This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

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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.

STUDY SYNOPSIS

Name of Sponsor/Company: Shire Development Inc. **Name of Finished Product:** FOSRENOL® **Name of Active Ingredient:** Lanthanum carbonate	Individual Study Table Referring to Part of the Dossier Volume: <Insert volume number> Page: <Insert page number>	(for National Authority Use only)

Title of Study:

A Phase IV, Open-Label, Multi-Centre Trial Evaluating the Conversion from Standard Phosphate Binder Therapy to FOSRENOL® in Chronic Kidney Disease Stage 5 Patients on Haemodialysis

Investigators:

Multi-centre study

Countries involved: Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, the Netherlands, Spain, and the United Kingdom.

Chief Coordinating Investigator: [redacted] MD, PhD

Study Centre(s):

Chief Coordinating Investigator's Address: [redacted] Italy.

Total number of centres: 70-80 centres were planned, 70 centres were selected at the time of study termination, 51 centres were initiated and supplied with study medication.

Publications (references):

Not applicable

Study period:	**Phase of development:**
22 May 2007 to 10 December 2007 (First subject consent date, last subject follow-up contact)	IV

Objectives:

Primary

- To assess the percentage of subjects who had serum phosphorus levels controlled to ≤1.78mmol/L (≤5.5mg/dL) following treatment with lanthanum carbonate compared to their previous phosphate binder therapy.

Secondary

- To assess if lanthanum carbonate can maintain serum phosphorus levels in subjects converting to lanthanum carbonate from their previous phosphate binder therapy
- To assess if lanthanum carbonate can reduce serum phosphorus levels in subjects converting to lanthanum carbonate from their previous phosphate binder therapy
- To assess the control of serum calcium, calcium-phosphate product, and intact parathyroid hormone (iPTH)
- To assess the average daily dose of lanthanum carbonate
- To assess the safety and tolerability of lanthanum carbonate.

The study was terminated early on 23 November 2007 due to insufficient enrolment of subjects to meet the study objectives according to planned timelines. At the time of the study termination, only 67 subjects were enrolled out of the planned enrolment of 760 subjects.

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Methodology:

This was designed as a prospective, open-label, multi-centre study to consist of a Screening Period lasting up to 2 weeks; Part 1 (Fixed Dose Period) lasting for 2 weeks; Part 2 (Dose Titration Period) lasting for 22 weeks; and a 30-day post-treatment follow-up telephone contact. Subjects were to perform study visits on the same day of the week, preferably on the first dialysis session of the week (Monday or Tuesday), throughout the study.

- **Screening Period:** The Screening Period was to last up to 2 weeks, during which 3 months of historical data on phosphate binder use (name, dose, and regimen) and serum phosphorus levels were to be collected. Subjects eligible to continue to Part 1 of the study were to meet all study inclusion and exclusion criteria.
- **Part 1 (Fixed Dose Period):** Following the Screening Period, eligible subjects were to enter Part 1 of the study. Two study visits, which included the Baseline Visit (Visit 0/Week 0) and Visit 1/Week 2 were to occur during Part 1.

  At the Baseline Visit (Visit 0/Week 0), subjects were to discontinue their previous phosphate binder therapy and were to begin treatment with 2250mg/day of lanthanum carbonate to be taken in three divided doses with meals or immediately following meals.

  Subjects were to continue dosing with 2250mg/day lanthanum carbonate and were to return to the study site 2 weeks following the Baseline Visit for the Visit 1/Week 2 visit.
- **Part 2 (Dose Titration Period):** Upon entry into Part 2, the starting dose of lanthanum carbonate (2250mg/day) was to be titrated (increased or decreased), as necessary, based on the Visit 1/Week 2 serum phosphorus results. Subjects were to continue this dose of lanthanum carbonate for 2 weeks. Six study visits, which included five dose titration visits (Visit 2/Week 4 through Visit 6/Week 20) and a final study visit (Visit 7/Week 24), were to occur during Part 2 of the study.

  Visit 2/Week 4 was to occur 2 weeks following Visit 1/Week 2. The total daily dose of lanthanum carbonate was to be titrated, as necessary, based on the Visit 2/Week 4 serum phosphorus results. Subjects were to continue the dose of lanthanum carbonate received at Visit 2/Week 4 for 4 weeks.

  Visit 3/Week 8 through Visit 7/Week 24 were to occur at 4-week intervals. At Visit 3/Week 8 through Visit 6/Week 20, the total daily dose of lanthanum carbonate was to be titrated, as necessary, based on each visit's serum phosphorus results. At Visit 7/Week 24, subjects were to have pre-dialysis blood samples drawn, and were to discontinue the use of the study drug.

  More frequent dose adjustments could occur, at the Investigator's discretion, during Part 2 to ensure optimal serum phosphorus control and subject safety.

  The daily dose of lanthanum carbonate was to be increased during the study until serum phosphorus levels were in the middle of the range of 1.13-1.78mmol/L (3.5-5.5mg/dL). The total daily dose, however, was not to be decreased below 1500mg/day or exceed 3000mg/day.
- **Follow-up contact:** Thirty days after the last dose of study drug, subjects were to be contacted via telephone to collect information on any ongoing non-serious AEs and SAEs, and to determine if any new SAEs had occurred since the last dose of study drug.

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Number of subjects (planned and analyzed):

Planned	760
Enrolled	67*
Withdrawn	67
Completed	0
Intent-to-Treat (ITT) for efficacy	62
Safety Population	67

* Of the 67 enrolled subjects, 44 used calcium as their previous primary phosphate binder therapy (calcium group), 22 used sevelamer as their previous primary phosphate binder therapy (sevelamer group), and one subject did not use a previous phosphate binder therapy.

Diagnosis and main criteria for inclusion:

Male or female subjects ≥18 years of age who were receiving a stable regimen of haemodialysis for chronic kidney disease (CKD) Stage 5 (haemodialysis two or three times per week for at least 2 months prior to screening) and were on a stable calcium-based phosphate binder and/or sevelamer dose (defined as no change in medication or dosage for at least the 1 month prior to screening) with a serum phosphorus level >1.78 and ≤2.43mmol/L (>5.5 and ≤7.5mg/dL).

Exclusion criteria included subjects who had a corrected serum calcium level <2.1mmol/L (<8.5mg/dL); an intact parathyroid hormone (iPTH) level >500pg/mL; a history of previous parathyroidectomy within the past 12 months; a life-threatening malignancy or current multiple myeloma, or known to be human immunodeficiency virus (HIV) positive; 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; or a clinically significant uncontrolled concurrent illness. Also excluded from the study were subjects receiving >3000mg/day elemental calcium (7500mg/day calcium carbonate) as a phosphate binder; >9600mg/day sevelamer; aluminium, magnesium, or combination therapy other than calcium and sevelamer as a phosphate binder; or those requiring treatment with cinacalcet HCl.

Test product, dose and mode of administration, batch number:

Lanthanum carbonate (FOSRENOL®, bulk drug manufactured for Shire Pharmaceutical Ltd. by Hamol Limited, Nottingham, UK) was administered orally every day in 500mg, 750mg, and 1000mg strength chewable tablets. Commercial drugs were over-labelled with clinical trial label.

Batch number/expiration dates: 500mg tablets ([redacted]30 April 2008 and [redacted]28 February 2008); 750mg tablets [redacted]31 May 2008); and 1000mg tablets ([redacted]31 July 2008).

Duration of treatment:

- Screening Period: Up to 2 weeks prior to start of treatment.
- Part 1 (Fixed Dose Period): Subjects were to start on lanthanum carbonate 2250mg/day with dose taken for 2 weeks.
- Part 2 (Dose Titration Period): Subjects completing Part 1 were to enter a 22-week period where dose titration was to occur based on serum phosphorus results.
- Post-treatment follow-up telephone contact: 30 days after last dose of study drug.

Reference therapy, dose and mode of administration, batch number:

None

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Criteria for evaluation:

Primary efficacy variable:

- The percentage of subjects achieving serum phosphorus levels of ≤1.78mmol/L (≤5.5mg/dL) following treatment with lanthanum carbonate at Week 12 compared to treatment with their previous phosphate binder therapy.

Secondary efficacy variables:

- The percentage of subjects achieving serum phosphorus levels of ≤1.78mmol/L (≤5.5mg/dL) following treatment with lanthanum carbonate at time points other than Week 12 compared to treatment with their previous phosphate binder therapy
- The maintenance of mean serum phosphorus levels at Week 2 following treatment with 2250mg/day of lanthanum carbonate compared to baseline
- The reduction of mean serum phosphorus levels from baseline
- Serum calcium, calcium-phosphate product, and iPTH
- Average daily dose of lanthanum carbonate.

Safety:

Safety was assessed based on AEs/SAEs, clinical laboratory test results, vital signs, physical examination findings, and other safety assessments (including ECG recordings and pregnancy tests results).

Statistical methods:

No inferential statistical tests were performed for this study as the study was terminated early and only 67 subjects were enrolled out of the planned enrolment of 760 subjects. All efficacy data were summarized by descriptive statistics or frequency counts and percentages as appropriate by three groups (calcium, sevelamer, and total). Post-hoc summaries of selected efficacy variables were summarized by four groups (calcium only, sevelamer only, both calcium and sevelamer, and total). Additional post-hoc summaries of the percentage of subjects in each category of serum iPTH level at baseline and Week 12 were presented.

Efficacy summaries were based on the ITT population consisting of all subjects who received at least one dose of study drug and had at least one follow-up assessment of the primary endpoint (i.e. at least one post-baseline serum phosphate level). In addition to this condition all subjects from site [redacted] were excluded from this population due to the substantial failure of this site to maintain adequate and accurate visit records. It was therefore agreed with relevant competent authorities and ethics committees that efficacy data from this site was deemed unreliable.

Safety summaries were based on all subjects who took at least one dose of study drug and had at least one post-dose safety assessment and included safety data from site [redacted] In addition to the protocol-specified tabulations of prior and concomitant medications by Anatomic, Therapeutic and Chemical (ATC) classification, post-hoc summaries of these medications were presented by Shire physician-specified classification.

SUMMARY – CONCLUSIONS:

EFFICACY RESULTS:

The protocol specifies Week 12 to assess the primary endpoint. At Week 12, a higher percentage of subjects in the total group (55.6%) compared to baseline (41.9%) had serum phosphorus levels controlled at ≤1.78mmol/L (≤5.5mg/dL). This met the protocol assumption of a difference ≥10% in control rate between Week 12 and baseline, although formal statistical testing was not performed. The result in the previous calcium group at Week 12 was similar to that in the total group; indicating at least a 10% increase in control rate at Week 12 compared to baseline.

Serum phosphorus levels following treatment with 2250mg/day of lanthanum carbonate for 2 weeks were maintained. After Week 2 when titration began, mean decreases from baseline in serum phosphorus levels in the total group were seen from Week 4 through Week 12, ranging from 0.107 to 0.159mmol/L (0.330 to 0.493mg/dL), which were clinically meaningful. Similar observations were made in the previous calcium group.

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After Week 2 when titration began, there were incremental mean decreases in serum phosphorus levels at each time point from Week 4 through Week 12, ranging from 0.118 to 0.170mmol/L (0.365 to 0.525mg/dL), which were also clinically meaningful. The reduction in serum phosphorus levels suggests a clinically meaningful decrease in phosphate burden.

There were small mean decreases from baseline in serum calcium levels following treatment with lanthanum carbonate in the total group (ranging from 0.006 to 0.057mmol/L [0.02 to 0.23mg/dL]). Similar mean decreases were observed in the previous calcium group (ranging from 0.032 to 0.065mmol/L [0.13 to 0.27mg/dL]). The mean decreases in serum calcium levels may be due to the switch from a calcium-based phosphate binder to lanthanum carbonate (a non calcium-based phosphate binder) as calcium supplementation was constant in this study. Again, this result indicates lanthanum carbonate treatment, as a non-calcium agent, reduces calcium burden which is often increased in haemodialysis patients who simultaneously receive calcium in the dialysate, calcium, and vitamin D.

There were mean decreases from baseline in serum calcium-phosphorus product levels following treatment with lanthanum carbonate consistent with the reductions in serum phosphorus and calcium levels.

There were modest mean increases from baseline in serum iPTH levels following treatment with lanthanum carbonate. In the total group, 21 (33.9%) subjects had serum iPTH levels <15.9pmol/L (<150pg/mL) and three (4.8%) subjects had levels ≥53pmol/L (≥500pg/mL) at baseline. At Week 12, two (11.1%) subjects had levels <15.9pmol/L (<150pg/mL) and two (11.1%) subjects had levels ≥53pmol/L (≥500pg/mL). These results suggest potential improvement in bone turnover especially in subjects who initially had had suboptimally low iPTH levels.

Serum phosphorus, calcium, and calcium-phosphorus product levels improved with lanthanum carbonate treatment, with subjects shifting away from suboptimally low iPTH levels, suggesting an overall trend in the improvement of CKD metabolism disorder.

SAFETY RESULTS:

The mean age of this study population (65.5 years) was older than that from previous studies and safety composites. There were no unexpected AEs or safety concerns in this study. The most common TEAEs were gastrointestinal disorders mostly attributed to constipation (six subjects, 9.0%) and nausea (five subjects, 7.5%). Treatment-emergent AEs which were considered drug-related by the Investigator were experienced by 10 (14.9%) subjects. Almost all the drug-related TEAEs were gastrointestinal disorders such as nausea (three subjects, 4.5%), constipation (two subjects, 3.0%) and diarrhoea (two subjects, 3.0%); these are AEs known to occur with lanthanum carbonate.

There was one death due to cardiac failure during the post-treatment follow-up period, which was considered by the Investigator as not related to the study drug.

Of the 14 (20.9%) subjects who experienced treatment-emergent SAEs, only one event (gastritis) was considered as drug-related by the Investigator. Most of the treatment-emergent SAEs were cardiac disorders and infections and infestations (four subjects, 6.0% each). Many of the serious events are known to be associated with chronic renal failure and/or comorbid conditions commonly associated with CKD including high prevalence of cardiovascular disorders, compromised immune system, metabolic imbalances, electrolyte imbalance, and dialysis access complications.

Six (9.0%) subjects experienced TEAEs resulting in withdrawal from the study; four (6.0%) subjects discontinued due to gastrointestinal events which were considered related to study drug by the Investigator.

As previously discussed in the efficacy section, modest mean increases from baseline in serum iPTH levels were observed during treatment starting at Week 2, which suggest potential improvement in bone turnover. There was an increase in serum bicarbonate levels during lanthanum carbonate treatment, suggesting an improvement of metabolic acidosis in this patient population. There were no clinically meaningful changes from baseline in the other laboratory parameters or in vital signs.

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 the report: 16 September 2008