment emergent adverse events: nausea ( $p < 0.001$ ), vomiting ( $p < 0.001$ ), diarrhea ( $p = 0.007$ ), abdominal pain ( $p = 0.009$ ) and headache ( $p = 0.031$ ).

The sponsor found that mortality and the incidence of adverse events were lower in the lanthanum group. To take into account a higher termination rate in the lanthanum group, the sponsor presented time-to-event analysis of the adverse events and deaths in Study LAM-IV-307. The sponsor concluded that time-to-event patterns were statistically significantly better ( $p < 0.04$ ) in the lanthanum group for the following adverse events: back pain, edema peripheral, dyspepsia, hypercalcaemia, and pneumonia ( $p < 0.04$ ). The sponsor also concluded that patient survival while on the study was statistically significantly higher in the lanthanum group as compared to the standard group ( $p = 0.027$ ). The sponsor's conclusions on the Safety Update (with additional 61 patients) were the same.

### **3. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE**

#### **3.1 STUDY LAM-IV-302**

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

##### **3.1.1 Design of Study LAM-IV-302**

This was a USA, randomized, double-blind, placebo-controlled, parallel group study to assess the ability of lanthanum carbonate to control serum phosphorus in chronic renal failure patients receiving hemodialysis. This study consisted of three phases: a one to three week washout during which patients stopped all phosphorus binding medication, a 6-week open-label dose titration, and a 4-week double blind randomized drug maintenance phase with a placebo arm. To be eligible to enter the open-label dose titration phase, patients' serum  $PO_4$  had to be  $> 5.9$  mg/dL after washout. Eligible patients were then titrated to the optimal dose of lanthanum required to reduce their serum phosphorus to  $< 5.9$  mg/dL using 5 pre-defined dose levels for six weeks. The five daily doses were lanthanum 375 mg, 750 mg, 1500 mg, 2250 mg, and 3000 mg, given BID or TID with food. Patients who completed the 6-week titration were then randomized to receive either lanthanum or placebo for 4-week maintenance treatment.

**Number of Patients.** The protocol planned 120 patients to be dose titrated with the intention of having 80 patients, whose serum phosphorus was  $\leq 5.9$  mg/dL at the end of titration, randomized into the drug maintenance phase (40 per treatment arm). One hundred and sixty-three patients were enrolled and entered the washout phase. Of these, 126 met the criteria for dose titration and

entered the open-label lanthanum titration phase. Of the 126 patients, 94 completed the dose titration and were randomized to the drug maintenance phase. All but one were included in the ITT population (N=93) which was used as the primary efficacy population (lanthanum: 49; placebo: 44). One patient was excluded from the ITT population because of the lack of post-randomization serum phosphorus levels. All of the 163 study participants were evaluated for safety.

**Diagnosis and Main Criteria for Inclusion.** Patients of either sex, 18 years and older with end stage renal disease, and who had been undergoing dialysis 3 times weekly for at least 2 months, were enrolled in the washout phase.

**Duration of Treatment.** The washout phase was two to three weeks, until patients' serum  $\text{PO}_4$  was  $> 5.9$  mg/dL. Dose titration lasted for 6 weeks and the randomized double-blind maintenance treatment lasted for 4 weeks.

### Primary Efficacy Variables

The efficacy measurements were patients' pre-dialysis serum phosphorus levels (PSPL), which were measured at the first dialysis session of each study week. The primary efficacy variable was defined as the last PSPL of a patient that was obtained during the maintenance treatment period. The control of serum phosphorus levels at study endpoint was also to be analyzed primarily for efficacy evaluation. The control of serum phosphorus levels was defined in the protocol as less than or equal to 5.9 mg/dL.

### Sponsor's Statistical Methods

The last serum phosphorus value obtained post randomization was a co-primary efficacy endpoint. It was analyzed using one-way ANCOVA for the intent-to-treat (ITT) population to compare differences in serum phosphorus between the active and placebo groups. The model included treatment (main effect) and the pre-randomization serum phosphorus value as the covariate. The ANCOVA was carried out using SAS PROC GLM. The null hypothesis stated that there were no differences in the post-randomization serum phosphorus between the two treatment groups. Based on the results from the ANCOVA model, t-test procedure was used to compare the average serum phosphorus of lanthanum versus placebo and to report differences in serum phosphorus between the two groups.

The control of serum phosphorus levels at study endpoint was another co-primary variable. The control of serum phosphorus levels was defined in the protocol as less than or equal to 5.9 mg/dL. This analysis was performed using the logistic regression model. The patient's pre-randomization status of  $\text{PO}_4 \leq 5.9$  mg/dL (controlled) vs.  $\text{PO}_4 > 5.9$  mg/dL (not controlled) was used as a covariate in the logistic regression model.

## Reviewer's Statistical Methods

The sponsor did not use any p-value adjustment for the two co-primary efficacy variables. To adjust for the two co-primary efficacy variables, this reviewer used the Bonferroni adjustment with the significance level of 0.025 (instead of the 0.05 level used by the sponsor). Otherwise, the reviewer agrees with the sponsor's primary efficacy methods. The sponsor's primary efficacy analysis was not stratified by center. This is acceptable because randomization was not stratified by center. Non-stratified randomization in this study is acceptable because most of the centers in this study were very small.

### 3.1.2 Efficacy Results in Study LAM-IV-302

Primary efficacy analyses were performed on the intent-to-treat (ITT) population. Supportive efficacy analyses were performed on the per-protocol (PP) population.

**The ITT population** included all patients randomized into the maintenance treatment period and having at least one serum phosphorus level available at both pre- and post-randomization. Of 94 patients randomized, 93 (98.9%) patients had valid primary efficacy data pre- and post-randomization; these 93 patients (placebo 44; lanthanum 49) were defined as the ITT population. One patient who was randomized to lanthanum treatment was withdrawn during the first week of the randomized double-blind phase due to adverse event. This patient did not have a post-randomization serum phosphorus level available.

**Per-protocol (PP)** population included those ITT patients whose average drug compliance was at least 80% over the randomized treatment duration and whose serum phosphorus was less than or equal to 5.9 mg/dL (or controlled) prior to randomization. Out of 93 ITT patients, 47 (50.5%) patients were included into the PP population.

#### **Demographic and Other Baseline Characteristics**

Of the 163 patients enrolled, 103 (63%) were male and 60 (37%) female, and 72 (44%) were whites, 69 (42%) black 14 (9%) Hispanic, and 8 (5%) other races. The average age was 60.5 years, height was 67.0 inches and the average post-dialysis weight was 170.8 lbs. The demographic characteristics of the ITT population were similar to the entire patient population enrolled and to those patients titrated, and similar between patients randomized to lanthanum versus placebo.

The balance between the treatment groups at baseline was examined relative to patients' demographic characteristics and baseline measurements. The variables analyzed included gender, age, race, weight, serum phosphorus levels prior to randomization (end of dose titration), daily doses used for maintenance period, number of years on dialysis, primary disease diagnosis, history of kidney transplant, dialysis schedule, and control of serum phosphorus pre-randomization. None of these variables predicted the patient's randomized treatment assignment ( $p > 0.17$ ).

### Primary Efficacy Results

This reviewer tested the two co-primary efficacy variables in this study at the 0.025 significance level using the Bonferroni adjustment.

#### Analysis of Serum Phosphorus Level Data

One of the co-primary efficacy parameters in this study was the serum phosphorus level at the end of the double-blind randomized phase. The serum phosphorus levels were the values obtained pre-dialysis at the first dialysis session of the last week of the double-blind period. These data are presented in Table 302.1. At the end of washout, the serum phosphorus level was 7.39 mg/dL in the placebo group and 7.69 mg/dL in the lanthanum group. There were no differences in the serum phosphorus concentrations between the two treatment groups at the end of washout ( $p=0.37$ ). During titration all patients received lanthanum carbonate. At the end of dose titration (prior to randomization), the serum phosphorus level decreased, by an average of 2.0 mg/dL, to 5.62 mg/dL in the placebo group and 5.49 mg/dL in the lanthanum group. There were no differences in the serum phosphorus concentrations between the two subsequent treatment groups at the end of dose titration or prior to randomization ( $p=0.69$ ).

**Table 302.1 Primary Efficacy Analysis in Study LAM-IV-302: Serum PO<sub>4</sub> Levels at Various Time Points**

Primary Efficacy Parameter:	Treatment Group		Test Statistics (treatment effect)
	Placebo (N=44)	Lanthanum (N=49)	
Serum PO <sub>4</sub> mg/dL (Mean ± s.d.)			
At End of Washout (prior to dose titration)	7.39 ± 1.60	7.69 ± 1.61	P = 0.3754 (1-way ANOVA)
At End of Dose Titration (prior to randomization or baseline)	5.62 ± 1.61	5.49 ± 1.48	P = 0.6942 (1-way ANOVA)
<b>At Study Endpoint (end of randomized treatment)</b>	<b>7.85 ± 1.96</b>	<b>5.94 ± 1.65 [-2.60, -1.23]*</b>	<b>P &lt; 0.0001*** (1-way ANCOVA)</b>
Mean change from baseline (end of dose titration) to end of randomized treatment (study endpoint)	2.23 ± 2.08 (<0.0001)**	0.45 ± 1.62 (0.0601)	P < 0.0001 (t-test)
* - 95% confidence interval for the difference from placebo.			
** - p-value compared to baseline (i.e., end of dose titration)			
***- To adjust for the two co-primary efficacy variables, significance level of 0.025 is used in this review.			

At study endpoint (end of randomized treatment), the serum phosphorus was 7.85±1.96 mg/dL for placebo and 5.94±1.65 mg/dL for lanthanum. The mean difference of -1.91 mg/dL in serum phosphorus concentrations between the two groups was statistically significant ( $p<0.0001$  in the ANCOVA model with the patient's baseline PO<sub>4</sub> as covariate). Results in the Per Protocol

population were similar to that in the ITT population ( $p < 0.001$ ) for this primary efficacy variable.

#### Analysis of the Control of Serum phosphorus

The other co-primary efficacy variable was control of the serum phosphorus at the end of the randomized treatment. Results are presented in Table 302.2. Prior to randomization, percent of ITT patients with serum phosphorus levels controlled (less than or equal to 5.9 mg/dL) was 71% for lanthanum group and 59% for placebo group, which did not produce statistically significant difference ( $p = 0.28$  by Fisher's exact test).

At the study endpoint, percent of ITT patients whose serum phosphorus levels were controlled was 59% for lanthanum group and 23% for placebo. The difference of 36% was statistically significant by logistic regression ( $p = 0.0011$ ). By adjusting the patient's pre-randomization status of serum  $PO_4$  controlled vs. not controlled, the logistic regression analysis found an odds ratio of 4.7 (95% CI: 1.9-11.9).

**Table 302.2. Primary Efficacy Analysis in Study 302: Serum Phosphorus Controlled vs. Not Controlled at Study Endpoint**

Population/Treatment	Number (%) of Patients with $PO_4 \leq 5.9$ mg/dL at Endpoint	Odds Ratio	95% CI	P- Value
ITT patients (N=93): Lanthanum Placebo	29 (59%) 10 (23%)	4.7*	1.9 - 11.9*	0.0011*
ITT patients whose $PO_4$ were $\leq 5.9$ mg/dL prior to randomization (N=61): Lanthanum Placebo	23 (66%) 8 (31%)	4.3	1.5 - 12.8	0.0084
* Logistic regression model was adjusted for the patient's pre-randomization status of $PO_4 \leq 5.9$ mg/dL vs. $PO_4 > 5.9$ mg/dL				

For the subgroup of the ITT patients whose serum phosphorus levels were less than or equal to 5.9 mg/dL (i.e., being controlled) prior to randomization, percent of patients whose serum phosphorus levels remained controlled at study endpoint was 66% for lanthanum group and 31% for placebo. The difference of 35%, which was almost the same as in the ITT population, was statistically significant using logistic analysis ( $p = 0.0084$ ) for this sub-population of ITT patients, consistent with the results of ITT population (Table 302.2).

**3.1.3 Safety in Study LAM-IV-302**

Proportion of patients with adverse events is presented in Table 302.3. Safety analysis found no statistically significant difference between lanthanum and placebo relative to the incidence of adverse events except possibly for the statistically significant difference in favor of placebo for musculo-skeletal system (p=0.034).

**Table 302.3 Proportion of Patients Post-Randomization with Adverse Events in Study LAM-IV-302.**

Body system	Treatment Group		
	Lanthanum Group (N = 50)	Placebo Group (N = 44)	P-value
At least one adverse event	29 (58.0%)	17 (38.6%)	0.060
Body as a whole	7 (14.0%)	5 (11.4%)	0.70
Gastro-intestinal system	9 (18.0%)	5 (11.4%)	0.36
Musculo-skeletal system	8 (16.0%)	1 (2.3%)	0.034*
Respiratory System	8 (16.0%)	2 (4.5%)	0.098

*Likelihood Ratio Chi-Square or Fisher's exact test in Reviewer's Analysis.*  
\* Statistically significant difference in favor of Placebo.

**3.1.4 Conclusions on Study LAM-IV-302**

Primary efficacy analysis of Study LAM-IV-302 showed that lanthanum was statistically significantly better than placebo relative to both co-primary efficacy endpoints, serum phosphorus concentration at the end of randomized treatment (p<0.0001) and proportion of patients with phosphorus level controlled at the end of randomized treatment (p=0.0011). Safety analysis found no statistically significant difference between lanthanum and placebo relative to the incidence of adverse events except possibly for the statistically significant difference in favor of placebo for musculo-skeletal system (p=0.034).

**3.2 STUDY LAM-IV-202**

**Title:** A Phase 2, Dose Ranging, Placebo-controlled Parallel Group Study to Assess The Efficacy and Safety of 'Lambda' for Reduction of Gastrointestinal Phosphate Absorption in Patients Receiving Haemodialysis or Continuous Ambulatory Peritoneal Dialysis (CAPD)

**3.2.1 Design of Study LAMIV-202**

This was an UK, Phase 2, prospective, multicenter, 4-week double-blind, randomized, placebo controlled, parallel group study. Washout phase was followed by open dose titration period of 4

weeks (Part 1) and then followed by double-blind placebo-controlled comparative phase of 4 weeks (Part 2).

**Randomization.** At screening, each patient received a study screening number, which was used during the dose titration phase. In Part 2 of the study, neither the patient nor the Investigator knew which treatment had been allocated. Treatment was assigned according to the randomisation schedule held centrally. The schedule randomized the patients in blocks of four at the 1:1 ratio of lanthanum carbonate to placebo. Each patient entering Part 2 was assigned their randomisation number as a study patient number (which was different from the screening number).

### **Sponsor's Statistical Methods**

The primary efficacy variable was the control of serum phosphate level at week 9 (visit 9). Patients who were not assessed at visit 9, had their last visit carried forward for this analysis. Each patient was classified at each visit as 'Controlled' (if serum phosphate was in the range 1.3 - 1.8 mmol/L) or 'Uncontrolled' (if serum phosphate has risen above 1.8 mmol/L). Values <1.3 mmol/L were considered to be uncontrolled. The proportion of controlled patients was summarised by visit, and differences between the treatment groups were assessed using a chi-square or Fisher's exact test.

The primary efficacy analysis was based on the Per Protocol population. This would exclude any patients who were considered to be major protocol violators. In addition, a supporting ITT population was defined as all patients who were randomised and who received at least one dose of medication. ITT population was the primary population for the safety analysis. There were two additional patients (in the placebo group) in this population and no difference in the interpretation of the results.

Demographic and baseline characteristics of the patients were summarised for each treatment group. For continuous data, the comparability of treatment groups was assessed using ANOVA or Wilcoxon rank sum test as appropriate. Nominal data were evaluated using Pearson chi-squared statistics.

### **Reviewer's Statistical Methods**

In contrast to the sponsor's approach, this reviewer considered ITT population to be the primary efficacy population and the Per Protocol population as the secondary efficacy population.

**3.2.2 Efficacy Results of Study LAM-IV-202****Disposition of Patients**

Of the 59 treated patients, 50 patients completed Part 1 and nine withdrew. A total of 36 patients entered Part 2 of the study; 17 were randomised to lanthanum carbonate and 19 to placebo. Of the 36 patients, 34 completed the study ( $p=0.10$ ); two placebo-treated patients withdrew (Table 202.1).

**Table 202.1. Patient Disposition in Part 2**

	All Patients			
	Lanthanum		Placebo	
	N	%	n	%
Entered	17		19	
Completed	17	100.0	17	89.5
Discontinued:	0		2	10.5
Adverse event			1	5.3
Protocol violation			1	5.3
Patients in the ITT population	17	100.0	19	100.0
Patients in the Per Protocol population	17	100.0	17	89.5

Caucasians made up 94% of the patients. There was a balanced distribution of patients between the two treatment groups relative to age ( $p=0.51$ ), gender ( $p=0.71$ ), duration of renal disease or dialysis ( $p\geq 0.79$ ), type of dialysis ( $p=0.96$ ) or previous transplant status ( $p=0.11$ ).

**Primary Efficacy Results in Part 2**

The primary efficacy variable was the control of serum phosphate level at the end of treatment. Last observation was carried forward for this analysis. Results are shown in Table 202.2. Primary efficacy analysis showed that lanthanum was statistically significantly better than placebo ( $p=0.008$ ) relative to the proportion of patients with the serum phosphate control at the end of the treatment. The result in the Per Protocol population supported the result in the ITT population ( $p=0.016$ ).

**Table 202.2. Efficacy Results in Study LAM-202. Percentage of patients with the serum phosphate control.**

<b>ITT Population (Primary efficacy analysis)</b>					
	<b>Lanthanum</b>		<b>Placebo</b>		<b>p-value</b>
	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>	
Week 5	13/17	76.5	14/19	73.7	1.00
End of treatment	11/17	64.7	4/19	21.1	0.008

<b>Per-Protocol Population (supporting analysis)</b>					
	<b>Lanthanum</b>		<b>Placebo</b>		<b>p-value</b>
	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>	
Week 5	13/17	76.5	12/17	70.6	1.00
End of treatment	11/17	64.7	4/17	23.5	0.016

Results for the CAPD patients were similar to those for the overall population. At week 9, phosphate was controlled in 6/10 (60.0%) of CAPD patients taking lanthanum carbonate and in 1/9 (11.1%) taking placebo ( $p = 0.057$ ). The proportions with controlled phosphate at the last visit were 6/10 (60.0%) and 1/11 (9.1%), respectively ( $p = 0.024$ ).

### 3.2.3 Safety in Study LAM-IV-202

There was no statistically significant difference between lanthanum and placebo relative to the proportion of patients with adverse events.

### 3.2.4 Conclusions on Study LAM-IV-202

Primary efficacy analysis of Study LAM-IV-202 showed that lanthanum was statistically significantly better than placebo ( $p=0.008$ ) relative to the proportion of patients with serum phosphate control at the end of treatment. There was no statistically significant difference between lanthanum and placebo relative to the proportion of patients with adverse events.

## 3.3 STUDY LAM-IV-204

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

### **3.3.1 Design of Study LAM-IV-204**

This was a USA, Phase 2, randomized, double-blind, placebo-controlled, parallel group, and dose ranging study of lanthanum carbonate in chronic renal failure subjects receiving hemodialysis. First, subjects enrolled into a placebo run-in phase during which they stopped all phosphate binding medications. To be eligible to enter the double-blind treatment phase, subjects' serum PO<sub>4</sub> had to be > 5.6 mg/dL. Eligible subjects were then randomized to six weeks of double-blind study drug treatment. Study drug was supplied as identical, round, chewable tablets. Daily doses were administered BID or TID with meals.

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

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

**Duration of Treatment:** The placebo run-in phase lasted from one to three weeks, until subjects' serum PO<sub>4</sub> was > 5.6 mg/dL. Double-blind treatment lasted for 6.

**The primary efficacy parameter** was the reduction in serum PO<sub>4</sub> levels from washout following six weeks of treatment.

#### **Sponsor's Statistical Methods**

The primary efficacy endpoint, the reduction in PSPL from end-of-washout (EOW) to end-of-treatment (EOT), was analyzed using a one-way ANOVA for the ITT population. The ITT population was defined as all randomized patients who had phosphorus levels available both pre- and post-randomization. The secondary efficacy analysis was based on the Per Protocol population defined as patients treated at least for 2 weeks with the average drug compliance of at least 80% over treatment duration.

Based on the results from the ANOVA model, Dunnett's test for multiple mean comparisons, was employed to compare the average PSPL changes or reductions (EOT – EOW) of the four lanthanum groups to placebo. For both the ANOVA and Dunnett's test, the type I error rate for rejecting a null hypothesis was 0.05.

**3.3.2 Efficacy Results in Study LAM-IV-204****Disposition of Subjects**

One hundred and ninety-six (196) subjects were enrolled in the study and entered the placebo run-in phase. Of these subjects 145 met the criteria for randomization to the double-blind treatment phase. Thirty-two, 28, 29, 30, and 26 subjects were randomized to receive placebo, lanthanum 225 mg/day, 675 mg/day, 1350 mg/day, and 2250 mg/day, respectively. Disposition of patients in the randomized part of the study is shown in Table 204.1. The numbers of subjects in each treatment group who completed the study were 15 (49%), 13 (46%), 20 (69%), 21 (70%), and 22 (85%), respectively ( $p=0.0085$ ).

**Table 204.1 Disposition of Patients in the Randomized Part of Study LAM-IV-204**

	P-value	Randomized Treatment				
		Placebo	La225 mg	La675 mg	La1350 mg	La2250 mg
Entered		32	28	29	30	26
Randomized		32	28	29	30	26
Completed	0.0085	15	13	20	21	22
Discontinued	0.0085	17	15	9	9	4
AEs (death)	0.39	3	4	4	1	1
Safety <sup>1)</sup>	0.032	13	7	5	5	2
Administrative <sup>2)</sup>	0.11	1	4	0	3	1
# of patients for assessment						
Efficacy		32	27 <sup>3)</sup>	29	30	26
Safety		32	28	29	30	26

<sup>1)</sup> Including efficacy-related safety criteria such as  $PO_4 > 10$  mg/dL (8),  $PO_4 \times Ca > 80$  mg<sup>2</sup>/dL<sup>2</sup> (25), and  $\Delta_{PTH} > 500$ ;

<sup>2)</sup> Including 7 protocol violations, 8 consent withdrawal, 2 kidney transplants, 1 lost-to-follow-up, 9 other administration reasons such as non-compliance and scheduled absence;

<sup>3)</sup> One patient had no serum phosphate data post randomization.

All subjects randomized into the treatment phase who had serum phosphorus levels available both pre- and post-randomization, were included for the ITT analysis. Out of 145 patients randomized, 144 (99.3%) patients had valid primary efficacy data pre- and post-randomization. These 144 subjects (Placebo: 32; lanthanum 225 mg/day: 27; 675 mg/day: 29; 1350 mg/day: 30; and 2250 mg/day: 26) were defined as the patient sample eligible for ITT analysis. Out of 144 ITT-eligible patients, 114 (79%) patients met the criteria for PP analysis.

Among the 144 patients of the ITT population, 80 (55%) were male and 64 (45%) female, and 102 (71%) were black, 36 (25%) whites, and 6 (4%) other races. There were no statistically

significant differences between the treatment groups relative to age, race, weight, and height ( $p \geq 0.47$ ). The distribution of male and female subjects across treatment groups was marginally significant ( $p = 0.058$ ).

There were no statistically significant differences ( $p > 0.081$ ) between the treatment groups relative to the baseline clinical characteristics: diabetes or hypertension vs. other diseases; urea reduction ratio; duration of hemodialysis; previous kidney transplant; hemodialysis schedule; meal routine; or daily calcium and phosphorus intake during washout.

### Primary Efficacy Results

The primary efficacy parameter was the change in the serum phosphorus level from the end of end of washout (EOW) to the end of treatment (EOT). The phosphate levels were the mean of the values obtained pre-dialysis at the dialysis sessions #2 and #3 of the corresponding study week. Table 204.2 shows that there were no differences in the EOW serum phosphate concentrations between the treatment groups ( $p = 0.10$ ). There was a statistically significant difference between the 5 treatment groups relative to the changes in phosphate concentrations from EOW to EOT ( $p < 0.0001$ ). Pairwise comparisons versus placebo by Dunnett's test showed that lanthanum 1350 mg/day and lanthanum 2250 mg/day were statistically significantly better than placebo ( $p < 0.001$ ) and the two lower lanthanum doses were not statistically different from placebo.

**Table 204.2 Primary Efficacy Analysis in the ITT population of Study LAM-IV-204  
Change in Serum PO<sub>4</sub> Level from End of Washout to End of Treatment**

	Treatment Group					p-value
	Placebo N=32	La225 N=27	La675 N=29	La1350 N=30	La2250 N=26	
Baseline Serum PO <sub>4</sub> (EOW) mg/dL	7.19 ± 1.35	6.55 ± 1.13	7.25 ± 1.44	6.81 ± 1.42	7.42 ± 1.20	0.103
Change in Serum PO <sub>4</sub> from EOW to EOT mg/dL	0.75 ± 1.47	0.66 ± 1.57	0.07 ± 1.85	-0.95 ± 1.39	-1.13 ± 2.01	< 0.0001

### 3.3.3 Safety in Study LAM-IV-204

Proportion of patients with adverse events is presented in Table 204.3. As is seen from Table 204.3, there was no statistically significant difference between lanthanum and placebo relative to the incidence of adverse events.

**Table 204.3 Proportion of Patients Post-Randomization with Adverse Events in Study LAM-IV-204.**

Adverse Event	Treatment Group		
	Lanthanum Groups (N = 113)	Placebo Group (N = 32)	P-value
At least one adverse event	76 (67%)	20 (63%)	0.62
At least one severe adverse event	17 (15%)	1 (3%)	0.12
Drug related nausea	11 (10%)	3 (9%)	1.0
Dialysis graft clotted	10 (9%)	0 (0%)	0.12
Abdominal pain	6 (5%)	0 (0%)	0.34

*Likelihood Ratio Chi-Square or Fisher's exact test in Reviewer's Analysis.*

**3.3.4 Conclusions on Study LAM-IV-204**

Primary efficacy analysis of Study LAM-IV-204 showed that there was a statistically significant difference between the 5 treatment groups relative to the changes in phosphate concentrations from baseline to the end of treatment ( $p < 0.0001$ ). Pairwise comparisons versus placebo by Dunnett's test showed that two higher doses, lanthanum 1350 mg/day and lanthanum 2250 mg/day, were statistically significantly better than placebo ( $p < 0.001$ ). The two lower lanthanum doses (675 mg/day and 225 mg/day) were not statistically different from placebo. Safety analysis found that there was no statistically significant difference between lanthanum and placebo relative to the incidence of adverse events.

**3.4 STUDY LAM-IV-307**

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

**3.4.1 Design of Study LAM-IV-307**

This is a USA, Phase 3, ongoing, open label, randomized, multicenter, comparator controlled, parallel group study of the long-term safety of lanthanum carbonate for controlling hyperphosphatemia in chronic renal failure patients undergoing hemodialysis three times per week. The study consisted of three phases: a screening and one- to three-week washout phase (Part 1), followed by a six-week dose-titration phase (Part 2), and finally, a long-term maintenance phase (Part 3), for a total of 24 months. To be eligible to enter the dose-titration phase, patients'  $PO_4$  levels had to be  $>5.9$  mg/dL. Eligible patients were randomized at a 1:1 ratio to receive either lanthanum carbonate or their pre-study standard phosphate binder. Five

daily doses of lanthanum were used: 375 mg, 750 mg, 1500 mg, 2250 mg, and 3000 mg. All patients received phosphate binder for up to 24 months.

All patients had PO<sub>4</sub> levels assessed weekly and their phosphate binder dose titrated for a period of six weeks. Patients randomized to the lanthanum arm received a starting dose of 750 mg daily unless, at the discretion of the Investigator, the patient required a starting daily dose of 1500 mg lanthanum. Doses were titrated as necessary up to a maximum of 3000 mg/day, and were adjusted based on the results of the PO<sub>4</sub> levels taken at the first dialysis session of the week. If the patient's PO<sub>4</sub> level dropped below 3.1 mg/dL the patient's lanthanum dose could have been reduced to 375 mg per day. Patients randomized to standard therapy had their dose of phosphate binder titrated according to the drug's label and current clinical practice.

### Number of Patients

A. The NDA filing date was April 30, 2002, with the data cut off date **October 31, 2001**. The protocol called for a total of at least 500 patients randomized to each arm. As of October 31, 2001, a total of 1,345 patients enrolled with 1,228 patients being randomized to treatment (616 lanthanum versus 612 standard therapy). A total of 110 patients were terminated prior to randomization, and 7 patients were still in the washout phase.

B. A four-month Safety Update was submitted on August 27, 2002. This update presented the interim safety data as of **May 30, 2002**. The update includes additional 61 patients whose data were not available in the original NDA. As of May 30, 2002, a total of 1289 patients were randomized (647 lanthanum versus 642 on standard therapy).

**Inclusion Criteria:** Patients of either sex, at least 12 years of age, with chronic renal failure, who had undergone hemodialysis for chronic renal failure three times per week for at least the previous two months, and who currently required phosphate binders for the treatment of hyperphosphatemia (PO<sub>4</sub> >5.9 mg/dL).

**Duration of Treatment:** The washout phase was one to three weeks (Part 1), dose titration lasted for six weeks (Part 2), and maintenance treatment lasted for 24 months (Part 3).

**The primary objective of this open label study** is to evaluate the **long-term safety** of lanthanum carbonate in chronic renal failure patients with hyperphosphatemia receiving hemodialysis.

### Reviewer's Statistical Methods

Study LAM-IV-307 is an open label trial. The primary objective was to evaluate the long-term safety of lanthanum carbonate as compared to the standard therapy. Efficacy was a secondary objective of this open-label study. Study LAM-IV-307 was not powered for non-inferiority efficacy analysis. The sponsor's statistical plan for the efficacy analysis did not pre-specify non-inferiority delta which is required by the ICH E9 Document for the efficacy analysis of the active control studies. For all these reasons, no conclusion could be drawn for non-inferiority and thus,

efficacy was not reviewed for this study. This review includes only safety analysis of Study LAM-IV-307.

#### **Sponsor's Statistical Methods:**

As there were more early terminations in the lanthanum group due to adverse events, survival analysis was performed for the adverse events that showed a between-group difference of at least 6% in incidence rate. Survival analysis included Kaplan-Meier estimates and log-rank tests. The time to event was defined as number of months from the time when patients were randomized to the first occurrence of an event under study.

### **3.5 SPONSOR'S SAFETY RESULTS AND CONCLUSIONS IN STUDY LAM-IV-307**

#### **3.5.1 Sponsor's Time-to-Event Analysis (October 31, 2001):**

The sponsor found that death rate and the incidence of most adverse events were lower in the lanthanum group. To take into account a higher termination rate in the lanthanum group, the sponsor presented time-to-event analysis of the adverse events and deaths in Study LAM-IV-307. Survival analysis was performed for the adverse events that showed a between-group difference of at least 6% in incidence rate.

The sponsor's conclusion was that time-to-event patterns were statistically significantly different ( $p < 0.04$ ) between the two treatments in favor of the lanthanum group for the following adverse events: back pain, edema peripheral, dyspepsia, hypercalcaemia, and pneumonia ( $p < 0.04$ ). The sponsor also concluded that patient survival while on the study in the lanthanum group was statistically significantly higher than in the standard group ( $p = 0.027$ ).

#### **3.5.2 Sponsor's Results on Safety Update (May 30, 2002)**

On August 27, 2002, the sponsor submitted a Safety Update, which included cumulative safety data from additional 61 patients whose data were not available in the original NDA submission. This update reflects data collected as of May 30, 2002, the cut-off date for the interim report of Study LAM-IV-307 and the safety update. The total number of patients in Study LAM-IV-307 on May 30, 2002, was 1289 (647 in the lanthanum group and 642 in the standard group).

The sponsor's conclusions on the Safety Update were very similar to the conclusions on the data of October 30, 2001. Time-to-event patterns were statistically significantly different ( $p < 0.04$ ) between the two treatments in favor of the lanthanum group for the following adverse events: back pain, edema peripheral, dyspepsia, hypercalcaemia, and pneumonia. While on the study, patient survival in the lanthanum group was statistically significantly higher than in the standard group ( $p = 0.015$ ).

**3.6 REVIEWER'S SAFETY RESULTS IN STUDY LAM-IV-307****3.6.1 Patient Disposition in Study LAM-IV-307 (October 31, 2001)**

A total of 1,345 patients were enrolled in the study. Of the 1,228 patients randomized, 616 patients (50.2%) were randomized to receive lanthanum carbonate, and 612 patients (49.8%) were randomized to standard therapy. The patient disposition is summarized in Table 307.1. Table 307.1 shows that lanthanum was statistically significantly ( $p < 0.001$ ) worse than standard therapy relative to proportion of patients who are remaining in the study and have completed. Lanthanum was statistically significantly worse than standard therapy relative to proportion of patients who withdrew due to adverse events ( $p < 0.0001$ ), protocol violations ( $p = 0.003$ ), consent withdrawal ( $p < 0.001$ ), exceeding safety criteria ( $p = 0.024$ ), and other ( $p = 0.005$ ). A total of 645 patients (52.5%) terminated after they had been randomized to treatment: 386 (63%) in the lanthanum group versus 259 (42%) in the standard therapy group,  $p < 0.001$ . Terminated patients were not followed in Study LAM-IV-307, and the study report does not provide any information on the survival of the patients who were terminated.

**Table 307.1 Patient Disposition in Study 307 (Cut off date of October 31, 2001)**

Treatment	Lanthanum N (%)	Standard N (%)	P-value
<b>Total enrolled</b>	<b>616</b>	<b>612</b>	
Number remaining in the study	196 (31.8)	289 (47.2)	0.001*
Number who have completed the study	34 (5.5)	64 (10.5)	0.001*
Number withdrawn	386 (62.7)	259 (42.3)	0.001*
Reasons for withdrawal:			
Adverse Event	80 (13.0)	17 (2.8)	0.0001*
Protocol Violation	13 (2.1)	2 (0.3)	0.003*
Withdrew Consent	81 (13.1)	26 (4.2)	0.001*
Patient Received Kidney Transplant	40 (6.5)	55 (9.0)	0.10
Lost to Follow-up	6 (1.0)	6 (1.0)	1.0
Death during the study	29 (4.7)	67 (10.9)	0.001
Other	95 (15.4)	62 (10.1)	0.005*
Exceeded Safety Criteria	42 (6.8)	24 (3.9)	0.024*
Two PO <sub>4</sub> evaluations > 10 mg/dL	28 (4.5)	16 (2.6)	0.067
Two PO <sub>4</sub> evaluations < 2.0 mg/dL	0 (0.0)	1 (0.2)	0.50
Two Ca*PO <sub>4</sub> products > 90mg <sup>2</sup> mg <sup>2</sup> /dL	8 (1.3)	4 (0.7)	0.25
Calcium > 11.5 mg/dL	1 (0.2)	1 (0.2)	1.0
Increase in PTH > 500 pg/mL from baseline	4 (0.6)	0 (0.0)	0.12
<i>Likelihood Ratio Chi-Square or Fisher's exact test in Reviewer's Analysis.</i>			
<i>* Statistically significant difference in favor of the Standard Therapy</i>			

**3.6.2 Extent of Exposure in Study LAM-IV-307 (October 31, 2001)**

Exposure to study drug by time interval is presented in Table 307.2. Table 307.2 shows that for most time intervals, patients in the Standard Therapy group had statistically significantly longer exposure to the study drug than the patients in the lanthanum group.

**Table 307.2 Duration of Exposure in Study LAM-IV-307 (October 31, 2001)**

Treatment Duration	Treatment Group		P-value
	Lanthanum Group N(%)	Standard Group N (%)	
	616	612	
< 1 month	53 (8.6%)	28 (4.6)	0.004*
≥ 1 to < 2 months	81 (13.1%)	34 (5.6%)	0.001*
> 2 to < 3 months	45 (7.3%)	27 (4.4%)	0.03*
≥ 3 to < 6 months	82 (13.3%)	58 (9.5%)	0.034*
≥ 6 to < 9 months	73 (11.9%)	63 (10.3%)	0.39
≥ 9 to < 12 months	39 (6.3%)	44 (7.2%)	0.55
≥ 12 to < 18 months	89 (14.4%)	91 (14.9%)	0.84
≥ 18 to < 24 months	120 (19.5%)	201 (32.8%)	0.001*
≥ 24 months	34 (5.5%)	66 (10.8%)	0.001*

*Likelihood Ratio Chi-Square in Reviewer's Analysis.*  
*\* Statistically significant difference in favor of Standard Therapy.*

Overall extent of exposure to the study drug in the two treatment groups is shown in Table 307.3. Table 307.3 shows that mean overall time of exposure in the lanthanum group was statistically significantly smaller than in the standard therapy group (284 days vs. 397 days,  $p < 0.0001$ ).

**Table 307.3 Overall Extent of Exposure to Study Drug in Study LAM-IV-307 (October 31, 2001)**

Total days	Treatment group		P-Value
	Lanthanum (N=616)	Placebo (N=612)	
Mean	284.3	397.0	<0.001
Median	198.5	415.5	
Standard Deviation	241.5	247.4	
Minimum	1	1	
Maximum	745	741	

**3.6.3 Adverse Events in Study LAM-IV-307 (October 31, 2001):**

The incidence rate for treatment-emergent adverse events was 90.9% for the lanthanum group and 92.3% for the standard therapy group ( $p=0.37$ ). Statistically significantly ( $p=0.0003$ ) more lanthanum patients experienced at least one drug-related AE compared with the standard therapy group: 124 (20.1%) versus 77 (12.6%). Statistically significantly ( $p<0.0001$ ) more lanthanum patients were withdrawn because of adverse events compared with the standard therapy group: 80 (13.0%) versus 17 (2.8%). A total of 312 patients (50.6%) in the lanthanum group and 390 (63.7%) in the standard therapy group experienced a serious AE ( $p<0.001$ ). Three serious AEs in lanthanum patients were related to study drug. A total of 37 lanthanum patients and 75 standard therapy patients have died post-randomization either during the study or within 30 days of their last dose of study drug, with  $p<0.001$  (Table 307.4).

**Table 307.4 Summary of Treatment-Emergent Adverse Events**

Category	Treatment Group		
	Lanthanum Group (N = 616)	Standard Group (N = 612)	P-value*
No. of patients with at least one treatment-emergent AE	560 (90.9%)	565 (92.3%)	0.37
No. of patients with at least one likely drug-related treatment-emergent AE	124 (20.1%)	77 (12.6%)	0.0003**
No. of patients withdrawn for adverse events as study outcome	80 (13.0%)	17 (2.8%)	<0.0001**
No. of patients with a SAE	312 (50.6%)	390 (63.7%)	<0.0001
No. of patients with a drug-related SAE	3 (0.49%)	0	0.25
No. of patients who died during study as study outcome	29 (4.7%)	67 (10.9%)	<0.0001
No. of patients who died during or within 30 days post study	37 (6.0%)	75 (12.3%)	<0.0001
*Likelihood Ratio Chi-Square or Fisher's exact test in reviewer's analysis			
** Statistically significant difference in favor of Standard Therapy.			

Incidence of drug related treatment emergent AEs is shown in Table 307.5. From this table it is seen that lanthanum was statistically significantly worse than standard therapy relative to the following drug related treatment emergent AEs: nausea ( $p<0.001$ ), vomiting ( $p<0.001$ ), diarrhea ( $p=0.007$ ), abdominal pain ( $p=0.009$ ) and headache ( $p=0.031$ ). Results in the Safety Update (with additional 61 patients) were very similar to the results in Table 307.5.

**Table 307.5 Summary of Drug-Related Treatment-Emergent Adverse Events (October 31, 2001)**

Drug related Adverse Event	Treatment Group		
	Lanthanum Group (N = 616)	Standard Group (N = 612)	P-value
At least one adverse event	124 (20.1%)	77 (12.6%)	0.0003*
Nausea	38 (6.2%)	8 (1.1%)	0.001*
Vomiting	19 (3.1%)	2 (0.3%)	0.001*
Diarrhea	19 (3.1%)	6 (1.0%)	0.007*
Headache	6 (1.1%)	0 (0%)	0.031*
Abdominal pain	13 (2.1%)	3 (0.5%)	0.009*
Constipation	15 (2.4%)	11 (1.8%)	0.44

*Likelihood Ratio Chi-Square or Fisher's exact test in Reviewer's Analysis.*  
\* Statistically significant difference in favor of Standard Therapy.

**3.6.4 Reviewer's Conclusions on Safety in Study LAM-IV-307**

Safety analysis of the open label, randomized, long-term Study LAM-IV-307 found that patients in the lanthanum group had a statistically significantly shorter drug exposure time and greater termination rate as compared to the standard therapy group ( $p < 0.001$ ). Lanthanum was statistically significantly worse than standard therapy relative to the proportion of patients who withdrew due to: adverse events (80 vs. 17,  $p < 0.0001$ ), protocol violations ( $p = 0.003$ ), consent withdrawal ( $p < 0.001$ ), exceeding safety criteria ( $p = 0.024$ ), and other ( $p = 0.005$ ). Statistically significantly more lanthanum patients experienced at least one drug-related adverse event compared with the standard therapy group: 124 (20.1%) versus 77 (12.6%),  $p < 0.001$ . Lanthanum was statistically significantly worse than standard therapy relative to the following drug related treatment emergent adverse events: nausea ( $p < 0.001$ ), vomiting ( $p < 0.001$ ), diarrhea ( $p = 0.007$ ), abdominal pain ( $p = 0.009$ ) and headache ( $p = 0.031$ ).

This reviewer does not agree with the sponsor's conclusions in Study LAM-IV-307 that lanthanum is safer than the standard therapy relative to mortality and most adverse events. In this study, termination rate in the lanthanum group was statistically significantly greater than in the standard therapy group (63% vs. 42%,  $p < 0.001$ ) and duration of exposure in the lanthanum group was statistically significantly shorter ( $p < 0.001$ ). Terminated patients were not followed regarding survival or adverse events. The log-rank tests in the sponsor's time-to-event analysis may give misleading results because they are based on the invalid assumption that censoring is random and the censoring distributions are the same in the two treatment groups. Because of the significantly shorter drug exposure time and greater termination rate in the lanthanum group and no follow-up of the terminated patients, safety comparisons in this open-label study may be biased in favor of lanthanum. For this reason, in this study, the safety results that are in favor of lanthanum, should be interpreted with great caution. On the other hand, the safety results that are in favor of the standard treatment can be considered as robust and conservative. To be conservative, this review presents mostly the safety results that are in favor of standard therapy.

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**STATISTICAL REVIEW AND EVALUATION**

**ADDENDUM**

**NDA #:** 21-468

**DRUG NAME:** Fosrenol (Lanthanum Carbonate Hydrate)

**INDICATION:** C J

**APPLICANT:** Shire Pharmaceutical Inc.

**DOCUMENTS REVIEWED:** Safety Update data of ongoing Study LAM-IV-307,  
10/3, 10/8, 11/22, 12/12 and 12/16/2002

**STATISTICAL REVIEWER:** Valeria Freidlin, Ph.D. (HFD-710)

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**STATISTICAL KEY WORDS:** ANCOVA, ANOVA, multiple comparisons, chi-square test, time-to-event analysis, log rank test, non-random censoring.

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### **3. SUMMARY OF STATISTICAL FINDINGS**

#### **3.1 Reviewer's Conclusions on Four-Month Safety Update of Study LAM-IV-307**

In the Four-Month Safety Update of the ongoing Study LAM-IV-307, lanthanum seems to prolong QT interval to a greater extent than the standard therapy. Because of the study deficiencies, the study data seem to be not adequate for mortality comparisons.

#### **3.2 Reviewer's Findings in Four-Month Safety Update of Ongoing Study LAM-IV-307**

##### **QT interval prolongation**

This Addendum reviews the data submitted after the statistical review was entered into DFS. The reviewer's analysis of the Four-Month Safety Update of the ongoing open-label Study LAM-IV-307 found that patients in the lanthanum group had a statistically significantly ( $p < 0.001$ ) shorter drug exposure time and greater termination rate as compared to the standard therapy group. Lanthanum was statistically significantly worse ( $p \leq 0.037$ ) than standard therapy relative to the number of all QTc events defined as QTc (Bazett correction) change from baseline  $\geq 30$  msec or  $\geq 60$  msec (Table 1). Lanthanum was statistically significantly worse ( $p \leq 0.026$ ) than standard therapy relative to the mean increase from baseline in QTc at Weeks 3, 7, and 14 (Table 2). Lanthanum was numerically worse than standard therapy relative to the mean QTc increase from baseline at Weeks 26 and 52, and at Month 24 (Table 2).

At Visit 21 (Month 24), numerically greater percentage of lanthanum patients had change from baseline  $\geq 30$  msec, as compared with the standard therapy group: 29 (26.6%) versus 35 (20.4%). At Month 24, statistically significantly ( $p = 0.048$ ) more lanthanum patients had QTc change from baseline  $\geq 60$  msec, as compared with the standard therapy group: 11 (10.1%) versus 7 (4.1%).

Because of the statistically significantly shorter drug exposure time and greater termination rate in the lanthanum group in this study, comparison of the percentages of patients with at least one QTc event at any time may be biased in favor of lanthanum. In spite of this, greater percentage of lanthanum patients experienced at least one QTc event compared with the standard therapy patients. Namely, 41.8% of lanthanum patients had change from baseline  $\geq 30$  msec, as compared with 40.2% of standard therapy patients, and 10.0% of lanthanum patients had change from baseline  $\geq 60$  msec, as compared with 9.3% of standard therapy patients.

Results for QTc with Bazett correction are supported by the results for QTf with Fredericia correction (see Tables 1-A, 2-A, 3-A, and 4-A) and by the results for QT without correction (see Tables 1-B, 2-B, 3-B, and 4-B).

## Mortality

In this study, termination rate in the lanthanum group was statistically significantly ( $p < 0.001$ ) greater than in the standard therapy group and terminated patients were not followed regarding mortality or adverse events. On October 23, 2002, this reviewer requested the sponsor to follow up all study patients terminated after randomization and find out whether they are alive or not. In the 11/21/02 submission, the sponsor provided mortality information for only 85% of the patients. The relative risk (rr) of mortality of lanthanum to standard therapy in the 11/21/02 submission increased (19.2% versus 22.7%,  $rr = 0.85$ ,  $p = 0.16$ ) as compared with the original 4/30/02 submission (2.4% versus 5.5%,  $rr = 0.44$ ,  $p = 0.027$ ). This contrast shows the importance of complete follow-up. The agency requested the sponsor again to submit 100% of mortality data and provide a breakdown by treatment group of who is missing and why the data were not submitted. These data are not submitted yet. Because of these deficiencies, this reviewer thinks that the study data are not adequate for mortality comparisons.

## 4. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

### 4.1 DESIGN OF STUDY LAM-IV-307

This is a USA, Phase 3, ongoing, open label, randomized, multicenter, comparator controlled, parallel group study of the long-term safety of lanthanum carbonate for controlling hyperphosphatemia in chronic renal failure patients undergoing hemodialysis three times per week. The study consisted of three phases: a screening and one- to three-week washout phase (Part 1), followed by a six-week dose-titration phase (Part 2), and finally, a long-term maintenance phase (Part 3), for a total of 24 months. To be eligible to enter the dose-titration phase, patients'  $PO_4$  levels had to be  $> 5.9$  mg/dL. Eligible patients were randomized at a 1:1 ratio to receive either lanthanum carbonate or their pre-study standard phosphate binder. Five daily doses of lanthanum were used: 375 mg, 750 mg, 1500 mg, 2250 mg, and 3000 mg. All patients received phosphate binder for up to 24 months.

All patients had their phosphate binder dose titrated for a period of six weeks. Patients randomized to the lanthanum arm received a starting dose of 750 mg daily unless, at the discretion of the Investigator, the patient required a starting daily dose of 1500 mg lanthanum. Doses were titrated as necessary up to a maximum of 3000 mg/day, and were adjusted based on the results of the  $PO_4$  levels taken at the first dialysis session of the week. If the patient's  $PO_4$  level dropped below 3.1 mg/dL the patient's lanthanum dose could have been reduced to 375 mg per day. Patients randomized to standard therapy had their dose of phosphate binder titrated according to the drug's label and current clinical practice.

### Number of Patients

A Four-Month Safety Update presented the interim safety data as of May 30, 2002. The update includes additional 61 patients whose data were not available in the original NDA. As of May 30, 2002, a total of 1289 patients were randomized (647 to lanthanum versus 642 to standard therapy).

**Inclusion Criteria:** Patients of either sex, at least 12 years of age, with chronic renal failure, who had undergone hemodialysis for chronic renal failure three times per week for at least the previous two months, and who currently required phosphate binders for the treatment of hyperphosphatemia ( $\text{PO}_4 > 5.9$  mg/dL).

**Duration of Treatment:** The washout phase was one to three weeks (Part 1), dose titration lasted for six weeks (Part 2), and maintenance treatment lasted for 24 months (Part 3).

**The primary objective of this open label study** is to evaluate the **long-term safety** of lanthanum carbonate in chronic renal failure patients with hyperphosphatemia receiving hemodialysis.

### Reviewer's Statistical Methods

Study LAM-IV-307 is an open label trial. The primary objective is to evaluate the long-term safety of lanthanum carbonate as compared to the standard therapy. In this Addendum, proportions of patients with QT interval events were compared using the likelihood ratio chi-square test. Mean changes from baseline in QT interval were compared between the two treatment groups using ANCOVA model with baseline QT measurement as covariate.

### 4.2 REVIEWER'S RESULTS IN FOUR-MONTH SAFETY UPDATE OF STUDY 307

The reviewer's analysis of the Four-Month Safety Update of the ongoing open-label Study LAM-IV-307 found that patients in the lanthanum group had a statistically significantly ( $p < 0.001$ ) shorter drug exposure time and greater termination rate as compared to the standard therapy group.

#### 4.2.1 QTc (Bazett Correction)

Number of all QTc (Bazett correction) events is shown in Table 1. As seen in Table 1, lanthanum was statistically significantly worse ( $p \leq 0.037$ ) than standard therapy relative to the number of all QTc events defined as QTc change from baseline  $\geq 30$  msec or  $\geq 60$  msec.

Mean change from baseline in QTc is shown in Table 2. As seen in Table 2, lanthanum was statistically significantly worse ( $p \leq 0.026$ ) than standard therapy relative to the mean increase from baseline in QTc at Weeks 3, 7, and 14. Lanthanum was numerically worse than standard therapy at Weeks 26 and 52, and at Month 24.

Number (%) of patients with QTc abnormalities at Visit 21 (Month 24) are shown in Table 3. As seen in Table 3, at Month 24, numerically greater percentage of lanthanum patients had change from baseline  $\geq 30$  msec, as compared with the standard therapy group: 29 (26.6%) versus 35 (20.4%). At Month 24, statistically significantly ( $p = 0.048$ ) more lanthanum patients had QTc change from baseline  $\geq 60$  msec, as compared with the standard therapy group: 11 (10.1%) versus 7 (4.1%).

Number (%) of patients with QTc abnormalities at any time are shown in Table 4. As seen in Table 4, more lanthanum patients experienced at least one QTc event compared with the standard therapy patients. Namely, 41.8 % of lanthanum patients had change from baseline  $\geq 30$  msec, as compared with 40.2 % of standard therapy patients, and 10.0 % of lanthanum patients had change from baseline  $\geq 60$  msec, as compared with 9.3 % of standard therapy patients.

#### 4.2.2 QTf (Fredericia Correction)

Number of all QTf (Fredericia correction) events is shown in Table 1-A. As seen in Table 1-A, lanthanum was marginally significantly worse ( $p \leq 0.056$ ) than standard therapy relative to the number of all QTf events defined as QTf change from baseline  $\geq 30$  msec or  $\geq 60$  msec.

Mean change from baseline in QTf is shown in Table 2-A. As seen in Table 2-A, lanthanum was statistically significantly worse ( $p \leq 0.0046$ ) than standard therapy relative to the mean increase from baseline in QTf at Weeks 7 and 14. Lanthanum was numerically worse than standard therapy at Weeks 3, 26, and 52, and at Month 24.

Number (%) of patients with QTf abnormalities at Visit 21 (Month 24) are shown in Table 3-A. As seen in Table 3-A, at Month 24, numerically greater percentage of lanthanum patients had change from baseline  $\geq 30$  msec, as compared with the standard therapy group: 26 (23.9%) versus 30 (17.4%). At Month 24, statistically significantly ( $p=0.023$ ) more lanthanum patients had QTf change from baseline  $\geq 60$  msec, as compared with the standard therapy group: 9 (8.3 %) versus 4 (2.3 %).

Number (%) of patients with QTf abnormalities at any time are shown in Table 4-A. As seen in Table 4-A, more lanthanum patients experienced at least one QTf event compared with the standard therapy patients. Namely, 36.2 % of lanthanum patients had change from baseline  $\geq 30$  msec, as compared with 35.0 % of standard therapy patients, and 6.6 % of lanthanum patients had change from baseline  $\geq 60$  msec, as compared with 6.3 % of standard therapy patients.

QT (no correction) wave prolongation results are shown in Tables 1-B, 2-B, 3-B, and 4-B.

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**4.2.3 Tables**

<b>Table 1. Number of all QTc Events (Bazett Correction) Safety Update of Study LAM-IV-307 (May 30, 2002)</b>					
QTc Event	Lanthanum (N=3290)		Standard Therapy (N=3700)		P-value
	N	%	N	%	
Change from Baseline in QTc $\geq$ 30 msec	504	15.3 %	502	13.6 %	0.037
Change from Baseline in QTc $\geq$ 60 msec	106	3.2 %	88	2.4 %	0.032

<b>Table 2. Mean Change from Baseline in QTc (Bazett Correction) Safety Update of Study LAM-IV-307 (May 30, 2002)</b>					
Visit (Week/Month)	Lanthanum		Standard Therapy		P-value
	N	Mean	N	Mean	
Baseline	639	424.7	632	425.9	0.47
QTc Change ( $\Delta$ ) from Baseline to:	N	$\Delta$	N	$\Delta$	P-value
Visit 3 (Week 3)	592	6.3	600	2.5	0.026
Visit 7 (Week 7)	517	8.3	575	3.2	0.0026
Visit 9 (Week 14)	457	7.5	537	1.2	0.0025
Visit 12 (Week 26)	360	6.1	481	3.2	0.35
Visit 15 (Week 52)	223	8.1	332	5.3	0.38
Visit 18 (Month 18)	137	6.9	249	7.6	0.70
Visit 21 (Month 24)	109	13.9	172	5.6	0.053

<b>Table 3. Number (%) Patients with QTc (Bazett Correction) Abnormalities at Visit 21 (Month 24) Safety Update of Study LAM-IV-307 (May 30, 2002)</b>					
QTc Abnormality	Lanthanum (N=109)		Standard Therapy (N=172)		P-value
	N	%	N	%	
Change from Baseline in QTc $\geq$ 30 msec	29	26.6 %	35	20.4 %	0.23
Change from Baseline in QTc $\geq$ 60 msec	11	10.1 %	7	4.1 %	0.048
QTc > 450 msec	35	32.1 %	51	29.7 %	0.66
QTc > 480 msec	10	9.2 %	11	6.4 %	0.39
QTc > 500 msec	2	1.8 %	5	2.9 %	0.57

<b>Table 4. Patients with QTc (Bazett Correction) Abnormalities at any Time Safety Update of Study LAM-IV-307 (May 30, 2002)</b>				
<b>QTc Interval Abnormality</b>	<b>Lanthanum (N=639)</b>		<b>Standard Therapy (N=632)</b>	
	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>
Change from Baseline in QTc $\geq$ 30 msec	267	41.8 %	254	40.2 %
Change from Baseline in QTc $\geq$ 60 msec	64	10.0%	59	9.3 %

<b>Table 1-A. Number of all QTf Events (Fredericia Correction) Safety Update of Study LAM-IV-307 (May 30, 2002)</b>					
<b>QTf (Fredericia Correction) Event</b>	<b>Lanthanum (N=3290)</b>		<b>Standard Therapy (N=3700)</b>		<b>P-value</b>
	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>	
Change from Baseline in QTf $\geq$ 30 msec	434	13.2 %	431	11.7%	0.051
Change from Baseline in QTf $\geq$ 60 msec	74	2.3 %	60	1.6 %	0.056

<b>Table 2-A. Mean Change from Baseline in QTf (Fredericia Correction) Safety Update of Study LAM-IV-307 (May 30, 2002)</b>					
	<b>Lanthanum</b>		<b>Standard Therapy</b>		<b>P-value</b>
	<b>N</b>	<b>Mean</b>	<b>N</b>	<b>Mean</b>	
<b>Baseline</b>	<b>639</b>	<b>408.4</b>	<b>632</b>	<b>410.0</b>	<b>0.34</b>
<b>QTf Change (<math>\Delta</math>) from Baseline to:</b>	<b>N</b>	<b><math>\Delta</math></b>	<b>N</b>	<b><math>\Delta</math></b>	<b>P-value</b>
Visit 3 (Week 3)	592	5.2	600	2.4	0.13
Visit 7 (Week 7)	517	7.1	575	2.5	0.0046
Visit 9 (Week 14)	457	7.4	537	1.1	0.0013
Visit 12 (Week 26)	360	6.0	481	3.3	0.33
Visit 15 (Week 52)	223	6.8	332	5.6	0.88
Visit 18 (Month 18)	137	7.1	249	7.5	0.64
Visit 21 (Month 24)	109	13.4	172	5.9	0.071

<b>Table 3-A. Number (%) Patients with QTf (Fredericia Correction) Abnormalities at Visit 21 (Month 24)</b>					
<b>Safety Update of Study LAM-IV-307 (May 30, 2002)</b>					
QTf Abnormality	Lanthanum (N=109)		Standard Therapy (N=172)		P-value
	N	%	N	%	
Change from Baseline in QTf $\geq$ 30 msec	26	23.9 %	30	17.4 %	0.19
Change from Baseline in QTf $\geq$ 60 msec	9	8.3 %	4	2.3 %	0.023
QTf $\geq$ 450 msec	22	20.2 %	23	13.4 %	0.13
QTf $\geq$ 480 msec	3	2.8 %	6	3.5 %	0.73
QTf $\geq$ 500 msec	1	0.9 %	2	1.2 %	0.84

<b>Table 4-A. Patients with QTf (Fredericia Correction) Abnormalities at any Time</b>				
<b>Safety Update of Study LAM-IV-307 (May 30, 2002)</b>				
QTf Interval Abnormality	Lanthanum (N=639)		Standard Therapy (N=632)	
	N	%	N	%
Change from Baseline in QTf $\geq$ 30 msec	231	36.2 %	221	35.0 %
Change from Baseline in QTf $\geq$ 60 msec	42	6.6%	40	6.3 %

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<b>Table 1-B. Number of all QT Events (No Correction) Safety Update of Study LAM-IV-307 (May 30, 2002)</b>					
QT Event	Lanthanum (N=3290)		Standard Therapy (N=3700)		P-value
	N	%	N	%	
Change from Baseline in QT > 30 msec	505	15.4 %	573	15.5 %	0.87
Change from Baseline in QT > 60 msec	124	3.8 %	120	3.2 %	0.23

<b>Table 2-B. Mean Change from Baseline in QT (No Correction) Safety Update of Study LAM-IV-307 (May 30, 2002)</b>					
	Lanthanum		Standard Therapy		P-value
	N	Mean	N	Mean	
Baseline	639	379.01	632	380.93	0.34
<b>QT Change (<math>\Delta</math>) from Baseline to:</b>	<b>N</b>	<b><math>\Delta</math></b>	<b>N</b>	<b><math>\Delta</math></b>	<b>P-value</b>
Visit 3 (Week 3)	592	3.5	600	2.3	0.89
Visit 7 (Week 7)	517	4.9	575	1.3	0.090
Visit 9 (Week 14)	457	6.9	537	1.26	0.019
Visit 12 (Week 26)	360	5.6	481	3.9	0.66
Visit 15 (Week 52)	223	4.6	332	6.5	0.27
Visit 18 (Month 18)	137	7.3	249	7.5	0.57
Visit 21 (Month 24)	109	12.6	172	6.9	0.37

<b>Table 3-B. Number (%) Patients with QT (No Correction) Abnormalities at Visit 21 (Month 24) Safety Update of Study LAM-IV-307 (May 30, 2002)</b>					
QT Abnormality	Lanthanum (N=109)		Standard Therapy (N=172)		P-value
	N	%	N	%	
Change from Baseline in QT > 30 msec	33	30.3 %	43	25.0 %	0.33
Change from Baseline in QT > 60 msec	14	12.8 %	10	5.8 %	0.043
QT $\geq$ 450 msec	9	8.3 %	10	5.8 %	0.43
QT $\geq$ 480 msec	2	1.8 %	5	2.9 %	0.57
QT $\geq$ 500 msec	2	1.8 %	2	1.2 %	0.65

<b>QT Interval Abnormality</b>	<b>Lanthanum (N=639)</b>		<b>Standard Therapy (N=632)</b>	
	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>
Change from Baseline in QT $\geq$ 30 msec	246	38.5 %	280	44.3 %
Change from Baseline in QT $\geq$ 60 msec	80	12.5 %	80	12.7 %

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