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Lanthanum carbonate: safety data after 10 years

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SUMMARY AT A GLANCE

Lanthanum carbonate is a non-calcium-based phosphate binder, and although it is a metal cation, its effects are not comparable with those of aluminium. This article discusses safety data of lanthanum with clinical studies showing no significant toxic effects after 10 years of follow-up.

ABSTRACT:

Despite 10 years of post-marketing safety monitoring of the phosphate binder lanthanum carbonate, concerns about aluminium-like accumulation and toxicity persist. Here, we present a concise overview of the safety profile of lanthanum carbonate and interim results from a 5-year observational database study (SPD405-404; ClinicalTrials.gov identifier: NCT00567723). The pharmacokinetic paradigms of lanthanum and aluminium are different in that lanthanum is minimally absorbed and eliminated via the hepatobiliary pathway, whereas aluminium shows appreciable absorption and is eliminated by the kidneys. Randomised prospective studies of paired bone biopsies revealed no evidence of accumulation or toxicity in patients treated with lanthanum carbonate. Patients treated with lanthanum carbonate for up to 6 years showed no clinically relevant changes in liver enzyme or bilirubin levels. Lanthanum does not cross the intact blood–brain barrier. The most common adverse effects are mild/moderate nausea, diarrhoea and flatulence. An interim Kaplan–Meier analysis of SPD405-404 data from the United States Renal Data System revealed that the median 5-year survival was 51.6 months (95% CI: 49.1, 54.2) in patients who received lanthanum carbonate (test group), 48.9 months (95% CI: 47.3, 50.5) in patients treated with other phosphate binders (concomitant therapy control group) and 40.3 months (95% CI: 38.9, 41.5) in patients before the availability of lanthanum carbonate (historical control group). Bone fracture rates were 5.9%, 6.7% and 6.4%, respectively. After more than 850 000 person-years of worldwide patient exposure, there is no evidence that lanthanum carbonate is associated with adverse safety outcomes in patients with end-stage renal disease.

INTRODUCTION

An elevated serum phosphate level (hyperphosphatemia) is one of the major clinical manifestations of end-stage renal disease (ESRD). Hyperphosphatemia is associated with cardiovascular events and increased all-cause mortality in patients with ESRD.[1–4] Observational studies have shown that the treatment of hyperphosphatemia with phosphate-binding agents reduces the risk of mortality compared with no treatment in patients with ESRD.[5–8] The main types of phosphate binder currently used in clinical practice are calcium based and non-calcium based (including iron based).[9] Lanthanum carbonate (LaC), a non-calcium-based binder, has been indicated for the management of hyperphosphatemia in patients with ESRD in the USA since 2005.[10] As of 30 April 2015, the estimated total worldwide patient exposure to LaC was 851 634 person-years

(tablets, 626 636 person-years; oral powder, 224 998 person-years [data on file, Shire, 2015]). In total, 6287 patients have been exposed to LaC during completed phase 1–4 clinical trials. Studies evaluating the safety of LaC monotherapy over 2,[11] 3[12] and 6 years[13] have consistently reported that LaC is well tolerated. Despite the positive safety profile of LaC, established by 17 phase 1–4 clinical studies[11–27] and 10 years of post-marketing safety monitoring, questions over the long-term safety of LaC persist. The historical toxicity of aluminium and the perception that lanthanum is chemically similar to aluminium engendered concerns that lanthanum could show aluminium-like accumulation and toxicity in the bone and central nervous system.[28–32] Owing to extensive safety concerns surrounding aluminium-based phosphate binders, their use in clinical practice is now limited, and non-aluminium-based binders are instead favoured.[33] A comparative review of the efficacy and safety of

calcium, sevelamer and LaC concluded that all three non-aluminium-based binders were effective at reducing serum phosphate levels and that they were generally well tolerated; however, treatment with calcium carbonate was associated with higher rates of hypercalcaemia.[34]

To date, there has been no comprehensive safety review of LaC compared with aluminium. Here, we present a detailed review of the key pharmacokinetic, toxicological and clinical studies that established the positive long-term safety profile of LaC and interim results from a 5-year observational database study of LaC safety in patients with ESRD (SPD405-404; ClinicalTrials.gov: NCT00567723).

OVERVIEW OF KEY STUDIES

Lanthanum pharmacokinetics

Given initial concerns that LaC treatment could lead to high systemic levels of lanthanum,[28] low gastrointestinal absorption and low plasma levels of lanthanum were important target characteristics. A phase 1 study conducted in healthy individuals[22] showed that the absolute bioavailability of lanthanum following a single 1000 mg oral dose of LaC was very low (mean ± SD: $0.00127 \pm 0.0008\%$), indicating that lanthanum is minimally absorbed from the gut. Furthermore, any absorbed lanthanum was almost entirely (>99%) bound to plasma proteins.[35] Hutchison *et al.* (2006)[12] also demonstrated that mean plasma lanthanum concentrations plateaued at nanomolar levels (2.5–9.7 nmol/L) in dialysis patients receiving long-term LaC treatment. Interestingly, plasma lanthanum levels were not statistically different at LaC doses of 750−3000 mg/day, indicating a nonlinear relationship between administered dose and plasma levels. This effect is probably caused by mechanisms that limit intestinal absorption of metals, including epithelial exfoliation.[36]

Because LaC is indicated for patients with impaired renal function, lanthanum excretion via a nonrenal route was an important characteristic. Damment *et al.* (2007)[35] showed that 99.3% of an oral lanthanum dose was recovered in the faeces of rats and that 86.0% of an intravenous dose was recovered in the bile of bile duct-cannulated rats. These results indicated that lanthanum is predominantly eliminated in the faeces via hepatobiliary excretion, although this has yet to be demonstrated in humans. Pennick *et al.* (2006)[22] showed that only 0.00003% of an oral dose of lanthanum was eliminated in the urine of healthy human participants, reflecting both negligible renal clearance and the poor bioavailability of lanthanum. In light of the nonrenal clearance of lanthanum, the expectation was that patients with impaired renal function would not be more susceptible to systemic accumulation of lanthanum than healthy individuals. This was confirmed by data demonstrating similar lanthanum exposure profiles in patients with ESRD and individuals with normal renal function.[37]

In contrast to lanthanum, oral ingestion of aluminium results in appreciable absorption from the gastrointestinal tract in healthy participants (0.06–0.1%),[38] ~50–80-fold higher than that seen with lanthanum. Moreover, aluminium is mainly (~95%) eliminated via the kidney with negligible biliary excretion (~2%).[39–42] Thus, patients with ESRD are particularly vulnerable to the deleterious effects of aluminium ingestion.[43]

Based on these data, the pharmacokinetic profiles of LaC and aluminium appear to be quite different (Fig. 1).
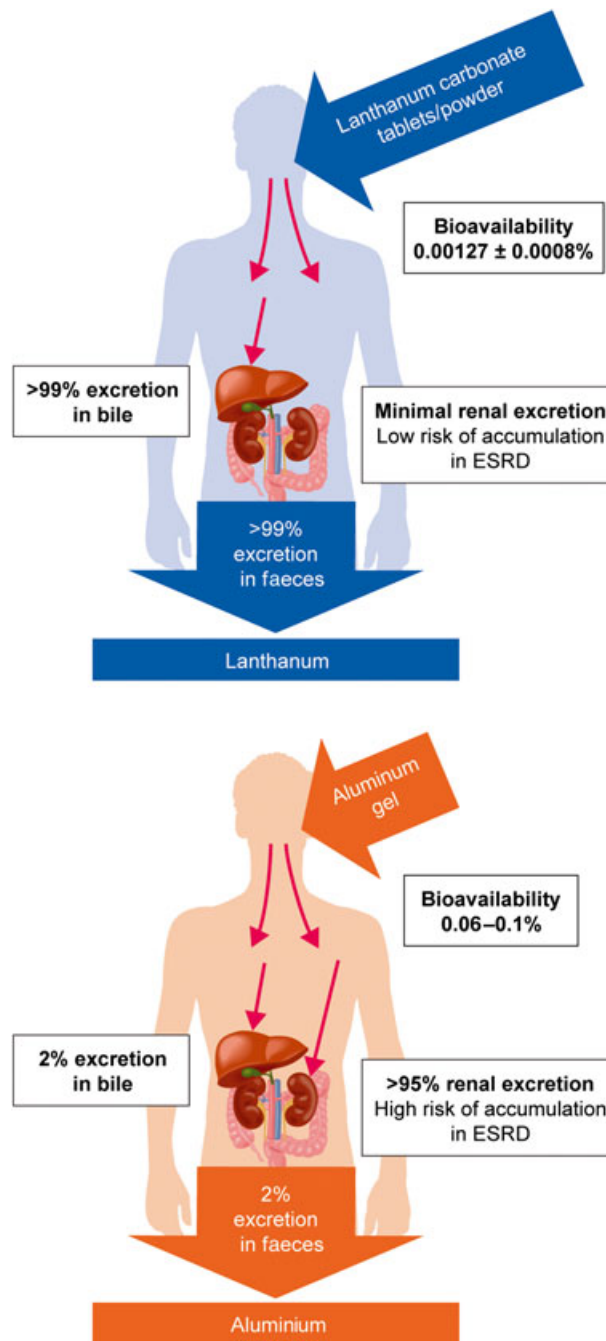
Fig. 1 Comparison of the pharmacokinetics of lanthanum and aluminium. ESRD, end-stage renal disease.

Effect of lanthanum on bone

Bone is known to be a major reservoir for divalent and trivalent cationic metals,[44] and the pathophysiological effects of aluminium on bone health are well documented.[28–32] Bone was therefore one of the key target organs in the safety evaluation of LaC. A phase 3, open-label study compared the effects of LaC and calcium carbonate on the evolution of renal bone disease in patients with ESRD.[16] Only 3.0% (1/33) of patients in the LaC group evolved towards adynamic bone compared with 20.0% (6/30) of patients receiving calcium carbonate. Additionally, a subset of patients in both groups had low bone turnover and hyperparathyroidism at baseline; however, these baseline characteristics evolved towards normalisation of bone turnover after 1 year of treatment in 71.0% (5/7) and 80.0% (4/5) of patients in the LaC group, respectively, and in 43.0% (3/7) and 50.0% (3/6) of patients in the calcium carbonate group, respectively. No statistical testing was performed because of the exploratory nature of this endpoint and the small sample size. A 2-year, open-label study[45] also investigated the evolution of renal bone disease in patients with ESRD who were switched to LaC or maintained on their previous phosphate binder. The proportion of patients with improvement or no change was higher in the LaC group than in the phosphate binder group for bone activation frequency (66.7% vs 55.0%), bone formation rate (74.2% vs 57.1%) and bone volume (84.4% vs 62.5%) at 2 years.

Bronner et al. (2008)[46] modelled the bone load of lanthanum in dialysis patients using bone lanthanum concentration data collected from three long-term trials (up to 5 years) of LaC. The model predicted a sevenfold increase in total bone lanthanum from $1.0\,\mu g/g$ to $6.6\,\mu g/g$ after 10 years of LaC treatment. A 3-year, prospective, open-label study of dialysis patients, performed by Shigematsu et al. (2011),[47] reported mean bone lanthanum levels at 3 years $(4.3\,\mu g/g)$ that were comparable with those predicted in the Bronner study.[46] In addition, there was no evidence of bone toxicity: all patients with normal bone turnover at baseline remained normal, while two patients with osteitis fibrosa and two patients with adynamic bone disease evolved towards normal bone turnover. Another study[48] reported mean bone lanthanum levels of $1.9\,\mu g/g$ after 3 years of LaC treatment and observed no differences in osteoblast numbers or mineral apposition rates in bone biopsies of patients treated with LaC compared with those receiving calcium carbonate.

Persy et al. (2006)[49] estimated the molar bone lanthanum (atomic mass, 138.9): calcium (atomic mass, 40.1) ratio to gain a better quantitative understanding of the potential for lanthanum to disrupt bone mineral structure. Assuming a maximum bone lanthanum concentration of $9.5\,\mu g/g$ $(0.0095\,mg/g)$, a bone calcium concentration of $120\,mg/g$ and homogeneous lanthanum distribution throughout the bone,[50] the molar bone lanthanum : calcium ratio was estimated to be 2×10^{-5}. This equates to 1 in 50 000 calcium atoms being replaced by lanthanum. Applying similar reasoning to aluminium, but assuming

that it is localised in only 1% of the total bone volume (based on the observation that aluminium is localised at the osteoid-calcification front), the molar bone aluminium : calcium ratio was estimated to be 6×10^{-2}, equating to 1 in 16 calcium atoms being replaced by aluminium.

These studies indicate that, unlike aluminium, LaC is unlikely to accumulate to clinically relevant levels in bone and is not associated with bone toxicity.

Effect of lanthanum on the liver

Lanthanum is predominantly excreted via the hepatobiliary pathway.[35] The subcellular localisation of lanthanum in liver tissue was determined using a combination of microscopy and spectroscopy techniques.[51,52] These studies demonstrated that lanthanum is present in the lysosomes of hepatocytes, and is concentrated both in the biliary pole of the hepatocyte and in the bile canaliculi, indicating that lanthanum undergoes transcellular transport in the liver. Hutchison et al. (2009)[18] reported an analysis of hepatic biochemical tests and liver-associated adverse events (AEs) in patients with ESRD who received LaC in four previous phase 3 trials and who were followed in a 2-year extension study for a total treatment duration of up to 6 years $(n = 93)$. Changes in transaminases, bilirubin and alkaline phosphatase observed during long-term treatment were minimal and similar to those reported in previous trials. Overall, there was no evidence of an increase in the incidence or severity of liver-related AEs with increasing treatment duration and no new types of liver-related AEs in patients who received LaC for up to 6 years.

Effect of lanthanum on the central nervous system

The seminal study of Alfrey et al. (1976)[53] was the first to present evidence of an association between aluminium accumulation in the brain and dialysis encephalopathy. Biochemical and epidemiological data subsequently confirmed that aluminium neurotoxicity is an aetiological factor in the development of this syndrome.[54–56] In contrast to aluminium, lanthanum cannot cross the tight junctions of the intact blood–brain barrier (BBB). It is for this reason that lanthanum is used as a tracer to assess the integrity of the BBB.[57–60] Bervoets et al. (2009)[51] reported no difference in brain levels of lanthanum in healthy rats and rats with chronic renal failure following treatment by oral gavage with LaC for 20 weeks. Lanthanum levels remained close to the limit of quantification $(4\,ng/g)$, and there was no evidence of increased levels with duration of treatment. A 2-year, open-label study[61] found no evidence of a difference in the rate of cognitive decline in patients with ESRD randomised to LaC or 'standard' phosphate binder therapy.[62]

In summary, there is currently no evidence to indicate that lanthanum crosses the intact BBB.

Effect of lanthanum on the gastrointestinal tract

Lanthanum carbonate forms insoluble complexes with phosphate in the gastrointestinal tract;[10,63] but safety pharmacology studies have shown no clinically significant effects on gastric emptying, intestinal transit time or aspirin-induced gastric lesions at LaC doses up to 13-fold higher than the clinical dose (3000 mg/day).[37] Hutchison *et al.* (2008)[13] reported safety data in patients who received long-term LaC monotherapy for up to 6 years. The majority of treatment-related adverse effects were related to the gastrointestinal tract (mainly mild/moderate nausea, diarrhoea and flatulence) and were consistent with those observed with other phosphate binders.[64] A meta-analysis of 16 randomised controlled trials[65] reported a higher rate of vomiting but a lower rate of abdominal pain with LaC compared with calcium-based binders. No significant differences were found in the incidences of nausea, constipation or dyspepsia.

The risk of gastrointestinal obstruction and perforation is increased in patients with ESRD compared with the general population.[66] There have also been reports of gastrointestinal obstruction, ileus, subileus and gastrointestinal perforation in patients treated with LaC.[67,68] However, analysis of pooled data from completed phase 2–4 clinical trials of LaC chewable tablet demonstrated a lower rate of gastrointestinal obstruction and ileus/subileus compared with active comparators (0.3% [18/5634] *vs* 0.8% [10/1184], respectively), and a similar incidence of gastrointestinal perforation (0.09% [5/5634] *vs* 0.08% [1/1184]) [data on file, Shire, 2015]. It should be noted that the current LaC label instructs that LaC chewable tablets must be chewed completely before swallowing, in order to prevent such adverse gastrointestinal events. The tablets may also be crushed completely to aid chewing, but intact tablets must not be swallowed whole.[69] These data, along with the findings from a cumulative review of safety data from all sources, show that there is currently not sufficient evidence to indicate that these AEs are directly related to LaC therapy.

Published case studies have demonstrated the presence of lanthanum particles in the gastrointestinal tract using radiographic techniques.[70–74] Additionally, two recent reports have documented lanthanum deposition in the human gastric mucosa[75,76]; however, the clinical significance of these observations is unclear. Absorption from the gastrointestinal tract has also been documented in the juvenile rat, with lanthanum detected in all measured tissues after dosing. Lanthanum levels of up to 90 000 ng/g wet tissue weight were observed in juvenile rats administered 2000 mg/kg doses of LaC by oral gavage (>16 times the human dose of 3 g/day). Dosing was then followed by a 28−29-day treatment-free period, where tissue levels of LaC decreased, except for in the glandular mucosa of the stomach where they remained high [Shire, unpublished data]; however, these data were not considered clinically significant. Overall, there is no evidence of an increase in the incidence of gastrointestinal-related AEs with increasing exposure to LaC.

Effect of lanthanum on the haematopoietic system

Hutchison *et al.* (2008)[13] reported that 6 years of LaC treatment did not result in adverse effects on haematological laboratory parameters, including serum total iron, ferritin and haemoglobin, transferrin saturation, haematocrit and mean cell volume. A *post hoc* analysis of two phase 3 studies also showed no evidence of iron accumulation in patients treated with LaC.[77] In contrast, aluminium toxicity is known to result in a microcytic, hypochromic anaemia that is refractory to iron and recombinant erythropoietin therapy.[78,79] The mechanism by which aluminium disrupts erythropoiesis is unclear but may involve effects on bone marrow erythroid progenitor cells[80] or haemoglobin synthesis.[79,81]

The conclusion from these studies is that LaC does not seem to have an effect on iron or haematological parameters.

OVERVIEW OF SPD405-404 STUDY

Background

The primary objectives of the SPD405-404 study are to compare all-cause mortality and bone fractures requiring hospitalisation in patients who received LaC with patients who received other phosphate binders.

Patients

Patients in the USA (≥18 years) who received a minimum of 12 consecutive weeks of treatment with LaC were recruited into SPD405-404 and formed the test group. The control arms (historical and concomitant), which included adult patients with ESRD receiving dialysis for at least 12 consecutive weeks, were identified from the United States Renal Data System (USRDS) database.[82] The historical control group comprised individuals whose data were in the database prior to 1 January 2000 (5 years before LaC became available in the USA), and as such, the comparison has limitations due to changes in standards of care; the concomitant therapy control group instead comprised patients who were treated for hyperphosphatemia with any phosphate binder other than LaC (same era as the test group). For each patient in the test group, a maximum of four other patients were selected from the USRDS database for inclusion in each of the control groups. Patients in the control groups were matched to those in the test group by age (5-year categories), sex and duration of dialysis (integer year categories, historical control group) or first year of commencement of dialysis (concomitant control group). To be eligible for matching, patients in the USRDS database (historical and concomitant therapy control groups) must have been alive and at least 18 years old at their respective screening date and have (1) at least one post-screening record in the database (i.e. treatment or hospitalisation data); (2) Medicare as the primary insurer at screening; and (3) more

than 12 consecutive weeks of dialysis at screening. It should be noted that control group membership was assigned based on the data available in the downloaded USRDS database. This study is being conducted in accordance with the ethical principles set out in the Declaration of Helsinki (1989). The protocol was approved at each centre by an Institutional Review Board. Patients in the test group provided written, informed consent before participating in the study.

Study design

This is a phase 4, observational database study of patients with ESRD in the USA. Patients will enter into the study at the screening assessment and will be contacted every 6 months during the observational period to record information on exposure to LaC or any other phosphate binder. Participant follow-up for primary and secondary endpoints is planned for up to 5 years via the USRDS database. Control arms were matched from USRDS data. Primary endpoints are time to and incidence of all-cause mortality, and time to first event and incidence of bone fractures requiring hospitalisation. Secondary endpoints are the time to first event and incidence of gastrointestinal disease, liver disease, malignancy, and major infectious episodes requiring hospitalisation. Endpoint data are obtained from the USRDS database. The USRDS records and data from SPD405-404 case report forms will be used in the summary and analysis. The USRDS data will be used if there are discrepancies between the databases. The interim analysis presented here was based on USRDS data through 2014, which was downloaded in May 2015.

Survival curves were generated using the Kaplan–Meier method. Statistical analyses were performed using SAS® version 9.4 (SAS Institute, Cary, NC, USA). Analyses were performed on the full analysis set, which comprises all patients enrolled in the study who had received LaC treatment for a minimum of 12 consecutive weeks and had at least one post-screening record in the USRDS database, plus their matched control patients. A multivariate regression analysis was conducted to compare time to all-cause mortality between the test group and the historical and concomitant therapy control groups, respectively, using a Cox proportional hazards model. The model adjusted for patient baseline characteristics and included the following covariate terms: age category, sex, body mass index, region, year of starting dialysis (test *vs* concomitant), duration of dialysis at screening (test *vs* historical), study group, type of dialysis, presence of diabetes and other comorbidities. Covariates were included using stepwise regression covariate selection with $\alpha = 0.1$ entry and removal significance levels. The stepwise regression began with the fixed terms in the model (age category, sex and study group). The fixed terms were not removed from the stepwise procedure.

Interim results

In total, 2136 patients were enrolled in the study, of whom 2027 were included in the full analysis set, along with 8112

Table 1 SPD405-404 study: patient disposition and baseline demographic characteristics

	Test group	Concomitant therapy control group	Historical control group
Enrolled patients, n	2136	N/A	N/A
Safety analysis set, n (%)†	2029 (95.0)	N/A	N/A
Full analysis set, n (%)‡	2027 (94.9)	8103	8112
Transplant recipients, n (%)	290 (14.3)	873 (10.8)	1225 (15.1)
Length of follow-up, months, mean (SD)	37.5 (21.39)	37.4 (21.72)	33.5 (21.58)
Length of follow-up for living patients w/o transplant, n (%)§			
< 60 months	3 (0.1)	5 (0.1)	3 (< 0.1)
60 months	718 (35.4)	2934 (36.2)	2202 (27.1)
Died during the follow-up period¶, n (%)	1050 (51.8)	4372 (54.0)	4846 (59.7)
Transplant recipient during the follow-up period, n (%)	290 (14.3)	873 (10.8)	1225 (15.1)
Age, years, mean (SD)	57.1 (14.54)	56.7 (14.58)	57.1 (14.59)
Sex, n (%)			
Male	1178 (58.1)	4707 (58.1)	4714 (58.1)
Female	849 (41.9)	3396 (41.9)	3398 (41.9)
Race, n (%)			
White	970 (47.9)	3940 (48.6)	4084 (50.3)
Non-white	1055 (52.0)	4163 (51.4)	4025 (49.6)
Black/African American	959 (47.3)	3529 (43.6)	3359 (41.4)
Asian	37 (1.8)	238 (2.9)	189 (2.3)
Other	59 (2.9)	396 (4.9)	477 (5.9)
Missing	2 (0.1)	0	3 (< 0.1)
BMI, kg/m^2, mean (SD)	30.31 (8.33)	29.00 (8.02)	26.34 (7.14)
Serum phosphate, mg/dL, mean (SD)	5.89 (1.77)	N/A	N/A
Presence of diabetes, n (%)	895 (44.2)	3920 (48.4)	2795 (34.5)
Duration of ESRD, years, mean (SD)	5.36 (5.01)	5.29 (4.96)	5.47 (4.96)

Percentages for the safety analysis set and full analysis set are based on enrolled patients. Other percentages are based on the full analysis set. †The safety analysis set comprises all patients who were registered to the study and had previously received lanthanum carbonate treatment for a minimum of 12 consecutive weeks (test group only). ‡The full analysis set consists of patients in the safety analysis set who also had at least one post-screening record in the United States Renal Data System database (test group) and their matched control patients (concomitant therapy and historical control groups). §The length of follow-up for living patients without a transplant is from screening until the date of their last available claim record in the United States Renal Data System database; the length of follow-up for patients who died or received a transplant is from screening until their death or transplant. The maximum length of follow-up is 60 months. ¶Thirty-four patients (1.7%) in the test group, 81 patients (1.0%) in the concomitant therapy control group and 164 patients (2.0%) in the historical control group had a transplant and died during the follow-up period. BMI, body mass index; ESRD, end-stage renal disease; N/A, not available; SD, standard deviation; w/o, without.

historical and 8103 concomitant therapy matched control patients. Baseline demographic characteristics in the test and control groups were similar (Table 1). A Kaplan−Meier analysis revealed that the median survival with 5 years follow-up was 51.6 months (95% CI: 49.1, 54.2) in patients who received LaC (test group) (Fig. 2), 48.9 months (95% CI: 47.3, 50.5) in patients treated with any other phosphate binder (concomitant therapy control group) (Fig. 2) and 40.3 months (95% CI: 38.9, 41.5) in patients before the availability of LaC (historical control group). Kaplan−Meier estimates of survival (95% CI) at month 60 were 0.44 (0.42, 0.46) *versus* 0.43 (0.42, 0.44) *versus* 0.35 (0.34, 0.36) for the test, concomitant therapy and historical control groups, respectively. A Cox proportional hazards model was also fitted; hazard ratios (95% CI) for the test group *versus* the concomitant therapy control group were 0.96 (0.90, 1.03), $P = 0.262$ and 0.76 (0.71, 0.82), $P < 0.001$ for the test group *versus* historical control group. The incidence of bone fractures was similar in the test, concomitant therapy and historical control groups: 5.9%, 6.7%, and 6.4%, respectively (Table 2). Given that the 'other' phosphate binders were mostly calcium based, these findings are consistent with the results of Jamal *et al.*[83] With regard to pathophysiological bone changes that
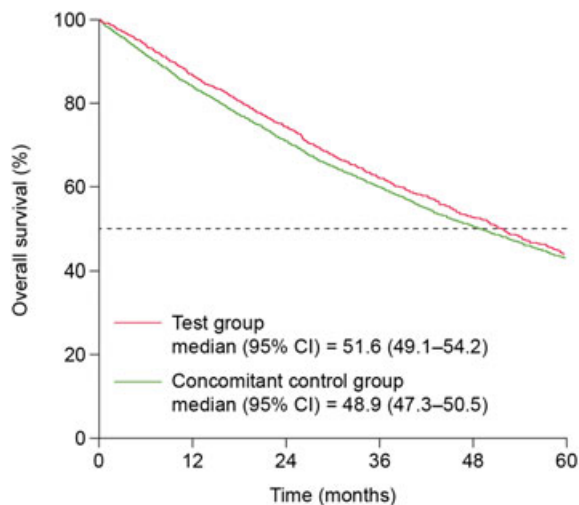
Fig. 2 Kaplan–Meier analysis of time to all-cause mortality based on United States Renal Data System data from 2014 (full analysis set). Horizontal reference line shows median survival time. CI, confidence interval.

Table 2 SPD405-404 study: rates of bone fracture requiring hospitalisation based on United States Renal Data System data from 2014 (Full analysis set†)

Test group (N = 2027)	Concomitant therapy control group (N = 8103)	Historical control group (N = 8112)
n (%)	n (%)	n (%)
120 (5.9)	546 (6.7)	519 (6.4)

†The full analysis set comprises patients in the safety analysis set who also had at least one post-screening record in the United States Renal Data System database (test group) and their matched control patients (concomitant therapy and historical control groups).

are a common complication in patients with ESRD,[84] bone fracture rates were similar across the three groups, corroborating that long-term LaC therapy is not associated with bone toxicity. However, it must be noted that there were very few bone fracture events.

Limitations of the USRDS include lack of continuous validation of its data capture, lack of complete comorbidity and laboratory data, survival bias, attrition bias, differences between test and historical control arms due to the different landscape in standard of care, limitations in matching control from registry database and lack of accuracy of cause-of-death reporting.[82]

CONCLUSIONS

LaC is a well tolerated phosphate binder that has been indicated for the management of hyperphosphatemia in patients with ESRD since 2005. Initial concerns that lanthanum could show aluminium-like accumulation and toxicity have been refuted by the pharmacokinetic, toxicological and clinical evidence summarised here. It is clear that the pharmacokinetic paradigms of lanthanum and aluminium are different: lanthanum is minimally absorbed and mainly eliminated via the hepatobiliary pathway, whereas aluminium shows appreciable absorption and is mainly eliminated via the kidneys. Randomised prospective studies of paired bone biopsies revealed no evidence of aluminium-like accumulation or toxicity, or mineralisation defects in patients treated with LaC. Patients treated with LaC for up to 6 years showed no clinically relevant changes in liver enzyme or bilirubin levels and no increase in the incidence of liver-associated AEs. Lanthanum does not cross the intact BBB, and there is no evidence of an adverse effect of lanthanum on cognitive functioning. Similar to other oral phosphate binders, the majority of adverse reactions in patients taking LaC are related to the gastrointestinal tract (mainly nausea, diarrhoea and flatulence) and are primarily mild/moderate in intensity. Recent reports have documented lanthanum deposition in the gastric mucosa; however, the clinical significance of this is unclear.

Interim results from study SPD405-404, a 5-year observational database study, indicate that all-cause mortality and bone fracture rates in patients treated with LaC are comparable with those in patients treated with other phosphate binders. Overall, after 10 years of continuous post-marketing safety monitoring and more than 850 000 person-years of worldwide patient exposure to LaC, there is no evidence that LaC is associated with adverse safety outcomes in patients with ESRD.

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