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Personally identifiable information (PII) within this document is either removed or redacted (i.e., specific content is masked irreversibly from view with a black bar) to protect personal privacy. Personally identifiable information includes:

- All named persons associated with the study
- Patient identifiers within text, tables, or figures
- By-patient data listings

Anonymized patient data may be made available subject to an approved research proposal submitted. Information which is considered intellectual property or company confidential was also redacted.

SYNOPSIS

Study number: SPD405-310	**Study drug:** Lanthanum Carbonate
Title of the study: A multi-centre, open label, randomised, parallel group pilot study to assess the efficacy and safety of lanthanum carbonate and sevelamer hydrochloride in patients receiving haemodialysis for end stage renal disease	
Investigators: Multicenter study Countries involved: United Kingdom (UK) and United States (US) Coordinating Principal Investigator: Dr [redacted]	
Study center(s): Coordinating Principal Investigator address: [redacted] UK Total number of centers: 6	
Publications (reference): None	
Study period: 07 Jan 2005 to 22 Aug 2005 (First patient screened, last patient completed)	**Clinical phase:** IIIb

Objectives:

Primary

To assess phosphate reduction and control (3.5-5.5mg/dL [1.1-1.8mmol/L]) in patients with end stage renal disease (ESRD) following administration of lanthanum carbonate or sevelamer hydrochloride.

Secondary

To assess:

- The effects of lanthanum carbonate and sevelamer hydrochloride on serum calcium and calcium-phosphate product levels
- The percentage of patients achieving a reduction in serum calcium-phosphate product to $\leq 54.6 mg^2/dL^2$ ($\leq 4.4 mmol/L^2$) following administration of lanthanum carbonate or sevelamer hydrochloride
- The average daily pill burden, dose levels and compliance
- The safety and tolerability of lanthanum carbonate
- Patient satisfaction with treatment.

Methodology:

This was a multicenter, open label, randomized, parallel group, pilot study to assess the efficacy and safety of lanthanum carbonate and sevelamer hydrochloride in hemodialysis patients with ESRD.

Patients were screened over a 3-week period, followed by a 1- to 3-week 'washout' from their current phosphate binder(s). Patients whose serum phosphate levels rose above 5.9mg/dL (1.9mmol/L) were randomized at baseline (Visit 0) in a 1:1 ratio to receive either lanthanum carbonate or sevelamer hydrochloride for 8 weeks. Patients had serum phosphate levels measured prior to their first dialysis session of the week (Monday or Tuesday). Phosphate binder dose was titrated at Visits 1-7 from a starting dosage of 1500-2250mg/day of lanthanum carbonate or 2400-4800mg/day of sevelamer hydrochloride, dependent upon the patient's baseline phosphate level, until an acceptable level of serum phosphate was reached, up to a maximum dose level of 6000mg or 12000mg, respectively.

Dose escalation was to occur if the serum phosphate level had not reached a value of 3.5mg/dL (1.1mmol/L) providing:

- The investigator thought that the next dose level would result in a phosphate level <3.5mg/dL (<1.1mmol/L)
- The patient was willing to receive the higher dose.

If the investigator did not feel it was in the interest of the patient to receive a higher dose, the reason was to be

specified in the case report form (CRF). At the discretion of the investigator, a patient could be allowed to skip the subsequent dose escalation. Administration of dosages above 4500mg/day lanthanum carbonate were to be discussed with the Shire Medical Safety Monitor.

Dose reduction could occur if:

- The current dose resulted in a phosphate value <3.5mg/dL (<1.1mmol/L) (this could have been reconsidered at a subsequent visit)
- The patient was not willing to continue at that dose (a reason was to be provided if possible)
- The investigator did not feel it was in the interest of the patient to receive that dose (a reason was to be provided if possible).

An end-of-study (or withdrawal) visit was held at the end of the treatment period (Visit 8), and a follow-up was conducted approximately 4 weeks after the last dose (Visit 9).

Number of patients (total and for each treatment arm):

Treatment was allocated using a 1:1 ratio for lanthanum carbonate:sevelamer hydrochloride. One patient in the sevelamer hydrochloride group withdrew consent after randomization and did not receive any study drug.

	Lanthanum Carbonate	Sevelamer Hydrochloride	Total
Planned	24	24	48
Randomized	27	28	55
Withdrawn	4	3	7
Completed	23	25	48
ITT for efficacy	27	27	54
PP for efficacy	23	25	48
Safety population	27	27	54

ITT Intention-to-treat, PP per protocol.

Diagnosis and main criteria for admission:

Inclusion Criteria:
Male or female patients ≥18 years of age receiving hemodialysis for ESRD with a level of serum phosphate >5.9mg/dL (>1.9mmol/L) after washout or sub-optimally treated with current phosphate binder. Patients (including those who had undergone renal transplantation in the past) must have received hemodialysis for chronic renal failure three times per week for at least the previous 2 months.

Exclusion Criteria:
Pregnant or lactating women. Patients with screening calcium <8.8mg/dL (<2.2mmol/L), parathyroid hormone (PTH) level >85pmol/L (>800pg/mL), or with significant abnormal laboratory values (excluding markers of pathologies associated with chronic renal failure), which in the opinion of the investigator excluded the patient from the study. Patients with clinically significant uncontrolled concurrent illness, a life-threatening malignancy or current multiple myeloma or known to be human immunodeficiency virus (HIV) positive. Patients with any significant bowel obstruction, active inflammatory bowel disease, gastrointestinal (GI) motility disorders, abnormal or irregular bowel motion or a history of major GI surgery within the last 6 months. Patients who had been in any other clinical trial within the last 30 days or who had taken lanthanum carbonate in the last year.

Test product, dose and mode of administration, batch no.:

Lanthanum carbonate 250, 500, 750 and 1000mg chewable tablets (optimized formulation), administered orally.

Batch numbers (US and UK sites): 250mg tablets: [redacted] and [redacted] 500mg tablets: [redacted] and [redacted] 750mg tablets: [redacted] and [redacted] 1000mg tablets: [redacted] and [redacted]

Duration of treatment:

- Duration of screening period: 3 weeks
- Duration of washout period: up to 3 weeks
- Duration of treatment period: 8 weeks
- Duration of follow-up: 30 days following the last dose
- Total maximum duration for any patient: 18 weeks.

Reference therapy, dose and mode of administration, batch no.:

Sevelamer hydrochloride 800mg tablets (RENAGEL®), administered orally.

Batch number: 800mg tablets: [redacted] and [redacted] (US sites); [redacted] (UK sites).

Criteria for evaluation:

Efficacy:
Primary: pre-dialysis serum phosphate level; percentage of patients achieving control of pre-dialysis serum phosphate levels in the target control range 3.5-5.5 mg/dL (1.1-1.8mmol/L).
Secondary: serum calcium and calcium-phosphate product levels; percentage of patients achieving a reduction in calcium-phosphate product; average daily pill burden, dose levels and compliance; patient satisfaction with treatment (assessed by patient questionnaire at Visit 8).

Safety: collection of adverse event (AE) data; physical examination including post-dialysis body weight, 12-lead electrocardiogram (ECG); pre-dialysis vital signs, pre-dialysis clinical laboratory tests (hematology and biochemistry). Blood samples were taken pre-dose and at Visits 4, 8 and 9 for measurement of plasma lanthanum concentrations. A validated inductively coupled plasma mass spectrometry (ICP-MS) method was used to measure lanthanum concentrations.

Statistical methods:

Primary efficacy analysis: Mean pre-dialysis serum phosphate levels and change from baseline were summarized and presented by treatment group at each visit and over the last 4 weeks of treatment. The number and percentage of patients maintaining control of their serum phosphate levels (3.5-5.5mg/dL) at each visit and over the last 4 weeks of treatment were also summarized (with 95% confidence intervals [CIs]). The summaries were repeated using the last observation carried forward (LOCF) procedure. The summaries were conducted using the per protocol (PP) population in addition to the intention-to-treat (ITT) population.

Secondary efficacy analysis: Mean pre-dialysis serum calcium levels and mean calcium-phosphate product levels, together with changes from baseline, were summarized by treatment group at each visit and over the last 4 weeks of treatment. The number and percentage of patients achieving serum calcium-phosphate product levels of $\leq 54.56 mg^2/dL^2$ ($\leq 4.44 mmol/L^2$) at each visit and over the last 4 weeks of treatment were also summarized (with 95% CIs) by treatment. The summaries were repeated using the LOCF procedure. Calcium values were corrected for albumin.

The average dose level was calculated at the end of the treatment period together with pill burden estimates and presented for each treatment group. Treatment compliance was calculated at each visit and summary statistics were presented for each treatment group. The proportion of patients who had maintained compliance (≥80%) throughout the study was also summarized. Patient questionnaire data were summarized.

Additional efficacy analysis: After finalization of the statistical analysis plan (SAP), additional summary statistics were defined for further assessment of serum phosphate levels and serum phosphate level control status (number and percentage of patients) using the following sub-groups: age; gender; race; phosphate level at baseline (baseline disease severity); dose level at final dose; geographical location; bio-intact PTH level at baseline; mono or combination therapy for hyperphosphatemia. In addition, graphical displays were prepared for: serum phosphate and dose level changes over time for individual patients; mean serum phosphate and dose level changes over time for the ITT population, and split by responders* and non-responders, and by baseline phosphate levels; mean PTH and dose level changes by responders* and non-responders.

* A responder was defined as a patient whose mean phosphate level in the last 4 weeks of treatment was controlled (i.e. it was in the range 3.5-5.5mg/dL).

Safety analysis: AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 7.0, and incidence tables were provided. Other safety data were tabulated and summary statistics calculated as appropriate. Mean plasma lanthanum concentration data were summarized by visit and treatment group. Additional safety presentations were defined for total number of treatment-emergent AEs (TEAEs) and GI disorders by dose level and by mono or combination therapy for hyperphosphatemia.

Summary – Results:

Patient demographics:

Patients in the lanthanum carbonate group were, on average, slightly older and had started on dialysis more recently than patients in the sevelamer hydrochloride group. The mean (standard deviation [SD]) age was 62.1 (16.18) years versus 55.1 (14.05) years, respectively, and the mean (SD) time since start of dialysis was 23.3 (3.06) months versus 47.0 (10.23) months, respectively. There were other differences, for example, in terms of cause of renal disease, with hypertension and diabetes being the most common causes in the lanthanum

carbonate group (37% and 26% of patients, respectively), whereas these were less common in the sevelamer hydrochloride group (15% and 15%, respectively), in which causes described as 'other' accounted for 41% of causes of renal disease.

Efficacy results:

Primary efficacy analysis:

In the last 4 weeks of treatment, the mean (standard error of the mean [SEM]) pre-dialysis serum phosphate levels were similar in the lanthanum carbonate and sevelamer hydrochloride groups: 6.05 (0.311) mg/dL and 6.33 (0.325) mg/dL, respectively, indicating similar control of serum phosphate in both groups (LOCF analysis; ITT population). Over the course of the treatment period, the average serum phosphate level generally decreased at each visit in both treatment groups, indicating constant improvements in serum phosphate level control over time. However, the mean level did not fall within the range defined for control of serum phosphate (3.5-5.5mg/dL) at any time point, for either treatment group.

Over the course of treatment, the percentage of patients who achieved controlled serum phosphate levels (in the range 3.5-5.5mg/dL) increased from baseline in both treatment groups. In the last week of treatment, 10 patients (37%) in the lanthanum carbonate group and 16 patients (59%) in the sevelamer hydrochloride group had controlled serum phosphate levels (LOCF analysis; ITT population). In the last 4 weeks of treatment (based on the mean pre-dialysis serum phosphate levels during the last 4 weeks of the treatment period), 9 patients (33%) in the lanthanum carbonate group and 11 patients (41%) in the sevelamer hydrochloride group had controlled serum phosphate levels.

Results of the PP population supported those of the ITT population.

Secondary efficacy analysis:

There were no notable changes in mean corrected serum calcium levels over the course of the treatment period, in both treatment groups. Mean (SEM) values for the last 4 weeks of treatment were 9.23 (0.128) mg/dL and 9.56 (0.139) mg/dL in the lanthanum carbonate and sevelamer hydrochloride groups, respectively, representing mean (SEM) changes from baseline of 0.12 (0.086) mg/dL and 0.25 (0.103) mg/dL, for the two treatment groups, respectively (LOCF analysis; ITT population).

In both treatment groups, the mean corrected serum calcium-phosphate product levels decreased over time. Mean (SEM) values for the last 4 weeks of treatment were 55.55 (2.802) mg^2/dL^2 and 60.42 (3.241) mg^2/dL^2 in the lanthanum carbonate and sevelamer hydrochloride groups, respectively, representing similar mean (SEM) changes from baseline of -14.88 (4.176) mg^2/dL^2 and -14.12 (2.816) mg^2/dL^2, for the two treatment groups, respectively (LOCF analysis; ITT population).

The percentage of patients achieving a reduction in corrected serum calcium-phosphate product level to ≤54.56mg^2/dL^2 generally increased over the course of the treatment period, in both treatment groups. In the last week of treatment, the percentage of patients with a reduction was 56% in the lanthanum carbonate group and 59% in the sevelamer hydrochloride group (LOCF analysis; ITT population). For the last 4 weeks of treatment, the percentage of patients with a reduction was 48% and 48%, for the two treatment groups, respectively.

The mean (SEM) number of tablets taken per day was less (45%) in the lanthanum carbonate group than in the sevelamer hydrochloride group: 2.8 (0.21) compared with 6.2 (0.55) tablets per day.

The mean prescribed daily dose increased over the course of the study in both treatment groups. In the lanthanum carbonate group, the maximum daily dose level was 6000mg. In the sevelamer hydrochloride group, the maximum was 12000mg. Overall, the mean (SEM) prescribed daily dose in the lanthanum carbonate group was less than in the sevelamer hydrochloride group: 2810.8 (160.85) mg versus 6120.5 (368.57) mg, respectively.

Overall mean compliance was similar in the lanthanum carbonate and sevelamer hydrochloride groups: 84% and 87%, respectively (safety population).

In terms of how easy or difficult the medication was to use in its current form, 12 of the 24 patients (50%) in the lanthanum carbonate group who responded described it in the range somewhat easy to extremely easy, and 12 (50%) described it as difficult to extremely difficult. In the sevelamer hydrochloride group, patients tended to find the medication easier to use, with 25 of 27 patients (93%) describing it as somewhat easy to extremely easy to use and only two patients (7%) describing it as difficult or very difficult.

In terms of taking the medication with the patients' daily food/drink schedule and how convenient or not it was to take the medication as instructed, the majority of respondents in both the treatment groups described it as somewhat easy to extremely easy or somewhat convenient to extremely convenient.

Changes in calcium supplement usage and changes in Vitamin D therapy during the treatment period occurred

in only a minority of patients. This suggests that the efficacy demonstrated in the study population was a result of the study drug treatment and not from changes in permitted supplemental medication.

Additional efficacy analysis:

In the lanthanum carbonate group, the mean dose level for responders increased from approximately 1700mg at Visit 1 to 2800mg at Visit 8. For non-responders in the lanthanum carbonate group, serum phosphate control was not achieved even with an increase in mean dose from approximately 1700mg at Visit 1 to 4600mg at Visit 8. In the sevelamer hydrochloride group, a greater increase in dose level was required to achieve control in the responders (approximately 2800mg to 6300mg at Visit 8), and an even larger increase in dose level was not successful in achieving control in non-responders (approximately 4000mg to 9300mg).

There was an apparent trend for serum phosphate levels to be less controlled at the end of the 8-week treatment period in patients who had a more severe hyperphosphatemia level at baseline. However, for patients with severe hyperphosphatemia in the lanthanum carbonate group, control of serum phosphate occurred faster and to a larger extent than for patients in the sevelamer hydrochloride group. For patients with mild baseline disease, better control was observed in the sevelamer hydrochloride group.

An assessment of serum phosphate by dose level at final dose showed that mean serum phosphate levels at the end of the treatment period were controlled in the range 3.5-5.5mg/dL for those patients who finished treatment on a low dose (mean serum phosphate levels were approximately 5mg/dL in both treatment groups). For those patients who finished on a medium dose, mean serum phosphate levels were slightly higher (approximately 6mg/dL), and those patients who finished on a high dose had the highest mean serum phosphate levels (approximately 7mg/dL).

In the last 4 weeks of treatment, controlled serum phosphate levels tended to be achieved by a higher percentage of patients in study centers in the US compared with patients in Europe (UK), in both treatment groups. In addition, a greater percentage of females compared with males achieved controlled serum phosphate in the last 4 weeks of treatment.

Changes in mean bio-intact PTH levels appeared to correlate with mean serum phosphate levels, particularly in responders.

Safety results:

In the lanthanum carbonate group, the most commonly reported TEAEs were GI disorders, particularly nausea (26%), vomiting (19%), diarrhea (15%) and constipation (11%). GI disorders were also most commonly reported in the sevelamer hydrochloride group. Other commonly occurring TEAEs in the lanthanum carbonate group were hypotension (15%) and hypertension (11%), but both TEAEs had a lower incidence in the sevelamer hydrochloride group (4% each). Overall, the number (and percentage) of patients who had a serious TEAE was slightly higher in the lanthanum carbonate group: 10 (37%) versus 5 (19%), respectively. However, all of the serious TEAEs, in both groups, were classified as unrelated to study drug. Five patients were withdrawn because of AEs: three of four patients in the lanthanum carbonate group experienced related GI disorders that resulted in their withdrawal (and one of these patients also reported abnormal thinking leading to withdrawal, classed as unrelated), and one patient was withdrawn due to unrelated cardiomyopathy, but this patient also later died as a result of the cardiomyopathy (classified as unrelated to study drug). One patient in the sevelamer hydrochloride group was withdrawn because of a related GI disorder.

There were a number of clinical laboratory test parameters for which patients in both treatment groups had a shift from normal values at baseline to low or high values at post-baseline time points. There were no apparent clinically significant trends in any parameter. One patient in the lanthanum carbonate group had a treatment-related abnormal liver function test that was recorded as a TEAE.

Mean systolic and diastolic blood pressure (BP) results showed a slight fluctuation over the 8-week treatment period, with a slight trend towards increasing mean diastolic BP, particularly at Visit 5 and onwards. There were no apparent clinically significant changes in physical examination or 12-lead ECG results.

Mean plasma lanthanum concentrations in the lanthanum carbonate group showed an increase from baseline (0.03ng/mL) to 0.34ng/mL at Visit 4 and 0.38ng/mL at Visit 8, and then decreased to 0.15ng/mL at the follow-up Visit (Week 12).

Conclusions:

This section contained Summary and Conclusion information which could be considered promotional in nature. This section has been removed to allow the reader to draw their own conclusions.

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Date of report

27 July 2006