MEDICAL REVIEW

NDA No.: 21-468
DRUG NAME: FOSRENOL™ (Lanthanum Carbonate) Chewable Tablets
SPONSOR: SHIRE PHARMACEUTICAL COMPANY
1901 Research Boulevard
Rockville, MD 20850
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INTRODUCTION AND BACKGROUND

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

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

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

At present, the most effective approach in the treatment of hyperphosphatemia associated with renal insufficiency is to lessen intestinal absorption by the administration of phosphate binders, i.e., aluminum- (off-label use) or calcium-based phosphate binding agents or more recently with RENAGEL® (sevelamer hydrochloride). Of note, although highly effective as a phosphate binder, long-term use (off-label) of aluminum salts has been shown to result in serious adverse events such as aluminum-related bone disease, dementia, myopathy, hypoparathyroidism, and death.

The clinical development program of FOSRENOL™ is centered on its ability to act as a phosphate binder and thus to treat hyperphosphatemia associated with end-stage renal disease.

DRUG ESTABLISHED AND PROPOSED TRADE NAME

The active ingredient in lanthanum carbonate chewable tablets is lanthanum (III) carbonate hydrate, an inorganic salt with the approximate formula $La_2(C0_3)_3.4H_20$. The sponsor's proposed trade name for lanthanum carbonate is FOSRENOL™.

DRUG CLASS

FOSRENOL™ (Lanthanum Carbonate) is a phosphate binder that acts in the lumen of the gastrointestinal tract to bind dietary phosphorus released from food during digestion. According to the sponsor, "the chemical basis for this being the ionic binding properties of La^{3+}, which has an overwhelming preference for oxygen donor atoms of which the most common ligands are carboxyl and phosphate ($P0_4$) groups. In the presence of HCl in the stomach, a proportion of administered lanthanum carbonate is converted to the more highly soluble chloride salt with the release of carbon dioxide. The relatively high solubility of the chloride salt implies a greater absorption potential of La^{3+}. The activity of lanthanum carbonate as a phosphate binder is dependent on the availability of soluble La^{3+} in the gastrointestinal tract and the high affinity of La^{3+} for $P0_4^{2-}$. This binding results in the formation of highly insoluble lanthanum phosphate salt, which cannot be absorbed and therefore is excreted, thus significantly reducing phosphate absorption."

SPONSOR'S PROPOSED INDICATION(S)

The sponsor is seeking the following indication "FOSRENOL™ is indicated for [redacted]

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

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

STATE OF ARMAMENTARIUM FOR INDICATION(S)
Currently, there are two drug products, PhosLo® and RENAGEL®, approved by the FDA for the treatment of hyperphosphatemia associated with end-stage renal disease. The active ingredients of PhosLo® and RENAGEL® are calcium acetate and sevelamer hydrochloride (polly [allylamine hydrochloride] crosslinked with epichlorohydrin), respectively. Both phosphate binders are approved for oral administration.

POSTMARKETING EXPERIENCE
FOSRENOL™ (lanthanum carbonate) has not been marketed.

DESCRIPTION OF CLINICAL DATA AND SOURCES[1]
The Clinical Pharmacology program consisted of 11 studies, 6 of which had both pharmacokinetic and pharmacodynamic components as objectives in the study (LAM-IV-101, 104, 105, 108, 109, 110). Of the remaining 5 studies, LAM-IV-111 and LAM-IV-112 obtained primarily pharmacokinetic data of lanthanum, and studies LAM-IV-113, 114, 115 obtained the pharmacokinetic parameters of the drugs concomitantly administered with lanthanum carbonate and, thus, were considered as pharmacodynamic studies.[2]

The efficacy of lanthanum carbonate has been evaluated in two placebo-controlled (LAM-IV-202 and 204) and in three active-controlled (LAM-IV-301, 302 and 307) clinical studies conducted in the US and Europe.

label says 302 is plbo

The safety of lanthanum carbonate has been evaluated in the aforementioned Phase I-II-and III studies. In addition, study LAM-IV-303 evaluated the effect of lanthanum carbonate, as compared with calcium carbonate, on bone formation through paired bone biopsies, and studies LAM-IV-205 and -308 had an uncontrolled design and were open-label safety extensions of lanthanum carbonate studies LAM-IV-204, and LAM-IV-205 and LAM-IV-302, respectively.

DEMOGRAPHICS AND OTHER CHARACTERISTICS OF STUDY POPULATION
In Phase I studies, the majority of subjects were male (81.6% of subjects who received lanthanum carbonate, 100% of subjects who received placebo) and Caucasian (84.9% and 82.9%, respectively). The mean age was similar for the two treatment groups: 29.5 years for subjects who received lanthanum carbonate, and 25.7 years for subjects who received placebo; ages ranged from 18 to 67 years.

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

Patients' demographics remain unchanged for the short-term Phase II-III studies. In the short-term Phase II-III studies, 298 patients were treated with lanthanum carbonate and 95 patients were treated with placebo.

[1] The reader is referred to the Appendix, Tables 1A-3A.
[2] The clinical pharmacology studies were reviewed by Drs. Dorantes and Stockbridge.

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

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

USE IN SPECIAL POPULATIONS

The studies submitted in support of this NDA did not evaluate patients within the pediatric age groups. The reader is referred to the Integrated Summary of Efficacy where the effectiveness of lanthanum carbonate in sub-populations based on age, race, and gender is presented.

INTEGRATED SUMMARY OF EFFICACY

The effectiveness of lanthanum carbonate in reducing and maintaining serum phosphate levels in hyperphosphatemic patients, male or female aged 18 or older, with end-stage renal disease (ESRD) undergoing hemo- or peritoneal-dialysis has been evaluated in five placebo- or active-controlled Phase II (LAM-IV-202 and 204) and III (LAM-IV-301, 302 and 307) clinical studies conducted in the US and Europe. The efficacy of lanthanum carbonate was assessed by examining the change from baseline in serum phosphate levels and the proportion of patients whose serum phosphate levels were controlled, i.e., serum phosphate ≤5.6 mg/dL for European studies (LAM-IV-202, and -301) and ≤5.9 mg/dL for the US studies (LAM-IV-204, -302, and -307). An intent to treat approach was used to evaluate efficacy.

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

Placebo-Controlled Studies LAM-IV-202, -204, and -302

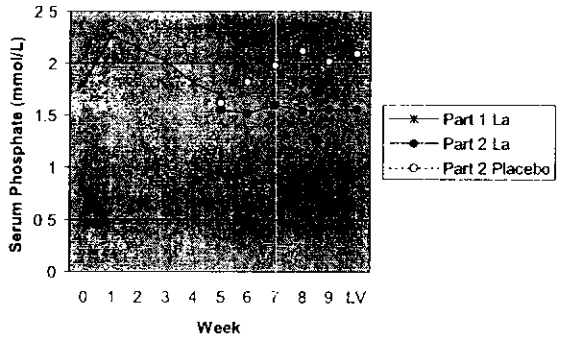
Protocol LAM-IV-202 (UK): This was a randomized, double blind, placebo controlled, parallel group, dose ranging study of lanthanum carbonate in subjects receiving hemodialysis or CAPD. The study had two parts: 1) 2-week washout period, followed by a four-week titration (lanthanum carbonate 375 mg to 2250 mg) until the serum phosphate reached and was maintained at a level between 1.3 mmol/L to 1.8 mmol/L, and 2) a four-week double blind, parallel group phase where patients were randomized to receive either their maintenance dose of lanthanum or placebo.

[3] Renagel® (sevelamer hydrochloride), and Phoslo® (calcium acetate) are FDA-approved phosphate binders, however Tums® an over the counter formulation of calcium carbonate has not been approved by the FDA for use as a phosphate binder.

Fifty-nine subjects entered the dose titration phase, 40 (67.8%) were male, 56 (94.9%) white, 2 (3.4%) Asian, and 1 (1.7%) Negroid. The average age was 54.7 years. The mean duration of dialysis treatment was 29.2 months; 66.1% of the subjects were undergoing CAPD at the time of the study.

Figure 1-ISE shows mean serum phosphorus level from screening to the end of Part 2. While mean serum phosphate level in patients who continued on lanthanum (n=17) remained stable, the mean serum phosphate level for those subjects who were switched from lanthanum to placebo (n=19) treatment in the Part 2 of the protocol gradually increased toward the baseline level. However, the observed numerical differences between treatment groups were no statistically significant.

Figure 1-ISE. Mean Serum Phosphorus Levels by Visit and Treatment Group – ITT Population



[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-202, Vol. 120, Tables XII and 24.1. La denotes Lanthanum carbonate. LV denotes Last Visit.]

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

Table 1-ISE. Number (%) of Patients with Controlled Serum Phosphates – ITT Population

	Lanthanum N=17 n(%)	Placebo N=19 n(%)	p-Value
Week 5	13(76.5)	14(73.7)	1.0
End of Treatment	11(64.7)	4(21.1)	0.008

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

dechotomous was 55.

Protocol LAM-IV-204 (US): This was a randomized, double blind, placebo controlled, parallel group, dose ranging study of lanthanum carbonate in subjects with ESRD receiving hemodialysis. Patients were randomly allocated, in a 1:1:1:1:1 ratio, to daily doses of lanthanum carbonate 225 mg, 675 mg, 1350 mg, 2250 mg or placebo. Study drug (chewable tablets) was taken three times a day with meals. The study had three phases: 1) 1 to 3-week single blind placebo run in[4], 2) followed by randomization of eligible subjects into a six week double blind treatment phase, and a 2 week, single blind placebo run out phase. The primary endpoint was the reduction of pre-dialysis serum phosphate levels from washout levels following six weeks of treatment.

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

[4] All phosphate binders were discontinued prior to starting this phase.

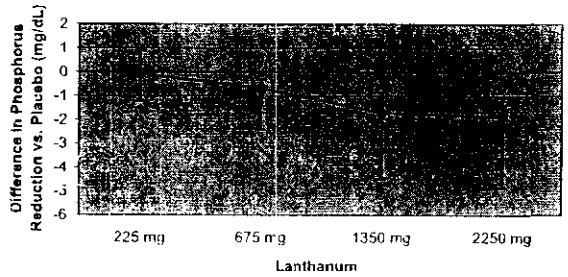
Table 2-ISE summarizes the results of baseline and the changes (mean±SD) in serum phosphate levels. Figure 2-ISE shows the change, point estimates and 95% confidence intervals, in the serum phosphorus level from the end of the placebo run-in phase to the end of treatment. There were no differences in baseline serum phosphate concentrations across treatment groups. The decreases in phosphate concentrations in the lanthanum doses of 1350 mg/day and 2250 mg/day were significantly greater ($p< 0.0001$) versus placebo.

Table 2-ISE. Baseline and Change (mean±SD) in Serum PO_4 Level (mg/dL) from End of Washout to End of Treatment – ITT Population

	Treatment Group					p-value
	Placebo N=32	La225 N=27	La675 N=29	La1350 N=30	La2250 N=26	
Baseline Serum PO_4	7.1±1.3	6.5±1.1	7.2±1.4	6.8±1.4	7.4±1.2	0.103
Change in Serum PO_4	0.7±1.4	0.6±1.5	0.07±1.8	-0.9±1.3	-1.1±2.0	<0.0001

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-204, Vol. 123, Table 6, (Dunnett's test).]

Figure 2-ISE. Primary Endpoint: Comparison of Placebo vs. Lanthanum (Point Estimates, 95% CI) – ITT Population



[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-204, Vol. 123, Table 6.]

Protocol LAM-IV-302 (US): This was a randomized (1:1 ratio to either lanthanum carbonate or placebo), placebo-controlled, double blind, parallel group study in patients with ESRD receiving hemodialysis. Lanthanum carbonate starting dose was 750 mg daily and titrated as needed up to 3000 mg daily[5] to achieve a serum phosphate level <5.9 mg/dL. The study had the following phases: screening and washout phase, six week open-label dose titration phase, and 4-week double-blind randomized drug maintenance phase with a placebo arm. The primary endpoint was defined by the sponsor "as the last pre-dialysis serum phosphorus level of a patient that was obtained during the maintenance treatment period." The control of serum phosphorus levels at study endpoint was also analyzed.

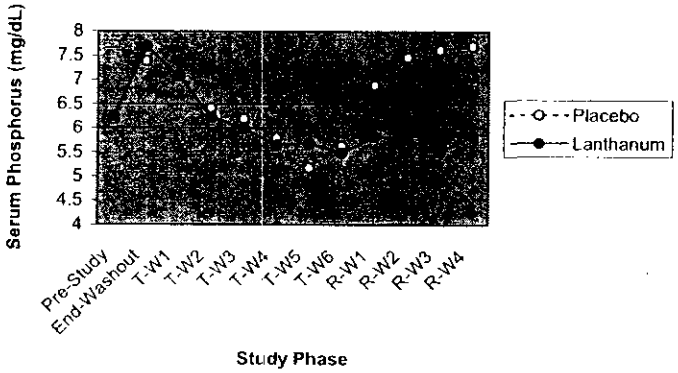
In the ITT population 61 (66%) patients were male and 32 (34%) female, 40 (43%) were whites, 37(40%) black, 9 (10%) Hispanic, and 7 (8%) Asian/other races. The average age was 60.3 years. The average time on dialysis prior to enter the study was 3.2 years.

The efficacy results are depicted in Figure 3-ISE. The pre-study serum phosphorus levels for the placebo and lanthanum groups were similar, 6.186 mg/dL vs. 6.251 mg/dL, respectively. There were no differences in the serum phosphorus concentrations between the two treatment groups at the end of washout (7.39 mg/dL placebo group and 7.69 mg/dL lanthanum group, p=0.3754). At the end of dose titration[6] the serum phosphorus level decreased to 5.62 mg/dL in the placebo group and to 5.49 mg/dL in the lanthanum group (p=0.6942).

[5] i.e., 750 mg, 1500 mg, 2250 mg, and 3000 mg daily with meals
[6] i.e., all patients received lanthanum carbonate prior to randomization.

Fifty subjects were randomized to the lanthanum carbonate group and 44 patients received placebo. At end of randomized treatment, the serum phosphorus (mean±SD) was 7.85±1.96 mg/dL for placebo and 5.94±1.65 mg/dL for lanthanum ($p<0.0001$). The mean difference in serum phosphorus concentrations between groups was -1.91 mg/dL, and the 95% confidence interval of the mean difference ranged from -2.6 mg/dL to -1.23 mg/dL. Serum phosphorus ranged from 5.51 mg/dL to 5.84 mg/dL for patients who continued lanthanum treatment[7], while the serum phosphorus increased to 6.89 mg/dL at the end of first randomized week and to 7.70 mg/dL at the end of the fourth randomized week for patients who discontinued lanthanum treatment ($p<0.01$ at week 1, $p<0.0001$ at weeks 2-4).

Figure 3-ISE. Mean Serum Phosphorus Levels over Time – ITT Population



[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-302, Vol. 182, Table 2.3.1. T-W denotes week in titration phase; R-W denotes week in randomization phase; *$p<0.01$; **$p<0.0001$.]

In seventy one percent and 59% of the patients in the lanthanum and placebo groups, respectively, their serum phosphorus was controlled (defined as ≤5.9 mg/dL, $p=0.275$). At the end of week fourth post randomization, the percent of patients whose serum phosphorus levels were controlled was 59% for the lanthanum group and 23% for placebo (mean difference of 36%, $p=0.001$).

Active-Controlled Studies LAM-IV-301, and -307

Protocol LAM-IV-301 (EU): This was an open-label, randomized[8] (2:1 ratio to either lanthanum carbonate or calcium carbonate[9]), active comparator controlled, parallel group study of lanthanum carbonate in patients with ESRD receiving hemodialysis. Lanthanum carbonate and calcium carbonate were taken (chew) after meals and titrated as needed from 375 mg to 3000 mg (elemental lanthanum) and 1500 mg to 9000 mg (elemental calcium), respectively, to achieve a phosphate level of ≤1.8 mmol/L. The study had the following periods: 1) 1 to 3-week screening and washout period, 2) randomization followed by 5-week dose titration period, 3) 20-week treatment phase, 4) a 24-week extension phase during which all patients received lanthanum carbonate, and 5) an optional 2-year extension phase.[10]

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

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[7] Below the study-defined clinically acceptable limit of ≤5.9 mg/dL.

[8] At each site "investigators delegated a member of staff not involved with the study to open an envelope when a patient was to be randomized and to direct the investigator to assign the treatment indicated."

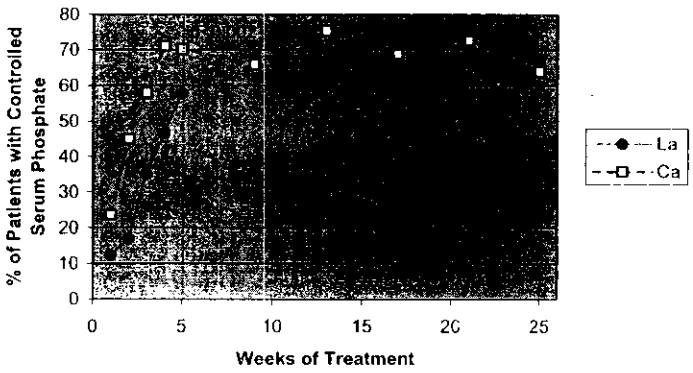
[9] The FDA for the treatment of hyperphosphatemia associated with ESRD has not approved calcium carbonate.

[10] This phase of the study is ongoing and not reported here

[11] Of note, thirty-three patients (23 from the lanthanum group and 10 from the calcium carbonate group) from one investigative center (site 99) were not included in the efficacy analyses because the sponsor deemed the efficacy data "unreliable."

Efficacy was determined according to the level of serum phosphate achieved after 5 weeks in the dose titration phase; serum phosphate levels ≤1.80 mmol/L were considered control. A secondary objective was the evaluation of maintenance of treatment control after 25 weeks of treatment, i.e., 5 weeks titration plus 20 weeks maintenance. Results of the analysis (intent-to-treat) of the primary endpoint are shown in Figure 4-ISE. The percentage of controlled patients, i.e., with serum phosphate levels ≤1.80 mmol/L, at the end of the 5 week dose titration (visit 6) was significantly higher in the calcium group than in the lanthanum group, 70.3% vs. 57.8%, respectively (Chi-square test, p<0.002). After 25 weeks of treatment the proportion of controlled patients in the calcium group was similar to that in the lanthanum group (63.9% vs. 65.8%, respectively, p=0.73).

Figure 4-ISE. Percent of Patients with Controlled Serum Phosphate – ITT Population



Week	1	2	3	4	5	9	13	17	21	25
La. N=	498	492	479	466	453	277	255	242	228	222
Ca. N=	253	238	231	212	209	152	138	131	117	122

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-301, Table 14.1.28.1. La denotes Lanthanum carbonate. Ca denotes Calcium carbonate.]

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

Eligible patients were randomized 1:1 (500 patients per arm) to either lanthanum carbonate up to a maximum of 3000 mg/day or their pre-study standard therapy, which was one or more of the commercially available phosphate binders, i.e., Renagel® (17%), Phoslo® (34.5%) or Tums® (calcium carbonate, 44.%).[12] The primary efficacy endpoint in this study was the predialysis PO_4 levels (PSPL), which were measured at the first dialysis sessions of study visits, including pre-study and washout.

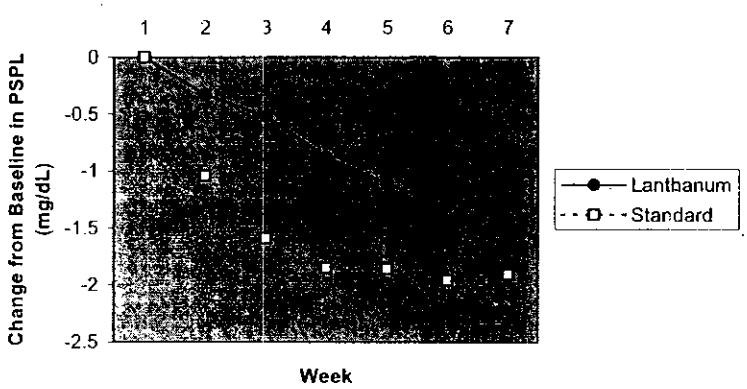
Fifty-nine percent of the study population was male with an average age of 55.3 years, race was evenly distributed between Caucasian and Black, 46.2% versus 43.0%, respectively

The primary efficacy endpoint in this study was the predialysis serum PO_4 levels (PSPL), which were measured at the first dialysis sessions of study visits week 1 to week 7, i.e., titration period (Figure 5-ISE). In both treatment groups serum PO_4 levels declined over time. However, when compared between treatment groups, the change from baseline serum phosphorus level to each follow-up week of dose titration, a greater reduction occurred for patients on standard therapy (p=0.000). At the end of dose

[12] Renagel® (sevelamer hydrochloride), and Phoslo® (calcium acetate) are FDA-approved phosphate binders, however Tums® and over the counter formula of calcium carbonate is not approved by the FDA for use as a phosphate binder.

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

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



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

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

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

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

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

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

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

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

Table 4-ISE. Proportion of Patients with Controlled Serum Phosphorus[♦] in Placebo-Controlled Studies (LAM-IV-202, 204 and 302) – ITT Population by Treatment Group and by Gender, Race, and Age

Sub group/Treatment	Baseline		4th Rx Week		End Point	
	n/N	%	n/N	%	n/N	%
Gender						
Male: Placebo	23/52	44.2	9/40	22.5	11/52	21.2
225-750mg/day	17/42	40.5*	14/35	40.0*	13/42	31.0*
1350-1500mg/day	12/26	46.2*	15/22	68.2**	12/26	46.2**
2250mg/day	10/29	34.5	19/28	67.9***	18/29	62.1***
3000 mg/day	10/12	83.3*	7/12	58.3	7/12	58.3
Female: Placebo	22/43	51.2	10/36	27.8	10/43	23.3
225-750 mg/day	6/25	24.0	4/20	20.0	5/25	20.0
1350-1500mg/day	11/19	57.9*	13/16	81.3***	14/19	73.7***
2250 mg/day	5/14	35.7	9/14	64.3*	7/14	50.0*
3000 mg/day	3/11	27.3**	5/8	62.5*	6/11	54.5*
Race						
White: Placebo	26/45	57.8	10/35	28.6	12/45	26.7
225-750 mg/day	12/20	60.0*	8/17	47.1*	10/20	50.0**
1350-1500mg/day	10/19	52.6	13/17	76.5**	10/19	52.6*
2250mg/day	12/18	66.7*	15/17	88.2***	13/18	72.2***
3000 mg/day	5/9	55.6	3/7	42.9	4/9	44.4
Black: Placebo	17/43	39.5	9/35	25.7	9/43	20.9
225-750 mg/day	10/42	23.8	10/34	29.4	7/42	16.7
1350-1500mg/day	11/23	47.8*	15/19	78.9***	14/23	60.9**
2250mg/day	2/22	9.1	13/22	59.1*	12/22	54.5**
3000 mg/day	4/10	40.0*	6/9	66.7*	6/10	60.0*
Age						
≤64 years:Placebo	27/57	47.4	9/46	19.6	9/57	15.8
225-750mg/day	15/46	32.6*	12/36	33.3	11/46	23.9
1350-1500mg/day	12/25	48.0**	13/20	65.0***	14/25	56.0***
2250mg/day	8/28	28.6	15/27	55.6**	13/28	46.4**
3000mg/day	7/14	50.0	9/13	69.2***	9/14	64.3***
≥65 years:Placebo	18/38	47.4	10/30	33.3	12/38	31.6
225-750mg/day	8/21	38.1	6/19	31.6	7/21	33.3
1350-1500mg/day	11/20	55.0	15/18	83.3**	12/20	60.0*
2250 mg/day	7/15	46.7	13/15	86.7**	12/15	80.0**
3000 mg/day	6/9	66.7	3/7	42.9	4/9	44.4

[Sponsor's analysis. NDA 21-468, Vol. 78, Table 8.7.22. [♦]Defined as serum phosphate levels ≤5.6 mg/dL for the UK study LAM-IV-202, and ≤5 9 mg/dL for the US studies LAM-IV-204 and -302. *p<0.05; **p<0.01; ***p<0.001.]

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

[ ]

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

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

Of note, the FDA has not approved calcium carbonate[13] for use as a phosphate binder. Notwithstanding, after 5 weeks of treatment, lanthanum carbonate was significantly less effective than calcium carbonate in controlling hyperphosphatemia in patients with end stage renal disease (LAM-IV-301). This disparity in effectiveness between the drugs was not longer present by week 25.

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

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

INTEGRATED SUMMARY OF SAFETY

The primary focus of this section is on the adequacy of safety testing and assessments carried out in the clinical development program with the main objective of delineating the safety profile of FOSRENOL™ (lanthanum carbonate). To this end the medical reviewer utilized NDA desk copies and the electronic version provided with the original submission, SAS datafiles[14] and as well as material provided by the sponsor in response to special requests, i.e., ECG[15], overall mortality[16] data and incidence of bone fractures. The safety information provided by the sponsor in the four-month safety update was also reviewed and the results were incorporated in this integrated review of safety.

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

Clinical Safety Data: Safety data from the following studies were examined: 1 clinical pharmacology Phase I studies in healthy volunteers and patients with ESRD (LAM-IV-101, 104, 105, 108, 109, 110, 111, 112, 113, 114, and 115)[17] and 8 Phase II-III studies (LAM-IV-202, 204, 205, 301, 302, 303, 307, and 308).

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

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

Study LAM-IV-303 evaluated a small number of patients, 49 in each lanthanum carbonate and calcium carbonate[18] groups, approximately two-thirds of these patients had bone biopsy data collected and were

[13] As per the sponsor, calcium carbonate has been approved in the following countries: United Kingdom, Netherlands, Sweden, Finland, Switzerland, Germany and Australia

[14] Dr. Valeria Freidlin, Ph.D. (HFD-710) performed the safety analyses on QT/QTc.

[15] NDA 21-468, Serial # 028, dated November 15, 2002

[16] NDA 21-468, Serial # 030, dated November 21, 2002.

[17] The reader is referred to the medical and pharmacokinetic reviews by Drs. Norman Stockbridge and Angelica Dorantes, respectively.

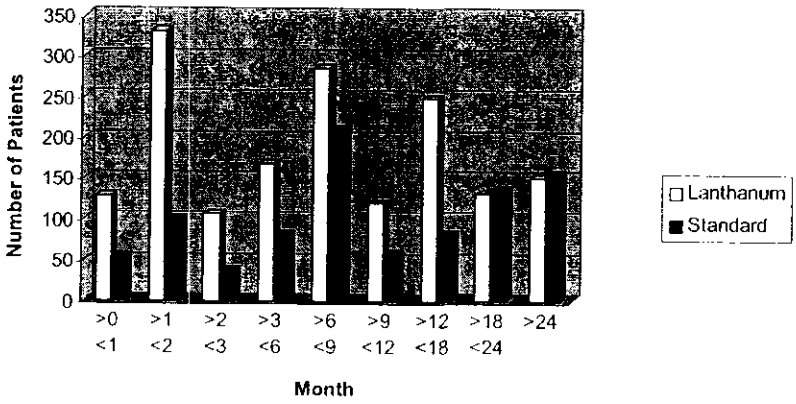
treated for approximately 12 months. Critical to the interpretation of the results from this clinical trial, the sponsor did not power the study to rule out an effect of lanthanum carbonate as compared with the active control on bone metabolism.

Studies LAM-IV-205 (n=42) and -308 (n=77), had an uncontrolled design and were open-label safety extensions of lanthanum carbonate studies LAM-IV-204, and LAM-IV-205 and LAM-IV-302, respectively. The contribution of these studies to the overall understanding of the safety of lanthanum carbonate because of the uncontrolled nature of the protocols' design is difficult, if not impossible, to weigh.

Studies LAM-IV-301 (lanthanum carbonate n=533 and calcium carbonate n=267) and -307 (lanthanum carbonate n=647 and standard therapy n=642) were long-term clinical trials, with an open-label and active-controlled design, conducted in Europe and the United States, respectively. However, the length of the comparative phase in study LAM-IV-301 was only 25 weeks, the remaining exposure to lanthanum carbonate is derived from the uncontrolled phase of the study. Thus the contribution of the results from this study to the understanding of the long-term safety of lanthanum is meager. Furthermore, the interpretation of the safety data from study LAM-IV-307, which is still ongoing, is significantly undermined because lanthanum-treated patients had a significantly higher rate of discontinuation and thus shorter drug exposure than those patients treated with standard therapy, 62.7% versus 42.3% and 284.3 days versus 397.0 days (p=0.001), respectively.[19]

Patient Exposure: Phase I studies randomized 179 subjects to lanthanum carbonate and 76 to placebo/other. According to the sponsor, "a total of 1672 patients received multiple doses of lanthanum carbonate (225 mg to 3000 mg) and 909 received active control phosphate binders in Phase II and III studies." However, of those only 151 (9.0%) and 155 (17.1%) patients were treated for ≥2 years with lanthanum carbonate or standard therapy, respectively. Figure 1-ISS depicts the number of patients receiving multiple doses of active treatment in Phase II and III studies over time.

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



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

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

[18] Calcium carbonate is not an FDA approved phosphate binder thus its safety profile, as compared with placebo, is unknown to the Division of Cardio-Renal Drug Products.
[19] Sponsor's analysis.

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

Subjects/Patients Discontinuations: In the Phase I studies 15.1% (n=27) of the subjects discontinued prematurely in the lanthanum group versus 6.6% (n=5) of the subjects receiving placebo/other. In the Phase II-III short-term studies[21] the rate of withdrawal was higher for those patients receiving lanthanum carbonate than for the placebo-treated patients, 32.2% (n=96) versus 28.4% (n=27). Similarly, in the Phase III long-term studies[22] the percentage of patients discontinuing lanthanum carbonate therapy was greater than for active control phosphate binders, 60.4% versus 41.4%.

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

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

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

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

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

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

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[20] NDA 21-468, Four-Month Safety Update

[21] Including LAM-IV-202, -204, and -302.

[22] Including LAM-IV-205, -301, -307 (interim data cut-off date of May 30, 2002) and –308.

which represents a follow-up rate of 96.8% with the mortality data available for 94.5% of patients treated with lanthanum or active controls. Of note, there are 138 patients remaining for whom the mortality status is not known, lanthanum carbonate only n=93, comparator only n=38, and comparator followed by lanthanum n=7.[23]

At the present, the updated mortality data indicate that mortality rates are higher in lanthanum-treated patients as compared with those subjects receiving active controls, **24.5%** versus **20.8%**, representing a difference between treatments of **3.7%** against lanthanum. These incidence rates are derived from the number of patients treated, regardless whether or not their vital status is known, and the number of deaths. If one corrects the denominator by the number of patients for whom their vital status is unknown, the difference between treatments is **4.4%** against lanthanum carbonate, i.e., mortality rates of **26.0%** {422x100/[1721-(93+7)]} for lanthanum carbonate versus **21.6%** [199x100/(958-38)] for active controls.

Although the retrieval of mortality data ensures "comparable follow-up" between treatments, the effect the imbalance in exposure to drug could have had on mortality remains and will remain unknown up until the time an adequate designed and powered mortality trial is performed.

Table 1-ISS. Number (%) of Deaths for Phase II-III Studies Patient Population

	Lanthanum [N] n (%)	**Standard [N] n (%)**
Four-Month Safety Update (May 30, 2002)	[1672] 68 (4.1)	[909] 83 (9.1)
Updated Mortality Data (October 30, 2002).	[1721] 376 (21 9)	[958] 186 (19.4)
Updated Mortality Data (December 19, 2002).	[1721] 422 (24 5)	[958] 199 (20.8)

[Sponsor's analysis, adapted from NDA 21-648, Four-Month Safety Update and Sponsor responses serial # 030 dated November 21, 2002, and serial #042 dated December 20, 2002.]

Treatment Emergent Adverse Events: Table 2-ISS summarizes the number and percentage of patients with treatment emergent adverse events which occurred at a rate >1% in the lanthanum group and at least with a rate 50% greater than in the placebo/other-treated patients in Phase I studies. As compared with placebo/other, single or multiple doses of lanthanum carbonate were associated with higher rates for nausea, vomiting, headache, abdominal pain, dizziness, myalgia, rash, and constipation.

Table 2-ISS. Number (%) of Patient in Phase I Studies with Treatment Emergent Adverse Events

Adverse Event	**Lanthanum-SD N=132 n (%)**	**Lanthanum-MD N=111 n (%)**	**Placebo/Other N=76 n (%)**
Nausea	34 (25.8)	12 (10.8)	2 (2.6)
Vomiting	27 (20.5)	6 (5.4)	1 (1.3)
Headache	22 (16.7)	15 (13.5)	2 (2.6)
Abdominal Pain	13 (9.8)	6 (5.4)	1 (1.3)
Dizziness	8 (6.1)	5 (4.5)	2 (2.6)
Myalgia	4 (3.0)	3 (2.7)	0 (0.0)
Rash	4 (3.0)	3 (2.7)	0 (0.0)
Constipation	3 (2.3)	3 (2.7)	0 (0.0)

[Sponsor's analysis, adapted from NDA 21-648, Four-Month Safety Update, Table 8.5.1. SD denotes single dose. MD denotes multiple doses.]

Table 3-ISS summarizes the number and percentage of patients with treatment emergent adverse events which occurred at a rate >1% in the lanthanum group and at least with a rate 50% greater than in the

[23] The reader is referred to the Appendix.

placebo-treated patients in short-term Phase II-III placebo-controlled studies. As was the case in Phase I studies the incidence of nausea, vomiting and abdominal pain was greater in lanthanum-treated patients than in patients receiving placebo. Of note, in comparison to placebo, administration of lanthanum carbonate was associated with a higher incidence of dialysis graft occlusion.

Table 3-ISS. Number (%) of Patient in Short-Term Phase II-III Placebo-Controlled Studies[♦] with Treatment Emergent Adverse Events*

Adverse Event	Lanthanum N=180 n (%)	Placebo N=95 n (%)
Nausea	19 (10.6)	5 (5.3)
Vomiting	17 (9.4)	4 (4.2)
Dialysis Graft Occlusion	14 (7.8)	1 (1.1)
Myalgia	13 (7.2)	4 (4.2)
Abdominal Pain	9 (5.0)	0 (0.0)
Hypertension	5 (2.8)	0 (0.0)
Skeletal Pain	5 (2.8)	0 (0.0)
Anemia	5 (2.8)	0 (0.0)
Arthralgia	4 (2.2)	1 (1.1)
Dyspnea	4 (2.2)	1 (1.1)

[Sponsor's analysis, adapted from NDA 21-648, Four-Month Safety Update, Table 8.5.5. [♦]LAM-IV-202, -204, and -302. *Treatment adverse events that occurred post-randomization and during the comparative phase of the study.]

Albeit, the safety data resulting from Phase I studies and short-term phase II-III placebo-controlled studies contribute to delineate the safety profile of short-term exposure to lanthanum carbonate, the long-term safety of lanthanum carbonate can not be inferred from such studies. In this regard, the long-term safety of lanthanum carbonate must be surmised from the active-controlled and open-label long-term studies LAM-IV-301, -303, and -307.[24] However, there are significant inadequacies with the design of the studies as well as a significant imbalance in drug exposure that together prevents the characterization of the long-term safety profile of lanthanum carbonate in this population with any degree of confidence.[25] Notwithstanding the marked deficiencies already mentioned, Table 4-ISS summarizes adverse events occurring with an incidence ≥10% by treatment group. Noteworthy, each adverse event, regardless of body system, with an incidence ≥10% invariably occurred at a greater rate in active control than in lanthanum carbonate, and the noted differences were statistically significant in 24 out of a total of 26 distinct adverse events, with p-values ranging from <0.05 to <0.001.

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

[24] The results of Study LAM-IV-303 are being discussed in the section: Studies specifically conducted to assess safety, below.

[25] This issue has been addressed in the section: Critical Pre-Clinical Safety Findings and Limitations of Clinical Data and Safety Testing, bullet #5, above.

Table 4-ISS. Treatment-Emergent Adverse Events with an Incidence ≥10% in Long-Term Studies

Adverse Event	Lanthanum N=1180 n (%)	Active-Control N=909 n (%)
Back Pain	79 (6.7)***	131 (14.4)
Chest Pain	124 (10.5)***	148 (16.3)
Fever	94 (8.0)***	115 (12.7)
Influenza-like Symptoms	95 (8.1)***	127 (14.0)
Leg Pain	84 (7.1)**	95 (10.5)
Malaise	71 (6.0)***	92 (10.1)
Pain	98 (8.3)***	132 (14.5)
Hypotension	138 (11.7)***	162 (17.8)
Edema Peripheral	87 (7.4)***	153 (16.8)
Dizziness	141 (11.9)***	168 (18.5)
Headache	151 (12.8)***	167 (18.4)
Dialysis Cath. Complication	91 (7.7)***	115 (12.7)
Dialysis Graft Complication	157 (13.3)***	211 (23.2)
Dialysis Graft Occlusion	145 (12.3)***	177 (19.5)
Abdominal Pain	143 (12.1)**	151 (16.6)
Constipation	110 (9.3)***	130 (14.3)
Diarrhea	202 (17.1)**	204 (22.4)
Dyspepsia	74 (6.3)***	103 (11.3)
Nausea	293 (24.8)	261 (28.7)
Vomiting	254 (21.5)	208 (22.9)
Hypercalcemia	25 (2.1)***	128 (14.1)
Myalgia	164 (13.9)***	183 (20.1)
Coughing	119 (10.1)***	164 (18.0)
Dyspnea	150 (12.7)***	196 (21.6)
URI	83 (7.0)***	106 (11.7)
Pruritus	83 (7.0)*	93 (10.2)

[Sponsor's analysis, adapted from NDA 21-648, Four-Month Safety Update, Table 8.5.6. *p<0.05; **p<0.01; ***p<0.001 compared to the comparator of the same study category using Fisher's exact test.]

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

[26] Sponsor's analysis, NDA 21-648, Four-Month Safety Update, Table 8.7.4

Table 5-ISS. Gastrointestinal Treatment-Emergent Adverse Events Leading to Discontinuations in Long-Term Phase II-III Studies

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

[Sponsor's analysis, adapted from NDA 21-648, Four-Month Safety Update, Table 8.7.4. *p<0.05; **p<0.01; ***p<0.001 compared to the comparator of the same study category using Fisher's exact test. NOS denotes not other specified.]

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

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

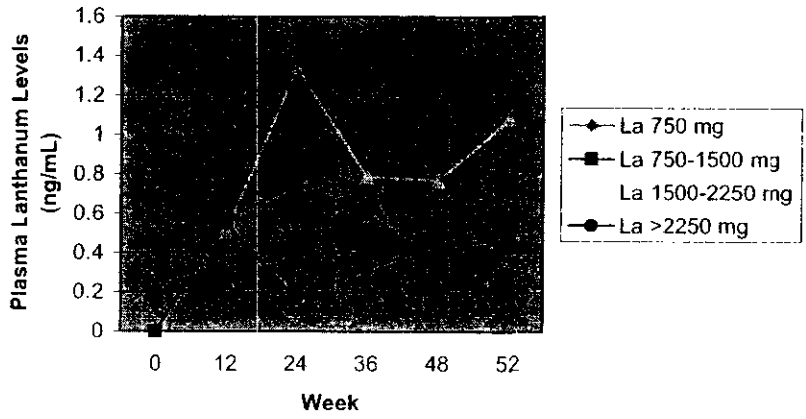
Mineralization lag time the primary efficacy endpoint of the study, defined as the mean time interval between deposition and mineralization of any volume of matrix averaged over the entire life span of the osteoid seam, is a key variable for the assessment of new bone formation. The median z-scores of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

Specific Findings of Safety Review

Plasma and Bone Tissue Levels of Lanthanum: Data on plasma and bone tissue levels of lanthanum from Study LAM-IV-303 is next presented. Plasma lanthanum levels were measured at weeks 0, 12, 24, 36, 48 and 52.[27] In lanthanum-treated patients there were increases in plasma lanthanum for all doses administered compared with baseline levels-in baseline plasma samples lanthanum was not detectable. Albeit the small sample size prevents one to be conclusive as to whether there is a dose relationship, plasma lanthanum levels appear to be dose-dependent (Figure 2-ISS).

[27] NDA 21-468, Protocol No. LAM-IV-303, Vol. 189, Table 30.

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

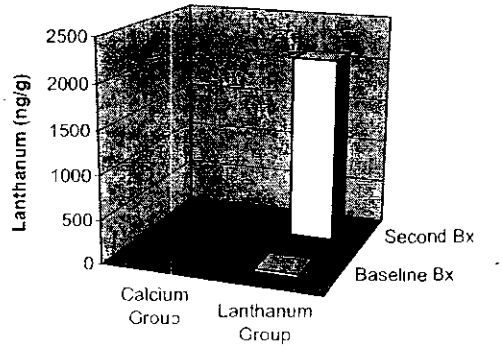


Week	La 750 mg n	La 750-1500 mg n	La 1500-2250 mg n	La >2250 mg n
0	19	6	0	0
12	13	21	3	3
24	12	22	3	2
36	10	19	4	3
48	15	14	4	2
52	11	15	5	3

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

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

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



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

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

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

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

ECG Data: Only in phase II-III studies carried out in the US the sponsor obtained ECG recordings. Thus there is not ECG data available for review from studies LAM-IV-301 and -303. Studies LAM-IV-204 and -302 enrolled few patients and were of short duration, 6 weeks and 4 weeks, respectively, and studies LAM-IV-205 and 308 had an uncontrolled design and also enrolled few patients.[29] Thus the evaluation of potential ECG abnormalities must rely on the results of study LAM-IV-307. Table 6-ISS summarizes important findings on QT interval changes from baseline observed in patients who has completed study LAM-IV-307. Of note, the incidence of QT changes from baseline ≥60 msec was two-fold greater in patients receiving lanthanum as compared with those subjects on standard therapy, $p<0.043$.[30] This finding raised the concern that long-term exposure to lanthanum may be associated with clinically significant prolongation of the QT interval. Similar results were obtained when the QT interval was corrected by heart rate, i.e., by using either the Fredericia or Bazzet formulas.[31]

Table 6-ISS. Number (%) of Patients from Study LAM-IV-307 with QT Interval Abnormalities at Visit 21* (24 Months)

QT Interval Abnormality	Lanthanum N=109		Standard Therapy N=172		p-Value
	n	%	n	%	
Δ from Baseline ≥30 msec	33	30.3	43	25.0	0.33
Δ from Baseline ≥60 msec	14	12.8	10	5.8	0.043
≥450 msec	9	8.3	10	5.8	0.43
≥480 msec	2	1.8	5	2.9	0.57
≥500 msec	2	1.8	2	1.2	0.65

[FDA's Analysis, Dr. Freidlin (HFD-710). *Visit 21 (24 months) represents the end of the study.]

Overdosage: There is no clinical experience with overdose of Fosrenol™.

Critical Pre- and Clinical Safety Findings and Limitations of Clinical Safety Data and Testing: Before reaching a conclusion as to whether FOSRENOL™ is approvable it is of importance to call attention to the following facts as well as deficiencies in the clinical development program:

1. Long-term use (off-label) of aluminum salts, which are effective phosphate binders, in patients with chronic renal failure or end-stage renal disease on dialysis has been shown to result unequivocally in serious adverse events such as aluminum-related bone disease, dementia, myopathy, hypoparathyroidism, and death.[32] Of note, aluminum and lanthanum are both trivalent

[28] Sponsor's response on rates of bone fractures by study dated December 24, 2002.See Appendix Table 4A.
[29] The reader is referred to the review by the biostatistician Dr. Freidlin (HFD-710).
[30] PR interval did not change.
[31] The reader is referred to the review by the biostatistician Dr. Freidlin (HFD-710).
[32] The subject has been reviewed in depth by Dr.Alfrey AC. Aluminum toxicity in patients with chronic renal failure. *Ther Drug Monit. 1993 Dec;15(6):593-*

cations and undergo gastrointestinal absorption and tissue accumulation. In view of the aluminum fiasco any substance like lanthanum that is absorbed and accumulates is suspicious, hence robust and adequate data on its long-term safety are necessary before such a drug can without hesitation be recommended for approval.

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

3. Pre-clinical studies performed by the sponsor[34] and by other investigators[35] in a chronic renal failure rat model indicate that lanthanum carbonate results in a dose-dependent decrease in bone formation and osteomalacia. In this regard, in study LAM-IV-303 the median z-scores of mineralization lag time obtained from bone biopsies indicate that patients in the lanthanum carbonate group had slower bone formation than those patients receiving the active control.

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

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

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[33] The reader is referred to the pharmacology and toxicology review by the FDA.
[34] The reader is referred to the pharmacology and toxicology review by the FDA.
[35] Behets GJ, *et al.* An assessment of the effects of lanthanum on bone in a chronic renal failure rat model. *J Am Soc Nephrol 2001; 12: A 3862.*
[36] The reader is referred to the biopharmacokinetic review by the FDA.
[37] Sponsor's analysis

thus its safety profile, as compared with placebo or standard therapy, is unknown to the Division of Cardio-Renal Drug Products. Finally, studies LAM-IV-301 and 307, in which the safety of lanthanum carbonate versus that of calcium carbonate or standard therapy is compared, had an open-label design, which could have led to significant underreporting of adverse events due to investigators' biases. Thus, because of the lack of adequate follow-up coupled with shorter drug exposure for the lanthanum group in study LAM-IV-307 in addition to the long-term studies' open-label design, safety comparisons are significantly biased unquestionably in favor of lanthanum carbonate treatment.

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

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

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

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

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

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

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

[38] Medical Review, Appendix, Table 8.3-2.
[39] According to the sponsor this corresponds to a follow-up rate of 96.8%.

RECOMMENDATIONS

The recommendation is that FOSRENOL™ (Lanthanum Carbonate) Chewable Tablets should not be approved

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

INDIVIDUAL DETAILED STUDY REVIEWS

Protocol LAM-IV-202: "A Phase II, Dose Ranging, Placebo Controlled, Parallel Group Study to Assess the Efficacy and Safety of "Lambda" for Reduction of Gastrointestinal Phosphate Absorption in Patients Receiving Hemodialysis or Continuous Ambulatory Peritoneal Dialysis (CAPD)."

The primary objective of this study was "to determine an efficacious dose of lanthanum for reduction and maintenance of serum phosphate at a level between 1.3 mmol/L to 1.8 mmol/L, to evaluate the absorption and safety profile of lanthanum carbonate in hemodialysis and CAPD patients. And to collect data on dose and frequency of established phosphate binders compared to effective doses of lanthanum in this patient population."

This Phase II study had a double blind, randomized, multicenter, placebo controlled, dose ranging and parallel group design. The study was conducted at 8 investigative sites in the UK. The study start date was June 1997 and the stop date was June 1999.

INVESTIGATIONAL PLAN[40]

Study Design: This was a randomized, double blind, placebo controlled, parallel group, dose ranging study of lanthanum carbonate in subjects receiving hemodialysis or CAPD. The study had two parts: 1) 2-week washout period, followed by a four-week titration (lanthanum carbonate 375 mg to 2250 mg) until the serum phosphate reached and was maintained at a level between 1.3 mmol/L to 1.8 mmol/L, and 2) a 4-week double blind, parallel group phase where patients were randomized to receive either their maintenance dose of lanthanum or placebo. Study drug (chewable tablets)[41] was taken three times a day with meals.

Dietary phosphate intake was monitored with the use of diet sheets and dietary cards. Phosphate binders were excluded from the time of screening until the end of the study. Compliance with study drug was assessed by tablet count.

Study Population: male or female patients aged 18 or older with end stage renal disease undergoing hemodialysis or CAPD for at least 6 months and a serum phosphate level ≥1.8 mmol/L, but <3.0 mmol/L, were enrolled in the study. Significant hypercalcemia or hyperparathyroidism defined as serum PTH >500 pg/mL, among others, excluded the patient from randomization into the study.

Efficacy Variables: The primary efficacy endpoint was the reduction and maintenance of serum phosphate levels between 1.3 mmol/L to 1.8 mmol/L with a predetermined maintenance dose of lanthanum carbonate compared with placebo in part 2 of the study.

Secondary efficacy variables included: 1) serum calcium, 2) PTH, and 3) calcium x phosphate product.

Safety: Evaluation of the safety of lanthanum carbonate was based upon the assessment of adverse events, and changes in routine safety laboratory parameters.

Statistical Methods: The sponsor did not power the study to determine statistical differences between treatments groups.

RESULTS

Amendments: The protocol was amended twice, the first was dated 18 August 1997 and the second, 21 January 1998. These amendments did not significantly affect the interpretation of the study.

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[40] For a complete description of the study protocol the reader is referred to NDA 21-468, Protocol LAM-IV-202, Vol 120.

[41] Chewable tablets containing 125 mg, and 250 mg of lanthanum.

Disposition of Subjects: A total of 105 subjects were screened and 59 completed the washout phase and entered the dose titration phase, i.e., Part 1. Fifty patients completed the titration period and 9 subjects withdrew, 2 because of adverse events, 3 at the patient's request, one each due to high phosphate and an other due to high PTH, and one due to protocol violation. Fourteen patients who have completed Part 1 were not randomized into Part 2 of the study, protocol violations 3 cases, non-compliance in one subject, 5 as per protocol for pilot group, and uncontrolled phosphate in 5 patients.

Thus a total of 36 patients entered Part 2 of the study. Seventeen patients were randomized to lanthanum carbonate and 19 subjects to placebo. Only two patients receiving placebo were discontinued prematurely from Part 2 of the study because of an adverse event and a protocol violation in the other.

Study Population: Out of the 59 subjects entering the dose titration phase 40 (67.8%) were male, 56 (94.9%) were white, 2 (3.4%) Asian, and 1 (1.7%) Negroid. The average age was 54.7 years. The mean duration of dialysis treatment was 29.2 months, 66.1% of the subjects were undergoing CAPD at the time of the study. Twenty five percent had a history of kidney transplant.

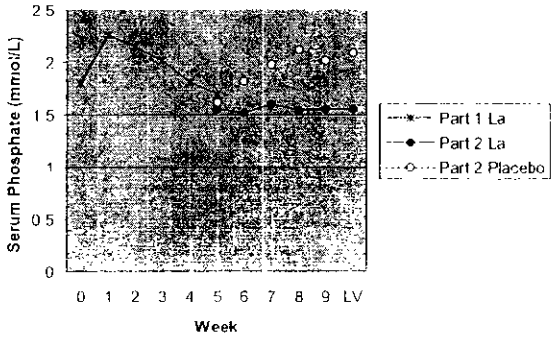
Treatment Compliance: According to the sponsor, "mean compliance was at least 94% for lanthanum carbonate and 93% for placebo patients."

Concomitant Medications: All 59 patients used concomitant medications. The most common treatment was erythropoietin, which was received by 75% of patients. Other commonly used were vitamin B (48%), vitamin C (44%), oral iron (32%) and iron/folic acid (32%), dihydropyridine derivatives (32%), aspirin (3 1%) and furosemide (3 1%). Overall the two groups were well balanced with respect to concomitant treatment but a higher proportion of placebo-treated than lanthanum -treated patients used ACE inhibitors, dihydropyridine derivatives, 112 receptor antagonists, HMG CoA reductase inhibitors, aspirin, sodium bicarbonate and alfacalcidol.

Efficacy Results: The primary efficacy endpoint was the reduction and maintenance of serum phosphate levels between 1.3 mmol/L to 1.8 mmol/L with a predetermined maintenance dose of lanthanum carbonate compared with placebo in part 2 of the study.

Figure 1 shows mean serum phosphorus level from screening to the end of Part 2. While mean serum phosphate level in patients who continued on lanthanum remained stable, the mean serum phosphate level for those subjects who were switched from lanthanum to placebo treatment in the Part 2 of the protocol gradually increased toward the baseline level. However, the observed numerical differences between treatment groups were no statistically significant.

Figure 1. Mean Serum Phosphorus Levels by Visit and Treatment Group – ITT Population



[Sponser's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-202, Vol 120, Tables XII and 24.1. LV denotes Last Visit.]

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

Table 1. Number (%) of Patients with Controlled Serum Phosphates – ITT Population

	Lanthanum N=17 n(%)	Placebo N=19 n(%)	p-Value
Week 5	13(76.5)	14(73.7)	1.0
End of Treatment	11(64.7)	4(21.1)	0.008

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

Mean serum calcium levels were comparable between treatment groups throughout the study. At the beginning of part 2 men serum PTH levels were similar between the groups, however thereafter mean levels were higher in the placebo group than in the lanthanum group.

Safety Results: The safety of lanthanum compared to placebo was characterized by evaluating the incidence of deaths, serious adverse events, discontinuations due to adverse events, clinical and laboratory adverse experiences; and changes in vital signs.

Extent of Exposure: In Part 1 of the study, 59 patients received at least one dose of study medication. 50 patients receiving approximately 4 weeks of treatment completed part 1 of the study. Seventeen of these patients were randomized to lanthanum carbonate in Part 2 of the study and therefore received (approximately) a further 4 weeks of lanthanum carbonate treatment. A further 19 patients switched to placebo after 4 weeks treatment with lanthanum carbonate.

Seven (10.8%) patients discontinued prematurely from the study, in part 1, because of adverse events. One (5.3%) placebo-treated patient withdrew from the study due to an adverse event.

Deaths: There were no deaths reported in this study.

Serious Adverse Events: Serious adverse events were reported for seven patients in total; six patients experienced serious adverse events during treatment with lanthanum carbonate (all during dose titration) and one during treatment with placebo. Serious adverse events include: peritonitis, hospitalization due to exacerbation of chest infection, episode of unsteadiness, coronary angioplasty, menorrhagia, anaphylasis reaction to vancomycin, hospitalization for blood transfusion.

Clinical and Laboratory Adverse Events: The number of patients reporting adverse events during either Part 1 or 2 of the study were too small to allow for any valid conclusion.

Vital Signs: Mean systolic and diastolic blood pressures, heart rate and respiration rate were by and large unchanged throughout the study.

ECG Data: The reader is referred to the ISS.

Protocol LAM-IV-204: "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."

The primary objective of this study was "to compare changes in serum phosphate levels from baseline to the end of treatment for four fixed doses of lanthanum and placebo. The secondary objective was "to determine the minimum and maximum clinically effective dose."

This Phase II study had a double blind, randomized, multicenter, placebo controlled, dose ranging and parallel group design. The study was conducted at 10 investigative sites in the USA. The study start date was April 6, 1998 and the stop date was November 11, 1998.

INVESTIGATIONAL PLAN[42]

Study Design: This was a randomized, double blind, placebo controlled, parallel group, dose ranging study of lanthanum carbonate in "chronic renal failure" subjects receiving hemodialysis. Patients were randomly allocated, in a 1:1:1:1:1 ratio, to daily doses of Lanthanum carbonate 225 mg, 675 mg, 1350 mg, 2250 mg or placebo. Study drug (chewable tablets)[43] was taken three times a day with meals. The study had three phases: 1) 1 to 3-week single blind placebo run in[44], 2) followed by randomization of eligible subjects into a six week double blind treatment phase, and a 2 week, single blind placebo run out phase.

Study Population: male or female patients aged 18 or older with end stage renal disease undergoing hemodialysis for at least 6 months and a serum phosphate level ≥5.6 mg/L were enrolled in the study. Significant hypercalcemia >11.0 mg/dL or hyperparathyroidism, defined as serum PTH >1000 pg/mL, among others, excluded the patient from randomization into the study.

The following medications were excluded from the time of screening until the end of the study: phosphate binders or other calcium-based compounds, OTC products containing aluminum, calcium, phosphates or magnesium, or sucralfate.

Compliance with study drug was assessed by tablet count.

Efficacy Variables: The primary endpoint was the reduction of pre-dialysis serum phosphate levels from washout levels following six weeks of treatment.

Secondary efficacy variables included: 1) to determine the minimum and maximum clinically effective dose, 2) to determine the time at which a significant reduction in serum phosphate was first achieved, and whether this reduction was sustained until the end of treatment for each dose group, 3) to determine the effects of lanthanum carbonate withdrawal on serum phosphate level, and 4) to evaluate the effects of dietary phosphorus and calcium intake on changes in serum phosphates levels.

Safety: Evaluation of the safety of lanthanum carbonate was based upon the assessment of adverse events, and changes in ECG and routine safety laboratory parameters.

Statistical Methods: Efficacy determined by the reduction in pre-dialysis serum phosphate levels from end-of-washout to end-of-treatment was analyzed using a one-way analysis of variance. The ITT population was the primary analysis population. The sponsor estimated that a sample size (n) of 23 per group was sufficient to give a power of 90%, given that the Type I error (α) was set to 0.05.

RESULTS

Amendments: According to the sponsor, there were not changes to the original protocol.

Protocol Violations: There were 44 patients with single protocol violations. Protocol violations leading to subject discontinuation included: poor compliance with study drug regimen (n=2), disallowed medication taken (n=2), serum phosphorus <5.6 mg/dL (n=1), and randomization error (n=2).

Unblinding: The sponsor did not report any case that required unblinding.

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[42] For a complete description of the study protocol the reader is referred to NDA 21-468. Protocol LAM-IV-204, Vol. 123.

[43] Chewable tablets containing 25 mg, 75 mg, 150 mg, and 250 mg of lanthanum.

[44] All phosphate binders were discontinued prior to starting this phase.

Disposition of Subjects: A total of 145 subjects were randomized to double blind treatment, placebo n=32, lanthanum 225 mg/day n=28, 675 mg/day n=29, 1350 mg/day n=30, and 2250 mg/day n=26 (Table 2).

Table 2. Subject Disposition

	Placebo N=32 n(%)	La-225mg N=28 n(%)	La-675mg N=29 n(%)	La-1350mg N=30 n(%)	La-2250mg N=26 n(%)
Completed	15(46.9)	13(46.4)	20(69.0)	21(70.0)	22(84.6)
Discontinued:	17(53.1)	15(53.6)	9(31.0)	9(30.0)	4(15.3)
AEs	3	4	4	1	1
Safety	13	7	5	5	2
Adm. or Other	1	4	0	3	1

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-204, Vol. 123, Table 2. AEs denotes adverse events including death; Safety denotes PO_4 >10 mg/dL, PO_4xCa >80 mg^2/dL^2 and Δ_{PTH} >500. Administrative or other includes 7 protocol violations, 8 consent withdrawal, 2 kidney transplant, 1 lost to follow-up, 9 other administration reasons such as non-compliance and scheduled absence.]

Study Population: Out of the 145 subjects randomized into the study, 145 were included in the ITT population[45], 80 (55%) were male, 102 (71%) were black, 36 (25%) whites, and 6 (4%) other races. The average age was 56.4 yeas. Sixty-eight (47%) patients had diabetes, 42 (29%) had hypertension, 11 (7%) had glomerulonephritis, 3 (2%) cystic kidney disease, 18 (12%) had other diseases as a primary diagnosis, and in2 (1%) subjects the cause of ESRD was unknown. Only 12(8%) of the subjects had a history of kidney transplant. Overall, albeit the number of patients randomized per group was small, there were no major differences/imbalances between the treatment groups in baseline demographic characteristics, blood pressure, prior therapies, and laboratory measures[46]. The mean duration of dialysis range from 2.5 to 4.3 years.

Treatment Compliance: According to the sponsor, "when assessed across treatment groups, compliance was similar during each of the three periods for the active drug treatment groups, ranging from 88% to 96%. However, there appeared to be a decrease over the course of the study for subjects in the placebo group, from 92% compliance during the run-in washout to 79% dining the run-out washout."

Concomitant Medications: N/A.

Efficacy Results: The primary endpoint was the reduction of pre-dialysis serum phosphate levels from washout levels following six weeks of treatment (Table 3 and Figure 2).

Figure 2 shows the change, point estimates and 95% confidence intervals, in the serum phosphorus level from the end of the placebo run-in phase to the end of treatment. There were no differences in baseline serum phosphate concentrations across treatment groups. The decreases in phosphate concentrations in the lanthanum doses of 1350 mg/day and 2250 mg/day were highly significantly greater ($p< 0.0001$) versus placebo (Table 3).

Table 3. Change in Serum PO_4 Level (mg/dL) from End of Washout to End of Treatment – ITT Population

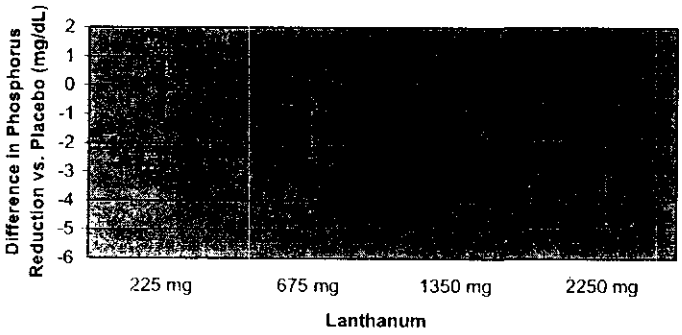
	Treatment Group					p-value
	Placebo N=32	La225 N=27	La675 N=29	La1350 N=30	La2250 N=26	
Baseline Serum PO_4	7.1±1.3	6.5±1.1	7.2±1.4	6.8±1.4	7.4±1.2	0.103
Change in Serum PO_4	0.7±1.4	0.6±1.5	0.07±1.8	-0.9±1.3	-1.1±2.0	<0.0001

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-204, Vol 123, Table 6, (Dunnett's test).]

[45] Subject 15-SA028 was w thdrawn during the first week of the randomized double blind phase for a kidney transplant

[46] NDA 21-468, Protocol No. LAM-IV-204, Vol. 13, Table 4.

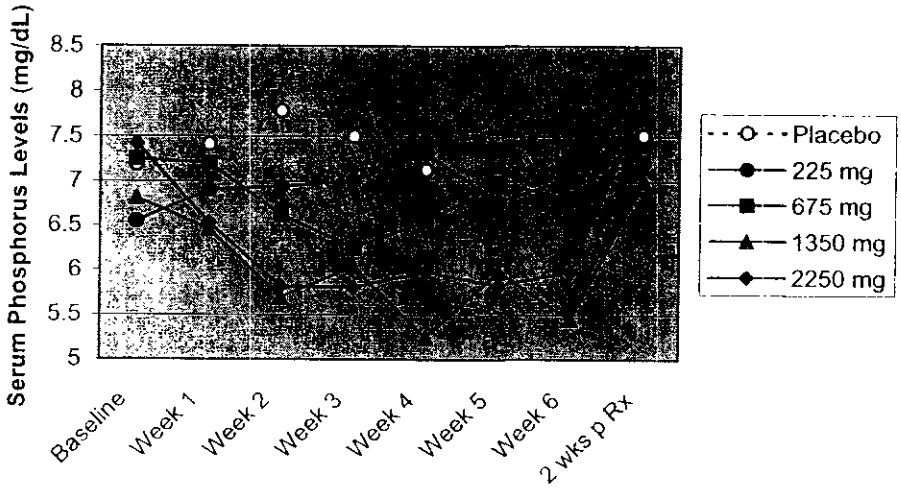
Figure 2. Primary Endpoint: Comparison of Placebo vs. Lanthanum (Point Estimates, 95% CI) – ITT Population



[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-204, Vol. 123, Table 6.]

Mean serum phosphorus levels at the end of each week are depicted in Figure 3. There is clear temporal and dose relationship between lanthanum and mean serum phosphorus levels.

Figure 3. Mean Serum Phosphorus Levels Over Time – ITT Population



[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-204, Vol. 123, Table 7.]

The effect of lanthanum at doses of 225 mg/day and 675 mg/day on serum phosphorus levels could not be distinguished from placebo. However when lanthanum was administered at doses of 1350 mg/day and 2250 mg/day controlled serum phosphorus levels, i.e., <6.0 mg/dL, at end of treatment in 56.7% and 50.0% of the patients, respectively.

The effect of stopping lanthanum treatment on serum phosphorus was assessed in the placebo run-out phase of the study (Figure 3). After two weeks of drug discontinuation, serum phosphorus concentrations increased to levels at or above baseline values.

Safety Results: The safety of lanthanum compared to placebo was characterized by evaluating the incidence of deaths, serious adverse events, discontinuations due to adverse events, clinical and laboratory adverse experiences; changes in vital signs, and ECG parameters.

Extent of Exposure: More than fifty percent of patients in each lanthanum dose were exposed to study drug

for 6 weeks: 57.1% (n=16), 79.3% (n=23), 73.3% (n=22), 88.5% (n=23) of the subjects for the 225 mg, 675 mg, 1350mg, and 2250 mg dose, respectively.

Deaths: There were two deaths reported in this study, one each in the 225 mg (myocardial infarction) and 1350 mg (worsening aortic valve stenosis) lanthanum groups.

Serious Adverse Events: Eighteen patients experienced serious adverse events post-randomization (Table 4). Five patients receiving lanthanum had an incident of clotted graft while none of the placebo-treated subjects had such event.

Table 4. Patients Who Experienced a Serious Adverse Event Post-Randomization

Treatment	Site # / Subject #	Serious Adverse Event
Placebo	13 / SA011	Uremia
La 225	11 / SA007	Clotted graft
	12 / SA001	Esophagitis, exacerbation of chronic pancreatitis, paracentral cervical disk herniation
	13 /SCO02	Clotted access graft
	14 / SA003	Clotted dialysis graft, Uremia
	14 SDO10	Accelerated hypertension, Pulmonary edema
	15 SA028	Chronic renal disease
	19 SB001	Aortic valve stenosis
La 675	14 / SA020	Clotted dialysis graft
	15 / SA018	Coronary artery stenosis
	18 / SB002	Atrial fibrillation, Worsening mitral valve regurgitation
La 1350	11 / SA010	Congestive heart failure
	11 / SA011	Clotted dialysis graft
	13 / SA006	Infected dialysis graft
	18 / SA008	Acute myocardial infarction
	20 / SB003	Hyperglycemia
La 2250	11 / SA006	Exacerbation of diabetic gastroparesis
	11 / SB002	Pneumoperitoneum

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-204, Vol. 123, Table 15.]

Clinical Adverse Events: Patients in the lanthanum group, as compared with those subjects randomized to the calcium group, had greater (at least two-fold) incidence of nausea (14% vs. 6%), vomiting (12% vs. 5%), hypotension (8% vs. 3), and abdominal pain (6% vs. 0%). Of note, while no patient receiving placebo had a dialysis graft clotted, 11 (10%) lanthanum-treated subjects had problems with dialysis graft clotting: 3 in the lanthanum 225 mg group; 2 lanthanum 675 mg, 2 lanthanum 350 mg; and 4 lanthanum 2250 mg (Table 5).

Table 5. Percent Incidence of Adverse Events Reported (≥5%) Post-Randomization by Treatment Group

Adverse Event	Placebo N=32 %	Lanthanum N=113 %
Nausea	6	14
Vomiting	6	12
Dialysis Graft Clotted	0	10
Hypotension	3	8

Abdominal Pain	0	6

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-204, Vol. 123, Table 14.

Laboratory Adverse Events: Overall reporting of laboratory abnormalities as adverse events was low. Hyperphosphatemic and hypocalcemic events were more frequent in patients receiving placebo than lanthanum (22% vs. 6% and 6% vs. 0%, respectively). Patients in the lanthanum group, as compared with those subjects randomized to the calcium group, had greater incidence of anemia (3% vs. 0%), and hyperglycemia (3% vs. 0%),

Vital Signs: According to the sponsor, mean systolic and diastolic blood pressures, heart rate and respiration rate were mostly unchanged during the treatment period.

ECG Data: The reader is referred to the ISS.

Protocol LAM-IV-205: "Long Term, Open Label Extension Study of Protocol LAM-IV-204"

The primary objective of this study was "to assess the long-term safety of lanthanum carbonate in hemodialysis patients who had received treatment in the previous study LAM-IV-204 and wished to continue treatment. The study was conducted at 6 investigative sites in the USA. The study start date was March 01, 1999 and the completion date was March 16, 2000.

INVESTIGATIONAL PLAN[47]

Study Design: This Phase III extension study had an open label, and multicenter design. Patients participating in this study were those who had received treatment in the previous study LAM-IV-204. The duration of the study was 48 weeks of treatment. Patients started study treatment at a daily dose of 300 mg, which could be titrated by the investigators based on pre-dialysis phosphorus levels up to 2250 mg/daily, i.e., 300, 450, 900, 1350, 1500 and 2250 mg/day.

Study compliance was assessed by tablet counts.

Study Population: Patients enrolled in this study had already met the inclusion and exclusion criteria for study LAM-IV-204 and had successfully completed the study.

Efficacy Variables: The primary endpoint was the control of pre-dialysis serum phosphate levels (PSPL, ≤6.0 mg/dL).

Safety: Evaluation of the safety of lanthanum carbonate was based upon the assessment of adverse events, and changes in ECG and routine safety laboratory parameters.

Statistical Methods: No sample size was determined statistically for this study.

RESULTS

Amendments: According to the sponsor, there were not changes to the original protocol.

Protocol Violations: There were 3 patients with single protocol violations. Protocol violations leading to subject discontinuation included: serum phosphorus >10 mg/dL (n=1), and randomization error (n=2).

Unblinding: N/A.

[47] For a complete description of the study protocol the reader is referred to NDA 21-468, Protocol LAM-IV-205, Vol. 127.

Disposition of Subjects: A total of 42 subjects were randomized to the study. Twenty six (62%) patients were discontinued prematurely (Table 6). The following adverse events caused patients' discontinuations: nausea (n=2), weakness (n=2), and one each for diarrhea, catheter complications, hyperkalemia, and fracture of right femur.

Table 6. Subject disposition

Reason for Withdrawal	**Lanthanum N=42 n(%)**
Completed	16(38.0)
Discontinued:	26(62.0)
AEs	8(19.0)
Withdrew Consent	10(24.0)
Protocol Violation	3(7.1)
Safety	3(7.1)
Adm. or Other	1(2.0)
Kidney Transplant	1(2.0)

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-205, Vol. 127, Table 4. AEs denotes adverse events including death; Safety denotes PO_4 >10 mg/dL, PO_4xCa >80 mg^2/dL^2.]

Study Population: Out of the 42 subjects randomized into the study, 40 were included in the ITT population[48], 22 (55%) were male, 34 (85%) were black, 5 (12.5%) whites, and 1 (2.4%) Asian/Pacific. The average age was 54.1 years. Demographic and baseline characteristics were in keeping with those already described in Protocol LAM-IV-204.

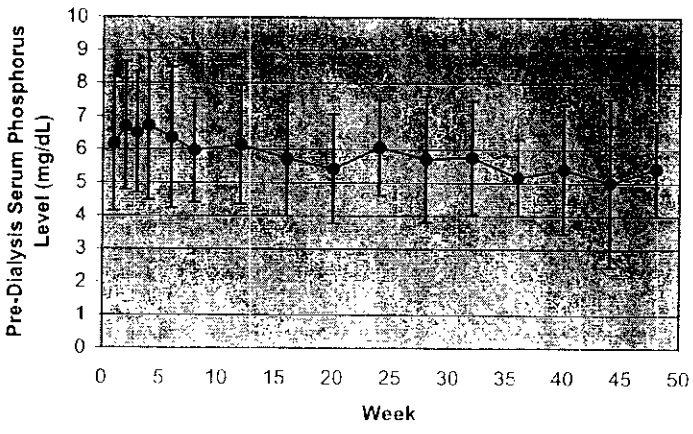
Treatment Compliance: Treatment compliance was 83%.

Concomitant Medications: N/A.

Efficacy Results: The primary endpoint was the maintenance of pre-dialysis serum phosphate levels at ≤6.0 mg/dL

Figure 4 shows mean (±SD) serum phosphorus levels throughout the study. For most of the time points mean pre-dialysis serum phosphate levels were at the pre-specified value of ≤6.0 mg/dL.

Figure 4. Mean (±SD) Pre-Dialysis Serum Phosphorus Level



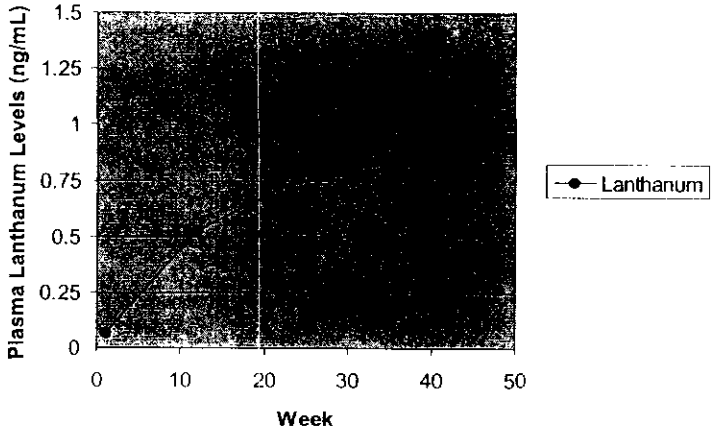
[48] Two subjects (31-SA001 and 31-SB003) did not receive study drug.

Week																
	1	2	3	4	6	8	12	16	20	24	28	32	36	40	44	48
N	37	32	31	36	33	32	30	28	24	22	19	17	13	6	5	12

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-205, Vol. 127, Table 2.2.1.]

Lanthanum plasma levels were measured at baseline and weeks 12, 24, 36, and 48. Figure 5 depicts plasma lanthanum levels overtime. The mean (±SD) plasma levels increased from a baseline level of 0.070 (±0.110) ng/mL to 0.527 (±0.871) ng/mL at week 12 and to 0.756 (±1.399) ng/mL at week 24, thereafter mean values declined to 0.543 (±0.488) ng/mL at week 36 and to 0.268 (±0.206) ng/mL at week 48. Of note, the number of patients who had a measurement declined significantly over time, less than one-third by week 48.

Figure 5. Mean Plasma Lanthanum Levels – Intent-to-Treat Population



Week					
	1	12	24	36	48
N	34	33	27	15	10

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-205, Vol. 127, Table 2.4.1.]

Safety Results: The safety of lanthanum was characterized by evaluating the incidence of deaths, serious adverse events, discontinuations due to adverse events, clinical and laboratory adverse experiences; changes in vital signs, and ECG parameters.

Extent of Exposure: Table 7 summarizes the exposure to lanthanum. Only four patients received lanthanum longer than one year.

Table 7. Exposure to Lanthanum – Intent to Treat Population

Treatment Duration	Lanthanum N=42 n(%)
≤1 month	6 (14.3)
2-3 months	6 (14.3)
4-6 months	8 (19.0)
7-9 months	13 (31.0)
10-12 months	5 (11.9)
>12 months	4 (9.5)

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-205, Vol. 127, Table 6.]

Deaths: There was no death reported during this study, however one death was reported within 30 days of the subject (Subject 18-SA006) stopping study drug. The subject died following unspecified complications after surgery.

Serious Adverse Events: Fifteen patients experienced 26 serious adverse events during the study (Table 8).

Table 8. Patients Who Experienced a Serious Adverse Event during the Study

Subject ID	Serious Adverse Event
14-SA002	Hyperkalemia, fluid overload
14-SA004	Fracture
14-SA005	Pancreatitis
14-SA010	Dialysis catheter infection
14-SA012	Dialysis graft infection
14-SA020	Renal transplant
14-SD003	Bone disorder
14-SD013	Dialysis graft occlusion
14-SD018	Sepsis, back pain, diverticulitis, pain, nausea, vomiting
18-SA002	Peripheral ischemia
18-SA006	Atrial fibrillation, fracture femur, cardiac arrest
18-SB007	Dialysis catheter occlusion
18-SB009	Dialysis catheter and graft occlusion
21-SA019	Renal transplant
21-SA029	Tachycardia supraventricular

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-205, Vol. 127, Table 9.]

Clinical Adverse Events: The most commonly reported adverse events were myalgia (76%), hypotension (67%), nausea (55%), cramps (52%), peripheral edema (50%), pain (41%), vomiting (41%), malaise (38%), dialysis catheter complications (36%), diarrhea (33%), and rhinitis (33%).

Laboratory Adverse Events: Overall reporting of laboratory abnormalities as adverse events by the investigators was very low. Hyperkalemia and hypoglycemia were reported in 7.1% and 2.4% of the patients, respectively.

Vital Signs: There were no clinically significant changes in mean systolic and diastolic blood pressures, heart rate and respiration rate during treatment.

ECG Data: The reader is referred to the ISS.

Protocol LAM-IV-301: "A Phase III, Open Label, Comparator Controlled Parallel Group Study to Assess the Efficacy and Safety of Lanthanum Carbonate for Reduction of Gastro-intestinal Phosphate Absorption and Maintenance of Control of Serum Phosphate in Chronic Renal Failure Patients Receiving Hemodialysis."

The primary objective of this study was "to assess the reduction of gastrointestinal phosphate absorption as measured by reduction in serum phosphate, after dosing with lanthanum carbonate compared to calcium carbonate in hemodialysis patients."

This Phase III study had an open-label, randomized, multicenter, multinational, comparator controlled, and parallel group design. The study was conducted at 67 investigative sites in the following countries: Belgium (11), The Netherlands (5), Germany (37), and United Kingdom (14). The study start date was September, 1998 and the completion of the treatment date was April, 2000. [ ] is still ongoing.

INVESTIGATIONAL PLAN[49]

Study Design: This was an open-label, randomized[50] (2:1 ratio to either lanthanum carbonate or calcium carbonate[51]), active comparator controlled, parallel group study of lanthanum carbonate in "chronic renal failure" patients receiving hemodialysis. Lanthanum carbonate and calcium carbonate were taken (chew) after meals and titrated as needed from 375 mg to 3000 mg (elemental lanthanum) and 1500 mg to 9000 mg (elemental calcium), respectively, to achieve a phosphate level of ≤1.8 mmol/L. The study had the following periods: 1) 1 to 3-week screening and washout period, 2) randomization followed by 5-week dose titration period, 3) 20-week treatment phase, 4) a 24-week extension phase during which all patients received lanthanum carbonate, a 5) [redacted]

Study Population: male or female patients aged 18 or older with "chronic renal failure" undergoing hemodialysis (3 per week for at least three months) and a serum phosphate level >1.8 mmol/L (>5.6 mg/L) were enrolled in the study. Significant hypercalcemia (≥3.0 mmol/L) or hyperparathyroidism (>1000 pg/mL) precluded the patient's randomization into the study.

Compliance with study drug was assessed by tablet count.

Efficacy Variables: The primary endpoint was reduction of serum phosphate to ≤1.8 mmol/L (≤5.6 mg/dL); patients achieving this target were considered to be controlled. Secondary parameters included: 1) the maintenance of serum phosphate to ≤1.8 mmol/L, 2) the long-term absorption profile of lanthanum in hemodialysis patients, 3) the effects of lanthanum carbonate on serum calcium and PTH levels, 4) the use of vitamin D therapy, and 5) the long-term safety and tolerability of lanthanum carbonate. Changes in dietary phosphorus intake were monitored twice during the study in a cohort of patients.

Safety: Evaluation of the safety of lanthanum carbonate was based upon the assessment of adverse events, and changes in ECG and routine safety laboratory parameters.

Statistical Methods: Efficacy was determined according to the level of serum phosphate achieved after 5 weeks in the dose titration phase. The ITT population was the primary analysis population. Assuming a 5% level of confidence (two-tailed) and a 90% power, 585 patients were required to detect a 10% difference in the proportion of controlled patients in the two groups.

RESULTS

Amendments: The original protocol was amended 5 times as follows:[53]

1. 24th August 1998: Errors in the Statistics sections were corrected and of timing of drug intake in relation to meals was clarified.
2. 26th November 1998: Guidelines for dietary assessment in a cohort of patients were introduced.
3. 23rd September 1999: This amendment comprised changes in CRO company name, personnel, selection of central laboratory, SAE reporting, timing of analysis of primary endpoint[54], and an increased in the number of patients recruited, up to 803.
4. 21st December 1999: The two-year extension was introduced to collect more information on safety.

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[49] For a complete description of the study protocol the reader is referred to NDA 21-468, Vol. 130, Protocol LAM-IV-301.

[50] At each site "investigators delegated a member of staff not involved with the study to open an envelope when a patient was to be randomized and to direct the investigator to assign the treatment indicated."

[51] Calcium carbonate is not approved in the USA for the treatment of hyperphosphatemia associated with ESRD.

[52] [redacted] and not reported here.

[53] For a complete description of amendments the reader is referred to NDA 21-468, Vol. 130, Protocol LAM-IV-301, pages 045-051.

[54] "The data recorded at the end of the titration (5 weeks) and the maintenance (26 weeks) phase will be analyzed..." was amended to: "The data recorded at the end of the titration (week 6) and the maintenance (Week 26) phase will be analyzed."

5. 17th January: This amendment comprised changes in CRO company address and telephone numbers.

Protocol Violations: Three hundred and six protocol violations were noted (196 [36.6%] in the lanthanum group and 110 [41.2%] in the calcium group).

Table 9 lists all the protocol deviations leading to patient withdrawal from the study by the investigator.

Table 9. Protocol Deviations that Caused Withdrawal of Patients by Investigator

Protocol Deviation	Patients Withdrew n
Poor compliance with study drug	8
Hemodialysis <3 times a week	2
Phosphate level ≤1.8 mmol/L	5
Concomitant phosphate binder	1
Hyperparathyroidism	2
Unspecified	20

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-301, Table 3.]

Unblinding: N/a.

Disposition of Subjects: A total of one thousand and thirteen patients were screened and 805 patients were randomized. Three patients were randomized but study drug was not dispensed and two patients returned all their medication. Thus a total of 800 patients received at least one dose of study drug, 533 received lanthanum carbonate and 267 received calcium carbonate. Of note, thirty-three patients from one investigative center (site 99) were not included in the efficacy analyses because the sponsor deemed the efficacy data unreliable. Safety data from these patients however was included in the safety evaluation. The ITT population, as defined by the sponsor, consisted of 767 patients (lanthanum carbonate n= 510 and calcium carbonate n= 257). During the course of the study 425 patients discontinued study medication, the reasons for discontinuation are given in Table 10.

Table 10. Patient Discontinuations

Reason for Discontinuation	Lanthanum N=533 n (%)	Calcium N=267 n(%)
Total	271(50.8)	154(57.6)
Protocol violation	24(8.8)	11(2.0)
Withdrew consent	43(8.0)	29(5.4)
Kidney transplant	23(4.3)	16(3.0)
Lost to follow up	5(0.9)	1(0.1)
Death	19(3.5)	11(2.0)
Adverse event	82(15.3)	47(8.8)
Serious adverse event	12(2.2)	4(0.7)
Other	63(11.8)	34(6.3)
Missing	1(0.2)	0(0)

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-301, Vol. 130, Table 2.]

Demographic and Other Baseline Characteristics: Table 11 summarizes demographic and other baseline characteristics, based on mean comparisons there were no major discrepancies between the groups. The patient population was primarily male (65.3%), white (96.2%) with a mean age of 57.7 years.

Table 11. Demographic and Other Baseline Characteristics

	Lanthanum N=510 n (%)	Calcium N=257 n(%)
Gender		
Male	341(66.9)	164(63.8)
Female	169(33.1)	93(36.2)
Race		
Caucasian	493(96.7)	246(95.7)
Black	9(1.8)	3(1.2)
Asian	4(0.8)	2(0.8)
Oriental	3(0.6)	4(1.6)
Hispanic	1(0)	1(0.4)
Other	0(0)	1(0.4)
Age		
Range	19-87	21-85
Mean±SD	57.0±14.3	58.4±13.3
Blood Pressure (mmHg, Mean±SD)	N=533	N=267
Systolic	145.9±21.2	147.0±24.3
Diastolic	79.6±12.0	79.6±12.0
Months on Hemodialysis (Mean±SD)	42.9±39.0	43.8±43.9
Previous Kidney Transplant	63(12.4)	33(12.8)

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-301, Vol. 130, Tables 4. 5.7.]

Renal History: Similar renal histories were recorded for the patients in both groups. The main causes of patients' chronic renal failure, in the lanthanum group vs. in the calcium group), were glomerulonephritis (29.6% vs. 25.3%), diabetes (14.3% vs. 14.8%), cystic kidney disease (11.8% vs. 15.6%), and hypertension (9.2% vs. 10.5%).

Concurrent Diseases: Concurrent diseases in patients in the ITT population were recorded at screening and during Part 4 of the study during which patients previously receiving calcium carbonate were switched to lanthanum carbonate. The incidences of these diseases were well balanced between the treatment groups and in terms of type and frequency were typical of chronic renal failure patient populations.

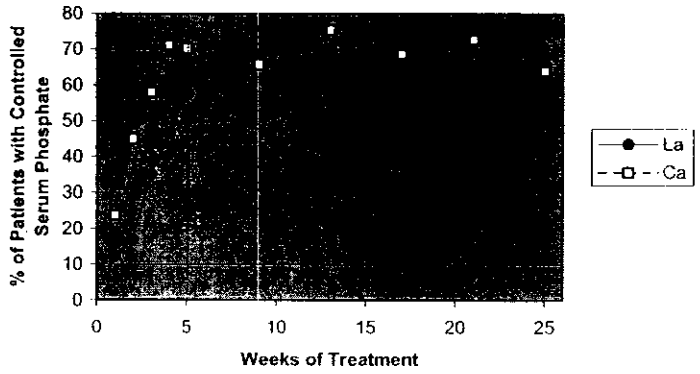
Concurrent Medications: The use of concomitant medications was well balanced between the two treatment groups throughout the study.[55]

Efficacy Results: Efficacy was determined according to the level of serum phosphate achieved after 5 weeks in the dose titration phase; serum phosphate levels ≤1.80 mmol/L were considered control. A secondary objective was the evaluation of maintenance of treatment control after 25 weeks of treatment, i.e., 5 weeks titration plus 20 weeks maintenance.

Results of the analysis (intent-to-treat) of the primary endpoint are shown in Figure 6. The percentage of controlled patients, i.e., with serum phosphate levels ≤1.80 mmol/L, at the end of the 5 week dose titration (visit 6) was significantly higher in the calcium group than in the lanthanum group, 70.3% vs. 57.8%, respectively (Chi-square test, $p<0.002$). After 25 weeks of treatment the proportion of controlled patients in the calcium group was similar to that in the lanthanum group (63.9% vs. 65.8%, respectively, $p=0.73$).

[55] NDA 21-468, Protocol No. LAM-IV-301, Vol 130, Table 8.

Figure 6. Percent of Patients with Controlled Serum Phosphate – ITT Population



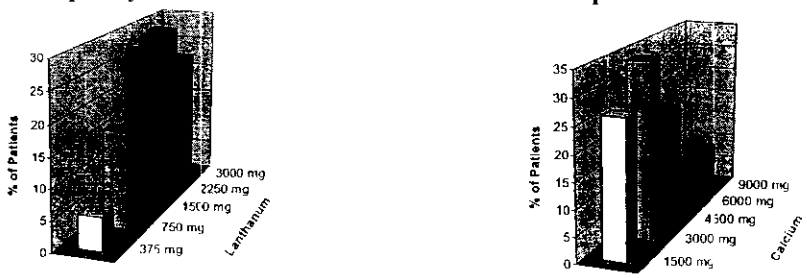
Week	1	2	3	4	5	9	13	17	21	25
La. N=	498	492	479	466	453	277	255	242	228	222
Ca. N=	253	238	231	212	209	152	138	131	117	122

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-301, Table 14.1.28.1]

Dietary assessment, i.e., intake of phosphate, protein, calcium, kilocalories, vitamin D and sodium, in a subset of patients from the ITT population (n=95) failed to show statistically significant differences in dietary intake.

Figure 7 illustrates the frequency of doses of study drug dispensed at week 5, i.e., end of titration phase, for both groups. At the end of the maintenance phase (not shown) the frequency of doses of lanthanum and calcium dispensed remained similar to those dispensed at week 5 of treatment. Over seventy percent of the patients receiving lanthanum required doses of 1500 mg/daily or greater to have their serum phosphate levels controlled.

Figure 7. Frequency of Doses of Lanthanum and Calcium Dispensed at Week 5.

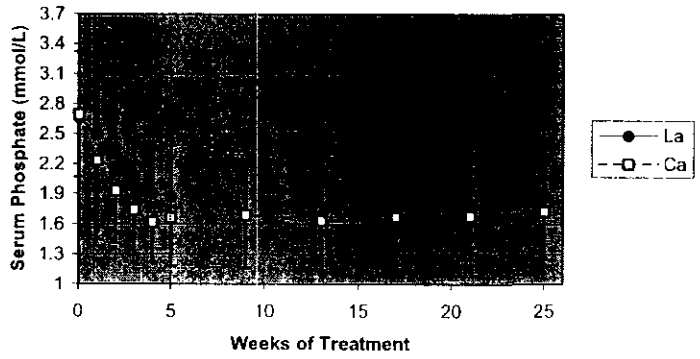


[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-301, Table 14.1.30.3]

Secondary efficacy variables included: the maintenance of serum phosphate to ≤1.8 mmol/L, the long-term absorption profile of lanthanum in hemodialysis patients, the effects of lanthanum carbonate on serum calcium and PTH levels, the use of vitamin D therapy, and the long-term safety and tolerability of lanthanum carbonate.

- The maintenance of serum phosphate to ≤1.8 mmol/L: Figure 8 depicts mean (±SD) serum phosphate levels (mmol/L) baseline through week 25 of treatment. At baseline the mean serum phosphate levels were 2.67±0.66 vs. 2.69±0.62, at week 5 were 1.87±0.51 vs. 1.66±0.48, and at week 25 were 1.76±0.56 vs. 1.82±0.51 for the lanthanum and calcium groups, respectively.

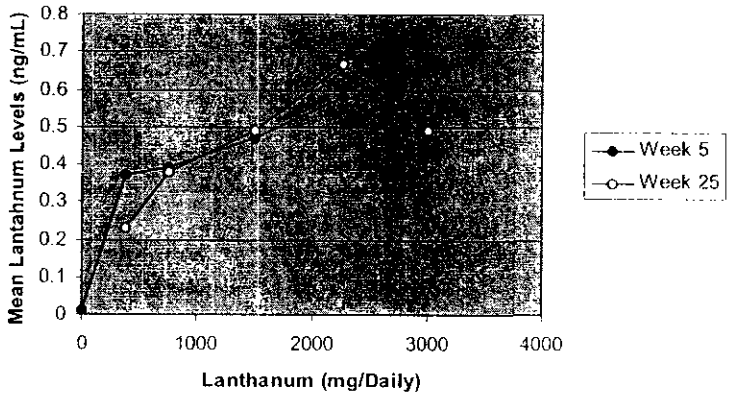
Figure 8. Serum Phosphate Levels (Mean±SD) – ITT Population



[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-301, Table 14.1.15.1.]

- The long-term absorption profile of lanthanum in hemodialysis patients: Serum lanthanum levels in the lanthanum group increased as compared with baseline with doses between 350 mg and 2250 mg and then plateau at the 3000 mg dosage (Figure 9). Overall the observed levels at week 5 were similar to those documented at week 25. In patients receiving calcium carbonate serum lanthanum levels remained unchanged throughout the study and essentially at baseline levels.

Figure 9. Summary of Lanthanum Levels in Lanthanum-Treated Patients – ITT Population.



[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-301, Table 14.1.]

- The effects of lanthanum carbonate on serum calcium[56] and PTH levels: Throughout the study mean serum calcium levels in patients the lanthanum group remained essentially unchanged, from the mean baseline value of 2.38mmol/L. Conversely, mean serum calcium levels in the calcium group increased slightly from the baseline value of 2.35mmol/L, however a dose response couldn't be demonstrated. Of note, 5.7% of lanthanum-treated and 37.9% of calcium-treated patients had hypercalcemic, i.e., serum calcium value above ULN, events by week 26 of treatment ($p<0.001$). At baseline the median PTH[57] values for the lanthanum group was 127 ng/L and for the calcium group .63 ng/L. At week 5 these values were 174 ng/L and 98 ng/L for the lanthanum and calcium groups, respectively, and at week 25 166 ng/L and 113.5 ng/L. The median change in PTH from screening to end of maintenance was 50 ng/L for the lanthanum group, and -49 ng/L for the calcium group. Thus lanthanum carbonate treatment increased PTH levels while calcium carbonate treatment decreased them.

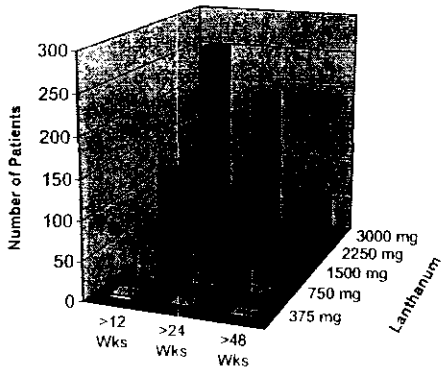
[56] NDA 21-468, Tables 14.1.A9.2 and 14.1A9.3.
[57] NDA 21-468, Table 14.1.17.1.

- The use of vitamin D[58] therapy: The sponsor assessed changes in vitamin D usage in the ITT population during the maintenance phase, in the lanthanum group, 11.9% of patients had changed vitamin D usage compared to 7.6% in the calcium group (p=0.452).

- The long-term safety and tolerability of lanthanum carbonate: This subject is being addressed in the safety results' section.

Extent of Exposure: A summary of the number of patients, grouped by final dose level, with at least 3,6 and 12 months of exposure is given in Figure 10. As expected, the number of patients treated with lanthanum diminished over time, 510 patients have at least 3 months exposure, 411 at least 6 months and only 178 have approximately one year of lanthanum exposure.

Figure 10. Number of Patients Treated with Lanthanum Carbonate by Dose.



[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-301, Vol. 130, Table 33.]

Safety Results: The safety of lanthanum compared to placebo was characterized by evaluating the incidence of deaths, serious adverse events, discontinuations due to AEs, clinical and laboratory adverse experiences; changes in vital signs, and ECG parameters. The analysis of safety was carried out on the ITT population.

Table 12 summarizes the frequency of adverse events, SAEs, discontinuations due to AEs and death for the titration and treatment phases as well as for the 24-weeks extension phase in which every patient received lanthanum. Except for the frequency of SAEs, which was higher in the calcium carbonate group, the incidence of AEs, discontinuations due to AEs and deaths was comparable among the groups for the titration and treatment phases combined.

Table 12. Summary of Adverse Events by Treatment Group

	Lanthanum N=533 n (%)	**Calcium N=267 n (%)**
Titration and Treatment Phase (25 Weeks)		
Patients with at least an adverse experience	414 (77.7)	213 (79.8)
Discontinued due to adverse experiences	132 (24.8)	58 (21.7)
Patients with a serious adverse experiences	114 (21.4)	80 (30.0)
Who died	12 (2.3)	7 (2.6)
24 Weeks Extension (all Pts. Received Lanthanum)	**N=518**	
Patients with at least an adverse experience	466 (90.0)	
With serious adverse experiences	136 (26.3)	

[58] NDA 21-468, Vol. 130, Table 14.1.34.1.

Discontinued due to adverse experiences	198 (38.2)	
Who died	21 (4.1)	

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-301, Vol. 130, Table 37.]

Deaths: There were a total of 40 deaths during the study. In the course of the titration and treatment phases there were 12 (2.3%) deaths in the lanthanum group and 7 (2.6%) in the calcium group. In the 24 weeks extension 21 (4.1%) deaths were reported in total, 12 (3.6%) deaths it the lanthanum/lanthanum group and 9 (4.9%) in the calcium/lanthanum group.

Serious Adverse Events: The frequency for the most serious adverse events reported in the titration and treatment phases were comparable between the treatment groups.[59]

Clinical Adverse Events: Table 13 summarizes the frequency (greater in subjects receiving lanthanum than calcium carbonate) of the most common clinical adverse events reported during the titration and treatment phases. More patients receiving lanthanum, as compared with those treated with calcium, reported nausea, vomiting, diarrhea, and abdominal pain. Also hyperparathyroidism was more commonly diagnosed in the lanthanum group than in the calcium group. Of importance, 5 (0.9%) patients receiving lanthanum carbonate had bone fractures while only one (0.4%) patient treated with calcium carbonate reported a fracture.

Table 13. Incidence of Adverse Events Reported by Treatment Group

Adverse Event	Lanthanum N=533 %	Calcium N=267 %
Nausea	15.9	12.7
Vomiting	18.4	11.2
Diarrhea	12.6	9.7
Abdominal Pain	4.9	3.4
Hyperparathyroidism	1.9	0.4

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-301, Vol. 131, Table 14.1.25.2.]

Laboratory Adverse Events: The number (%) of patients with specific laboratory adverse events was very small and similar between the groups. Hypercalcemia is the exception in that was reported in 20.2% of the subjects receiving calcium versus 0.4% of lanthanum-treated patients.

Vital Signs: According to the sponsor, mean systolic and diastolic blood pressures, heart rate and respiration rate were mostly unchanged during the study.

ECG Data: The sponsor did not obtain electrocardiograms in this study.

Protocol LAM-IV-302: "A Phase III, Dose Titration, Randomized, Double Blind, Placebo Controlled Parallel Group Study to Assess the Efficacy and Safety of Lanthanum Carbonate for Reduction and Maintenance of Serum Phosphate Levels in Chronic Renal Failure Patients Receiving Hemodialysis."

The primary objective of this study was "to assess the maintenance of serum phosphate levels within the clinically acceptable limits which was defined as ≤5.9 mg/dL by continue use of lanthanum carbonate compared to placebo in chronic renal failure patients receiving hemodialysis and with hyperphosphatemia which was defined as serum phosphorus levels >5.9 mg/dL."

This Phase III study had a double blind, randomized, multicenter, placebo controlled, parallel group and dose titration design. The study was conducted at 14 investigative sites in the USA. The study start date was October 11, 1999 and the stop date was July 31, 2000.

[59] NDA 21-468, Vol. 131, Table 14.1.26.3.

INVESTIGATIONAL PLAN[60]

Study Design: This was a randomized (1:1 ratio to either lanthanum carbonate or placebo), placebo-controlled, double blind, parallel group study in chronic renal failure patients receiving hemodialysis. Lanthanum carbonate starting dose was 750 mg daily and titrated as needed up to 3000 mg daily[61] to achieve a serum phosphate level <5.9 mg/dL. The study had the following phases: screening and washout phase, six week open-label dose titration phase, and 4-week double-blind randomized drug maintenance phase with a placebo arm.

Study Population: male or female patients aged 18 or older with "chronic renal failure" undergoing hemodialysis (3 per week for at least two months) and a serum phosphate level >5.9 mg/dL were enrolled in the study. Significant hypercalcemia (>11.0 mg/dL) or hyperparathyroidism (>1000 pg/mL) precluded the patient's randomization into the study.

Compliance with study drug was assessed by tablet count.

Efficacy Variables: The primary endpoint was defined "as the last pre-dialysis serum phosphorus level of a patient that was obtained during the maintenance treatment period." The control of serum phosphorus levels at study endpoint was also analyzed.

Secondary endpoints included: 1) the pre-dialysis serum phosphorus levels obtained during the dose titration period and maintenance treatment period, 2) the weekly serum calcium, 3) the weekly serum calcium-phosphorus product, and 4) the weekly PTH levels obtained during the randomized treatment period."

Safety: Evaluation of the safety of lanthanum carbonate was based upon the assessment of adverse events, and changes in ECG and routine safety laboratory parameters.

Statistical Methods: Efficacy was determined according to the last level of serum phosphate obtained post randomization. The ITT population was the primary analysis population.

RESULTS

Amendments: The original protocol (dated on June 21, 1999) was amended twice. The first amendment was dated on September 16. 1999, "the changes included a change of medical monitor and typographical errors in addition to reducing the maximum limit of the calcium-phosphorus product to 80 mg^2/dL^2, clarifying timing of repeat testing for laboratory tests leading to withdrawal of patients, documentation required of previous phosphate binders, instructions for dispensing study medications and a change of protocol number for the open label safety study patients could be enrolled to following completion of this current study." The second amendment was issued on December 8, 1999. "The changes made in this amendment were for the purpose of clarification, such as instructions for rapid notification of serious adverse events, name change of emergency contact information, duration of screening period prior to study enrollment, eligibility criteria for entering dose titration. The amendment made it clear: dose during the titration phase could be increased or decreased no more than 2 levels at one study visit; and Vitamin D supplementation was permitted."

Protocol Violations: Overall, protocol deviations were reported in 66 patients. Of those noted for deviations, 40(61%, 40/66) patients were approved to continue the study. Seventeen (26%, 17/66) patients were not approved for continuation; however. 3 of them completed the study and were included in ITT population: Patient 307-031 (lanthanum), Patient 307-03 7 (placebo), and Patient 307-048 (placebo). Five patients were terminated under the termination category of protocol violation as listed in the CRF: poor

[60] For a complete description of the study protocol the reader is referred to NDA 21-468, Protocol LAM-IV-302, Vol. 182.
[61] i.e., 750 mg, 1500 mg, 2250 mg, and 3000 mg daily with meals.

compliance with study drug regimen 307-005 and 307-044, disallowed medication (calcium) taken 307-040, enrolled after enrollment closed 307-054 and 307-056

Unblinding: N/A.

Disposition of Subjects: A total of one hundred and sixty-three patients from 14 sites were enrolled in the study and entered the washout phase, 126 (77%) met the criteria for entering dose-titration phase, and 94[(75%), Lanthanum n=50, Placebo n=44] completed the 6-week dose titration and were randomized into the double-blind maintenance phase with 46 (92%) patients receiving lanthanum and 36 (82%) placebo-treated patients completing the study (Table 14).

Table 14. Patient Disposition

	Lanthanum N=50 n (%)	**Placebo N=44 n (%)**
Completed	46(92.0)	36(81.8)
Discontinued	4 (8.0)	8 (18.2)
Withdrew consent	0 (0.0)	1 (2.3)
Kidney transplant	0 (0.0)	2 (4.5)
Adverse event	2 (4.0)	1 (2.3)
Safety*	1 (2.0)	3 (6.8)
Protocol violation/other	1 (2.0)	1 (2.3)

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-302, Vol. 182, Table 2. *Including efficacy-related safety criteria defined as two consecutive values of PO_4 >10 mg/dL, PO_4xCa >90 mg^2/dL^2, Ca >110 mg/dL, and Δ_{PTH} >500 pg/mL.]

Demographic and Other Baseline Characteristics: 103 patients enrolled (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. Fifty-two (32%) and 65 patients (40%) randomized into the study had a history of diabetes and hypertension, respectively. Only 18 (11%) patients had glomerulonephritis as the primary diagnosis. Prior therapies to control hyperphosphatemia included calcium acetate (49%), calcium carbonate (42%), Renagel® (6%).[62] The average time on dialysis prior to enter the study was 2.9 years.

Mean serum phosphorus levels were similar at pre-study (i.e., before washout) between patients randomized to lanthanum (6.25 mg/dL) vs. placebo (6.19 mg/dL).

Overall, based on means comparison, there were no significant differences/imbalances between the treatment groups in demographic and other baseline characteristics.

Compliance with study drug: For the ITT population the mean drug compliance was similar across the two periods: 90% for dose titration and 87% for maintenance treatment. When assessed across treatment groups. compliance was similar during each of the two periods for the two treatment groups, ranging from 86% to 90%.

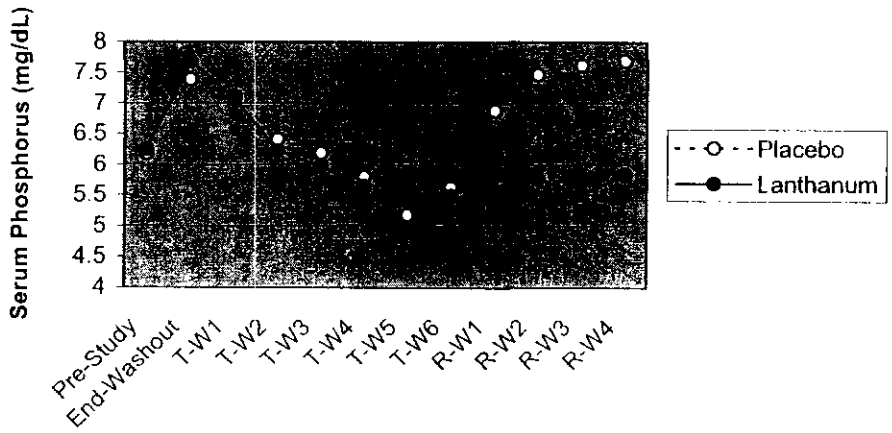
Efficacy Results: The primary endpoint was defined "as the last pre-dialysis serum phosphorus level of a patient that was obtained during the maintenance treatment period." The control of serum phosphorus levels at study endpoint was also analyzed. Secondary endpoints included: 1) the pre-dialysis serum phosphorus levels obtained during the dose titration period and maintenance treatment period, 2) the weekly serum calcium, 3) the weekly serum calcium-phosphorus product, and 4) the weekly PTH levels obtained during the randomized treatment period."

[62] NDA 21-468, Protocol LAM-IV-302, Vol. 182, Table 4.

The pre-study serum phosphorus levels for the placebo and lanthanum groups were similar, 6.186 mg/dL vs. 6.251 mg/dL, respectively. There were no differences in the serum phosphorus concentrations between the two treatment groups at the end of washout (7.39 mg/dL placebo group and 7.69 mg/dL lanthanum group, p=0.3754). At the end of dose titration[63] the serum phosphorus level decreased to 5.62 mg/dL in the placebo group and to 5.49 mg/dL in the lanthanum group (p=0.6942).

At end of randomized treatment, the serum phosphorus (mean±SD) was 7.85±1.96 mg/dL for placebo and 5.94±1.65 mg/dL for lanthanum (p<0.0001). The mean difference in serum phosphorus concentrations between groups was -1.91 mg/dL, and the 95% confidence interval of the mean difference ranged from -2.6 mg/dL to -1.23 mg/dL. Serum phosphorus ranged from 5.51 mg/dL to 5.84 mg/dL for patients who continued lanthanum treatment[64], while the serum phosphorus increased to 6.89 mg/dL at the end of first randomized week and to 7.70 mg/dL at the end of the fourth randomized week for patients who discontinued lanthanum treatment (p<0.01 at week 1, p<0.0001 at weeks 2-4). Figure 11 depicts serum phosphorus levels throughout the study.

Figure 11. Mean Serum Phosphorus Levels Over Time – ITT Population



[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-302, Vol. 182, Table 2.3.1. T-W denotes week in titration phase; R-W denotes week in randomization phase; *p<0.01; **p<0.0001.]

In seventy one percent and 59% of the patients in the lanthanum and placebo groups, respectively, their serum phosphorus were controlled (defined as ≤5.9 mg/dL, p=0.275). At the end of week four post randomization, the percent of patients whose serum phosphorus levels were controlled was 59% for the lanthanum group and 23% for placebo (mean difference of 36%, p=0.001).

There were no statistically significant differences in serum calcium levels between lanthanum- and placebo-treated patients throughout the study.

There were no differences in the calcium-phosphorus product between the two treatment groups at the end of both washout and dose titration phases. However at study endpoint, this product was 66.59±18.30 mg^2/dL^2 for placebo and 52.37±14.89 mg^2/dL^2 for lanthanum (mean difference of -14.22 mg^2/dL^2 p<0.0001).

Mean PTH levels were no different between the two treatment groups at the end of both washout (p=0.3067) and dose titration periods (p=0.5894). At study endpoint, the PTH level was 291.80±194.82 pg/mL for placebo and 209.41±152.65 pg/mL for lanthanum (p=0.006).

[63] i.e., all patients received lanthanum carbonate prior to randomization.
[64] Below the study-defined clinically acceptable limit of ≤5.9 mg/dL.

Extent of Exposure: Of the 126 patients who entered the dose titration phase, 94 (75.0%) completed the 6-week dose titration and were randomized into the double-blind maintenance phase with 82 (87.0%) patients completing the study (46 subjects in the lanthanum group versus 36 subjects in the placebo group). Exposure to lanthanum carbonate by dose during the maintenance phase is summarized in Table 15.

Table 15. Exposure to Lanthanum Carbonate by Dose during the Maintenance Phase

Duration of Treatment	La 375-750 N=11 n(%)	La 1500 N=25 n(%)	La 2250 N=37 n(%)	La 3000 N=53 n(%)
≤1 week	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)
2 weeks	1 (9.1)	3 (12.0)	1 (2.7)	0 (0.0)
3-4 weeks	1 (9.1)	4 (16.0)	6 (16.2)	3 (5.7)
5-6 weeks	1 (9.1)	2 (8.0)	2 (5.4)	5 (9.4)
7-8 weeks	4 (36.4)	8 (32.0)	14 (37.8)	24 (45.3)
9-10 weeks	1 (9.1)	6 (24.0)	8 (21.6)	15 (28.3)
>10 weeks	2 (18.2)	2 (8.0)	6 (16.2)	6 (11.3)

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-302, Vol. 182, Table 8.]

Safety Results: The safety of lanthanum compared to placebo was characterized by evaluating the incidence of deaths, serious adverse events, discontinuations due to adverse events, clinical and laboratory adverse experiences; changes in vital signs, and ECG parameters. The analysis of safety was carried out on the ITT population.

Deaths: Three deaths were reported during the study. Patient 303-003, a 64-year-old white female with diabetes as primary diagnosis, died during the washout period and did not receive any study drug. Patient 309-010, an 86-year-old white male, also died during the washout period, from pneumonia. The third patient to die was Patient 307-011, a 60-year old black male diagnosed with hypertension, who died during the titration period and was on lanthanum for six (6) weeks. His final daily lanthanum dose was 1500 mg. The cause of death was cardiac arrest, following hospitalization for ventricular arrhythmia.

Serious Adverse Events: Post-randomization, 4 serious adverse events in 4 patients (8%, 4/50) were reported for the lanthanum-treated group; and 10 in 4 patients (9.1%, 4/44) were reported for the placebo-treated group. The number of serious adverse events per category was too small to allow for any valid conclusion.

A total of fifteen patients were discontinued from the study for adverse events as follows: 2 patients during the washout period, 10 during the titration period, and 3 during the maintenance period. Seven of these discontinuations which occurred during the titration or the maintenance phases in lanthanum-treated patients were due to gastrointestinal manifestations including nausea, vomiting diarrhea and flatulence.

Clinical Adverse Events: Table 16 summarizes the most common clinical adverse events reported post-randomization. The patients reported small number of adverse events per category post-randomization. Of note, patients in the lanthanum group, as compared with those subjects randomized to the placebo group, had greater incidence of nausea (6% vs.4.5%), vomiting (6.0% vs. 2.3%), abdominal pain (6% vs. 0%), dialysis graft occlusion (6.0% vs. 2.3), and dialysis graft complication (4.0% vs. 2.3%).

Table 16. Percent Incidence of Adverse Events Reported Post-Randomization by Treatment Group

Adverse Event	Lanthanum N=126 %	Placebo N=44 %
Nausea	6.0	4.5
Vomiting	6.0	2.3
Abdominal Pain	6.0	0.0
Dialysis Graft Occlusion	6.0	2.3
Dialysis Graft complication	4.0	2.3

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-302, Vol. 182, Table 3.4.4.]

Laboratory Adverse Events: Laboratory adverse events reported by the investigators during the study were too small to reach any valid conclusion.[65]
Vital Signs: Vital signs (systolic and diastolic blood pressures, pulse. respiration rate. and temperature) were measured weekly. Based on the comparison of the mean values there were not significant differences between the treatment groups.

ECG Data: The reader is referred to the ISS.

Protocol LAM-IV-303: "A Phase III, Multi-Center, Open Label Study to Investigate the Effect of Lanthanum Carbonate Compared with Calcium Carbonate on Renal Bone Disease in Chronic Renal Failure Patients Receiving Hemodialysis."

The primary objective of this study was "to investigate the effect of lanthanum compared with calcium carbonate on renal bone disease", secondary objectives included "to investigate the concentration of lanthanum and calcium within bone and to evaluate long-term safety and tolerability of lanthanum in this patient population."

INVESTIGATIONAL PLAN[66]

Study Design: This was an open-label, multi-center, randomized (1:1 ratio of lanthanum carbonate to calcium carbonate), comparator controlled, parallel group study of lanthanum carbonate in "chronic renal failure" patients receiving hemodialysis. The study had the following periods: 1) screening period, 2) tetracycline labeling followed by baseline bone biopsy and randomization to either lanthanum carbonate or calcium carbonate, 3) titration and treatment phase, and 4) tetracycline labeling followed by final bone biopsy (transiliac) at week 52. Lanthanum carbonate and calcium carbonate were taken (chew) after meals and titrated up to 3750 mg/day of lanthanum or 9000 mg/day of calcium.

Study Population: male or female patients aged 18 or older with "chronic renal failure" undergoing hemodialysis and requiring phosphate binders were enrolled in the study.

Compliance with study drug was assessed by tablet count.

Efficacy Variables: The primary response variables included mineralization lag time, % osteoid surface, % osteoid volume, % osteoblast surface, bone formation rate, % osteoclast surface and mean erosion rate. The secondary response variables were cortical bone thickness and volume, trabecular bone mean osteoid thickness, volume, wall thickness, % mineralizing surfaces, mean apposition rate, eroded surface, trabecular thickness, trabecular number and separation, activation frequency, % labeled osteoid seams, adjusted apposition rate, aluminum staining, the concentration of lanthanum, aluminum and calcium, and the adverse event profile.

Safety: Evaluation of the safety of lanthanum carbonate was based upon physical examination and the assessment of adverse events, and changes in vital signs, ECG and routine safety laboratory parameters.

Statistical Methods: "It was planned that 100 patients would be randomized in a 1:1 ratio of lanthanum to calcium carbonate treatment. Assuming a drop out rate of 44%, it was estimated that 56 patients would complete the study. There was limited data available on which to base the sample size estimates, therefore numbers were based on practical rather than statistical considerations."

RESULTS

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[65] NDA 21-468, Protocol LAM-IV-302, Vol. 182, Tables 8.3.1 and 8.3.2.
[66] For a complete description of the study protocol the reader is referred to NDA 21-468, Vol. 189, Protocol LAM-IV-303.

Amendments: The original protocol was amended 4 times.[67] The conduct of the study or the interpretation of the results was not significantly affected by the amendments.

Protocol Violations: According to the sponsor "there were 15 protocol deviations (8 in the lanthanum group and 7 in the calcium group, recorded in all patients randomized). The most frequent protocol deviation was poor compliance (6 in the lanthanum group and 6 in the calcium group) where the patients had taken less than 80% of their study medication. Other protocol deviations included a patient not receiving dialysis at randomization, a patient receiving a prohibited medication, and a patient who did not receive the study treatment that they had been randomized to."

Unblinding: N/A.

Disposition of Subjects: A total of ninety-eight patients were randomized into the study. Forty-nine and 48 patients in the lanthanum and calcium groups, respectively, had baseline bone biopsy. A second bone biopsy was obtained in 36 and 35 patients receiving lanthanum and calcium, respectively. Thirty-four patients in each treatment group completed the study thus fifteen patients in each group discontinued the study prematurely. The reasons for discontinuation are summarized in Table 17.

Table 17. Patient Discontinuations

Reason for Discontinuation	**Lanthanum** N=49 n	**Calcium** N=49 n
Investigator decision	0	1
Protocol violation	0	1
Kidney transplant	5	5
Death	6	5
Serious adverse event	1	1
Other	3	2

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-303, Vol. 189, Table 5.]

Demographic and Other Baseline Characteristics: The study population was mainly male (60%), Caucasian (93%) with an average age of 55 years. Overall, when comparing mean values, there were not significant differences in demographic and others baseline characteristics between the groups (Table 18). At screening most of the patients were undergoing hemodialysis, lanthanum n=38 vs. calcium n=34, while the remaining subjects receiving peritoneal dialysis, lanthanum n=12 vs. calcium n=17.[68]

Table 18. Demographic and Other Baseline Characteristics

	Lanthanum N=49 n (%)	**Calcium** N=49 n(%)
Gender		
Male	31(63)	28(57)
Female	18(37)	21(43)
Race		
Caucasian	45(92)	46(94)
Black	0(0.0)	0(0.0)
Asian	1(2.0)	1(2.0)
Mixed Race	2(4.0)	2(4.0)
Oriental	0(0.0)	0(0.0)
Hispanic	0(0.0)	0(0.0)
Other	1(2.0)	0(0.0)

[67] For a complete description of amendments the reader is referred to NDA 21-468, Vol. 189, Protocol LAM-IV-303, pages 052-055.

[68] Three patients were both hemodialysis and peritoneal dialysis patients.

Age		
Range	27-80	18-75
Mean±SD	55.9±13.5	54.0±15.2
Blood Pressure (mmHg, Mean±SD)		
Systolic	149.6±18.4	146.4±20.2
Diastolic	85.2±12.4	85.1±13.7

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-303, Vol. 189, Tables 6,7.]

Renal History: The most common primary diagnoses were diabetes 20% and 31% for the lanthanum and calcium carbonate groups, respectively, cystic kidney disease: 12% and 16% and unknown cause: 20% and 8%. Residual renal function as assessed by creatinine clearance was 5.81 mL/min in the lanthanum group and 5.33 mL/min in the calcium group of patients.

Concurrent Diseases: As expected, cardiovascular disease was most common. For lanthanum and calcium groups, respectively, the incidences for essential hypertension were 80% and 78%, anemia in 67% of patients in both groups, other primary cardiomyopathies on 10% and 14% of patients and chronic ischemic heart disease in 14% and 6% of patients. Type II or unspecified type diabetes were present in 22% and 14% of patients, type I insulin-dependent diabetes in 8% and 10% of patients, background diabetic retinopathy in 10% and 14% of patients, and hyperparathyroidism in 14% and 12% of patients in the lanthanum and calcium groups, respectively.

Concurrent Medications: The usage of concomitant medications, commonly taken by a population with end-stage renal disease, was well balanced between the two treatment groups.

Extent of Exposure: In total, the patients were treated with study drugs for 50 weeks.

Treatment Compliance: N/A

Efficacy Results: The interpretation of the bone biopsy results is equivocal because according to the sponsor the "number [of patients studied] were based on practical rather than statistical considerations." Thus the study was not powered to demonstrate treatment differences. Notwithstanding, the results from baseline and follow-up bone biopsies (63 pairs) suitable for histomorphometric measurements are next presented.[69]

Of note, the median z-scores of mineralization lag time indicate that patients in the lanthanum carbonate group had slower bone formation than those patients receiving the active control, +0.8 versus +3.975, respectively.

Table 19. Summary of Bone Histomorphometric Measurements by Teatment Group.

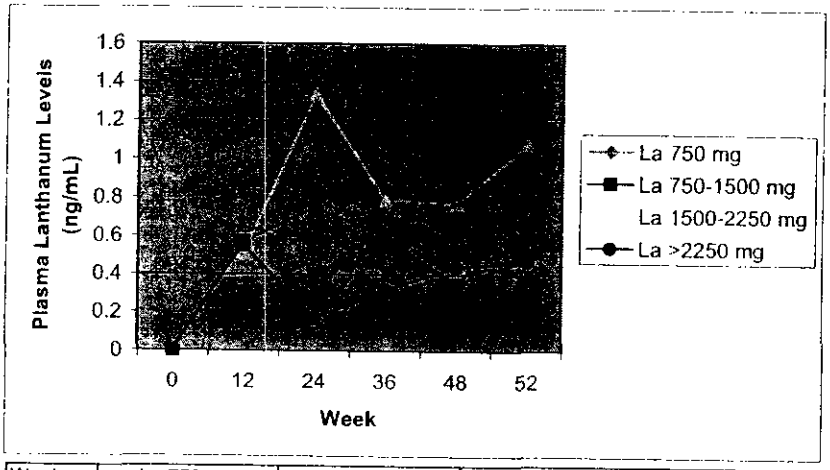
Variable	Lanthanum		Calcium		95%CI*
	n	Median	n	Median	
Mineralization Lag Time(Days)	32	-4.1	30	-35.8	-31.7, 91.5
% Osteoid Surface	33	-2.3	30	-1.9	-6.81, 3.92
% Osteoid Volume	33	0.13	30	-0.28	-0.69, 1.35
% Osteoblast Surface	33	1.9	30	-3.8	-4.4, 11.9
Bone Formation Rate ($\mu m^3/\mu m^2$/year)	32	1.3	30	0.08	-10.7, 9.4
% Osteoclast Surface	33	-0.1	30	-0.1	-0.62, 0.54
Mean Erosion Depth (μm)	33	-1.8	30	-1.9	-2.34, 2.15

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-303, Vol. 189, Tables10-15. *Non parametric 95% confidence interval for median treatment difference]

[69] . Baseline biopsies were not included in this analysis where no follow-up biopsy had been obtained. In addition, the sponsor provided median values for the primary variables "since the data ranges for both groups were skewed..."

Plasma lanthanum levels were measured at visits 3, 8, 11, 14, 17 and 20.[70] In lanthanum-treated patients there were increases in plasma lanthanum for all doses administered compared with baseline levels which were undetectable (Figure 12). Albeit the small sample size prevents one to be conclusive as to whether there is a dose relationship, plasma lanthanum levels appear to be dose-dependent.

Figure 12. Plasma Lanthanum Levels by Visit and Dose Level in Lanthanum Group – ITT Population

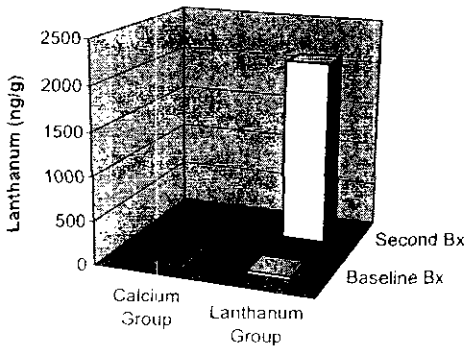


Week	La 750 mg n	La 750-1500 mg n	La 1500-2250 mg n	La >2250 mg n
0	19	6	0	0
12	13	21	3	3
24	12	22	3	2
36	10	19	4	3
48	15	14	4	2
52	11	15	5	3

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

Figure 13 illustrates bone lanthanum concentrations at baseline and after 52 weeks of treatment. While bone lanthanum concentration remained essentially unchanged in the calcium group, mean±SD 52.2±54.8 vs. 102.5±165.8 ng/g, in the Lanthanum group there was a marked, over a 50-fold, increase in bone lanthanum concentration, from (mean±SD) 40.4±21.8 to 2104.8±1356.9 ng/g.

Figure 13. Summary of Bone Lanthanum Concentration by Treatment Group.



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

[70] NDA 21-468, Protocol No. LAM-IV-303, Vol. 189, Table 30.

Bone calcium and aluminum concentrations by treatment group are provided in Table 20. In both groups bone calcium and aluminum levels increased slightly, not statistically significant, between the baseline and second biopsies.

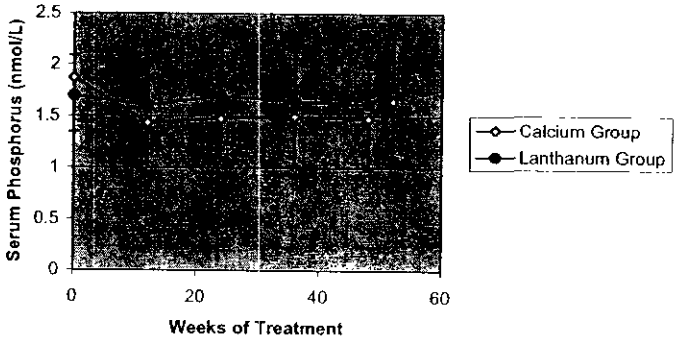
Table 20. Summary of Bone Calcium and Aluminum Concentrations by Teatment Group.

Variable	Lanthanum		Calcium	
	n	Mean±SD	n	Mean±SD
Bone Calcium Concentration (mg/g)				
Baseline Bx	43	100.2±37.8	46	111.6±36.1
Second Bx	34	120.3±33.5	35	125.3±51.8
Bone Aluminum Concentration (µg/g)				
Baseline Bx	43	6.4±3.8	46	8.1±9.5
Second Bx	33	9.7±8.5	35	10.0±11.0

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-303, Vol. 189, Table 17. *Where individual bone sample values were below the limit of quantitation (LOQ) the LOQ value was used to determine the concentration.]

Serum phosphorus levels at baseline and visits (12,24,36,48, and 52 weeks) during the study by treatment group are depicted in Figure 14. Throughout the study serum phosphorus levels were similar between the groups and on average both treatment groups showed reasonable well-controlled phosphate levels during the study.

Figure 14. Serum Phosphorus Levels (Mean±SD) Over Time by Treatment Group.



[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-303, Vol. 189, Table 18.]

The mean serum calcium levels were similar in both groups throughout the study.[71] According to the sponsor, in the majority of calcium carbonate-treated patients rigorous control of serum calcium was maintained through adjustments in calcium content of the dialysate and reduction in vitamin D_3.

As a result of comparable serum levels for phosphorus and calcium between the treatment groups, the mean calcium x phosphorus product were comparable between the treatment groups throughout the study.[72]

The mean (±SD) PTH levels at twelve weeks interval during the study by treatment group are given in Table 21. Throughout the study mean PTH levels for the lanthanum group remained stable and were higher than the mean levels obtained in the calcium group. Calcium carbonate admin stration was associated with a trend toward lower PTH levels (Table 21).

[71] NDA 21-468, Protocol No. LAM-IV-303, Vol. 189, Table 19.
[72] NDA 21-468, Protocol No. LAM-IV-303, Vol. 189, Table 20.

Table 21. Summary of PTH Levels (pmol/L) by Teatment Group.

Weeks on Treatment	Lanthanum		Calcium	
	n	Mean±SD	n	Mean±SD
0	49	30.9±29.6	49	28.6±23.5
12	42	31.8±25.0	46	20.1±21.1
24	39	35.1±27.9	43	18.7±25.8
36	35	30.5±26.9	41	23.5±29.7
48	34	30.0±36.3	37	23.1±30.1
52	36	30.9±24.2	36	26.6±31.2

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-303, Vol. 189, Table 23.]

Safety Results: The safety of lanthanum compared to placebo was characterized by evaluating the incidence of deaths, serious adverse events, discontinuations due to AEs, clinical and laboratory adverse experiences; changes in vital signs, and ECG parameters. The analysis of safety was carried out on the ITT population.

Extent of Exposure: Of the 98 patients randomized into the study, 34 patients in each group (total: 68) completed the study. These patients were therefore treated with either lanthanum or calcium carbonate for approximately one year in each case.

Deaths: There were a total of 12 deaths reported in this study, six (12.2%) in the lanthanum group and 6 (12.2%) in the calcium carbonate group. Cardiovascular events were the leading cause of death.

Serious Adverse Events: Thirty-four (69%) patients receiving lanthanum and 29 (59%) subjects treated with calcium reported at least one serious adverse event. The number of SAEs reported in each category is small. Nevertheless, the lanthanum group, as compared with the calcium group, had greater incidence of cardiac failure (8% vs. 4%), dialysis graft occlusion (14% vs. 6%), diarrhea (4% vs. 0%), anemia (6% vs. 0%), and dyspnea (4% vs. 0%).

Clinical Adverse Events: Overall, 94 (96%) patients in the safety population reported a total of 703 treatment emergent AEs during the study. Patients in the lanthanum group, as compared with those subjects randomized to the calcium group, had greater (at least two-fold) incidence of cardiac failure (8% vs. 4%), hypertension aggravated (10% vs. 4%), hypotension (14% vs. 4%), dizziness (6% vs. 2%), headache (14% vs. 2%), dialysis graft occlusion (14% vs. 6%) dialysis graft occlusion (14% vs. 6%), hyperparathyroidism (6% vs. 2%), hypocalcemia (29% vs. 12%), arthralgia (10% vs. 2%), and dyspnea (6% vs. 0%). Fractures were reported in 2 patients receiving calcium but none in the lanthanum group.

Laboratory Adverse Events: Reporting of laboratory abnormalities as adverse events was overall low. Hypercalcemic events were more frequent in patients receiving calcium than lanthanum (35% vs. 6%). Conversely, patients in the lanthanum group, as compared with those subjects randomized to the calcium group, had greater incidence of hypocalcemia (29% vs. 12%).

Vital Signs: According to the sponsor, mean systolic and diastolic blood pressures and pulse were mostly unchanged during the treatment period.

ECG Data: The reader is referred to the ISS.

Protocol LAM-IV-307: "An Open Label, 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."

The primary study objective was "to evaluate the long-term safety of lanthanum carbonate in chronic renal failure patients with hyperphosphatemia receiving hemodialysis."

This Phase III study had an open-label, randomized, multicenter, comparator controlled, and parallel group design. It is ongoing and being conducted at 96 investigative sites in the USA. The study start date was July 29, 1999. The date of interim data cut-off was October 31, 2001.

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Study Design: This was an open-label, randomized, multicenter, Phase III, comparator controlled, parallel group study of the long tern safety of lanthanum carbonate for controlling hyperphosphatemia in chronic renal failure patients undergoing hemodialysis three times per week. The study had the following periods: 1) screening and 1 to 3-week washout period, 2) randomization followed by 6-week dose titration period (phosphate binders to be titrated to achieve a PO_4 level of ≤5.9 mg/dl), and 3) a 24 months maintenance phase.

Eligible patients were randomized 1:1 (~500 patients per arm) to either lanthanum carbonate up to a maximum of 3000 mg/day or their pre-study standard therapy, which was one or more of the commercially available phosphate binders, i.e., Renagel® (17%), Phoslo® (34.5%) or Tums® (calcium carbonate, 44.%).[74]

Study Population: male or female patients aged 12 years or older with "chronic renal failure" undergoing hemodialysis (3 per week for at least two months) and a serum phosphate level >5.9 mg/L were enrolled in the study. Significant hypocalcemia <7.9 mg/dL) precluded the patient's randomization into the study.

Compliance with study drug was assessed by tablet count.

Efficacy Variables: The primary efficacy endpoint in this study was the predialysis PO_4 levels (PSPL), which were measured at the first dialysis sessions of study visits, including pre-study and washout. Other endpoints included pre-dialysis serum calcium levels, PTH, and the calcium-phosphorus product.

Safety: Safety was evaluated by monitoring vitals signs including ECG, physical examinations, mini mental state examination, hematology panels, biochemistry panels and adverse events. In addition, measurements analyzed for safety in a subset of patients included: cognitive function testing, and bone biopsy.

Statistical Methods: The primary objective of this study was to assess drug safety. Other objectives included assessing the maintenance of control of serum phosphorus with long-term use of lanthanum carbonate compared to standard therapy.

Of note, no statistical sample size estimation was performed for this study.

RESULTS

Amendments: There were seven amendments made to the original protocol dated June 8, 1999[75] The conduct of the study or the interpretation of the results was not significantly affected by the amendments.

Protocol Violations: Twenty-one patients were terminated from the study because of protocol violations. Six of these patients were withdrawn before randomization; the other 15 were withdrawn following randomization (13 from lanthanum and 2 from standard therapy).

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[73] For a complete description of the study protocol the reader is referred to NDA 21-468, Vol. 206, Protocol LAM-IV-307.

[74] Renagel® (sevelamer hydrochloride), and Phoslo® (calcium acetate) are FDA-approved phosphate binders, however Tums® and over the counter formula of calcium carbonate is not approved by the FDA for use as a phosphate binder.

[75] For a complete description of amendments the reader is referred to NDA 21-468, Vol. 206, Protocol LAM-IV-307, pages 043-044.

Unblinding: N/A.

Disposition of Subjects: A total of 1,345 patients were enrolled in the study, at 96 sites in the USA. The disposition of the enrolled patients is presented in Table 22.[76]

Of note, the sponsor did not follow-up patients who were discontinued from the study, thus the study report does not provide any information on safety including survival for those patients.

One hundred and ten patients (8.2%) were terminated prior to randomization and 7 patients (0.5%) were still in the washout phase based on the information available. The rest of 1,228 patients were randomized to one of the two treatments. Of those randomized, 616 patients (50.2%) were randomized to receive lanthanum carbonate, and 612 patients (49.8%) were randomized to standard therapy. Six hundred and forty-five patients (52.5%) withdrew after they had been randomized to treatment, 386 (62.7%) lanthanum versus 259 (42.3%) standard therapy patients ($p<0.001$).[77]

Thus, in the lanthanum group fewer patients completed the study and more patients discontinued the study because of adverse events ($p<0.0001$), protocol violations ($p<0.003$), withdrew consent ($p<0.001$), exceeded the safety criteria ($p<0.024$), or other ($p<0.005$) than in the standard therapy group.[78]

Table 22. Patient Disposition

	Lanthanum N=616 n (%)	**Standard N=612 n (%)**
Number remaining in the study	196 (31.8)	289 (47.2)
Number who have completed the study	34 (5.5)	64 (10.5)
Number withdrawn	386 (62.7)	259 (42.3)
Reasons for discontinuation:		
Adverse event	80 (13.0)	17 (2.8)
Protocol violation	13 (2.1)	2 (0.3)
Withdrew consent	81 (13.1)	26 (4.2)
Kidney transplant	40 (6.5)	55 (9.0)
Lost to follow-up	6 (1.0)	6 (1.0)
Death	29 (4.7)	67 (10.9)
Other	95 (15.4)	62 (10.1)
Exceeded safety criteria	42 (6.8)	24 (3.9)

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-307, Vol. 206, Table 2.]

Demographic and Other Baseline Characteristics: Fifty-nine percent of the study population was male with an average age of 55.3 years, race was evenly distributed between Caucasian and Black, 46.2% versus 43.0%, respectively. Overall, when comparing mean values, there were not significant differences in demographic and others baseline characteristics between the groups (Table 23).

Table 23. Demographic and Other Baseline Characteristics

	Lanthanum N=616 n(%)	**Standard** N=612 n(%)
Gender		
Male	347(56.3)	365(59.6)
Female	269(43.7)	247(40.4)

[76] As of the October 31, 2001 data cut-off date for this study report, 98 patients (Lanthanum Group: 34; Standard Group: 64) have completed the study and the remaining 492 patients are still participating in either the dose titration phase or maintenance phase of the study based on the CRF information available.
[77] FDA's Statistical Review: Dr. Freidlin (HFD-710), page 23.
[78] FDA's Statistical Review: Dr. Freidlin (HFD-710), page 23.

Race		
Caucasian	276(44.8)	288(47.1)
Black	279(45.3)	251(41.0)
Hispanic	50(8.1)	52(8.5)
Asian/PI	2(0.3)	9(1.5)
Native American	6(1.0)	6(1.0)
Other	3(0.5)	9(1.0)
Age		
Mean±SD	54.2±14.4	55.5±14.4
Primary Renal Disease Diagnosis		
Diabetes	214(35.7)	218(36.2)
Hypertension	192(32.0)	176(29.2)
Glomerulonephritis	64(10.7)	75(12.4)

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-307, Vol. 206, Tables 3 & 4.]

Renal History: The most common primary diagnoses were diabetes, hypertension and glomerulonephritis.

Concurrent Diseases: N/A

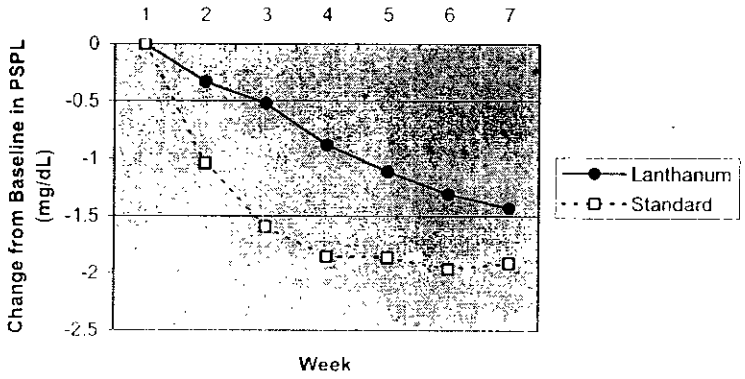
Concurrent Medications: The usage of phosphate binders, commonly taken by a population with end-stage renal disease, was well balanced between the two treatment groups, lanthanum group versus standard therapy group: Calcium carbonate 44.6% vs. 44.0%, Calcium acetate 34.9% vs. 34.5% and Renagel 15.6% vs. 17.0%.

Treatment Compliance: In the ITT population, 341 (56.8%) of the 600 lanthanum patients with compliance measurements had an 80% or greater compliance as did 360 (59.7%) standard therapy patients.

Efficacy Results: The primary efficacy endpoint in this study was the predialysis serum PO_4 levels (PSPL), which were measured at the first dialysis sessions of study visits week 1 to week 7, i.e., titration period (Figure 15).

In both treatment groups serum PO_4 levels declined over time. However, when compared between treatment groups, the change from baseline serum phosphorus level to each follow-up week of dose titration, a greater reduction occurred for patients on standard therapy (p=0.000). At the end of dose titration, week 7 the mean (±SD) change from baseline serum phosphorus level was -1.43±2.19 for the lanthanum group versus -1.91±2.20 for the standard therapy group, p<0.000. The data indicate that standard therapy is superior to lanthanum treatment in reducing serum phosphorus levels in patients with end stage renal disease, and thus controlling hyperphosphatemia.

Figure 15. Change from Baseline in PSPL during the Titration Phase (Weeks 1-7) – ITT Population



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

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

The changes from baseline serum phosphorus level during the maintenance phase, weeks 7 to 52, are summarized in Table 24. The changes from baseline in PSPL were greater in the standard therapy group at weeks 7, 10, 14 and 26 than in the lanthanum group. At week 52 there were no statistically significant differences between the groups.

Table 24. Change From Baseline In PSPL During The Maintenance Phase (Weeks 7-52) - ITT Population Of The Safety Update (May 30, 2002).

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

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

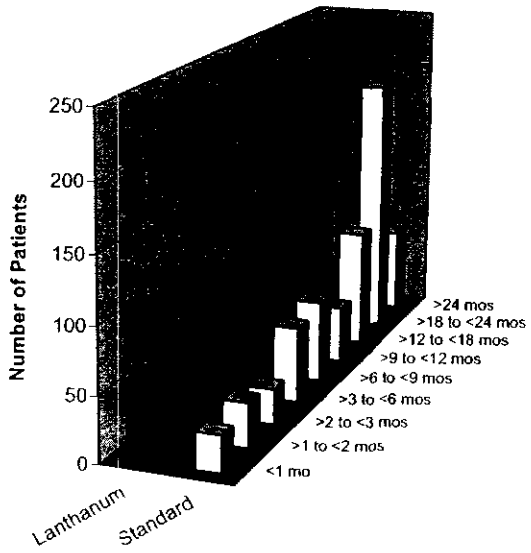
At the end of the titration phase (week 7), the proportion of patients in whom the PSPL was controlled (defined as ≤5.9 mg/dL) was greater in the standard group than in the lanthanum group (57.2% vs. 43.2%, p=0.0001). At 2 years, the values were 42.5% versus 38.2% for the standard and lanthanum groups, respectively.

Serum calcium levels, calcium-phosphorus product and PTH levels were also analyzed in this study for efficacy assessment. The control of Ca x PO_4 was defined as within the clinically acceptable range of 43 mg^2/dL^2 to 60 mg^2/dL^2. Mean serum calcium levels at baseline were similar between groups, however at the end of the titration phase (p=0.000) and throughout the maintenance phase the values in the standard group were higher than in the lanthanum group (p=0.000). Of note, serum PTH levels, at the end of the titration phase (p=0.000) and throughout the maintenance phase, in the standard group were higher than in the lanthanum group, p=0.000 and p=0.000. Therefore, calcium-phosphorus product in the lanthanum group was numerically larger than in the standard group at the end of the titration phase and throughout the maintenance phase.

Extent of Exposure: A summary of the number of patients, by treatment group, with at least 1 and more than 24 months of exposure is given in Figure 16.

As of the cut-off date, October 31, 2001, significantly fewer patients have been exposed to lanthanum therapy as compared to standard treatment. One-hundred twenty (19.5%) lanthanum patients have been treated for ≥18 to <24 months, compared to 201 (32.8%) standard therapy patients (p=0.001). And only 34 (5.5%) lanthanum patients have been treated for ≤24 months, compared to 66 (10.8%) standard therapy patients (p=0.001). As expected, there is also a marked imbalance for the mean days of exposure to study drug between the groups, 284.3±241.5 days for the lanthanum group versus 397.0±247.4 for the standard therapy group (p=0.001).

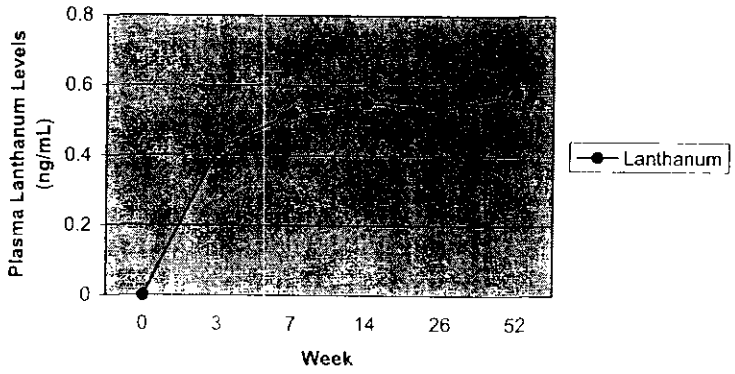
Figure 16. Extent of Exposure



[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-307, Vol. 206, Table 14.1.11.1.]

Plasma lanthanum levels were measured at Screening, Weeks 3, 7 (maintenance baseline), 14, 26, and 52. The mean concentrations and changes from the screening visit are presented in Figure 17.[79] The mean plasma lanthanum level at screening was below the limit of quantification, . —— ng/mL. By Week 3 (mid point of the titration phase) the mean plasma lanthanum concentration was 0.42 ng/mL and at the start of the maintenance period (Week 7) the mean was 0.52 ng/mL. At the remaining visits at which lanthanum levels were measured Weeks 14, 26 and 52, the means were 0.55, 0.53, 0.58 ng/mL, respectively. All these changes were statistically significantly different from zero (p=0.00).[80]

Figure 17. Mean Plasma Lanthanum Levels in Lanthanum Group – ITT Population



[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No LAM-IV-307, Vol. 206, Table 14.2.5.]

Safety Results: The safety of lanthanum compared to standard therapy was characterized by evaluating the incidence of deaths, serious adverse events, discontinuations due to AEs, clinical and laboratory adverse

[79] Plasma lanthanum levels (at screening and final visit) for the standard therapy patient; were not analyzed for this study report.

[80] FDA's Statistical Review, Dr. Freidlin (HFD-710), page 21.

experiences; changes in vital signs, and ECG parameters. The analysis of safety was carried out on the ITT population.

Critical to the interpretation of the safety data is the fact that the sponsor did not follow-up patients who were discontinued from the study, thus the study report does not provide any information on safety including survival for those patients. This lack of follow-up becomes even more important because there was a statistically significantly greater rate of withdrawal in the lanthanum group than in the standard therapy group. The aforementioned deficiency coupled with the marked discrepancy in drug exposure renders the safety results, primarily those in which lanthanum's rates are equal or lower than standard therapy, uninterpretable. In this regard the incidence of fractures were 26 (4.2%) in the lanthanum carbonate group versus 29 (4.7) in the standard therapy group.

Table 25 summarizes the frequency of adverse events, serious adverse events, discontinuations due to AEs and death post randomization, i.e., for the titration and maintenance phases.

The frequency of patients with at least one AE was comparable among the groups for the titration and treatment phases combined, however the incidence of discontinuations due to AEs was more than four-fold higher in the lanthanum group than in the standard therapy group (13.0% vs. 2.8%, p=0.0001). In the lanthanum group more than half of the discontinuations were due to nausea, vomiting, gastrointestinal upset, diarrhea and emesis while the reasons for withdrawal in the standard therapy group was more diverse. The findings support the notion that lanthanum carbonate therapy is significantly less well tolerated than standard therapy.

As compared with the lanthanum group, twice as many patients died during or within 30 days post study in the standard therapy group (12.3% vs. 6.0%). This particular finding is discussed in detail below.

Table 25. Summary of Adverse Events by Treatment Group

	Lanthanum N=616 n (%)	**Standard N=612 n (%)**
Patients with at least an adverse experience	560 (90.9)	565 (92.3)
Discontinued due to adverse experiences	80 (13.0)	17 (2.8)
Patients with a serious adverse experiences	312 (50.6)	390 (63.7)
Who died during study as study outcome	29 (4.7)	67 (10.9)
Who died during or within 30 days post study	37 (6.0)	75 (12.3)

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No LAM-IV-307, Vol. 206, Table 7.]

Deaths: There were a total of 96 deaths during the study, 29 (4.7%) in the lanthanum group and 67 (10.9%) in the standard therapy group, and 112 deaths during the study or within 30 days post study, 37 (6.0%) in the lanthanum group and 75 (12.3%) in the standard therapy group. Because of the statistically significant shorter exposure to lanthanum, due to greater discontinuation rates, as compared to standard therapy ($p<0.001$)[81], this lower death rate most likely represents an underestimation of the exact rate since once a patient was discontinued from the study no follow-up vital status was attained.

Serious Adverse Events and Clinical Adverse Events: Overall, the standard therapy group had a higher incidence of serious adverse events[82] and treatment emergent clinical adverse events (regardless of cause)[83] than the lanthanum group. Again this finding almost certainly reflects the significant imbalance in withdrawal rates, and thus exposure to study drug, between the two treatment groups. In addition, the open-label design could have led to significant underreporting of adverse events due to investigators' biases.

[81] FDA's Statistical Review. Dr. Freidlin (HFD-710), page 23.
[82] NDA 21-468, Protocol LAM-IV-307, Vol. 206, Table 14.3.1.5.
[83] NDA 21-468, Protocol LAM-IV-307, Vol. 206, Table 14.3.1.2.

Laboratory Adverse Events: The number (%) of patients with specific laboratory adverse events was very small. Interpretation of these results is again hampered by the significant imbalance in withdrawal rates, leading to dissimilar exposure to study drug, between the two treatment groups. Notwithstanding, the lanthanum group had higher means values of PTH and lower serum calcium levels than the group of patients receiving standard therapy.

Vital Signs: Vital signs (systolic and diastolic blood pressures, heart rate, respiration rate, temperature, and post-dialysis weight) for the randomized population as assessed remained stable throughout the study and the were not major differences between treatment groups.[84]

ECG Data: The reader is referred to the ISS.

Protocol LAM-IV-308: "A Long Term, Open Label, Extension Study of Protocols LAM-IV-205 and LAM-IV-302."

The primary objective of this study was "to assess the long-term safety of lanthanum carbonate in hemodialysis patients who had received treatment in the previous studies LAM-IV-205[85] or LAM-IV-302 and wished to continue treatment.

This Phase III extension study had an open label, uncontrolled and multicenter design. The study was conducted at 13 investigative sites in the USA. The study start date was December 27, 1999 and the last completion date was July 25, 2001.

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Study Design: This Phase III extension study had an open label, and multicenter design. Patients participating in this study were those who had received treatment in the previous studies LAM-IV-205 or LAM-IV-302 and wished to continue treatment. The duration of the study was 12 months.

The initial dose of study drug was the same as the final dose in the prior study. During the course of the study the dose could be titrated up to 3000 mg daily in order to maintain the serum phosphate level at ≤5.9 mg/dL.

Study Population: Patients enrolled in this study had already met the inclusion and exclusion criteria for studies LAM-IV-205 or LAM-IV-302.[87]

Efficacy Variables: The primary efficacy endpoint was the control of pre-dialysis serum phosphate levels (PSPL, ≤5.9 mg/dL).

Safety: Evaluation of the safety of lanthanum carbonate was based upon the assessment of adverse events, and changes in ECG and routine safety laboratory parameters. Serum lanthanum levels were also measured.

Statistical Methods: N/A.

RESULTS

Amendments: The original protocol (dated October 8, 1999) was amended twice. The amendments did not

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[84] NDA 21-468, Protocol LAM-IV-307, Vol. 207, Table 14.3.5.1.
[85] Protocol LAM-IV-205 was an open label extension of Protocol LAM-IV-204.
[86] For a complete description of the study protocol the reader is referred to NDA 21-468, Protocol LAM-IV-308, Vol. 279.
[87] The information on study population, etc. is provided on the reviews of studies LAM-IV-205 and LAM-IV-302.

substantially change the conduct of the study and thus the interpretation of the results.

Protocol Violations: Protocol deviations leading to patient's withdrawal were reported in 5 cases. Four patients began taking an excluded medication while on study and one patient was withdrawn for non-compliance.

Unblinding: N/A.

Disposition of Subjects: A total of 77 patients were enrolled in the study, 66 from study LAM-IV-302 and 11 from study LAM-IV-205. The disposition of subjects is summarized in Table 26.

Table 26. Patient Disposition

	Lanthanum N=77 n (%)
Completed	32(41.6)
Discontinued	45 (58.4)
Withdrew consent	12 (15.6)
Kidney transplant	5 (6.5)
Adverse event	8 (10.4)
Safety*	6 (7.8)
Protocol violation	5 (6.5)
Other	7 (9.1)

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-308, Vol. 279, Table 2. *Including efficacy-related safety criteria defined as two consecutive values of PO_4 <2.0 mg/dL PO_4 >10 mg/dL, PO_4xCa >80 mg^2/dL^2, Ca >110 mg/dL, and Δ_{PTH} >500 pg/mL.]

Demographic and Other Baseline Characteristics: Fifty patients (64.9%) were male and 27 (35.1%) female, 25 (32.5%) were Caucasian, 41 (53.2%) Black, 6 (7.8%) Hispanic, and 2 (2.6%) Asian/Pacific. Seventeen patients (22.1%) were in the 18-50 year age group, 25 (32.5%) in the 51-64 year age group, and the remaining 35 patients (45.5%) were 65 years of age or older; the mean age was 60.9 ± 12.5 years.

Compliance with Study Drug: For the ITT population the mean drug compliance was 82.1%. Forty-six (59.9%) of the 77 patients had an 80% or greater compliance.

Efficacy Results: According to the sponsor, "by the sixth week of lanthanum treatment 66% of the patients had their PSPL controlled, which is similar to the level of control seen in earlier studies. During the remainder of the study more than 63% of patients had controlled PSPL values, except at Week 20 (55%) and the final visit (Week 52, at which 53% had controlled PSPL values)."

Extent of Exposure: Exposure to lanthanum carbonate is summarized in Table 27. The mean (±SD) time of exposure is 232 6±128.9 days.

Table 27. Exposure to Lanthanum Carbonate by Dose during the Maintenance Phase

Duration of Treatment	**Lanthanum N=77 n(%)**
≤1 month	6 (7.8)
2-3 month	14 (18.2)
4-6 month	13 (16.9)
7-9 months	7 (9.1)
10-12 months	33 (42.9)
>12 months	4 (5.2)

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-308, Vol. 279, Table 4.]

Safety Results: The safety of lanthanum was characterized by evaluating the incidence of deaths, serious adverse events, discontinuations due to adverse events, clinical and laboratory adverse experiences; changes in vital signs, and ECG parameters. The analysis of safety was carried out on the ITT population.

Deaths: Three deaths were reported during the study or within 30 days post study. The causes of death include one each: uremia, cardiac arrest, and myocardial infarction.

Serious Adverse Events: A total of thirty-seven patients experience a serious adverse event during the study. Five patients discontinued the study prematurely because of renal transplant, one each due to worsening hyperparathyroidism, myocardial infarction and cerebral vascular disorder. Six (7.8%) patients had dialysis graft complications, 5 (6.5%), 5 (6.5%) vascular disorders, 4 (5.2%) osteomyelitis, 4 (5.2%) myocardial infarction, and 3 heart failure (3.9%).

Clinical Adverse Events: A total of 888 adverse events were reported in 72 (93.5%) of the 77 patients who were treated with study drug. Table 28 summarizes the most common clinical adverse events reported by the patients while on study drug. Three patients had bone fractures.

Table 28. Percent Incidence of Adverse Events Reported during Treatment

Adverse Event	Lanthanum N=77 %
Nausea	26.0
Edema peripheral	23.4
Myalgia	20.8
Vomiting	18.2
Dialysis Graft Occlusion	18.2
Hypotension	16.9
Dizziness	16.9
Headache	15.6
Diarrhea	13.0
Abdominal Pain	13.0

[Sponsor's analysis. Adapted from: NDA 21-468, Protocol No. LAM-IV-308, Vol. 279, Table 6.]

Six patients discontinued because of non-fatal adverse events. Four of the discontinuations were due to gastrointestinal manifestations including nausea, vomiting and diarrhea or constipation. Two patients were discontinued for either an elevated PTH or hyperparathyroidism.

Laboratory Adverse Events: Albeit there were as expected laboratory changes from baseline, the incidence of laboratory adverse events reported by the investigators during the study were too small to reach any valid conclusion.

Vital Signs: Vital signs (systolic and diastolic blood pressures, pulse. respiration rate. and temperature) were measured weekly. Based on the comparison of mean values there were not persistent significant changes from baseline values.

ECG Data: The reader is referred to the ISS.

APPENDIX

Table 1A. Description of Human Pharmacokinetics Studies

Protocol No. Country/Sites	Study Start Date/Status	Study Design	Study Medication	Number of Subjects Randomized	Age Range (mean) %M/F % B/W/O	Treatment Duration
LAM-IV-105 UK/1	01/29/97	Phase 1, randomized, double blind, placebo-controlled, single- and multiple dose, drug absorption study in healthy volunteers. Part 1: 8-way, single rising dose. Part 2: t.i.d. dosing for 3 days.	Part 1: La 500, 1000, 1500, 2500, 4000, 6000 and 9000 mg or matching placebo. Part 2: 9000 mg or matching placebo.	Total = 14 Part 1: 14 La vs. 12 Placebo. Total = 12 Part 2: 10 La vs. 2 Placebo.	22-50 years (31 years) 100/0 0/0/100	Part 1: 8 single doses with a 7 day interval between doses. Part 2: t.i.d. dosing for 3 days.
LAM-IV-108 Japan/1	08/31/98 Complete	Phase 1, randomized, double blind, placebo-controlled, single dose, 5-way crossover PK study in healthy volunteers.	La 250, 500, 1000 and 2000 mg or matching placebo.	Total = 10 La = 10 Placebo = 10	22-25 years (24 years) 100/0 0/0/100	5 single doses with 2-day interval between doses.
LAM-IV-109 Japan/1	07/06/99 Complete	Phase 1, randomized, double blind, placebo-controlled, parallel group multi dose PK study in healthy volunteers.	La 3000 mg (divided in 3 doses) or matching placebo.	Total = 9 La = 6 Placebo = 3	21-26 years (23 years) 100/0 0/0/100	t.i.d. dosing for 5 days.
LAM-IV-110 UK/1	08/09/99 Complete	Phase 1, randomized, open label, 3-way crossover multi-dose food effect PK study in healthy volunteers	La 3000 mg (divided in 3 doses) per day with food or 30-minute after food.	Total = 36 La = 36	18-44 years (25 years) 64/36 0/100/0	t.i.d. dosing for 3 days.
LAM-IV-111 US/1	12/21/00 Complete	Phase 1, randomized, open label, parallel group single and multiple dose PK study in healthy volunteers and patients with CRF on hemodialysis.	Part 1: La 1000 mg or Part 2: 3000 mg (divided in 3 doses) daily with food.	Total = 18 La = 18 (8 volunteers vs. 10 patients with CRF)	27-67 years (48 years) 61/39 28/39/33	Part 1: 2 single doses with 14 days interval between doses. Part 2: t.i.d. dosing for 11 days.
LAM-IV-112 UK/1	08/09/99 Complete	Phase 1, randomized, open label, 3-way crossover single-dose citrate effect PK study in healthy volunteers.	La 1000 mg alone, or with orange juice, or with 2 Effercitrate® (3 g K^+ citrate + 0.5 g of citric acid).	Total = 25 La = 25	23-49 years (34 years) 48/52 0/100/0	3 single doses with a 14 day interval between doses.

[Sponsor's analysis. Source: NDA 21-468, Vol. 1.2, Table 3-44, pages 3-152 to 3-157.]

Table 2A. Description of Clinical Pharmacology Studies

Protocol No. Country/Sites	Study Start Date/Status	Study Design	Study Medication	Number of Subjects Randomized	Age Range (mean) %M/F % B/W/O	Treatment Duration
LAM-IV-108 Japan/1	08/31/98 Complete	Phase 1, randomized, double blind, placebo-controlled, single dose, 5-way crossover study in healthy volunteers.	La 250, 500, 1000 and 2000 mg or matching placebo.	Total = 10 La = 10 Placebo = 10	22-25 years (24 years) 100/0 0/0/100	5 single doses with 2-day interval between doses.
LAM-IV-109 Japan/1	07/06/99 Complete	Phase 1, randomized, double blind, placebo-controlled, parallel group multi dose study in healthy volunteers.	La 3000 mg (divided in 3 doses) or matching placebo.	Total = 9 La = 6 Placebo = 3	21-26 years (23 years) 100/0 0/0/100	t.i.d. dosing for 5 days.
LAM-IV-110 UK/1	08/09/99 Complete	Phase 1, randomized, open label, 3-way crossover multi-dose food effect study in healthy volunteers.	La 3000 mg (divided in 3 doses) per day with food or 30-minute after food.	Total = 36 La = 36	18-44 years (25 years) 64/36 0/100/0	t.i.d. dosing for 3 days.
LAM-IV-111 US/1	12/21/00 Complete	Phase 1, randomized, open label, parallel group single and multiple dose study in healthy volunteers and patients with CRF.	La 1000 mg or 3000 mg (divided in 3 doses) daily with food.	Total = 18 La = 18 (8 volunteers vs. 10 patients with CRF)	27-67 years (48 years) 61/39 28/39/33	Part 1: 2 single doses with 14 days interval between doses. Part 2: t.i.d. dosing for 11 days.
LAM-IV-112 UK/1	08/09/99 Complete	Phase 1, randomized, open label, 3-way crossover single-dose citrate effect study in healthy volunteers.	La 1000 mg alone, or with orange juice, or with 2 Effercitrate® (3 g K^+ citrate + 0.5 g of citric acid).	Total = 25 La = 25	23-49 years (34 years) 48/52 0/100/0	3 single doses with a 14 day interval between doses.
LAM-IV-113 UK/1	02/07/01 Complete	Phase 1, randomized, open label, 2-way crossover multi-dose study in healthy volunteers.	Warfarin single 10 mg with La 4000 mg or warfarin 10 mg alone.	Total = 14 La = 14 Warfarin = 14	18-28 years (24 years) 100/0 0/100/0	La: 1000 mg t.i.d. for 1 day + a 4th A.M. dose of 1000 mg. Warfarin: 2 single doses with 14 days interval between doses.
LAM-IV-114 UK/1	03/05/01 Complete	Phase 1, randomized, open label, 2-way crossover multi-dose study in healthy volunteers	Digoxin single 0.5 mg with La 4000 mg or digoxin 0.5 mg alone.	Total = 14 La = 14 Digoxin = 14	21-29 years (23 years) 100/0 0/100/0	La: 1000 mg t.i.d. for 1 day + a 4th A.M. dose of 1000 mg. Digoxin: 2 single doses with 14 days interval between doses.
LAM-IV-115 UK/1	03/26/01 Complete	Phase 1, randomized, open label, 2-way crossover multi-dose study in healthy volunteers.	Metoprolol single 100 mg with La 4000 mg or metoprolol 0.5 mg alone.	Total = 14 La = 13 Metoprolol = 13	18-33 years (24 years) 100/0 0/100/0	La: 1000 mg t.i.d. for 1 day + a 4th A.M. dose of 1000 mg. Metoprolol: 2 single doses with 8 days interval between doses.

[Sponsor's analysis. Source: NDA 21-468, Vol. 1.2, Table 3-46, pages 3-202 to 3-215.]

Table 3A. Description of Efficacy Studies

Protocol No. Country/Sites	Study Start Date/Status	Study Design	Study Medication	Number of Subjects Randomized	Age Range (mean) %M/F % B/W/O	Treatment Duration
LAM-IV-202 UK/8	06/23/97 Complete	Phase 2, multicenter, randomized, double blind, placebo-controlled, dose ranging study in patients with ESRD.	La 250, 375, 750, 1500 and 2250 mg daily or matching placebo.	Total = 36 La = 17 Placebo = 19	29-79 years (55 years) 56/44 3/97/0	Dose titration: 4 weeks. Randomized Rx: 4 weeks.
LAM-IV-204 US/10	04/06/98 Complete	Phase 2, multicenter, randomized, double blind, placebo-controlled, parallel group study with 4 fixed lanthanum doses in patients with ESRD.	La 225, 675, 1350 and 2250 mg daily or matching placebo.	Total = 145 La = 113 Placebo = 32	23-84 years (56 years) 56/44 71/25/4	Randomized Rx: 6 weeks.
LAM-IV-301 UK/14 Germany/37 Belgium/11 Netherlands/5	10/05/98 Complete	Phase 3, multinational, multicenter, randomized, open label, active-controlled, parallel group study in patients with ESRD.	La 375, 750, 1500, 2250, and 3000 mg daily or Ca carbonate 1500, 3000, 4500, 6000, and 9000 mg daily.	Total = 800 La = 533 Ca Carbonate = 267	19-87 years (59 years) 66/34 1/97/2	Dose titration: 5 weeks. Maintenance: 5 months. Extension on La: 6 months + 2 years.
LAM-IV-302 US/14	10/11/99 Complete	Phase 3, multicenter, randomized, double blind, placebo-controlled, parallel group study in patients with ESRD.	La 250, 375, 750, 1500 and 2250 mg daily or matching placebo.	Total = 94 La = 50 Placebo = 44	21-83 years (60 years) 66/34 40/43/17	Dose titration: 6 weeks. Randomized Rx: 4 weeks.
LAM-IV-303 Belgium/1 Czech Rep./1 France/1 Germany/1 Italy/1 Macedonia/1 Poland/1 Portugal/1 South Africa.2 Spain/1 UK/3 Yugoslavia/4	05/?/99 Complete	Phase 3, multinational, multicenter, randomized, open label, comparator-controlled, parallel group study in patients with ESRD undergoing dialysis to assess the effect on bone disease.	La titrated up to 3750 mg daily or Ca carbonate titrated up to 9000 mg daily.	Total = 98 La = 49 Placebo = 49	18-80 years (55 years) 60/40 00/93/7	Tetracycline Bone labelling and 1st Bx: 2 weeks. Dose titration: 6 weeks. Randomized Rx: 44 weeks. Tetracycline Bone labelling and 2nd Bx: 4 weeks.
LAM-IV-307 US/96	07/29/99 Ongoing	Phase 3, multicenter, randomized, open label, active-controlled, parallel group study in patients with ESRD.	La 375, 750, 1500, 2250, and 3000 mg daily or standard therapy.	Total = 1228 La = 616 Standard Rx = 612	19-91 years (55 years) 59/41 43/46/11	Dose titration: 6 weeks. Maintenance Rx: 23 months.

[Sponsor's analysis. Source: NDA 21-468, Vol. 1.2, Table 3-47, pages 3-213 to 3-215.]

Table 8.8-2 Number of Subjects/Patients Receiving Study Medication in the Lanthanum Carbonate Development Program

Development Phase	Treatment Groups			
	LaC	ACPB	Placebo/Other[1]	Total[2]
Phase 1 Studies:				
SD: LAM-IV-101 (UK)	10	0	2	12
LAM-IV-104 (UK) Part 1	7	0	4	11
Part 2	12	0	4	12
LAM-IV-108 (JA)	10	0	10	10
LAM-IV-112 (UK)	25	0	0	25
MD: LAM-IV-109 (JA)	6	0	3	9
LAM-IV-113 (UK)	14	0	14	14
LAM-IV-114 (UK)	14	0	14	14
LAM-IV-115 (UK)	13	0	13	14
SD and MD: LAM-IV-105 (UK) Part 1	14	0	12	14
Part 2	10 (10)	0	2 (2)	12 (12)
LAM-IV-110 (NI) Part 1	36	0	0	36
Part 2	36 (36)	0	0	36 (36)
LAM-IV-111 (US) Part 1	8/10[3]	0	0	8/10[3]
Part 2	8/10 (8/10)[3]	0	0	8/10 (8/10)[3]
Phase 1 Subtotal:	**179**	**0**	**76**	**189**
Phase 1 SD Subtotal:	132	0	32	138
Phase 1 MD subtotal	111	0	44	117
Phase 2-3 Studies:				
Complete:				
Short-Term DB: LAM-IV-202 (UK)	59	0	19	59
LAM-IV-204 (US)	113	0	32	145
LAM-IV-302 (US)	126	0	44	126
Long-Term OL: LAM-IV-205 (US)	42 (34)	0	0	42 (40)
LAM-IV-301 (EU)				
Parts 1-3	533	267	0	800
Part 4	507 (324)	0	0	507 (507)
Part 5	161 (158)	0	0	161 (161)
LAM-IV-308 (US)[4]	77 (11/66)	0	0	77 (11/66)
LAM-IV-303 (EU)[5]	49	49	0	98
On-going - Long-Term OL: LAM-IV-307 (US)	647	642	0	1289
Phase 2-3 Subtotal:	**1672**	**909**	**95**	**2421**
Short-Term Subtotal:	298	0	95	330
Long-Term Subtotal:	1474	909	0	2197
SD Studies[2]: In healthy adults	122	0	32	128
In patients with CRD	10	0	0	10
SD Studies Subtotal	132	0	32	138
MD Studies[2]: In healthy adults	101	0	46	107
In patients with CRD	1682	909	95	2431
MD Studies Subtotal:	1783	909	141	2538
Completed Studies Subtotal[2]. (without LAM-IV-303)	1204	267	171	1321
On-going Studies Subtotal[2]:	647	642	0	1289
Grand Total: (without LAM-IV-303)	**1851**	**909**	**171**	**2610**

LaC = lanthanum carbonate; ACPB = active control phosphate binder; SD = single dose; MD = multiple doses; DB = double-blind; OL = open-label; CRD = chronic renal disorder; US = Unites States; UK = United Kingdom; JA = Japan; NI = Northern Ireland; EU = Europe; () = number of patients who rolled over from a previous study or crossed over to an alternate treatment were subtracted from the calculation of the grand total

1 Includes single doses of Warfarin/Digoxin/Metoprolol for LAM-IV-113/LAM-IV-114/LAM-IV-115.

2 Patients who entered into a follow-up study(s) or crossed over to an alternate treatment(s) were counted only once

3 Healthy/hemodialysis subjects

4 12-month extension of LAM-IV-205/302

5 Numbers of patient enrollments for the corresponding study not included in the calculation of the grand total.

Data Source: Appendix Table 8.1.1

Summary of Patients Whose Mortality Data Were Not Available				
Active Treatment(s) Received in Study(s)	No. Patients w/o Mortality Data	Mean Age (years)	Lanthanum Exposure (day) Mean (SD)	Comparator Exposure (day) Mean (SD)
Lanthanum only (n=1535)	93 (6%)	53.5	206 (226.4)	---
Comparator only (n=772)	38 (5%)	54.1	---	385 (228.6)
Comparator & Lanthanum (n=186)	7 (4%)	59.1	141 (75.8)	152 (46.7)

Reason No Mortality Data Obtained	Number of Patients
Patient moved/transferred to another dialysis unit	44
Patient received kidney transplant/no longer under the care of Investigator	11
Site closed/unable to locate Investigator	9
Site refused to provide data	56
Other	18
TOTAL	138

Listing of reasons by patients appears in Appendix 4.

Table4A. Bone Fractures During the Comparative Phase

	Fracture n/%	Discontinuation n/%	Mean (±SD) Exposure (months)
Study LAM-IV-202			
Lanthanum N=59	0/0.0	23/39.0	1.3±0.5
Comparator N=?	?	?	?
Study LAM-IV-204			
Lanthanum N=113	0/0.0	37/32.7	1.2±0.4
Comparator N=?	?	?	?
Study LAM-IV-301			
Lanthanum N=528	5/0.94	204/38.3	3.9±2.2
Comparator N=266	1/0.37	83/31.1	3.7±2.4
Study LAM-IV-302			
Lanthanum N=126	0/0.0	36/28.6	1.7±0.6
Comparator N=?	?	?	?
Study LAM-IV-303			
Lanthanum N=49	0/0.0	15/30.6	10.1±3.8
Comparator N=47	2/4.08	15/30.6	11.1±2.5
Study LAM-IV-307			
Lanthanum N=619	28/4.33	421/65.1	10.2±8.4
Comparator N=605	37/5.76	293/45.6	14.1±8.6

[Sponsor's analysis, adapted from NDA 21-468, response to request dated December 24, 2002.]

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

/s/

Juan Carlos Pelayo
12/31/02 09:11:06 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION

TO *(Division/Office)*	FROM: Norman L Stockbridge M.D , Ph.D. Acting Director,
Dr Charles Capen Department of Vet Pathology Ohio State University, Columbus Ohio 43210 capen.2@0su edu Tel. 614 229 OHIO	Division of Cardio-Renal Drug Products, HFD 110

DATE	IND NO	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 19, 2004		21,468	Photomicrographs of bones from normal and uremic rats given lanthanum carbonate	July 1, 2004

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
LANTHANUM CARBONATE		Phosphate Binder	August 8, 2004

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- X☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	X☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please provide description and interpretation of labeled photomicrographs of bone from slides obtained from uremic and normal rats given lanthanum. The slides have been stained with van Gieson. The bones are undecalcified and embedded in methacrylate. Photomicrographs from uremic rats are labeled "B,X or H" and rat with normal renal function are labeled "C". Slides cannot be provided as these belong to the sponsor of NDA.

If you have any questions please contact the Project Manager Denise Hinton 301 594 5333 or Dr A O Williams: 301 594 5381

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL FEDEX ☐ HAND
SIGNATURE OF RECEIVE	SIGNATURE OF DELIVERER

General Comments:

The quality of the bone sections overall is quite poor making interpretation difficult.

Rats with Normal Renal Function & Lanthanum Carbonate

- The subperiosteal surface is highly irregular suggesting increased bone resorption and fibrous replacement but few osteoclasts are present
- Periosteal thickening is uncertain as it depends upon location of section (eg. near tendinous insertion?)
- Slight increase in thickness of osteoid seams on trabecular surfaces.

Rats with Chronic Renal Failure & Lanthanum Carbonate

- Highly irregular subperiosteal surface with marked increase in osteoclasts and osteoblasts with reparative fibroplasia
- Increased thickness of growth plate
- Striking increase in thickness of osteoid seams on endosteal and trabecular surfaces (Osteomalacia). This most likely represents a failure of mineralization rather than demineralization. Lesion is similar to that reported in experimental uremic rats fed a low phosphorus diet. I assume the serum phosphorus in the rats with CRD and administered Lanthanum Carbonate was reduced following the administration of a phosphate binder.

(see reference: The **Effects of Uremia and Dietary Phosphorus on the Bone of Rats:** W.G. Lieuallen, S.E. Weisbrode, R.L. Horst, and L.A. Nagode: *Bone*, 11, 41-46 (1990)

NDA 21-468
Fosrenol (lanthanum carbonate)
250 and 500 mg Chewable Tablets

Safety Update

(See Dr. William's 14Jul04 and Dr. Freidlin's 17May04 reviews)