PROTOCOL: SPD405-207

TITLE:	A 3-part Open-label Study to Assess the Pharmacokinetics of Lanthanum Carbonate, Compare the Efficacy, Safety and Tolerability of 8 Weeks of Treatment With Lanthanum Carbonate and Calcium Carbonate using a Crossover design and Investigate the Efficacy and Safety of 8 Months of Treatment With Lanthanum Carbonate in Hyperphosphataemic Children and Adolescents Aged 10 years to <18 Years With Chronic Kidney Disease on Dialysis
DRUG:	SPD405, Lanthanum carbonate
IND:	Non - IND
EUDRACT NO.:	2012-000171-17
SPONSOR:	Shire Pharmaceutical Development Ltd. Hampshire International Business Park Chineham, Basingstoke Hampshire, RG24 8EP
PRINCIPAL/ COORDINATING INVESTIGATOR:	PPD
PROTOCOL VERSION AND DATE:	Version 6.0 (Amendment 5), 18 Oct 2016

PROTOCOL SIGNATURE PAGE

Sponsor's Approval

This protocol has been approved by Shire

Signature:	**Date:**
PPD PPD , M PPD , PhD, PPD	PPD

Investigator's Acknowledgement

I have read this Shire protocol SPD405-207.

Title: A 3-part Open-label Study to Assess the Pharmacokinetics of Lanthanum Carbonate, Compare the Efficacy, Safety and Tolerability of 8 Weeks of Treatment With Lanthanum Carbonate and Calcium Carbonate using a Crossover Design and Investigate the Efficacy and Safety of 8 Months of Treatment With Lanthanum Carbonate in Hyperphosphataemic Children and Adolescents Aged 10 years to <18 Years With Chronic Kidney Disease on Dialysis

I have fully discussed the objective(s) of this study and the contents of this protocol with the Sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to my participation as an Investigator for this study to be terminated.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the Sponsor.

Investigator Name, Address, and Telephone Number: (please hand print or type)	

Signature: **Date:**

SUMMARY OF CHANGES

	Protocol Amendments	
	Summary of Change(s) Since Last Version of Approved Protocol	
Amendment Number: 5.0	**Amendment Date: 18 Oct 2016**	**Global/Country/Site-Specific: Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Removed the active comparator (calcium carbonate) treatment arm given the extreme difficulty in recruiting enough subjects to obtain the originally proposed sample size of at least 50 subjects required for the Per-protocol Set for a cross-over non-inferiority study. The original design of Part 2 of Study SPD405-207 was crossover non-inferiority to allow a formal comparison of the efficacy of lanthanum carbonate with calcium carbonate (Part 2a). Under the modified study design, Part 2a has been removed and subjects will only be treated with 8 weeks of lanthanum carbonate in Part 2b of the study for short-term efficacy and safety assessments.		Study Synopsis, Section 3.1
Adjusted planned sample size from 72 to 65, with the target to enroll at least 35 subjects (instead of at least 50) who complete 8 weeks of treatment with lanthanum carbonate and are assessable for the primary endpoint, due to low replenishment of eligible subjects and the discontinuation of subjects enrolled in the study, in agreement with Paediatric Committee of the European Medicine Agency.		Study Synopsis, Section 3.1, Section 9.13.
Added that Part 1, single dose, pharmacokinetic assessment of lanthanum carbonate, is complete and the interim clinical study report interpreting and summarizing the data is available.		Study Synopsis, Section 3.1
Modified the primary objective as follows since the study design no more allows a formal comparison of the efficacy of lanthanum and calcium carbonate: "To ~~compare~~ **summarize** the percentage of subjects achieving age-specific Kidney Disease Outcomes Quality Initiative (KDOQI) targets for serum phosphorus in hyperphosphatemic children and adolescents with chronic kidney disease (CKD) who are on dialysis, ~~following treatment with calcium carbonate for 8 weeks and lanthanum carbonate for 8 weeks~~ **following 8 weeks of treatment with lanthanum carbonate.**"		Study Synopsis, Section 2.2.1
Added or modified secondary objectives to assess efficacy for the subjects who have completed 8 weeks of treatment with calcium carbonate followed by 8 weeks of treatment with lanthanum carbonate since the study design no longer allows a formal comparison of the efficacy of lanthanum and calcium carbonate after 8 weeks of treatment: <u>Addition</u> "**To summarize the percentage of subjects achieving KDOQI targets for serum phosphorus in hyperphosphatemic children and adolescents with CKD who are on dialysis following treatment with calcium carbonate for 8 weeks and lanthanum carbonate for 8 weeks**." <u>Modification</u> "To ~~compare~~ **summarize** mean changes from baseline in serum phosphorus, calcium and calcium-phosphorus product in hyperphosphatemic children and adolescents with CKD who are on dialysis, following treatment with calcium carbonate for 8		Study Synopsis, Section 2.2.2

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weeks and lanthanum carbonate for 8 weeks."		
Added a secondary objective to assess efficacy for 8 weeks of lanthanum carbonate arm only: "**To assess mean changes from baseline in serum phosphorus, calcium and calcium-phosphorus product in hyperphosphatemic children and adolescents with CKD who are on dialysis, following treatment with lanthanum carbonate for 8 weeks**."		Study Synopsis, Section 2.2.2
Reordered the list of secondary objectives to emphasize the focus of the study on safety by moving the objective "To investigate the safety profile in hyperphosphatemic children and adolescents with CKD on dialysis treated with calcium carbonate and/or lanthanum carbonate" first in the order. This objective was modified to clarify that it encompassed subjects who enrolled in the cross over design part of the study as well as those who are treated with lanthanum carbonate only.		Study Synopsis, Section 2.2.2
Modified the following secondary objective to add flexibility for up to 8 months of treatment: "To investigate the efficacy (serum phosphorus, calcium, and calcium-phosphorus product) and safety of **up to** 8 months of treatment with lanthanum carbonate in children and adolescents aged 10 years to <18 years (Parts 2 and 3 of the study combined)."		Study Synopsis, Section 2.2.2

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Description of Change and Rationale		**Section(s) Affected by Change**
Divided Part 2 into Part 2a and Part 2b, where Part 2a is the originally proposed single sequence, 2-treatment period, study design (8 weeks of calcium carbonate treatment followed by 8 weeks of lanthanum carbonate treatment); Part 2b is the modified Part 2a with 1 treatment period with 8 weeks of lanthanum carbonate treatment only. Also specified wherever needed, throughout the amended protocol, that no new subjects will be included in Part 2a and that all new subjects will be enrolled in Part 2b only under Version 6.0 of the protocol.		Study Synopsis, Section 3
Specified that at the conclusion of Part 2a and 2b subjects may continue to receive open-label lanthanum carbonate for up to 6 additional months of therapy in Part 3; clarified that as noted in Section 6.2.1, Dosing (Hypercalcemia) subjects who participated in Part 2a, Treatment Period 1/calcium carbonate treatment arm, but who discontinued due to hypercalcemia, may continue to receive open-label lanthanum carbonate for up to 6 additional months of therapy.		Study Synopsis, Section 3.1
Increased the number of clinical sites from 30 to 36 to achieve the target recruitment for the planned sample size.		Study Synopsis, Section 3.4
Removed the upper limit of serum parathyroid hormone (~~Serum PTH >700pg/mL~~) from the exclusion criteria to facilitate enrollment since the specified maximum PTH level for exclusion was too low in the opinion of the investigators as higher PTH levels are tolerated in children with chronic kidney disease (CKD). Consequently, the stopping rule specifying PTH level >1200pg/mL was also removed.		Study Synopsis, Section 4.2, Section 4.4.1, Section 12 (Appendix 2)
As a result of the change in the study design, it is no longer necessary to replace subjects who discontinue Part 2 to ensure that 35 subjects enter Part 3 of the study.		Section 4.4
Updated study duration to 64 months (extended to 2018).		Study Synopsis
Added a table to separately present the schedule of assessments for Part 2b and Part 3 and updated the "Study Schedule" (Study Procedures)		Table 3, Section 7.1
Added a study schematic to depict Part 2b and Part 3.		Figure 2
Corrected an error in the text related to washout period 2 in Part 2a, where calcium carbonate was mentioned instead of lanthanum carbonate: "If a subject has started ~~calcium~~ **lanthanum** carbonate based on local laboratory results, the subject will be allowed to continue the study even if central laboratory results do not agree."		Section 7.1.2.4
Removed the text specifying that lanthanum carbonate will be provided to study participants at the end of study completion if the participant has benefited from and desires to continue dosing with lanthanum. The need for additional care of subjects after study does not exist anymore in the country that had originally requested it since there are no active clinical sites. No request for this additional supply of lanthanum carbonate has been received from other countries to date.		Section 7.1.4
Specified the approximate volume of blood collected from all subjects who will enter Part 2b (8 weeks of lanthanum carbonate treatment only) of the study and will undergo assessments for Part 2b and 3.		Section 7.2.5
Updated statistical methods to align with the removal of the cross over design, reduction in the planned sample size and the shift in the focus of the study to safety. • Modified or redefined analysis populations as follows to align with changes in		Study Synopsis, Section 9.5, Section 9.6, Section 9.7, Section 9.8, Section 9.9, Section 9.10, Section 9.11,

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the study design: ○ Modified the definition of Full Analysis Set to: Subjects who have taken at least 1 dose of investigational product and who have at least 1 phosphate assessment during Part 2 or Part 3. ○ Redefined Safety Analysis Set 2 to include Part 3 (long-term safety); therefore, removed Safety Analysis Set 3 and added **Safety Completer Set (SCS)** to include subjects who received 8 weeks of lanthanum carbonate treatment from Part 2 or Part 3 of the study. ○ Redefined Per-protocol Set and divided it into Set 1 and Set 2. ○ **Per-protocol Set 1** includes subjects in the Full Analysis Set who complete 8 weeks of calcium carbonate treatment followed by 8 weeks of lanthanum carbonate treatment and who have serum phosphate assessment data available to allow summarizing the percentage of subjects achieving age-specific KDOQI target. Only subjects who have serum phosphate levels equal to or above the age-specific KDOQI targets at study entry and between the calcium carbonate treatment and lanthanum carbonate treatment at Visit 2.4 will be included in this set. ○ **Per-protocol Set 2** includes subjects in the Full Analysis Set who complete 8 weeks of treatment with lanthanum carbonate and who have serum phosphate assessment data available to allow summarizing the percentage of subjects achieving age-specific KDOQI target. Subjects who have serum phosphate levels equal to or above the age-specific KDOQI targets prior to the start of lanthanum carbonate treatment will be included in this set. ○ Modified summarization of subject disposition, demographic and baseline characteristics, intent for listing and analyzing investigational product exposure, and methods for listing prior and concomitant medication to align with the changes made to the definition of Safety Analysis Sets. Clarified that the Full Analysis Set and PP2 Sets will be used for the primary endpoint analyses, while the FAS, PP1, and PP2 Sets will be used for the secondary efficacy endpoint analyses. The FAS and PP1 Sets will be used to summarize the percentage of subjects achieving age-specific KDOQI targets after 8 weeks of calcium carbonate treatment followed by 8 weeks of lanthanum carbonate. Updated primary and secondary variables to align with the changes made to the primary and secondary objectives and to the definition of analysis populations. The analysis of efficacy measures for the primary endpoint is descriptive under Version 6.0 of the protocol. Therefore, local laboratory data may be used if central laboratory data is missing. Added the following for analysis: "Serum phosphate levels tested at a central laboratory will be used for the analysis. **In case of missing central laboratory data, local laboratory data will be used**." Specified that height and weight will be measured at Visits 2.0, 2.4, 2.8, and 3.5 (Parts 2a and 3) and Visits 1.0, 2.4, and 3.5 (Parts 2b and 3).		Section 9.12, Section 9.13

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Description of Change and Rationale		**Section(s) Affected by Change**
Adjusted the planned sample size to include at least 35 subjects, who will complete 8 weeks of treatment with lanthanum carbonate and are assessable for the primary endpoint. Added that a sample size of 35 subjects is necessary in order to observe at least one event with a true event rate of 5% at a probability of 83.4%.		
Applied editorial changes throughout the document for clarity.		Study Synopsis and sections, as needed

See APPENDIX 1 for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

In the event of a Serious Adverse Event (SAE), the Investigator must fax or e-mail the Shire Pharmaceuticals Clinical Trial Serious Adverse Event Form within 24 hours to the Shire Pharmacovigilance Department:

Shire Pharmacovigilance SAE Fax Number: PPD

or

PPD

For protocol- or safety-related issues during normal business hours (9.00 until 17.00 Central European Time), the Investigator must contact the ICON Medical Monitor:

PPD MD MA

Tel: PPD

Fax: PPD

For protocol- or safety-related issues outside of normal business hours, the Investigator must contact the ICON 24/7 Medical Help Desk Numbers as below:

All countries globally for chargeable calls please call PPD

If you wish to make a toll-free call please dial the number relevant to your country. This service is only available for landline telephones and not mobile phones.

All current toll-free numbers can also be found at https://icophone.iconplc.com.

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

Please use the information below as applicable to report the Product Quality Complaint:

Origin of Product Quality Complaint	E-mail Address
North and South America	PPD
European Union (EU) and Rest of World	PPD

Telephone numbers (provided for reference if needed):

Shire, Wayne, PA (USA)
PPD or PPD

Shire, Basingstoke, Hampshire (UK)
PPD

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ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase (SGPT)
AST	aspartate transaminase (SGOT)
AUC	area under the curve
AUC_{0-t}	area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
CFR	Code of Federal Regulations
CKD	chronic kidney disease
C_{max}	maximum plasma concentration
CRF	case report form
CRO	Contract Research Organization
ECG	electrocardiogram
EOS	End of Study
EU	European Union
FAS	Full Analysis Set
FGF-23	fibroblast growth factor 23
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
KDOQI	Kidney Disease Outcomes Quality Initiative
LAR	legally authorized representative
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
PP	Per-protocol
PTH	parathyroid hormone
RBC	red blood cell
SAE	serious adverse event
SCS	Safety Completer Set
$t_{½}$	apparent terminal-phase disposition half-life

TEAE	treatment-emergent adverse event
TRAP	tartrate-resistant acid phosphatase
WBC	white blood cell
λ_z	apparent terminal-phase disposition rate constant

DEFINITIONS

Term	Definition
Abuse	Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.
Adverse Event	Any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
Adverse Event Relationship	**Related:** The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident. **Not Related:** The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.
Adverse Event Severity	**Mild:** A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. **Moderate:** A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject. **Severe:** A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Term	Definition
Baseline	Baseline is the last assessment prior to the first dose of investigational product in each treatment period.
Investigational Product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical (ie, human) study. Investigational product also includes biologics, medical devices, and 'Investigational Medicinal Product' (IMP) as referenced in the European Communities (EC) Directive 2001/20/EC. It includes a product with a marketing authorization (ie, marketed product) when: • Used or assembled (eg, formulated, packaged) in a way different from the approved form, • Used for an unapproved indication, or • Used to gain further information about an approved use.
Medication Error	An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the Sponsor only as defined in this protocol (see Section 8.1.7).
Misuse	Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol).
Overdose	Intentional or unintentional intake of a dose of an investigational product exceeding a pre-specified total daily dose of 3000mg of lanthanum or 6500mg calcium.
Primary Completion Date	The date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome (Last Subject Last Visit in most cases). Note: This date is used to ascertain timing for study results posting.
Product Quality Complaint	Any communication received which suggests that the quality or performance of a Shire marketed product or investigational product does not meet expectations or that the product did not meet the specifications defined in the regulatory applications/ licenses/marketing authorizations for the product. Examples (but not limited to): • Wrong product (label and contents are different products) • Correct product but wrong strength

Term	Definition
	• Product contamination • Product mix ("rogues" within a pack) • Counterfeit or deliberately tampered-with product within the distribution chain • Label or leaflet missing information, or providing misleading information • Missing label on primary packaging • Inadequate/faulty closure • Empty capsule • Overfilled capsule • Bottle fill shortage or overage • Vial fill shortage or overage • Broken/chipped tablets • Broken/damaged capsules • Broken/cracked vial
Screen Failure	A subject who has given informed consent and failed to meet the inclusion and/or meet at least 1 of the exclusion criteria and/or has not been randomized or administered investigational product(s) as defined by the protocol.
Serious Adverse Event	Any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose: • Results in death • Is life-threatening • Requires inpatient hospitalization or prolongation of existing hospitalization • Results in persistent or significant disability/incapacity • Is a congenital abnormality/birth defect • Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event (SAE) when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic

Term	Definition
	bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalisation; or the development of drug dependency or drug abuse.
Study Completion Date	Last Subject Last Visit (or last dose) including the follow-up period as defined in the protocol for the LAST site OR in other words, the latest site completion date for the protocol. This date determines the timing for the Clinical Study Report and notification timelines for competent authorities (as required).

STUDY SYNOPSIS

Protocol number: SPD405-207	**Drug:** Lanthanum carbonate	
Title of the study: A 3-part Open-label Study to Assess the Pharmacokinetics of Lanthanum Carbonate, Compare the Efficacy, Safety, and Tolerability of 8 Weeks of Treatment with Lanthanum Carbonate and Calcium Carbonate using a Crossover Design, and Investigate the Efficacy and Safety of 8 Months of Treatment with Lanthanum Carbonate in Hyperphosphataemic Children and Adolescents Aged 10 years to <18 Years With Chronic Kidney Disease on Dialysis		
Number of subjects (total and for each treatment arm): At least 8 evaluable subjects in Part 1 (single-dose pharmacokinetic assessment). After completion of Part 1, subjects will enter Part 2 (short-term efficacy and safety assessments). The study is planned to enroll at least 35 subjects who complete 8 weeks of treatment with lanthanum carbonate and are assessable for the primary endpoint. Approximately 65 subjects may be enrolled to achieve this target.		
Investigator(s): Multi-site study in the European Union, Russian Federation, and Republic of Turkey		
Site(s): Up to 36 sites are planned **Coordinating Principal Investigator:** PPD, MD, PhD, Medical University of Bialystok, Poland, University Children's Clinical Hospital of Bialystok, Ul. Waszyngtona 17, 15-274 Bialystok, Poland		
Study period (planned): Apr 2012 to Jul 2018	**Clinical phase:**	2

Objectives:

Primary:

To summarize the percentage of subjects achieving age-specific Kidney Disease Outcomes Quality Initiative (KDOQI) targets for serum phosphorus in hyperphosphatemic children and adolescents with chronic kidney disease (CKD) who are on dialysis, following 8 weeks of treatment with lanthanum carbonate.

Secondary:

1. To investigate the safety profile in hyperphosphatemic children and adolescents with CKD on dialysis treated with calcium carbonate and/or lanthanum carbonate.
2. To summarize the percentage of subjects achieving KDOQI targets for serum phosphorus in hyperphosphatemic children and adolescents with CKD who are on dialysis following treatment with calcium carbonate for 8 weeks and lanthanum carbonate for 8 weeks.
3. To assess mean changes from baseline in serum phosphorus, calcium and calcium-phosphorus product in hyperphosphatemic children and adolescents with CKD who are on dialysis, following treatment with lanthanum carbonate for 8 weeks.
4. To summarize mean changes from baseline in serum phosphorus, calcium and calcium-phosphorus product in hyperphosphatemic children and adolescents with CKD who are on dialysis, following treatment with calcium carbonate for 8 weeks and lanthanum carbonate for 8 weeks.
5. To describe the pharmacokinetics (maximum plasma concentration [C_{max}] and area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration [AUC_{0-t}]; body-weight-normalized) of lanthanum carbonate in hyperphosphatemic children and adolescents aged 10 years to <18 years with CKD who are on dialysis, after a single dose of lanthanum carbonate oral powder formulation is administered (Part 1 of the study).
6. To investigate the efficacy (serum phosphorus, calcium, and calcium-phosphorus product) and safety of up to 8

months of treatment with lanthanum carbonate in children and adolescents aged 10 years to <18 years (Parts 2 and 3 of the study combined).

7. To investigate biochemical markers of bone metabolism including bone alkaline phosphatase (ALP), tartrate-resistant acid phosphatase (TRAP), osteocalcin, fibroblast growth factor 23 (FGF-23), parathyroid hormone (PTH), sclerostin and fetuin-A in children and adolescents aged 10 years to <18 years with CKD who are on dialysis.
8. To investigate growth in children and adolescents aged 10 years to <18 years with CKD who are on dialysis.

Rationale:

Lanthanum carbonate is a phosphate binding medication indicated for the control of hyperphosphatemia in adult patients with end-stage renal disease receiving dialysis, as well as adult CKD patients not on dialysis with serum phosphorus ≥5.5mg/dL (1.78mmol/L). Currently, there are no data on lanthanum carbonate in pediatric patients. The data from this study will provide pharmacokinetic, safety and efficacy information in this population compared to a standard calcium-based phosphate binder.

Investigational products, dose, and mode of administration:

Lanthanum carbonate oral powder packaged in 250mg sachets and calcium carbonate as 500mg tables.

Part 1: An age-appropriate single dose of lanthanum carbonate oral powder will be given following breakfast.

Part 2a, Treatment Period 1: Calcium carbonate will be orally administered either alone or mixed with food, the total daily dose will be based on standard clinical practice in order to achieve or maintain serum phosphorus levels in accordance with KDOQI age guidelines.

Part 2a, Treatment Period 2: Lanthanum carbonate oral powder will be administered mixed with food; the total daily dose will be divided between meals, and will be titrated, as appropriate to achieve or maintain serum phosphorus levels in accordance with KDOQI age guidelines or until a maximum daily dose of 3000mg is reached.

Part 2b: Lanthanum carbonate oral powder will be administered mixed with food; the total daily dose will be divided between meals, and will be titrated, as appropriate to achieve or maintain serum phosphorus levels in accordance with KDOQI age guidelines or until a maximum daily dose of 3000mg is reached.

Part 3: Lanthanum carbonate oral powder will be administered mixed with food. The dosage of lanthanum carbonate will be determined by the Investigator based on serum phosphorus levels taken at each study visit up to a maximum dose of 3000mg/day.

Methodology:

This is a 3-part study:

- Part 1: Single-dose pharmacokinetic assessments of lanthanum carbonate in at least 8 subjects. Part 1 is complete and an interim clinical study report interpreting and summarizing the data is available.
- Part 2a: Open-label, active comparator crossover period. Subjects participating in Part 1 will begin Part 2 immediately following the completion of the pharmacokinetic assessments. Subjects not participating in Part 1 will enter Part 2a. During Part 2a, all subjects will receive calcium carbonate for the first 8 weeks (Treatment Period 1), followed by treatment with lanthanum carbonate for 8 weeks (Treatment Period 2). If needed, there will be a washout period up to 3 weeks between treatment with calcium carbonate (Treatment Period 1) and lanthanum carbonate (Treatment Period 2). No new subjects will be enrolled in Part 2a under Version 6.0 of the protocol.
- Part 2b: Open-label treatment period. Part 2b is modified Part 2a, where subjects will receive treatment with lanthanum carbonate only for 8 weeks. All new subjects will be enrolled in Part 2b only under Version 6.0 of the protocol.
- Part 3: Subjects in Part 2a (including subjects in Treatment Period 1/calcium carbonate treatment arm who discontinued due to hypercalcemia; refer to Section 6.2.1, Dosing, Hypercalcemia) and Part 2b may continue to receive open-label lanthanum carbonate for up to 6 additional months of therapy.

Screening:

There will be a 2-week screening period during which eligibility will be determined. Subjects who are eligible to participate will enter a washout period of up to 3 weeks if the phosphorus level is not above KDOQI required levels. During the washout period the existing phosphate binder treatment will be discontinued until phosphate levels have risen above 6.0mg/dL (1.94mmol/L) in subjects aged under 12 years or >5.5mg/dL (1.78mmol/L) in subjects aged over 12 years. At the end of the washout period, subjects will be assessed for inclusion in the study based on their serum phosphorus levels.

Treatment Period:

Part 1. At least 8 subjects will undergo pharmacokinetic sampling following a single dose of lanthanum carbonate in order to assess the plasma concentration-time relationship of lanthanum carbonate. At the completion of the pharmacokinetic assessment period, these subjects will enter Part 2 of the study.

Part 2a. Subjects who meet eligibility criteria and who are not participating in Part 1 will be enrolled into Part 2a (Treatment Period 1) and will receive calcium carbonate for the first 8 weeks. At the completion of the first 8 weeks of Part 2a, if required subjects will enter a washout period of up to 3 weeks duration and will then cross over to Part 2a to receive lanthanum carbonate treatment for 8 weeks (Treatment Period 2). No new subjects will be enrolled in Part 2a under Version 6.0 of the protocol.

Part 2b. Subjects who meet eligibility will be enrolled into Part 2b and will receive lanthanum carbonate treatment for 8 weeks. All new subjects will be enrolled in Part 2b only under Version 6.0 of the protocol.

Part 3. At the conclusion of Part 2 (2a and 2b), subjects may continue to receive open-label lanthanum carbonate for up to 6 additional months of therapy (including subjects who participated in Part 2a, Treatment Period 1/calcium carbonate treatment arm, but who discontinued due to hypercalcemia; refer to Section 6.2.1, Dosing, Hypercalcemia).

Dosing information:

Part 1: Lanthanum carbonate oral powder will be administered in the morning following breakfast on the day after receiving dialysis treatment.

Subjects aged between 10 and 12 years will receive a dose of 500mg lanthanum (as lanthanum carbonate hydrate; SPD405) and subjects aged 12 years and over will receive 1000mg lanthanum (as lanthanum carbonate hydrate; SPD405).

Part 2a, Treatment Period 1: Calcium carbonate may be started at the dose taken by the subject prior to starting the study or equivalent. For new subjects dosing will be based on standard clinical practice and the dose will be titrated 2-weekly as appropriate, until the target serum phosphorus level is achieved, or until a maximum daily dose of 6500mg is reached. Once serum phosphorus control is achieved, the dose of calcium carbonate will be maintained until the end of the 8-week calcium carbonate treatment period.

Part 2a, Treatment Period 2: At the end of the first 8-week treatment period of Part 2a (ie, Treatment Period 1), all subjects will begin 8 weeks of treatment with lanthanum carbonate following a washout period of 3 weeks, or until phosphorus level is above KDOQI required levels, whichever is sooner. Lanthanum carbonate will be mixed with food and given 3 times a day. If the subject has only 2 meals a day the lanthanum carbonate dose will split equally across the 2 meals with a single dose not exceeding 1000mg. The starting total daily dose of lanthanum carbonate is 1500mg for all subjects. The total daily dose will be titrated 2-weekly, as appropriate, until the target serum phosphorus level is achieved, or until a maximum daily dose of 3000mg is reached. Once serum phosphorus control is achieved or the maximum dose is reached, the dose of lanthanum carbonate will be maintained until the end of the 8-week treatment period. No new subjects will be enrolled in Part 2a under Version 6.0 of the protocol.

Part 2b: Subjects will begin 8 weeks of treatment with lanthanum carbonate. Lanthanum carbonate will be mixed with food and given 3 times a day. If the subject has only 2 meals a day the lanthanum carbonate dose will split equally across the 2 meals with a single dose not exceeding 1000mg. The starting total daily dose of lanthanum carbonate is 1500mg for all subjects. The total daily dose will be titrated 2-weekly, as appropriate, until the target serum phosphorus level is achieved, or until a maximum daily dose of 3000mg is reached. Once serum phosphorus control is achieved or the maximum dose is reached, the dose of lanthanum carbonate will be maintained until the end of the 8-week treatment period. All new subjects will be enrolled in Part 2b only under Version 6.0 of the protocol.

Part 3: Subjects who complete participation in Part 2 (2a or 2b) may continue to receive lanthanum carbonate for an additional 6 months (including subjects who participated in Part 2a, Treatment Period 1/calcium carbonate treatment arm, but who discontinued due to hypercalcemia). The dosage of lanthanum carbonate will be determined by the Investigator based on serum phosphate levels taken at each study visit up to a maximum dose of 3000mg/day.

Safety Follow-up: A safety follow-up telephone call will be made to all subjects or their parent/legally authorized representative (LAR) 7-14 days following the last dose. In the event of early discontinuation due to kidney transplantation, the safety follow-up call will be 30±7 days from the last dose.

Inclusion and exclusion criteria:

Inclusion Criteria:

1. Aged 10 years to <18 years of age at the time of consent.
2. Subject or parent/LAR understand and are able, willing, and likely to fully comply with the study procedures and restrictions defined in this protocol.
3. Male, or non-pregnant, non-lactating female who agrees to comply with any applicable contraceptive requirements of the protocol.
4. Established CKD, on dialysis, and requires treatment for hyperphosphatemia with a phosphate binder.
5. Serum phosphorus levels after a washout period of up to 3 weeks as follows:
   - Age <12 years: Serum phosphorus >6.0mg/dL (1.94mmol/L)
   - Age 12 years and older: Serum phosphorus >5.5mg/dL (1.78mmol/L)
6. Ability to provide written, signed, and dated (personally or via an LAR) informed consent/and assent, as applicable, to participate in the study.

Exclusion Criteria:

Subjects are excluded from the study if any of the following criteria are met.

1. Current or recurrent disease (eg, cardiovascular, liver, unstable and uncontrolled gastrointestinal, malignancy, or other conditions) other than CKD or end-stage renal disease that could affect the action, absorption or disposition of the investigational product, or clinical or laboratory assessments.
2. Current or relevant history of physical or psychiatric illness, any medical disorder (except for CKD or end-stage renal disease and related co-morbidities) that may require treatment or make the subject unlikely to fully complete the study, or any condition that presents undue risk from the investigational product or procedures.
3. Unable to eat semi-solid foods or on Total Enteral Alimentation.
4. Known or suspected intolerance or hypersensitivity to the investigational product(s), closely related compounds, or any of the stated ingredients.
5. History of alcohol or other substance abuse within the last year.
6. Current use of any medication (including over-the-counter, herbal, or homeopathic preparations) that could affect (improve or worsen) the condition being studied, or could affect the action, absorption, or disposition of the investigational product(s), or clinical or laboratory assessment.
7. Weight and age of subject are outside of local applicable criteria for blood sample volume limits.
8. Use of another investigational product within 30 days prior to receiving the first dose of investigational product.

Maximum duration of subject involvement in the study:

- Planned duration of screening period: Up to 2 weeks if washout not required, otherwise up to 5 weeks
- Planned duration of enrollment period: 64 months
- Planned duration of treatment period: Part 1 - 48 hours, Part 2a - 16 weeks (+ up to 3 weeks for washout between treatments) or Part 2b - 8 weeks, Part 3 - up to 6 months
- Planned duration of follow-up: 7-14 days or 30 ± 7 days in case of kidney transplantation

Endpoints and statistical analysis:

Primary Efficacy Measure:

- The percentage of subjects achieving age-specific KDOQI targets for serum phosphate level following 8-weeks of treatment with lanthanum carbonate will be descriptively summarized. The KDOQI serum phosphorus targets are defined as:
  - Adolescents aged ≥12-<18 years: ≤5.5mg/dL (1.78mmol/L)
  - Children aged 10 years -<12 years: ≤6.0mg/dL (1.94mmol/L)

Secondary Measures:

- The percentage of subjects with serum phosphorus levels below the age-specific KDOQI targets following 8 weeks of treatment with calcium carbonate followed by 8 weeks of treatment with lanthanum carbonate, will be descriptively summarized. The KDOQI serum phosphorus targets are defined as:
  - Adolescents aged ≥12-<18 years: ≤5.5mg/dL (1.78mmol/L)
  - Children aged 10 years -<12 years: ≤6.0mg/dL (1.94mmol/L)
- Changes from baseline in serum phosphorus, calcium and calcium-phosphorus product in hyperphosphatemic children and adolescents with CKD who are on dialysis, following treatment with

lanthanum carbonate for 8 weeks.

- Changes from baseline in serum phosphorus, calcium and calcium-phosphorus product in hyperphosphatemic children and adolescents with CKD who are on dialysis, following treatment with calcium carbonate for 8 weeks and lanthanum carbonate for 8 weeks.
- Change from baseline in serum phosphorus, calcium and calcium-phosphorus product levels at the last visit of each 8-week treatment period during Part 2 and monthly during the 6-month extension phase (Part 3).
- Biochemical bone markers: bone ALP, osteocalcin, TRAP, FGF-23, PTH, sclerostin and fetuin-A before and after each treatment period in Part 2, and at the end of Part 3.
- Height and weight at:
    - Visits 2.0, 2.4, 2.8, and 3.5 (Parts 2a and 3)
    - Visits 1.0, 2.4, and 3.5 (Parts 2b and 3).

Safety Assessments:

Safety will be assessed by the collection of adverse events (AEs), vital signs, physical examinations, and clinical laboratory tests (chemistry and hematology).

Pharmacokinetics:

Blood samples for pharmacokinetic evaluation will be collected during all 3 study periods (Parts 1, 2, and 3). Plasma lanthanum concentrations will be determined by a previously validated method utilizing inductively coupled plasma mass spectrometry.

Part 1. Blood samples for determination of single-dose lanthanum pharmacokinetics will be collected pre-dose and at 3, 5, 6, 8, 12, 24, and 48 hours after dosing. Plasma lanthanum concentrations will be analyzed by non-compartmental methods to determine pharmacokinetic parameters including, but not limited to, $AUC_{0-t,}$ area under the plasma concentration-time curve from time zero to 48 hours (AUC_{0-48}), C_{max}, time to C_{max}, and, if appropriate, apparent terminal half-life ($t_{1/2}$) and apparent terminal-phase disposition rate constant (λ_z) and area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$).

Summary statistics (number of observations, mean, standard deviation, coefficient of variation, median, maximum, minimum, and geometric mean) will be determined for all pharmacokinetic parameters.

Part 2 (Part 2a (Treatment Period 2) and Part 2b) and Part 3. Pharmacokinetics will be evaluated during lanthanum carbonate dosing using a sparse sampling approach. Blood samples (at least 2 per subject) for pharmacokinetic assessments will be collected during Parts 2a (Treatment Period 2), 2b and 3 from defined time-windows (to be selected from: 0-2 hours, 2-4 hours and 4-6 hours, after the first dose/meal of the day, so as to cover the full dosing interval). Plasma concentration-time data for Parts 2a (Treatment Period 2), 2b and 3 will be combined with those from Part 1 and subjected to population pharmacokinetic analysis using NONMEM software to determine estimates of steady-state systemic exposure ($C_{max,}$ C_{min} [minimum plasma concentration], and area under the plasma concentration-time curve at steady-state) and relationships of systemic exposure to dose and to safety findings explored if appropriate.

STATISTICAL METHODS

Analysis Populations

Screened Set – The set of subjects who have signed informed consent.

Enrolled Set – Subjects who have signed informed consent and have begun some study procedures (eg, dispensed investigational product, current drug has been withdrawn).

Safety Analysis Set 1 – Enrolled subjects who have taken 1 dose of investigational product in Part 1 and who have completed at least 1 follow-up safety assessment.

Safety Analysis Set 2 – Enrolled subjects who have taken 1 dose of investigational product in Part 2 or Part 3 and who have completed at least 1 follow-up safety assessment.

It is noted that safety assessments from the period when a subject is exposed to calcium carbonate will be summarized for calcium carbonate treatment. Safety assessments from the period when a subject is exposed to lanthanum carbonate will be summarized for lanthanum carbonate treatment.

Safety Completer Set (SCS) – Subjects who receive at least 8 weeks of lanthanum carbonate treatment from either Part 2 or Part 3 of the study.

Full Analysis Set (**FAS**) – Subjects who have taken at least 1 dose of investigational product and who have at least 1 phosphate assessment during Part 2 or Part 3.

Per-protocol Set 1 (PP1) – Subjects in the Full Analysis Set who complete 8 weeks of calcium carbonate treatment followed by 8 weeks of lanthanum carbonate treatment and who have serum phosphate assessment data available to allow summarizing the percentage of subjects achieving age-specific KDOQI target. Only subjects who have serum phosphate levels equal to or above the age-specific KDOQI targets at study entry and between the calcium carbonate treatment and lanthanum carbonate treatment at Visit 2.4 will be included in this set.

Per-protocol Set 2 (PP2) – Subjects in the Full Analysis Set who complete 8 weeks of treatment with lanthanum carbonate and who have serum phosphate assessment data available to allow summarizing the percentage of subjects achieving age-specific KDOQI target. Subjects who have serum phosphate levels equal to or above the age-specific KDOQI targets prior to the start of lanthanum carbonate treatment will be included in this set.

Pharmacokinetic Set 1 - Subjects in the Safety Analysis Set 1 for whom the primary pharmacokinetic data are considered sufficient and interpretable. Subjects in Part 1 who vomited may be excluded from Pharmacokinetic Set 1.

Pharmacokinetic Set 2 - Subjects in Safety Analysis Sets 1 or 2 for whom the primary pharmacokinetic data are considered sufficient and interpretable will be included in Pharmacokinetic Set 2.

Efficacy Analyses

The FAS and PP2 Sets will be used for the primary endpoint analyses.

For the primary endpoint, the percentage of subjects achieving age-specific KDOQI targets for serum phosphate level after 8 weeks of lanthanum carbonate treatment will be calculated along with a 95% confidence interval. The FAS and PP2 Sets will be used for this summarization.

The FAS, PP1, and PP2 Sets will be used for the secondary efficacy endpoint analyses.

For the secondary endpoint, the percentage of subjects achieving age-specific KDOQI targets after 8 weeks of calcium carbonate treatment followed by 8 weeks of lanthanum carbonate will be calculated along with a 95% confidence interval, separately, for each treatment arm.

For the long-term assessment, efficacy and safety variables will be summarized using the FAS and Safety Analysis Set 2 respectively, for each visit using descriptive statistics as follows:

- For continuous data: number of observations, mean, standard deviation, standard error, minimum, maximum, median, and 95% confidence interval
- For categorical data: number of observations and percentages.

Safety Analyses

All safety variables will be summarized using the defined Safety Analysis Sets. Summaries will be presented by treatment group and overall.

The number of events, incidence, and percentage of treatment emergent AEs (TEAEs) will be calculated overall, by system organ class, and by preferred term. Treatment-emergent AEs will be further summarized by age group, severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be summarized/listed. Clinical laboratory tests, vital signs, and ECG findings

will be summarized. Potentially clinically important findings will also be summarized or listed.

Expected Number of Subjects:

Pharmacokinetic Assessment

From Study LAM-IV-111, the mean±standard deviation AUC_{0-t} was 3.099±2.888ng hr/mL and C_{max} was 0.296±0.177ng hr/mL for a 1000mg single dose of lanthanum carbonate. Assuming the standard deviations from Study LAM-IV-111, a sample size of 8 subjects will have 80% assurance that the 2-sided 95% confidence interval for the AUC_{0-t} will be no wider than ±2.86ng.hr/mL and 80% assurance that 2-sided 95% confidence interval for C_{max} is no wider than ±0.18ng /mL.

Efficacy – Percentage of Subjects Achieving KDOQI Target for Serum Phosphorus

Originally, the sample size of at least 50 subjects for the PP set had been chosen based on practical considerations and on agreement with the Paediatric Committee of the European Medicines Agency. In order to obtain a PP Set of 50 subjects, a sample size of approximately 72 subjects were to be enrolled in Part 2. This assumed 70% of the subjects are eligible for the PP Set. This sample size has 81% power to show that the lower limit of the 95% confidence interval for the difference (LC – CC) in the percentage of subjects achieving serum phosphorus target is above the non-inferiority margin of -18%.

However, given the extreme difficulty in recruiting enough subjects to obtain at least 50 subjects for the PP set for the assessment of non-inferiority, serious consideration had to be given to adjust the sample size and focus of the study to safety, in order to complete it. The sample size has been adjusted to include at least 35 subjects, who complete 8 weeks of treatment with lanthanum carbonate and are assessable for the primary endpoint. This study is still useful in collecting information, where there is a void, regarding the use of lanthanum carbonate in the pediatric population.

Safety – Investigation of the Safety profile in hyperphosphatemic children and adolescents with CKD on dialysis treated with lanthanum carbonate.

A sample size of 35 subjects is necessary in order to observe at least one event with a true event rate of 5% at a probability of 83.4%.

STUDY SCHEDULE(S)

Table 1: Schedule of Assessments for Part 1, Part 2a (Treatment Periods 1 and 2), and Part 3

	Part 1 Subjects who enrol into Part 1 will omit the first washout in Part 2 (Visit window ±3 days)			Part 2a (Visit window ±3 days)								Part 3 (Visit window ±1 week)		
Visit	**1.0**	**Washout W1[j]**	**1.1[a]**	**2.0[b]**	**Washout W1[j]**	**2.1**	**2.2-2.3**	**2.4**	**Washout W2[j]**	**2.5-2.7**	**2.8**	**3.0-3.4**	**3.5/End of Study[c]**	**Safety Follow-up call[k]**
Week	**–5**	**-4 to -1**	**-4 to -1**	**0**	**0-3 weeks duration**	**2[d]**	**4, 6[d]**	**8[d]**	**0-3 week duration**	**10, 12, 14[d]**	**16[d]**	**20, 24, 28, 32, 36**	**40[d]**	**41-42[d]**
Informed consent	✔			✔										
In/exclusion criteria	✔			✔	✔[j]									
Medical and renal history	✔			✔										
Demographics	✔			✔										
12-lead ECG	✔			✔							✔		✔	
Physical examination	✔		✔	✔									✔	
Vital signs, height and weight	✔		✔	✔				✔			✔		✔	

Table 1: Schedule of Assessments for Part 1, Part 2a (Treatment Periods 1 and 2), and Part 3

	Part 1 Subjects who enrol into Part 1 will omit the first washout in Part 2 (Visit window ±3 days)			Part 2a (Visit window ±3 days)								Part 3 (Visit window ±1 week)		
Visit	**1.0**	**Washout W1[j]**	**1.1[a]**	**2.0[b]**	**Washout W1[j]**	**2.1**	**2.2-2.3**	**2.4**	**Washout W2[j]**	**2.5-2.7**	**2.8**	**3.0-3.4**	**3.5/End of Study[c]**	**Safety Follow-up call[k]**
Week	**–5**	**-4 to -1**	**-4 to -1**	**0**	**0-3 weeks duration**	**2[d]**	**4, 6[d]**	**8[d]**	**0-3 week duration**	**10, 12, 14[d]**	**16[d]**	**20, 24, 28, 32, 36**	**40[d]**	**41-42[d]**
Local laboratory tests[f]		✔		✔	✔	✔	✔		✔	✔		✔		
Central laboratory phosphate confirmation		✔			✔				✔					
Biochemistry	✔			✔				✔			✔		✔	
Hematology	✔			✔									✔	
Biochemical bone markers	✔			✔				✔			✔		✔	
Pregnancy test (where applicable)	✔			✔									✔	
Lanthanum pharmacokinetics			✔							✔ [g]		✔ [h]		

Table 1: Schedule of Assessments for Part 1, Part 2a (Treatment Periods 1 and 2), and Part 3

	Part 1 Subjects who enrol into Part 1 will omit the first washout in Part 2 (Visit window ±3 days)			Part 2a (Visit window ±3 days)								Part 3 (Visit window ±1 week)		
Visit	**1.0**	**Washout W1[j]**	**1.1[a]**	**2.0[b]**	**Washout W1[j]**	**2.1**	**2.2-2.3**	**2.4**	**Washout W2[j]**	**2.5-2.7**	**2.8**	**3.0-3.4**	**3.5/End of Study[c]**	**Safety Follow-up call[k]**
Week	**–5**	**-4 to -1**	**-4 to -1**	**0**	**0-3 weeks duration**	**2[d]**	**4, 6[d]**	**8[d]**	**0-3 week duration**	**10, 12, 14[d]**	**16[d]**	**20, 24, 28, 32, 36**	**40[d]**	**41-42[d]**
Investigational product dispensed			✔	✔[e]	✔[e]	✔	✔	✔	✔	✔	✔[i]	✔		
Investigational product collected						✔	✔	✔		✔	✔	✔	✔	
Dose adjustment (as needed) and compliance						✔	✔	✔		✔	✔	✔	✔	
Record adverse events	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Record concomitant medication	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Dialysis adequacy	✔			✔		✔	✔	✔		✔	✔	✔	✔	
Confirmation of dietary advice	✔			✔		✔	✔	✔		✔	✔	✔	✔	

[a] Visit 1.1 should be scheduled for the day after dialysis. See Table 2 for a detailed schedule of assessments.

Table 1: Schedule of Assessments for Part 1, Part 2a (Treatment Periods 1 and 2), and Part 3

	Part 1 Subjects who enrol into Part 1 will omit the first washout in Part 2 (Visit window ±3 days)			Part 2a (Visit window ±3 days)								Part 3 (Visit window ±1 week)		
Visit	**1.0**	**Washout W1[j]**	**1.1[a]**	**2.0[b]**	**Washout W1[j]**	**2.1**	**2.2-2.3**	**2.4**	**Washout W2[j]**	**2.5-2.7**	**2.8**	**3.0-3.4**	**3.5/End of Study[c]**	**Safety Follow-up call[k]**
Week	**–5**	**-4 to -1**	**-4 to -1**	**0**	**0-3 weeks duration**	**2[d]**	**4, 6[d]**	**8[d]**	**0-3 week duration**	**10, 12, 14[d]**	**16[d]**	**20, 24, 28, 32, 36**	**40[d]**	**41-42[d]**

[b] For subjects who have completed Part 1, laboratory and other assessments can be completed from Visit 1.0, no further blood samples are required. A consent form to participate in Part 2a must be signed.

[c] Assessments scheduled for Visit 3.5 should also be carried out at the time of discontinuation for all subjects who withdraw from the study early or as close as possible to the time of discontinuation. These assessments are not required for subjects post-transplantation, however a safety follow-up call is required.

[d] Visit weeks may be variable depending on duration of washout (+3 weeks).

[e] Investigational product will be dispensed at Visit 2.0 if eligible, however if a washout is required then investigational product will be dispensed at visit W1.

[f] Local laboratory assessments for phosphorus, serum calcium, and calcium phosphorus product in Parts 1 and 2 are for titration purposes, as required, and will not be analyzed; data from Visits 3.0-3.4 will be collected and assessed.

[g] Visit 2.6 only; Each subject will have at least 2 samples taken for pharmacokinetic assessment. These should be taken during defined time windows (to be selected from: 0-2 hours, 2-4 hours and 4-6 hours, after the first dose/meal of the day). Note: If the sampling is not done at Visit 2.6, blood sampling for pharmacokinetics must be taken at an alternative visit during Part 2.

[h] Visit 3.3 only; Each subject will have at least 2 samples taken for pharmacokinetic assessment. These should be taken during defined time windows (to be selected from: 0-2 hours, 2-4 hours and 4-6 hours, after the first dose/meal of the day). Note: If the sampling is not done at Visit 3.3, blood sampling for pharmacokinetics must be taken at an alternative visit during Part 3.

[i] For subjects entering Part 3 only.

[j] Only for subjects completing the washout.

Table 1: Schedule of Assessments for Part 1, Part 2a (Treatment Periods 1 and 2), and Part 3

	Part 1 Subjects who enrol into Part 1 will omit the first washout in Part 2 (Visit window ±3 days)			Part 2a (Visit window ±3 days)								Part 3 (Visit window ±1 week)		
Visit	**1.0**	**Washout W1[j]**	**1.1[a]**	**2.0[b]**	**Washout W1[j]**	**2.1**	**2.2-2.3**	**2.4**	**Washout W2[j]**	**2.5-2.7**	**2.8**	**3.0-3.4**	**3.5/End of Study[c]**	**Safety Follow-up call[k]**
Week	**–5**	**-4 to -1**	**-4 to -1**	**0**	**0-3 weeks duration**	**2[d]**	**4, 6[d]**	**8[d]**	**0-3 week duration**	**10, 12, 14[d]**	**16[d]**	**20, 24, 28, 32, 36**	**40[d]**	**41-42[d]**

[k] Safety follow-up call to be made 7-14 days following last dose of investigational product. For subjects discontinued due to kidney transplantation, the safety follow up call to be made 30 ± 7 days from the last dose.

Table 2: Detailed Schedule of Assessments for Visit 1.1 in Part 1

Hour (in relation to dosing time)	**Pre-dose**	**0**	**3**	**5**	**6**	**8**	**12**	**24**	**48**
Physical examination									✔ [a]
Vital signs (blood pressure and pulse)[b]	✔							✔	✔ [a]
Lanthanum carbonate single dose		✔							
Pharmacokinetic blood sampling[c]	✔		✔	✔	✔	✔	✔	✔	✔
Record adverse events	✔	✔	✔	✔	✔	✔	✔	✔	✔
Record concomitant medications	✔	✔	✔	✔	✔	✔	✔	✔	✔

[a] An attempt to perform these assessments and procedures should be made for any subject who withdraws or is removed early from the study, as well as those subjects completing the 48 hour period.

[b] Vital signs will be taken within 15 minutes of nominal dosing time.

[c] The samples should be drawn within ±5 minutes of the nominal in the first 4 hours after taking the investigational product, ±15 minutes up to 24 hours after taking the investigational product and within ±60 minutes thereafter.

Table 3: Schedule of Assessments for Part 2b and Part 3

	Part 2b (Visit window ±3 days)				Part 3 (Visit window ±1 week)		
Visit	**1.0[a]**	**Washout W1[b]**	**2.1-2.3**	**2.4**	**3.0-3.4**	**3.5/End of Study[c]**	**Safety Follow-up call[j]**
Week	**0**	**0-3 weeks duration**	**2, 4, 6[d]**	**8[d]**	**12, 16, 20, 24, 28**	**32[d]**	**33-34[d]**
Informed consent	✔						
In/exclusion criteria	✔	✔[b]					
Medical and renal history	✔						
Demographics	✔						
12-lead ECG	✔			✔		✔	
Physical examination	✔					✔	
Vital signs, height and weight	✔			✔		✔	
Local laboratory tests[e]	✔	✔	✔		✔		
Central laboratory phosphate confirmation		✔					
Biochemistry	✔			✔		✔	
Hematology	✔					✔	
Biochemical bone markers	✔			✔		✔	

Table 3: Schedule of Assessments for Part 2b and Part 3

	Part 2b (Visit window ±3 days)				Part 3 (Visit window ±1 week)		
Visit	**1.0[a]**	**Washout W1[b]**	**2.1-2.3**	**2.4**	**3.0-3.4**	**3.5/End of Study[c]**	**Safety Follow-up call[j]**
Week	**0**	**0-3 weeks duration**	**2, 4, 6[d]**	**8[d]**	**12, 16, 20, 24, 28**	**32[d]**	**33-34[d]**
Pregnancy test (where applicable)	✔					✔	
Lanthanum pharmacokinetics			✔[f]		✔[g]		
Investigational product dispensed	✔[h]	✔[h]	✔	✔[i]	✔		
Investigational product collected			✔	✔	✔	✔	
Dose adjustment (as needed) and compliance			✔	✔	✔	✔	
Record adverse events	✔	✔	✔	✔	✔	✔	✔
Record concomitant medication	✔	✔	✔	✔	✔	✔	✔
Dialysis adequacy	✔		✔	✔	✔	✔	
Confirmation of dietary advice	✔		✔	✔	✔	✔	

[a] A consent form to participate in Part 2b must be signed.

[b] Only for subjects completing washout.

[c] Assessments scheduled for Visit 3.5 should also be carried out at the time of discontinuation for all subjects who withdraw from the study early or as close as possible to the time of discontinuation. These assessments are not required for subjects post-transplantation; however a safety follow-up call is required.

Table 3: Schedule of Assessments for Part 2b and Part 3

	Part 2b (Visit window ±3 days)				Part 3 (Visit window ±1 week)		
Visit	**1.0[a]**	**Washout W1[b]**	**2.1-2.3**	**2.4**	**3.0-3.4**	**3.5/End of Study[c]**	**Safety Follow-up call[j]**
Week	**0**	**0-3 weeks duration**	**2, 4, 6[d]**	**8[d]**	**12, 16, 20, 24, 28**	**32[d]**	**33-34[d]**

[d] Visit weeks may be variable depending on duration of washout (+3 weeks).

[e] Local laboratory assessments for phosphorus in Part 2b are for titration purposes, as required, and will not be analyzed; data from Visits 3.0-3.4 will be collected and assessed.

[f] Visit 2.2 only; Each subject will have at least 2 samples taken for pharmacokinetic assessment. These should be taken during defined time windows (to be selected from: 0-2 hours, 2-4 hours and 4-6 hours, after the first dose/meal of the day). Note: If the sampling is not done at Visit 2.2, blood sampling for pharmacokinetics must be taken at an alternative visit during Part 2b.

[g] Visit 3.3 only; Each subject will have at least 2 samples taken for pharmacokinetic assessment. These should be taken during defined time windows (to be selected from: 0-2 hours, 2-4 hours and 4-6 hours, after the first dose/meal of the day). Note: If the sampling is not done at Visit 3.3, blood sampling for pharmacokinetics must be taken at an alternative visit during Part 3.

[h] Investigational product will be dispensed at Visit 1.0 if eligible, however if a washout is required then investigational product will be dispensed at visit W1.

[i] For subjects entering Part 3 only.

[j] Safety follow-up call to be made 7-14 days following last dose of investigational product. For subjects discontinued due to kidney transplantation, the safety follow up call to be made 30 ± 7 days from the last dose.

1. BACKGROUND INFORMATION

1.1 Condition Background and Current Treatment

Chronic kidney disease

Lanthanum carbonate has been developed as a phosphate-binding agent for the treatment of hyperphosphatemia associated with chronic kidney disease (CKD). Control of serum phosphate levels is fundamental in the management of CKD, which leads to progressive decline in the kidney's ability to excrete phosphate, produce active vitamin D (calcitrol), and maintain calcium homeostasis.

CKD is associated with complex metabolic, bone and vasculature abnormalities that together encompass a syndrome defined in 2006 as CKD-mineral and bone disorder (Moe et al. 2006). Hyperphosphatemia and secondary hyperparathyroidism are implicated as central components in CKD- mineral and bone disorder.

The pathophysiological consequences of positive phosphate balance and hyperphosphatemia include hyperparathyroidism and the associated renal osteodystrophy. Hyperphosphatemia and hyperparathyroidism in CKD is a vicious cycle with serious consequences. The associated high turnover bone disease manifests with bone pain, bone fracture, bone deformity, osteopenia, myopathy, arthritis, resistance to erythropoietin due to marrow fibrosis, growth failure in children, and extraskeletal calcification.

Serum phosphorus levels vary depending on age (Kidney Disease Outcomes Quality Initiative [KDOQI] Guideline 4, 2005).

A limited number of clinical studies have been conducted in the pediatric population with phosphate binders (Pieper et al. 2006; Alon et al. 1986; Clark et al. 1989; Mahdavi et al. 2003; Salusky et al. 2005). Currently the only such products with an approved indication in children are calcium-based binders and aluminium hydroxide.

1.2 Product Background

Lanthanum carbonate contains lanthanum carbonate hydrate, an inorganic salt with the chemical formula $LA_2(CO_3)_3.4H_20$. Lanthanum carbonate is a phosphate binder.

Always refer to the latest version of the SPD405 Investigator's Brochure (IB) for the most accurate and current information regarding the efficacy and safety of SPD405.

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

The European guideline on prevention and treatment of renal osteodystrophy in children with chronic renal failure recommends calcium-based phosphate binders as first-line treatment for hyperphosphatemia and calcium-free binders in cases of hypercalcemia (Klaus et al. 2006). Aluminium and sevelamer are included in this latter category. Aluminium use is not

recommended because of known toxicities to bone and central nervous system and sevelamer is not licensed for use in children. Lanthanum carbonate is also a calcium-free binder but no clinical studies have been conducted in children.

This study is intended to provide pharmacokinetic, safety and efficacy data on lanthanum carbonate in pediatric patients as compared to a standard calcium-based phosphate binder.

2.2 Study Objectives

2.2.1 Primary Objective

To summarize the percentage of subjects achieving age-specific Kidney Disease Outcomes Quality Initiative (KDOQI) targets for serum phosphorus in hyperphosphatemic children and adolescents with chronic kidney disease (CKD) who are on dialysis, following 8 weeks of treatment with lanthanum carbonate.

2.2.2 Secondary Objectives

1. To investigate the safety profile in hyperphosphatemic children and adolescents with CKD on dialysis treated with calcium carbonate and/or lanthanum carbonate.
2. To summarize the percentage of subjects achieving KDOQI targets for serum phosphorus in hyperphosphatemic children and adolescents with CKD who are on dialysis following treatment with calcium carbonate for 8 weeks and lanthanum carbonate for 8 weeks.
3. To assess mean changes from baseline in serum phosphorus, calcium and calcium-phosphorus product in hyperphosphatemic children and adolescents with CKD who are on dialysis, following treatment with lanthanum carbonate for 8 weeks.
4. To summarize mean changes from baseline in serum phosphorus, calcium and calcium-phosphorus product in hyperphosphatemic children and adolescents with CKD who are on dialysis, following treatment with calcium carbonate for 8 weeks and lanthanum carbonate for 8 weeks.
5. To describe the pharmacokinetics (maximum plasma concentration [C_{max}] and area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration [AUC_{0-t}]; body-weight-normalized) of lanthanum carbonate in hyperphosphatemic children and adolescents aged 10 years to <18 years with CKD who are on dialysis, after a single dose of lanthanum carbonate oral powder formulation is administered (Part 1 of the study).
6. To investigate the efficacy (serum phosphorus, calcium, and calcium-phosphorus product) and safety of up to 8 months of treatment with lanthanum carbonate in children and adolescents aged 10 years to <18 years (Parts 2 and 3 of the study combined).
7. To investigate biochemical markers of bone metabolism including bone alkaline phosphatase (ALP), tartrate-resistant acid phosphatase (TRAP), osteocalcin, fibroblast growth factor 23 (FGF-23), parathyroid hormone (PTH), sclerostin and fetuin-A in children and adolescents aged 10 years to <18 years with CKD who are on dialysis.

8. To investigate growth in children and adolescents aged 10 years to <18 years with CKD who are on dialysis.

3. STUDY DESIGN

3.1 Study Design

This 3-part study has been approved by the Paediatric Committee of the European Medicines Agency as part of the Paediatric Investigational Plan for lanthanum carbonate. Pharmacokinetic data will be collected during the study as there are currently no data on lanthanum carbonate in pediatric patients under the age of 18 years. The data from this study will be evaluated against historical systemic exposure data in adults. The pharmacokinetic assessment is combined with the efficacy and safety sections to reduce the number of studies to be performed and to ease subject enrollment.

Part 1: Single-dose, pharmacokinetic assessment

This part of the study was a single-dose pharmacokinetic assessment of lanthanum carbonate in at least 8 subjects. There was a 2-week screening period during which eligibility was determined for Part 1. Subjects who were eligible to participate entered a washout period of up to 3 weeks if the phosphorus level was not above KDOQI required levels. During the washout period the existing phosphate binder treatment was discontinued until phosphate levels had risen above 6.0mg/dL (1.94mmol/L) in subjects aged under 12 years or >5.5mg/dL (1.78mmol/L) in subjects aged over 12 years. At the end of the washout period, subjects were assessed for inclusion in the study based on their serum phosphorus levels.

Subjects participating in Part 1 could begin Part 2a immediately following the completion of the pharmacokinetic assessments. Subjects not participating in Part 1 entered Part 2a after screening at Visit 2/Week 0 (see Table 1).

Part 1 is complete and an interim clinical study report interpreting and summarizing the data is available.

Part 2a: Open-label, active comparator crossover period

Originally, the design of Part 2 of Study SPD405-207 was a crossover non-inferiority one to allow a formal comparison of the efficacy of lanthanum carbonate with calcium carbonate. It was a single-sequence design (8 weeks of calcium carbonate followed by 8 weeks of lanthanum carbonate) to minimize disruption to the subjects. The comparator calcium carbonate was selected to meet the comparator criteria outlined by Pediatric Committee of the European Medicines Agency. Since the originally proposed study included only 1 sequence (calcium carbonate for the 1st treatment period and lanthanum carbonate for the 2nd treatment period) blinding was not applicable, thus the study was open-label. As shown in the study schematic in Figure 1, all subjects were to receive lanthanum carbonate in period 2 of the crossover and had the option to continue on to Part 3 of the study on the same treatment for up to 6 months. If needed, there was a washout period for up to 3 weeks between treatment with calcium carbonate (Treatment Period 1) and lanthanum carbonate (Treatment Period 2). Subjects who discontinued calcium carbonate treatment period/Treatment Period 1 due to hypercalcemia in Part 2 of the

originally proposed study could also continue to Part 3 to receive lanthanum carbonate treatment (see Section 4.4.1 and Section 6.2.1 [Dosing, Hypercalcemia]) for up to 6 additional months.

No new subject will be enrolled in Part 2a under Version 6.0 of the protocol.

Part 2b: 8-week lanthanum carbonate treatment

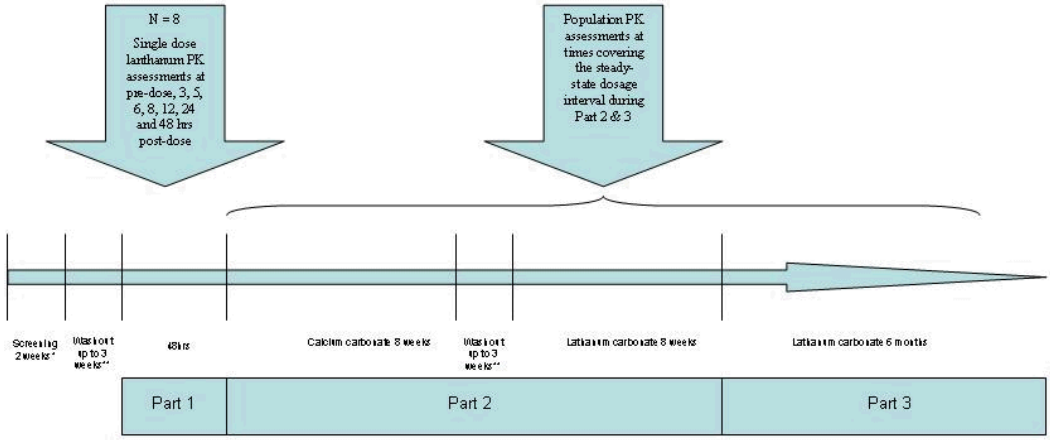
Given the extreme difficulty in recruiting enough subjects to obtain the originally proposed sample size of 50 subjects required for the Per-protocol Set for a cross-over non-inferiority study, the active comparator (calcium carbonate) treatment arm was removed (see Part 2a) in Part 2b; serious consideration had to be given to adjust the sample size and focus of the study to safety, in order to complete it. The sample size has been adjusted to include at least 35 subjects who will complete 8 weeks of treatment with lanthanum carbonate and will be assessable for the primary endpoint. As shown in the study schematic in Figure 2, eligible subjects will be enrolled in Part 2b after screening at Visit 1/Week 0 (see Table 3) to receive 8 weeks of lanthanum carbonate treatment only under Version 6.0 of the protocol. Subjects in Part 2b will have the option to continue on to Part 3 of the study on the same treatment for up to 6 additional months.

Part 3: 6-month lanthanum carbonate treatment

Subjects in Part 2a (including subjects in Treatment Period 1/calcium carbonate treatment arm who discontinued due to hypercalcemia; see Section 4.4.1 and Section 6.2.1 [Dosing, Hypercalcemia]) and Part 2b may continue to receive open-label lanthanum carbonate for up to 6 additional months of therapy.

The doses selected for Part 1 of the study were those that were suggested for use in children in clinical practice and those in Part 2 are based on known phosphate binder values for maintaining phosphate level balance.

Figure 1: Study Design Flow Chart- Part 1, Part 2a (Treatment Periods 1 and 2) and Part 3

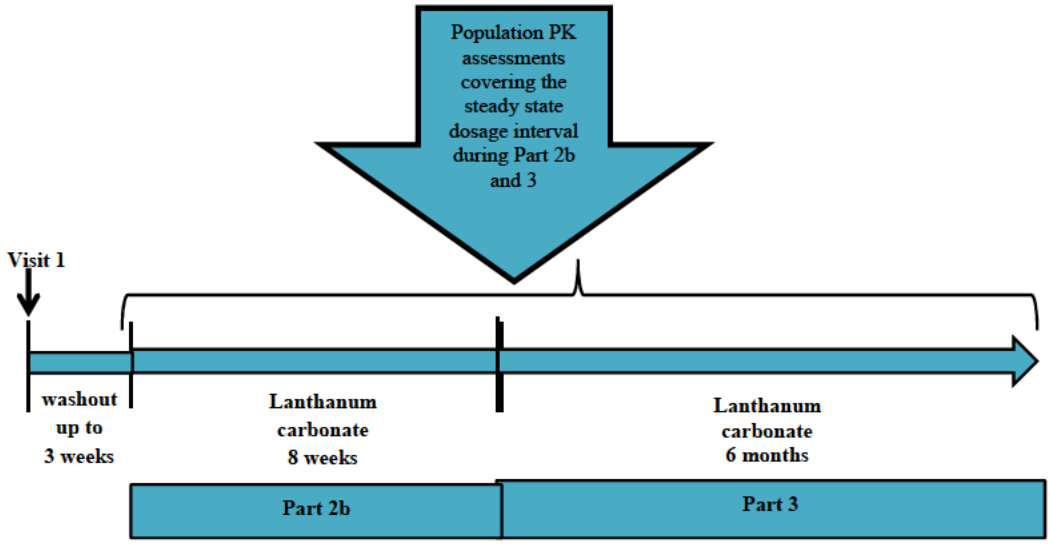


* Screening is only required once, either at Part 1 for subjects participating, otherwise at Part 2.

** The washout is only required if phosphorus is below KDOQI guidelines.

Note: The schematic in Figure 1 is applicable to the originally proposed open-label cross over study design.

Figure 2: Study Design Flow Chart- Part 2b and Part 3



***Eligible subjects will enter Part 2b to receive 8 weeks of lanthanum carbonate treatment only under Version 6.0 of the protocol. Screening will occur at Visit 1, Week 0. The washout (W1) is only required if phosphorus is below KDOQI guidelines.**

3.2 Number and Type of Subjects

Children and adolescents aged 10 years to <18 years with CKD who are on dialysis, will be eligible to participate, providing they are on solid food.

Subjects were recruited to provide at least 8 evaluable subjects in Part 1 (single-dose pharmacokinetic assessment). After completing participation in Part 1, subjects entered Part 2a (short-term efficacy and safety assessments). Part 1 of the study is complete. No new subject will enroll in Part 2a under Version 6.0 of the protocol.

The study is planned to enroll at least 35 subjects who complete 8 weeks of treatment with lanthanum carbonate and are assessable for the primary endpoint. Approximately 65 subjects may be enrolled to achieve this target. Under Version 6.0 of the protocol, all new subjects will be enrolled in Part 2b (modified Part 2a) and will be treated with lanthanum carbonate only (see Section 3.1).

3.3 Investigational Product

Lanthanum carbonate oral powder packaged in 250mg sachets will be administered following breakfast in Part 1. In Parts 2a, 2b, and 3, the lanthanum carbonate powder will be mixed with soft food, the total daily dose being divided between meals and titrated as appropriate to achieve or maintain serum phosphate levels in accordance with KDOQI age guidelines or until a maximum daily dose of 3000mg is reached.

Calcium carbonate (500mg tablets) was orally administered either alone or mixed with food, and dosing was based on standard clinical practice in order to achieve or maintain serum phosphorus levels in accordance with KDOQI age guidelines. Calcium carbonate was administered during

Part 2a only (see Table 1). Under Version 6.0 of the protocol, only lanthanum carbonate will be administered for 8 weeks of treatment in Part 2b (see Table 3).

3.4 Sites and Regions

Up to 36 sites are expected to participate in this study, from European Union, Russian Federation, and Republic of Turkey.

4. STUDY POPULATION

4.1 Inclusion Criteria

The subject cannot be enrolled in the study before all of the following inclusion criteria (including test results) are met.

1. Aged 10 years to <18 years of age at the time of consent.
2. Subject or parent/legally authorized representative (LAR) understand and are able, willing, and likely to fully comply with the study procedures and restrictions defined in this protocol.
3. Male, or non-pregnant, non-lactating female who agrees to comply with any applicable contraceptive requirements of the protocol.
4. Established CKD, on dialysis, and requires treatment for hyperphosphatemia with a phosphate binder.
5. Serum phosphorus levels after a washout period of up to 3 weeks as follows:
   - Age <12 years: Serum phosphorus >6.0mg/dL (1.94mmol/L)
   - Age 12 years and older: Serum phosphorus >5.5mg/dL (1.78mmol/L)
6. Ability to provide written, signed and dated (personally or via an LAR) informed consent/and assent, as applicable, to participate in the study.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met.

1. Current or recurrent disease (eg, cardiovascular, liver, unstable and uncontrolled gastrointestinal, malignancy, or other conditions) other than CKD or end-stage renal disease that could affect the action, absorption or disposition of the investigational product, or clinical or laboratory assessments.
2. Current or relevant history of physical or psychiatric illness, any medical disorder (except for CKD or end-stage renal disease and related co-morbidities) that may require treatment or make the subject unlikely to fully complete the study, or any condition that presents undue risk from the investigational product or procedures.
3. Unable to eat semi-solid foods or on Total Enteral Alimentation.
4. Known or suspected intolerance or hypersensitivity to the investigational product(s), closely related compounds, or any of the stated ingredients.

5. History of alcohol or other substance abuse within the last year.
6. Current use of any medication (including over-the-counter, herbal, or homeopathic preparations) that could affect (improve or worsen) the condition being studied, or could affect the action, absorption, or disposition of the investigational product(s), or clinical or laboratory assessment.
7. Weight and age of subject are outside of local applicable criteria for blood sample volume limits.
8. Use of another investigational product within 30 days prior to receiving the first dose of investigational product.

4.3 Reproductive Potential

All females must have a negative serum beta human chorionic gonadotropin pregnancy test at Visit 1.0 and/or Visit 2.0. Females must abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Condoms should be used with the following acceptable contraceptives:

- Intrauterine devices
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring).

Other acceptable contraception methods are:

- Double barrier methods (eg, condoms and diaphragms with spermicidal gel or foam).

Sexually active females should have been using an acceptable form of contraception for at least 4 weeks prior to enrollment. All females must be advised to use acceptable contraceptives throughout the study period and for 30 days following the last dose of investigational product. If hormonal contraceptives are used they should be administered according to the package insert. Females who are not currently sexually active must agree to use acceptable contraception, as defined above, if they become sexually active during the period of the study and 30 days following the last dose of investigational product.

4.3.1 Restrictions

None.

4.4 Withdrawal of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The Investigator or Sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The withdrawal of a subject from investigational product by the Investigator should be discussed where possible with the Medical Monitor before the subject stops investigational product.

If investigational product is permanently discontinued, regardless of the reason, the final evaluations are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified follow-up. Comments (spontaneous or

elicited) or complaints made by the subject must be recorded in the source documents. The reason for termination, date of stopping investigational product, and the total amount of investigational product taken must be recorded on the case report form (CRF) and source documents.

4.4.1 Subject Stopping Criteria

Subjects must be removed from study if any 1 or more of the following events occur:

- Violation of inclusion/exclusion criteria at study entry
- Taking another non-study phosphate binder (on either calcium carbonate and lanthanum carbonate arms) rather than the investigational product during the study
- Kidney transplant during the study. Subjects should be followed 30±7 days post-transplant
- Pregnancy
- Serum phosphorus rises above 10.0mg/dL (3.23mmol/L) during the study (however this does not apply during the washout periods)
- Calcium level rises to >11.5mg/dL (2.88mmol/L) during the first treatment period of Part 2a (calcium carbonate). Subjects may continue to Part 3 but must complete all procedures for Visit 2.4 prior to commencing Part 3.

See APPENDIX 2 for guidelines on phosphorus and calcium levels.

4.4.2 Reasons for Discontinuation

The reason for withdrawal must be determined by the Investigator and recorded in the subject's medical record and on the CRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the CRF.

If an adverse event (AE) is a reason for discontinuation, then "adverse event" must be recorded as the reason for discontinuation on the CRF.

Reasons for discontinuation include but are not limited to:

- Death
- Withdrawal by subject
- Lost to follow-up
- Lack of efficacy
- Physician decision
- Pregnancy
- Kidney transplant
- Other (must be specified. eg, met stopping 1 or more stopping criteria).

Reasons for possible discontinuation (to be determined by Sponsor and Investigator discussion) include but are not limited to:

- Adverse event
- Protocol violation
- Non-compliance with study drug
- Progressive disease.

4.4.3 Subjects 'Lost to Follow-up" Prior to Last Scheduled Visit

At least 3 documented attempts must be made to contact any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). One of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return any unused investigational product and return to the site for final safety evaluations.

5. PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Treatment

Prior treatment includes all treatment (including over-the-counter, herbal treatments, vitamins, non-pharmacological treatment such as psychotherapy as appropriate), received within 30 days of, and discontinued prior to, the date of first dose of investigational product. Prior treatment information must be recorded on the appropriate CRF page.

Subjects taking growth hormone must have started their treatment at least 2 months prior to Visit 1.0 (Part 1, Table 1 or Part 2b and 3, Table 3) or Visit 2.0 (Part 2a and 3, Table 1).

Treatment with proton pump inhibitors must be initiated at least 4 weeks prior to Visit 1.0 (Part 1, Table 1 or Part 2b and 3, Table 3) or Visit 2.0 (Part 2a and 3, Table 1).

Table 4 details the washout period for common prior treatments and highlights excluded medications.

Table 4: Common Excluded Treatments and Washout Period

Treatment	Washout	Examples (if applicable)
Cinacalcet hydrochloride	Up to 3 weeks[a]	MIMPARA
Sevelamer hydrochloride	Up to 3 weeks[a]	RENAGEL, RENVELA

[a] Until phosphate levels are <6.0mg/dL (1.94mmol/L) for subjects under 12 years or <5.5mg/dL (1.78mmol/L) for subjects aged 12 years and over

5.2 Concomitant Treatment

Concomitant treatment taken between the dates of the first and last dose of investigational product, inclusive, must be listed on the appropriate CRF page.

Treatments not listed in Table 4 above are considered allowable.

Subjects who require treatment with Vitamin D analogues should maintain a stable dose throughout the study unless modification is required due to hypercalcaemia as specified in Section 6.2.1. Vitamin D therapy including dose, unit, route, regimen, indication and dates of use, and the calcium concentration of the dialysate will also be recorded in the CRF.

Treatment with cinacalcet hydrochloride, or with compounds containing phosphate or magnesium, aluminum, or calcium that are used as a phosphate binder are prohibited during the study.

Contraceptives for females should be taken at least 4 weeks prior to enrollment and continued throughout the duration of the study and for 30 days following the last dose of investigational product.

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The test product is lanthanum carbonate, which will be provided in 250mg sachets in powder form. Additional information is provided in the current SPD405 IB and Summary of Product Characteristics.

The reference/comparator product in Part 2a is calcium carbonate which is provided in 500mg tablet form. Additional information is provided in the Summary of Product Characteristics.

6.2 Administration of Investigational Product(s)

6.2.1 Dosing

Both calcium carbonate tablets and lanthanum carbonate powder are to be taken orally.

Part 1: Lanthanum carbonate oral powder will be administered in the morning following breakfast at Visit 1.1, which is the day after dialysis treatment.

Subjects aged between 10-12 years will receive a single dose of 500mg lanthanum (as lanthanum carbonate hydrate; SPD405) and subjects aged >12 years will receive a single 1000mg dose of lanthanum (as lanthanum carbonate hydrate; SPD405).

Part 2a, Treatment Period 1: Calcium carbonate may be started at the dose taken by the subject prior to starting the study or equivalent. For new subjects, dosing will be based on standard clinical practice. The total daily dose may be adjusted as appropriate, until the target serum phosphorus level is achieved or until a maximum daily dose of 6500mg is reached. Once serum phosphorus control is achieved, the dose of calcium carbonate will be maintained until the end of the 8-week calcium carbonate treatment period.

Investigational product will be dispensed at Visit 2.0 if eligible, however if a washout is required then investigational product will be dispensed at visit W1.

Part 2a, Treatment Period 2: At the end of the first 8-week treatment period of Part 2a, all subjects will begin 8 weeks of treatment with lanthanum carbonate following a washout period of up to 3 weeks if necessary (see Section 7.1.2.4). Subjects reaching a level of phosphorus equal to or greater than the age-appropriate KDOQI guidance (aged under 12 years: serum phosphorus >6.0mg/dL [1.94mmol/L] and aged 12 years and older: serum phosphorus >5.5mg/dL [1.78mmol/L]) will be withdrawn from washout and commence treatment with lanthanum carbonate.

Lanthanum carbonate will be started at a total daily dose of 1500mg mixed into meals for all subjects. Lanthanum carbonate will be mixed with food and given 3 times a day. If the subject has only 2 meals a day the lanthanum carbonate dose will split equally across the 2 meals with a single dose not exceeding 1000mg. The total daily dose will be titrated as appropriate, until the target serum phosphorus level is achieved in accordance with KDOQI age guidelines or until a maximum daily dose of 3000mg is reached. Once serum phosphorus control is achieved, the dose of lanthanum carbonate will be maintained until the end of the 8-week lanthanum carbonate treatment period.

Part 2b: Eligible subjects will begin 8 weeks of treatment with lanthanum carbonate if they have phosphate levels equal to or greater than the age appropriate KDOQI guidance (serum phosphorus >6.0mg/dL [1.94mmol/L] for subjects aged under 12 years; >5.5mg/dL [1.78mmol/L] for subjects aged 12 years and older) at Visit 1, Week 0. Eligible subjects with serum phosphate levels below the age appropriate KDOQI guidance at Visit 1, Week 0 will enter a washout period (W1) of up to 3 weeks (see Table 3).

Lanthanum carbonate will be mixed with food and given 3 times a day. If the subject has only 2 meals a day the lanthanum carbonate dose will split equally across the 2 meals with a single dose not exceeding 1000mg. The starting total daily dose of lanthanum carbonate is 1500mg for all subjects. The total daily dose will be titrated 2-weekly, as appropriate, until the target serum phosphorus level is achieved, or until a maximum daily dose of 3000mg is reached. Once serum phosphorus control is achieved or the maximum dose is reached, the dose of lanthanum carbonate will be maintained until the end of the 8-week treatment period. All new subjects will be enrolled in Part 2b only under Version 6.0 of the protocol.

Part 3: Subjects who complete participation in Part 2 (2a or 2b) may continue to receive lanthanum carbonate for an additional 6 months (including subjects who participated in Part 2a, Treatment Period 1/calcium carbonate treatment arm, but who discontinued due to hypercalcemia). The dosage of lanthanum carbonate will be determined by the Investigator based on serum phosphate levels taken at each study visit up to a maximum dose of 3000mg/day.

Hypophosphatemia During Parts 2 and 3

(See APPENDIX 2 for guidelines on phosphate and calcium level management.)

If the serum phosphate is <4mg/dL (1.29mmol/L) for adolescents aged 12-18 years, or <4.5mg/dL (1.45mmol/L) for subjects aged 10 years to <12 years, we advise that the Investigator monitor the phosphate levels carefully and consider reducing the binder dose by 25% depending on the rate at which the phosphorus is falling when prior laboratory testing is reviewed.

If the serum phosphate is <3.5mg/dL (1.13mmol/L) for adolescents aged 12-18 years, or <4mg/dL (1.29mmol/L) for subjects aged 10 years to <12 years, the binder should be stopped and serum phosphate levels monitored closely.

The binder should be resumed at 50% of the prior dose when the serum phosphorus is >4mg/dL (1.29mmol/L) for adolescents, and >4.5mg/dL (1.45mmol/L) for subjects aged 10 years to <12 years.

Hypocalcemia During Parts 2 and 3

Subjects whose serum levels of corrected total calcium are below the lower limit (<8.8mg/dL [2.20mmol/L]) should receive therapy to increase serum calcium levels. This must be taken between meals and/or at bedtime.

Hypercalcemia

If hypercalcaemia (serum calcium >10.2mg/dL (2.54mmol/L) develops during administration of calcium carbonate in Part 2a (Treatment Period 1) of the study, active vitamin D sterols should be decreased by 50%, the dose of calcium carbonate should be decreased by 25%, and the subject should be monitored. If after 2 weeks hypercalcemia persists, active vitamin D sterols should be stopped. If after another 2 weeks from onset of hypercalcemia it persists, the subject should be withdrawn from Part 2a. If the Investigator believes there are no contraindications and the subject is willing to continue, the subject can start Part 3.

If hypercalcemia (serum calcium >10.2mg/dL (2.54mmol/L) develops during administration of lanthanum carbonate, active vitamin D sterols should be decreased by 50%. If after 2 weeks hypercalcemia persists, active vitamin D sterols should be stopped until required.

6.2.2 Blinding the Treatment Assignment

Not Applicable.

6.2.3 Allocation of Subjects to Treatment

This is an open-label study. Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), this number is assigned to subjects according to the sequence of presentation for study participation.

6.2.4 Unblinding the Treatment Assignment

Not Applicable.

6.3 Labelling, Packaging, Storage, and Handling

6.3.1 Labelling

All investigational product is labelled with a minimum of the protocol number, medication identification number, dosage form (including product name and quantity in pack), directions for use, storage conditions, expiry date (if applicable), batch number and/or packaging reference, the statements ‘For clinical trial use only’ and ‘Keep out of reach of children’, and the Sponsor's

name and address. Any additional labelling requirements for participating countries and/or controlled substances will also be included on the label.

Space is allocated on the label so that the site representative can record a unique subject identifier and initials.

Additional labels may, on a case-by-case basis, be applied to the investigational product in order to satisfy local or institutional requirements, but must not:

- Contradict the clinical study label
- Obscure the clinical study label
- Identify the study subject by name.

Additional labels may not be added without the Sponsor's prior full agreement.

6.3.2 Packaging

Lanthanum carbonate is packaged in the following labelled containers: cartons containing 50 of the 250mg sachets.

Calcium carbonate is supplied in a white high-density polyethylene bottle with a white round cap with a plastic ring pull seal, containing 100 tablets.

Changes to Sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the Sponsor.

6.3.3 Storage

The Investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle/carton labels as they are distributed.

Investigational product must be stored in accordance with labelled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The Investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified Min/Max Thermometer) would require manual resetting upon each recording. The Sponsor must be notified upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The Sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive

documentation as necessary. Under no circumstances should product be dispensed to subjects until the impact is determined and product is deemed appropriate for use by Sponsor.

6.3.4 Handling

There are no special investigational product handling instructions.

6.4 Investigational Product Quality Complaints

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products).

6.5 Drug Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The Investigator or designee will acknowledge receipt of the investigational product documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The Investigator has overall responsibility for administering/dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the Investigator. This delegation must be documented in the applicable study delegation of authority form.

The Investigator or his/her designee (as documented by the Investigator in the applicable study delegation of authority form) will dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All dispensing will be documented on the CRFs and/or other investigational product record. The Investigator is responsible for assuring the retrieval of all study supplies from subjects.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the Sponsor. If such transfer is authorized by the Sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The Sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

At the end of the study, or as instructed by the Sponsor, all unused stock, subject-returned investigational product, and empty/used investigational product packaging are to be sent to a nominated contractor on behalf of the Sponsor. Investigational products being returned to the

Sponsor's-designated contractors must be counted and verified by clinical site personnel and the Sponsor (or designated Contract Research Organization; CRO). For unused supplies where the original supplied tamper-evident feature is verified as intact, the tamper-evident feature must not be broken and the labelled amount is to be documented in lieu of counting. All certificates of delivery/drug receipts should be signed by the site representative to confirm contents of shipment. Shipment return forms, when used, must be signed prior to shipment from the site. Returned investigational products must be packed in a tamper-evident manner to ensure product integrity. Contact the Sponsor for authorisation to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the Sponsor's satisfaction.

6.6 Subject Compliance

Subjects must be instructed to bring their unused investigational product and empty/used investigational product packaging to every visit. Drug accountability must be assessed at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (eg, bottles, cartons) or at the individual count level for opened containers/packaging. The pharmacist/nominated person will record details on the drug accountability form.

At each visit the investigational product dispensed at the previous visit will be counted, compliance calculated and the container returned to the subject until exhausted.

7. STUDY PROCEDURES

7.1 Study Schedule

See Table 1 and Table 3 for study procedures.

7.1.1 Screening Period

7.1.1.1 Part 1: Screening Visit Part 1 (Visit 1.0, Week -5)

The Investigator or designee will obtain written informed consent/assent from the subject/LAR prior to any study-related procedures being performed.

Each subject will be assigned a 7-digit number using the unique site number and the order of the subject as they present eg, the first subject at Site 101 would be 101-0001, the second 101-0002.

- All inclusion/exclusion criteria will be assessed and demographic characteristics recorded.
- Significant medical and renal history (in the Investigators' opinions) will be recorded.
- A full physical examination as well as height, weight, and vital signs will be performed.

- A 12-lead electrocardiogram (ECG) will be undertaken to exclude any underlying cardiac diseases.
- Blood samples will be taken for biochemistry, hematology, and biochemical bone markers.
- All females will undergo a serum pregnancy test.
- All concomitant medication and ongoing AEs will be recorded.
- Confirmation of dialysis adequacy and dietary advice will be made.

If all criteria are met except the phosphate level, the subject will enter the washout period for Part 1.

A screen failure will be considered to be a subject who has given informed consent and failed to meet the inclusion and/or meet at least 1 of the exclusion criteria and has not been administered investigational product(s) as defined by the protocol.

Subjects cannot be re-screened once they have been designated as a screen failure.

7.1.1.2 Part 2a: Screening Visit (Visit 2.0; Week 0)

The Investigator or designee will obtain written informed consent/assent from the subject/LAR prior to any study-related procedures being performed, irrespective of whether the subject has already completed Part 1 of the study.

Subjects who have completed Part 1 do not need to have a further blood sample taken and all of the study information itemized below can be obtained from their Visit 1.0 assessments. Upon completion of Visit 2.0, these subjects will enter Visit 2.1.

Each subject will be assigned a unique 7-digit number in the order that they present in the clinic, regardless if they start at Part 1 or Part 2 of the study eg, the first subject at Site 001 would be 001-0001, the second 001-0002.

- All inclusion/exclusion criteria will be assessed and demographic characteristics recorded (Version 5.0 of the protocol).
  - Eligibility can be based on local laboratory results; however blood samples must be submitted to the central laboratory to obtain central laboratory results. Phosphorus levels and serum pregnancy results must be taken from samples within 7 days of planned enrollment, and PTH samples must be taken within 3 months of planned enrollment.
- Significant medical and renal history (in the Investigator's opinion) will be recorded, including the last assessment of glomerular filtration rate taken from the medical record.
- A full physical examination including height, weight, and vital signs will be performed.
- A 12-lead ECG will be undertaken to exclude any underlying cardiac diseases.
- Blood samples will be taken for biochemistry, hematology and biochemical bone markers.
- All females will undergo a serum pregnancy test.

- All concomitant medication and ongoing AEs will be recorded.
- Confirmation of dialysis adequacy and dietary advice will be made.
- Investigational product will be dispensed to subjects who do not require a washout and have already reached a level of phosphorus equal to or greater than the age appropriate KDOQI guidance (aged under 12 years: serum phosphorus >6.0mg/dL [1.94mmol/L] and aged 12 years and older: serum phosphorus >5.5mg/dL [1.78mmol/L]). If a subject has started calcium carbonate based on local laboratory results, the subject will be allowed to continue in the study even if central laboratory results do not agree.

7.1.1.3 Part 2b: Screening Visit (Visit 1.0; Week 0)

The Investigator or designee will obtain written informed consent/assent from the subject/LAR prior to any study-related procedures being performed. Upon completion of Visit 1.0 for Part 2b, these subjects will enter Visit 2.1. All new eligible subjects will directly enter Part 2b under Version 6.0 of the protocol.

Each subject will be assigned a unique 7-digit number in the order that they present in the clinic, eg, the first subject at Site 001 would be 001-0001, the second 001-0002.

- All inclusion/exclusion criteria will be assessed and demographic characteristics recorded (Version 6.0 of the protocol).
  - Eligibility can be based on local laboratory results; however blood samples must be submitted to the central laboratory to obtain central laboratory results. Phosphorus levels and serum pregnancy results must be taken from samples within 7 days of planned enrollment, and PTH samples must be taken within 3 months of planned enrollment.
- Significant medical and renal history (in the Investigator's opinion) will be recorded, including the last assessment of glomerular filtration rate taken from the medical record.
- A full physical examination including height, weight, and vital signs will be performed.
- A 12-lead ECG will be undertaken to exclude any underlying cardiac diseases.
- Blood samples will be taken for biochemistry, hematology and biochemical bone markers.
- All females will undergo a serum pregnancy test.
- All concomitant medication and ongoing AEs will be recorded.
- Confirmation of dialysis adequacy and dietary advice will be made.
- Investigational product will be dispensed to subjects who have a level of serum phosphorus equal to or greater than the age appropriate KDOQI guidance (aged under 12 years: serum phosphorus >6.0mg/dL [1.94mmol/L] and aged 12 years and older: serum phosphorus >5.5mg/dL [1.78mmol/L]).
- If all criteria are met except the phosphate level, the subject will enter the washout period W1 for Part 2b.

7.1.1.4 Washout (W1)

Part 1 (between Visits 1.0 and 1.1)

Subjects must stop taking any phosphate binder medication for up to 3 weeks prior to the first dose of investigational product if their phosphate levels are <6.0mg/dL (1.94mmol/L) for subjects under 12 years or <5.5mg/dL (1.78mmol/L) for subjects aged 12 years and over.

If a subject under 12 years already has phosphate levels >6.0mg/dL (1.94mmol/L) or >5.5mg/dL (1.78mmol/L) for subjects aged 12 years and older, the subject may proceed directly to the next part of the study (Visit 1.1). If a subject has started lanthanum carbonate based on local laboratory results, the subject will be allowed to continue in the study even if central laboratory results do not agree.

Blood sample(s) will be taken locally during the washout period to ensure the phosphorus reaches the KDOQI required level. When reached the phosphate level should be confirmed by taking a sample (between 0.1-0.7mL depending on each country's specific requirements) which will be analyzed by the central laboratory. However study medication can be dispensed based on the local laboratory result.

Any AEs or changes to concomitant medication will be recorded.

Part 2a (between Visits 2.0 and 2.1) and Part 2b (between Visit 1.0 and 2.1)

Subjects must stop taking any phosphate binder medication for up to 3 weeks prior to the first dose of investigational product if their phosphate levels are <6.0mg/dL (1.94mmol/L) for subjects under 12 years or <5.5mg/dL (1.78mmol/L) for subjects aged 12 years and over.

If a subject aged under 12 years already has phosphate levels >6.0mg/dL (1.94mmol/L) or >5.5mg/dL (1.78mmol/L) for subjects aged 12 years and older, the subject may proceed directly to the next part of the study (Visit 2.1). If a subject has started calcium carbonate or lanthanum carbonate based on local laboratory results, the subject will be allowed to continue in the study even if central laboratory results do not agree.

If phosphate levels reach >6.0mg/dL (1.94mmol/L) for subjects aged under 12 years or >5.5mg/dL (1.78mmol/L) for subjects aged 12 years and older during the washout, the subject will be withdrawn from washout and start the next part of the study (Visit 2.1).

Blood sample(s) will be taken locally during the washout period to ensure the phosphorus reaches the KDOQI required level. When reached, the phosphate level should be confirmed by taking a sample (between 0.1-0.7mL depending on each country's specific requirements) which will be analyzed by the central laboratory. However subjects can be enrolled based on the local laboratory result.

Any AEs or changes to concomitant medication will be recorded.

Subjects who have participated in Part 1 do not need to have a washout prior to entering Part 2 (not applicable to part 2b).

Subjects who have completed the washout (W1) and have phosphate levels equal to or greater than the age appropriate KDOQI guidance (serum phosphorus >6.0mg/dL [1.94mmol/L] for subjects aged under 12 years; >5.5mg/dL [1.78mmol/L] for subjects aged 12 years and older) will:

- Part 2a: Be dispensed calcium carbonate at either the dose taken by the subject prior to starting the study or at a dose determined by the Investigator for new subjects based on standard clinical practice.
- Part 2b: Be dispensed lanthanum carbonate with the starting total daily dose as 1500mg for all subjects. The total daily dose will be titrated 2-weekly, as appropriate, until the target serum phosphorus level is achieved, or until a maximum daily dose of 3000mg is reached.
- Have any AEs that occurred since the last visit recorded.
- Have a review of any concomitant medication taken since the last visit undertaken and changes recorded.

7.1.2 Treatment Period

7.1.2.1 Part 1: Visit 1.1/ Week -5 to -1 (±3 Days)

Visit 1.1 should be scheduled on the day after dialysis. See Table 2 for a detailed schedule of assessments for this visit.

- Subjects aged between 10 and 12 years will receive a single dose of 500mg lanthanum (as lanthanum carbonate hydrate) and subjects aged 12 years and over will receive a single 1000mg dose lanthanum (as lanthanum carbonate hydrate; SPD405).
- Blood samples for pharmacokinetic analyses will be taken pre-dose and at 3, 5, 6, 8, 12, 24, and 48 hours after dosing.
- Vital signs (blood pressure and pulse) will be recorded pre-dose, and at 24 and 48 hours after dosing.
- A physical examination will be done at 48 hours post-dose.
- Adverse events and changes to concomitant medication will be recorded.

7.1.2.2 Part 2a: Visits 2.1-2.3 (Weeks 2, 4, and 6; ±3 Days)

- Subjects will attend the clinic every 2 weeks for scheduled study visits, starting from the first dose of investigational product
- Phosphate and calcium levels will be measured locally for titration purposes.
- The investigational product dispensed at the previous visit will be counted, compliance calculated and the container returned to the subject until exhausted. If necessary, a new container of investigational product will be dispensed.
- The dose of calcium carbonate will be adjusted as required at each visit.
- Any AEs that occurred since the last visit will be recorded.

- A review of any concomitant medication taken since the last visit will be undertaken and changes recorded.
- Confirmation of dialysis adequacy and dietary advice will be made.

7.1.2.3 Part 2a: Visit 2.4 (Week 8; ±3 Days)

- Vital signs, height, and weight will be measured.
- Blood samples will be taken for biochemistry, and biochemical bone markers.
- Investigational product will be collected and drug accountability performed.
- Any AEs that occurred since the last visit will be recorded.
- A review of any concomitant medication taken since the last visit will be performed and changes recorded.
- Confirmation of dialysis adequacy and dietary advice will be made.
- If phosphate levels remain >6.0mg/dL (1.94mmol/L) for subjects aged under 12 years or >5.5mg/dL (1.78mmol/L) for subjects aged 12 years and older, the subject may be dispensed lanthanum carbonate at a total daily dose of 1500mg to be taken with meals. If phosphate levels are below these levels the subject must enter a washout period of up to 3 weeks or until the targeted levels are reached, whichever is earliest. If a subject has started lanthanum carbonate based on local laboratory results, the subject will be allowed to continue the study even if central laboratory results do not agree.

7.1.2.4 Part 2a: Washout (W2)

Subjects will be asked to stop taking calcium carbonate and will not be taking a phosphate binder, for up to 3 weeks or until phosphate levels, to be measured locally, of >6.0mg/dL (1.94mmol/L) for subjects aged under 12 years or >5.5mg/dL (1.78mmol/L) for subjects aged 12 years and older are reached, whichever is sooner. The phosphate level should be confirmed by taking a sample (between 0.1-0.7mL depending on each country's specific requirements) which will be analyzed by the central laboratory. If a subject has started lanthanum carbonate based on local laboratory results, the subject will be allowed to continue the study even if central laboratory results do not agree.

Any AEs or changes to concomitant medication will be recorded.

Subjects who complete the 3-week washout (W2) will be dispensed lanthanum carbonate at a starting daily dose of 1500mg to be taken with meals.

Subjects whose phosphate levels do not rise above 6.0mg/dL (1.94mmol/L) for subjects aged under 12 years or >5.5mg/dL (1.78mmol/L) for subjects aged 12 years and older during the washout period may be dispensed lanthanum carbonate for Part 3 at a daily dose determined by the Investigator based on serum phosphorus levels taken at each study visit up to a maximum daily dose of 3000mg which will be taken with meals.

If phosphate levels do not reach the required levels then the subject cannot enter the second treatment period of Part 2, however they can proceed to Part 3.

7.1.2.5 Part 2a: Visits 2.5-2.7 (Weeks 10, 12, and 14, Nominally; ±3 Days)

- Subjects will attend the clinic every 2 weeks for scheduled study visits.
- At Visit 2.6 only, blood samples will be taken to measure lanthanum pharmacokinetics (2 samples to be selected from: 0-2 hours, 2-4 hours, or 4-6 hours). **Note:** If the sampling is not done at Visit 2.6, blood sampling for pharmacokinetics must be taken at an alternative visit during Part 2.
- Phosphate levels will be measured locally at Visits 2.5, 2.6 and 2.7 only, for titration purposes.
- The investigational product dispensed at the previous visit will be counted, compliance calculated and the container returned to the subject until exhausted. If necessary, a new container of investigational product will be dispensed.
- The dose of lanthanum carbonate will be adjusted and dispensed as required.
- Any AEs that occurred since the last visit will be recorded.
- A review of any concomitant medication taken since the last visit will be undertaken and changes recorded.
- Confirmation of dialysis adequacy and dietary advice will be made.

7.1.2.6 Part 2a: Final Visit (Visit 2.8; Week 16 Nominally; ±3 Days)

- A 12-lead ECG will be performed.
- Vital signs, height and weight will be measured.
- Blood samples will be taken for biochemistry, and biochemical bone markers.
- Any unused lanthanum carbonate will be collected and drug accountability performed
- Any AEs that occurred since the last visit will be recorded.
- A review of any concomitant medication taken since the last visit will be performed and changes recorded.
- Confirmation of dialysis adequacy and dietary advice will be made.
- For subjects entering Part 3, lanthanum carbonate will be dispensed at a dose determined by the Investigator based on serum phosphorus levels taken at each study visit up to a maximum dose of 3000mg/day.

7.1.2.7 Part 2b: Visits 2.1-2.3 (Weeks 2, 4, and 6; Nominally; ±3 Days)

- Subjects will attend the clinic every 2 weeks for scheduled study visits, starting from the first dose of investigational product.
- At Visit 2.2 only, blood samples will be taken to measure lanthanum pharmacokinetics (2 samples to be selected from: 0-2 hours, 2-4 hours, or 4-6 hours). **Note:** If the sampling is not done at Visit 2.2, blood sampling for pharmacokinetics must be taken at an alternative visit during Part 2b.

- Phosphate levels will be measured locally at Visits 2.1, 2.2 and 2.3 only, for titration purposes.
- The investigational product dispensed at the previous visit will be counted, compliance calculated and the container returned to the subject until exhausted. If necessary, a new container of investigational product will be dispensed.
- The dose of lanthanum carbonate will be adjusted and dispensed as required.
- Any AEs that occurred since the last visit will be recorded.
- A review of any concomitant medication taken since the last visit will be undertaken and changes recorded.
- Confirmation of dialysis adequacy and dietary advice will be made.

7.1.2.8 Part 2b: Final Visit (Visit 2.4; Week 8; Nominally; ±3 Days)

- A 12-lead ECG will be performed.
- Vital signs, height and weight will be measured.
- Blood samples will be taken for biochemistry, and biochemical bone markers.
- Any unused lanthanum carbonate will be collected and drug accountability performed.
- Any AEs that occurred since the last visit will be recorded.
- A review of any concomitant medication taken since the last visit will be performed and changes recorded.
- Confirmation of dialysis adequacy and dietary advice will be made.
- For subjects entering Part 3, lanthanum carbonate will be dispensed at a dose determined by the Investigator based on serum phosphorus levels taken at each study visit up to a maximum dose of 3000mg/day.

7.1.2.9 Part 3 (Visits 3.0-3.4: Weeks 20, 24, 28, 32, and 36; ±1 Week <u>for Part 2a</u>; Weeks 12, 16, 20, 24, and 28 <u>for Part 2b</u>)

- Subjects who have successfully completed Part 2 of the study will continue to be dispensed lanthanum carbonate for a further 6 months.
- Subjects will attend the clinic once every month for scheduled study visits.
- At Visits 3.0-3.4 the local lab results for serum calcium, serum phosphorus, and calcium phosphorus product will be taken for analysis.
- At Visit 3.3 only, blood samples will be taken to measure lanthanum pharmacokinetics (2 samples to be selected from: pre dose to 2 hours, 2-4 hours, and 4-6 hours). **Note:** If the sampling is not done at Visit 3.3, blood sampling for pharmacokinetics must be taken at an alternative visit during Part 3.
- The dose of lanthanum carbonate will be adjusted and dispensed as required and any unused lanthanum carbonate will be collected, and drug accountability performed.
- Any AEs that occurred since the last visit will be recorded.

- A review of any concomitant medication taken since the last visit will be undertaken and changes recorded.
- Confirmation of dialysis adequacy and dietary advice will be made.

7.1.2.10 End of Part 3 (Visit 3.5: Week 40/ End of Study for Part 2a; Week 32/End of Study for Part 2b; ±1 Week)

- A full physical examination including vital signs, weight and height will be carried out.
- 12-lead ECG will be performed.
- Blood samples will be taken for biochemistry, hematology, and biochemical bone markers.
- All females will undergo a serum pregnancy test.
- All AEs and concomitant medication will be recorded.
- Confirmation of dialysis adequacy and dietary advice will be made.
- The primary reason for withdrawal will be recorded, if applicable.
- All returned study medication will be counted and recorded, and compliance calculated.
- An End of Study (EOS) Visit should be performed for all subjects in the study, including those subjects who discontinue early.

7.1.3 Follow-up Period

The safety follow-up call for this protocol is 7-14 days following last dose of investigational product (Table 1 and Table 3). Subjects who discontinue due to kidney transplantation, will have their safety follow-up call after 30±7 days from the last dose.

The telephone call is initiated by the site staff to query for serious adverse events (SAEs), AEs, and concomitant treatments.

7.1.4 Additional Care of Subjects After the Study

Not Applicable.

7.2 Study Evaluations and Procedures

7.2.1 Demographic and Other Baseline Characteristics

Patient demographic details, medical history, vital signs, including height, weight, physical examination, biochemistry, hematology, serum pregnancy test, type of dialysis (hemodialysis or peritoneal), vitamin D levels, and concomitant medication data will be obtained at Visit 1.0 (Part 1, Table 1 or Part 2b and 3,Table 3) or Visit 2.0 (Part 2a and 3,Table 1).

7.2.2 Efficacy

The primary efficacy endpoint is the percentage of subjects achieving age-specific KDOQI targets for serum phosphate level following 8 weeks of treatment with lanthanum carbonate.

The KDOQI serum phosphate targets are defined as:

- Adolescents aged ≥12-18 years: ≤5.5mg/dL (1.78mmol/L)
- Children aged 10 years to <12years: ≤6.0mg/dL (1.94mmol/L)

The secondary efficacy endpoints will be evaluated by analysis of, phosphorus PTH, ALP, bone ALP, osteocalcin, TRAP, FGF-23, sclerostin and fetuin-A taken from blood samples at Visits 2.0, 2.4, 2.8 and 3.5 for Part 2a (see Table 1) and at Visits 1.0, 2.4, and 3.5 for Part 2b (see Table 3).

7.2.3 Safety

7.2.3.1 Medical and Medication History

Medical and renal history will be recorded.

7.2.3.2 Physical Examination

Abnormalities identified at Visit 1.0 (see Table 1 and Table 3) or Visit 2.0 (see Table 1), will be documented in the subject's source documents and on the medical history CRF. Changes after these visits will be captured as AEs on the AE CRF page, as deemed by the Investigator.

7.2.3.3 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). Adverse events are collected from the time informed consent is signed.

7.2.3.4 Vital Signs

Blood pressure should be determined by cuff (using the same method, the same arm, and in the same position throughout the study). Any clinically significant deviations from baseline vital signs which are deemed clinically significant in the opinion of the Investigator are recorded as an AE.

Height and weight will be measured as part of the vital signs assessments.

7.2.3.5 Clinical Laboratory Evaluations

The name and address of the each clinical laboratory used in this study will be maintained in the Investigator's files at each site.

All clinical laboratory assays will be performed according to the laboratory's normal procedures. Reference ranges are supplied by the laboratory and used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The Investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition may be, at the discretion of the Investigator or Sponsor, repeated until confirmed, explained, or resolved as soon as possible.

The following clinical laboratory assessments will be performed:

Biochemistry

Blood samples (approximately 4.0mL) for biochemistry will be taken according to the Schedule of Assessments (see Table 1 and Table 3). The following parameters will be assessed:

Sodium	Aspartate aminotransferase (AST)
Potassium	Alanine aminotransferase (ALT)
Calcium	Alkaline phosphatase (ALP)
Urea	Gamma glutamyl transferase (GGT)
Creatinine	Total bilirubin
Albumin	Magnesium
Total protein	Serum phosphorus
25-hydroxy Vitamin Da,	

[a] 25-hydroxy Vitamin D will be measured at baseline and EOS only

Changes from baseline will be recorded as an AE if clinically relevant.

Hematology

Blood samples (approximately 500µL) for hematology will be taken according to the Schedule of Assessments (see Table 1 and Table 3). The following parameters will be assessed:

Hemoglobin	Mean corpuscular hemoglobin (MCH)
Hematocrit	Mean corpuscular hemoglobin concentration (MCHC)
Red blood cells	White blood cell count – total and differential
Mean corpuscular volume (MCV)	Platelet count

Changes from baseline will be recorded as an AE if clinically relevant.

Biochemical Bone Markers

Blood samples (approximately 3.0mL) for biochemical bone markers will be taken according to the Schedule of Assessments (see Table 1 and Table 3). The following parameters will be assessed:

TRAP	FGF-23
Osteocalcin	Bone ALP
PTH[a]	Sclerostin
Fetuin- A	

Changes from baseline will be recorded as an AE if clinically relevant.

7.2.3.6 Pregnancy Test

A serum pregnancy test is performed on all female subjects at Visit 1.0, and/or Visit 2.0, and at the final visit (Visit 3.5), or if pregnancy is suspected, or on withdrawal of the subject from the study (see Table 1 and Table 3).

7.2.3.7 Electrocardiogram

An ECG will be carried out at Visit 1.0, at Visits 2.0, 2.8 and 3.5/EOS for Part 2a (see Table 1), and at Visits 1.0, 2.4, and 3.5/EOS for Part 2b (see Table 3).

The ECG must be assessed by either a cardiac specialist or by a study physician who is trained to perform this assessment.

7.2.4 Others

7.2.4.1 Clinical Pharmacology Assessments

Blood Sampling for Lanthanum Pharmacokinetic Evaluation

Actual pharmacokinetic blood sample collection times relative to the time of dosing will be monitored. The Sponsor's expectation is that the Investigator will ensure that every effort is made to collect all pharmacokinetic blood samples at the precise protocol-scheduled time.

Blood samples (1mL each) for pharmacokinetic evaluation will be collected during all 3 study periods (Parts 1, 2 [2a and 2b], and 3).

Part 1. Blood samples for determination of single-dose lanthanum pharmacokinetics will be collected at pre-dose and at 3, 5, 6, 8, 12, 24, and 48 hours after dosing.

Part 2 (2a or 2b) and Part 3. Pharmacokinetics will be evaluated during lanthanum carbonate dosing using a sparse sampling approach. Blood samples (at least 2 per subject) for pharmacokinetic assessments will be collected during Parts 2 (2a or 2b) and 3 in defined time windows (to be selected from: 0-2 hours, 2-4 hours and 4-6 hours after the first dose/meal of the day, so as to cover the full dosing interval).

The actual time that the sample was taken will be recorded; it should be within ±5 minutes of the nominal in the first 4 hours after taking the investigational product, ±15 minutes up to 24 hours after taking the investigational product (Parts 1, 2, and 3), and within ±60 minutes thereafter (Part 1 only).

Samples drawn outside these parameters will be considered a protocol deviation.

7.2.4.2 Pharmacodynamic Assessments

Not Applicable.

7.2.4.3 Quality of Life Assessments

Not Applicable.

7.2.4.4 Health Outcomes Assessments

Not Applicable.

7.2.5 Volume of Blood to be Drawn From Each Subject

Table 5: Volume of Blood to be Drawn From Each Subject

Assessment		Sample Volume (mL)	Number of Samples	Maximum Total Volume (mL)
Pharmacokinetic samples		1.0[a]	12	12.0
Safety	Biochemistry with β-HCG[a]	4.0	4	16.0
	Hematology	0.5	2	1.0
	Biochemical bone markers	3.0	4	12.0
	Centrally confirmed phosphate[b]	0.1-0.7[c]	2	1.4
Total mL				42.4

HCG=human chorionic gonadotropin

[a] β-HCG testing for all female subjects will be analyzed from the biochemistry samples so no additional blood volume is required

[b] Only for those subjects who require confirmation of their phosphate levels from the central laboratory, during the washout periods

[c] Volume will vary according to country

In the originally proposed study, it was expected that approximately 41.0mL of blood will be taken from all subjects, regardless of sex; a maximum of 42.4mL of blood will be taken from those subjects who require confirmation of their phosphate levels during both washouts in Part 2 (41.7mL if they only require confirmation during 1 of the washouts).

Under Version 6.0 of the protocol, subjects will enter Part 2b, after screening at Visit 1.0/Week 0 for this part, for 8 weeks of lanthanum carbonate treatment only. They will undergo assessments for Part 2b and 3 as presented in Table 3. It is expected that approximately 34mL of blood will be taken from all subjects, regardless of sex.

Note: The above amount of blood to be taken for each assessment is an estimate. The amount of blood to be taken may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment. However, the total volume drawn over the course of the study should be approximately 41.0mL (maximum of 42.4mL). When more than 1 blood

assessment is to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An ***Adverse Event*** **(AE)** is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (International Conference on Harmonisation [ICH] Guidance E2A 1995).

All AEs should be captured on the AE CRF.

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.3 and are to be recorded on the appropriate AE pages in the CRF and in source documents. Where possible, a diagnosis, rather than a list of symptoms, should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE CRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), an outcome is reached, stabilization (the Investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained regardless of whether the subject is still participating in the study. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate CRF).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A Physician/Investigator must make the assessment of relationship to investigational product for each AE. The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as 'not related'. Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered 'related'. The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship	Definition
Related	Yes	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	No	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the CRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved With Sequelae
- Recovering/Resolving
- Unknown

8.1.4 Symptoms of the Disease Under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease. However, significant worsening of the symptoms should be recorded as an AE.

8.1.5 Clinical Laboratory Evaluations

A change in the value of a clinical laboratory investigation can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory values which were not present at baseline, further clinical or laboratory investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal clinical laboratory values.

The Investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory parameter is clinically significant and therefore represents an AE.

8.1.6 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.3.

Any report of pregnancy for any female study participant must be reported within 24 hours to the Shire Pharmacovigilance Department using the Shire Pharmaceuticals Investigational and Marketed Products Pregnancy Report Form. The female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the Investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days post-partum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Pharmaceuticals Clinical Trial Serious Adverse Event Form. Note: An elective abortion is not considered an SAE.

In addition to the above, if the Investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Pharmaceuticals Clinical Trial Serious Adverse Event Form as well as the Shire Pharmaceuticals Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine human chorionic gonadotropin test or ultrasound result will determine the pregnancy onset date.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the Sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described

in Section 8.2. Note: The 24 hours reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol).
- **Overdose** – Intentional or unintentional intake of a dose of an investigational product exceeding a pre-specified total daily dose of 3000mg of lanthanum and 6500mg of calcium.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the Sponsor only as defined below.

Cases of subjects missing doses of product are not considered reportable as medication errors. Medication errors should be collected/reported for all products under investigation. The administration and/or use of the unassigned treatment is always reportable as a medication error. The administration and/or use of an expired product should be considered as a reportable medication error.

All investigational product provided to pediatric subjects should be supervised by the parent/LAR/caregiver.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for lanthanum carbonate for this study is the current SPD405 IB which the Sponsor has provided under separate cover to all Investigators, and the Summary of Product Characteristics.

The reference for safety information for the comparator/reference product in this study (calcium carbonate) is the Summary of Product Characteristics which the Sponsor has provided under separate cover to all Investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the Investigator to the Shire Pharmacovigilance Department within 24 hours of the first awareness of the event. Note: The 24 hours reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) unless they result in an SAE.

The Investigator must complete, sign, and date the Shire Pharmaceuticals Clinical Trial Serious Adverse Event Form and verify the accuracy of the information recorded on the form with the

corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or e-mail the form to the Shire Pharmacovigilance Department.

8.2.3 Serious Adverse Event Definition

A ***Serious Adverse Event*** **(SAE)** is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening

  NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event; Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE.

However, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meets serious criteria must be reported as SAE(s).

8.2.4 Serious Adverse Event Collection Timeframe

All SAEs (regardless of relationship to study) are collected from the time the subject signs informed consent until the defined follow-up period stated in Section 7.1.3, and must be reported to the Shire Pharmacovigilance Department within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the Investigator at any interval after the study has completed must be reported to the Shire Pharmacovigilance Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the

event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject prior to study entry or leading up to the onset date of the SAE or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (ie, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product).

8.2.7 Regulatory Agency, Institutional Review Board, Independent Ethics Committee, and Site Reporting

The Sponsor and the Clinical CRO are responsible for notifying the relevant regulatory authorities and European Union (EU) central Independent Ethics Committees (IECs) of related, unexpected SAEs.

In addition the Sponsor and the Clinical CRO are responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SPD405 program.

The Investigator is responsible for notifying the local Institutional Review Board (IRB), local IEC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The Investigators' authorized site personnel must enter the information required by the protocol on the CRF. A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the Investigator's Meeting. It is expected that site personnel will complete the CRF entry within 5 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRO's data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Statistical Analysis Process

Details regarding the statistical methods and definitions will be provided in the statistical analysis plan.

To preserve the integrity of the statistical analysis and study conclusions, the statistical plan will be finalized prior to database lock.

PRA International will perform all pre-defined statistical analyses after the database is locked. Statistical analyses of efficacy and safety data will be performed using Version 9.1 or higher of SAS® (SAS Institute, Cary, NC 27513).

All data will be summarized overall.

9.4 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

No formal interim analysis is planned for this study. However, descriptive analyses of efficacy and safety data will be provided in Q4 2014 to assist with regulatory interactions if the recruitment targets have not been met. Adaptive design has not been selected for this study and there will not be a Data Monitoring Committee.

9.5 Selection of Subjects to be Included in the Analyses

Screened Set – The set of subjects who have signed informed consent.

Enrolled Set – Subjects who have signed informed consent and have begun some study procedures (eg, dispensed investigational product, current drug has been withdrawn).

Safety Analysis Set 1 – Enrolled subjects who have taken 1 dose of investigational product in Part 1 and who have completed at least 1 follow-up safety assessment.

Safety Analysis Set 2 – Enrolled subjects who have taken 1 dose of investigational product in Part 2 or Part 3 and who have completed at least 1 follow-up safety assessment.

It is noted that safety assessments from the period when a subject is exposed to calcium carbonate will be summarized for calcium carbonate treatment. Safety assessments from the

period when a subject is exposed to lanthanum carbonate will be summarized for lanthanum carbonate treatment.

Safety Completer Set (SCS) – Subjects who receive at least 8 weeks of lanthanum carbonate treatment from either Part 2 or Part 3 of the study.

Full Analysis Set (**FAS**)–Subjects who have taken at least 1 dose of investigational product and who have at least 1 phosphate assessment during Part 2 or Part 3.

Per-protocol Set 1 (PP1) – Subjects in the Full Analysis Set who complete 8 weeks of calcium carbonate treatment followed by 8 weeks of lanthanum carbonate treatment and who have serum phosphate assessment data available to allow summarizing the percentage of subjects achieving age-specific KDOQI target. Only subjects who have serum phosphate levels equal to or above the age-specific KDOQI targets at study entry and between the calcium carbonate treatment and lanthanum carbonate treatment at Visit 2.4 will be included in this set.

Per-protocol Set 2 (PP2) – Subjects in the Full Analysis Set who complete 8 weeks of treatment with lanthanum carbonate and who have serum phosphate assessment data available to allow summarizing the percentage of subjects achieving age-specific KDOQI target. Subjects who have serum phosphate levels equal to or above the age-specific KDOQI targets prior to the start of lanthanum carbonate treatment will be included in this set.

Pharmacokinetic Set 1 - Subjects in the Safety Analysis Set 1 for whom the primary pharmacokinetic data are considered sufficient and interpretable. Subjects in Part 1 who vomited may be excluded from Pharmacokinetic Set 1.

Pharmacokinetic Set 2 - Subjects in Safety Analysis Sets 1 or 2 for whom the primary pharmacokinetic data are considered sufficient and interpretable will be included in Pharmacokinetic Set 2.

9.6 Subject Disposition

Part 1: Subjects who are in each applicable analysis set, as well as those subjects who complete Part 1, and those subjects who prematurely discontinue from Part 1 will be summarized using descriptive statistics. In addition, for subjects who prematurely discontinue from Part 1 of the study, the reasons for discontinuation will be summarized.

Part 2 (2a and 2b): All subjects from Safety Analysis Set 2 (including those who entered the study in Part 2b) who are in each applicable analysis set, as well as those subjects who complete Part 2, those subjects who prematurely discontinue from Part 2, and those subjects who entered Part 3 will be summarized by treatment group using descriptive statistics. In addition, for subjects who prematurely discontinue from Part 2, the reasons for discontinuation will be summarized by treatment group. Subjects who entered Part 3 due to hypercalcemia in Part 2 will also be summarized.

Part 2a (Treatment Period 2), Part 2b, and Part 3 Combined (lanthanum carbonate only): All subjects from Safety Analysis Set 2 who are in each applicable analysis set, as well as those subjects who complete the study, and those subjects who prematurely discontinue from the study

will be summarized using descriptive statistics. In addition, for subjects who prematurely discontinue, the reasons for discontinuation will be summarized.

9.7 Demographic and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented separately for Pharmacokinetic Set 1 and for Pharmacokinetic Set 2. Part 1 will be summarized using the Safety Analysis Set 1. Part 2 will be summarized by treatment group using Safety Analysis Set 2, the FAS, the PP1, the PP2 for lanthanum carbonate treatment only (Part 2a, Treatment Period 2 and Part 2b), and the SCS for 8 weeks of lanthanum carbonate treatment only in Parts 2 and 3 combined.

Continuous variables such as subject age, weight, height, and body mass index will be summarized using number of observations, mean, standard deviation, median, minimum, and maximum values. Categorical variables such as subject sex and race will be summarized using number of observations and percentages for each category.

Medical history will be listed.

9.8 Investigational Product Exposure

Data regarding exposure to lanthanum carbonate in Part 1 will be listed for Safety Analysis Set 1.

Part 2: Summary statistics for the duration of exposure to investigational product in Part 2 will be presented by treatment group for Safety Analysis Set 2. Compliance rates will be summarized by treatment.

Part 2 and 3 Combined (lanthanum carbonate only): Summary statistics for the duration of exposure to investigational product will be presented for the SCS and the Safety Analysis Set 2. Compliance rates will be summarized.

9.9 Prior and Concomitant Medication

Prior and concomitant medications will be coded using the World Health Organization drug dictionary (WHODRUG/2006QA or newer version).

Prior medications in Part 1 and Part 2 for Safety Analysis Set 1 and Safety Analysis Set 2, respectively, will be summarized by preferred drug name. Concomitant medications in Part 2 for Safety Analysis Set 2 will be summarized by preferred drug name and treatment group. Concomitant medications to the lanthanum carbonate treatment in Part 1, using Safety Analysis Set 1, and in Part 2 and Part 3 combined, using the Safety Analysis Set 2 and the SCS, will be summarized by preferred drug name.

9.10 Efficacy Analyses

9.10.1 Primary Efficacy Variable

The primary efficacy variable for the study is the percentage of subjects achieving age-specific KDOQI targets for serum phosphate level following 8-weeks of lanthanum carbonate treatment. The KDOQI serum phosphorus targets are defined as:

- Adolescents aged ≥12-<18 years: ≤5.5mg/dL (1.78mmol/L)
- Children aged 10 years -<12 years: ≤6.0mg/dL (1.94mmol/L)

For the primary endpoint, the percentage of subjects achieving age-specific KDOQI targets for serum phosphate levels after 8 weeks of lanthanum carbonate treatment will be descriptively summarized and calculated along with a 95% confidence interval. The FAS and PP2 Sets will be used for this descriptive summarization. Serum phosphate levels tested at a central laboratory will be used for the analysis. In the case of missing central laboratory data, local laboratory data will be used.

Handling of missing data rules will be described in the statistical analysis plan.

9.10.2 Secondary Variables

The secondary analyses will be carried out using the analysis populations of FAS, PP1, and PP2.

Secondary variables are:

- The percentage of subjects with serum phosphorus levels below the age-specific KDOQI targets following 8 weeks of treatment with calcium carbonate followed by 8 weeks of treatment with lanthanum carbonate will be descriptively summarized and will be calculated along with a 95% confidence interval, separately, for each treatment arm. The FAS and PP1 Sets will be used for this summarization. The KDOQI serum phosphorus targets are defined as:
  - Adolescents aged ≥12-<18 years: ≤5.5mg/dL (1.78mmol/L)
  - Children aged 10 years -<12 years: ≤6.0mg/dL (1.94mmol/L)
- Changes from baseline in serum phosphorus, calcium and calcium-phosphorus product in hyperphosphatemic children and adolescents with CKD who are on dialysis, following treatment with lanthanum carbonate for 8 weeks.
- Changes from baseline in serum phosphorus, calcium and calcium-phosphorus product in hyperphosphatemic children and adolescents with CKD who are on dialysis, following treatment with calcium carbonate for 8 weeks and lanthanum carbonate for 8 weeks.
- Change from baseline in serum phosphorus, calcium and calcium-phosphorus product levels at the last visit of each 8-week treatment period during Part 2 and monthly during the 6-month extension phase (Part 3).
- Biochemical bone markers: bone ALP, osteocalcin, TRAP, FGF-23, PTH, sclerostin and fetuin-A before and after each treatment period in Part 2, and at the end of Part 3.

- Height and weight at:
  - Visits 2.0, 2.4, 2.8, and 3.5 (Parts 2a and 3)
  - Visits 1.0, 2.4, and 3.5 (Parts 2b and 3).

For the long-term assessment, efficacy and safety variables will be summarized using the Safety Analysis Set 2 for each visit using descriptive statistics as follows:

- For continuous data: number of observations, mean, standard deviation, standard error, minimum, maximum, median, and 95% confidence interval
- For categorical data: number of observations and percentages.

Summary statistics (number of observations, mean, standard deviation, coefficient of variation, median, minimum, maximum and geometric mean) will be determined for all pharmacokinetic parameters.

9.10.3 Tertiary Efficacy Variables

Not Applicable.

9.11 Safety Analyses

All safety variables will be summarized using the defined Safety Analysis Sets (Safety Analysis Set 1, Safety Analysis Set 2, and SCS; see Section 9.5). Summaries will be presented by treatment group and overall.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities, Version 13.0.

The number of events, incidence, and percentage of treatment-emergent adverse events (TEAEs will be calculated overall, by system organ class, and by preferred term. Treatment-emergent AEs will be further summarized by age group, severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be summarized/listed. Clinical laboratory tests, vital signs, and ECG findings will be summarized. Potentially clinically important findings will also be summarized or listed.

9.12 Other Analyses

9.12.1 Pharmacokinetic Analyses

Part 1

Plasma lanthanum concentrations will be analyzed by non-compartmental methods to determine pharmacokinetic parameters including, but not limited to, area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUC_{0-t}), area under the plasma concentration-time curve from time zero to 48 hours (AUC_{0-48}), C_{max}, time to C_{max}, and, if appropriate, apparent terminal half-life ($t_{½}$) and apparent terminal-phase disposition rate constant (λ_z) and area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$).

Summary statistics (number of observations, mean, standard deviation, coefficient of variation, median, minimum, maximum, and geometric mean) will be determined for all pharmacokinetic parameters.

Parts 2 and 3

Plasma concentration-time data for Part 2a (Treatment Period 2), Part 2b, and Part 3 will be combined with those from Part 1 and subjected to population pharmacokinetic analysis using NONMEM to determine estimates of steady-state systemic exposure ($C_{max,}$ minimum plasma concentration [C_{min}] and area under the plasma concentration-time curve [AUC] at steady-state) and relationships of systemic exposure to dose and to safety findings explored if appropriate.

9.13 Sample Size Calculation and Power Considerations

Part 1 (Pharmacokinetic Assessment)

From Study LAM-IV-111, the mean±standard deviation AUC_{0-t} was 3.099±2.888ng.hr/mL and C_{max} was 0.296±0.177ng.hr/mL for a 1000mg single dose of lanthanum carbonate in subjects with renal failure who were receiving dialysis. Assuming the standard deviations from Study LAM-IV-111, a sample size of 8 subjects will have 80% assurance that the 2-sided 95% confidence interval for the AUC_{0-t} will be no wider than ±2.86ng.hr/mL and 80% assurance that 2-sided 95% confidence interval for C_{max} is no wider than ±0.18ng.hr/mL.

Parts 2 and 3 (Efficacy – Percentage of Subjects Achieving KDOQI Target for Serum Phosphorus)

Originally, the sample size of at least 50 subjects for the PP set had been chosen based on practical considerations and on agreement with the Paediatric Committee of the European Medicines Agency. In order to obtain a PP Set of 50 subjects, a sample size of approximately 72 subjects were to be enrolled in Part 2. This assumed 70% of the subjects are eligible for the PP Set. This sample size has 81% power to show that the lower limit of the 95% confidence interval for the difference (LC – CC) in the percentage of subjects achieving serum phosphorus target is above the non-inferiority margin of -18%.

However, given the extreme difficulty in recruiting enough subjects to obtain at least 50 subjects for the PP set for the assessment of non-inferiority, serious consideration had to be given to adjust the sample size and focus of the study to safety, in order to complete it. The sample size has been adjusted to include at least 35 subjects, who complete 8 weeks of treatment with lanthanum carbonate and are assessable for the primary endpoint. This study is still useful in collecting information, where there is a void, regarding the use of lanthanum in the pediatric population.

For the investigation of safety profile in hyperphosphatemic children and adolescents with CKD on dialysis treated with lanthanum carbonate, a sample size of 35 subjects is necessary in order to observe at least one event with a true event rate of 5% at a probability of 83.4%.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations and ICH Good Clinical Practice (GCP) Guideline E6 (1996) and EU Directive 2001/20/EC.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the Sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and inter/national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The Sponsor ensures that Local Regulatory Authority requirements are met before the start of the study. The Sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any Regulatory Authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

The Sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the Indemnity document is supplied to the Investigator before study initiation, per local country guidelines.

The Sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied to the CRO as necessary.

10.1.3 Public Posting of Study Information

The Sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating Investigators' names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Independent Ethics Committees

The Sponsor will provide a summary of the Clinical Study Report within 1 year of the end of the study completion date to the competent authority of the Member State(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. The Sponsor will provide the IECs with a copy of the same summary.

10.1.5 Study Suspension, Termination, and Completion

The Sponsor may suspend or terminate the study or part of the study at any time for any reason. If the study is suspended or terminated, the Sponsor will ensure that applicable regulatory agencies and IRBs/IECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

The Sponsor will make an EOS declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The Investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC and applicable regulatory requirements and guidelines.

It is the Investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The Investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The Investigator will maintain a list of appropriately qualified persons to whom the Investigator has delegated significant study-related tasks. *Curriculum vitae* for Investigators and sub-investigators are provided to the study Sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the Investigator should, with the subject's consent, inform them of the subject's participation in the study.

A Coordinating Principal Investigator is appointed to review the final Clinical Study Report for multi-site studies. Agreement with the final Clinical Study Report is documented by the signed and dated signature of the Coordinating Principal Investigator (multi-site study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2 Protocol Adherence and Investigator Agreement

The Investigator and any co-investigators must adhere to the protocol as detailed in this document. The Investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an Investigator Agreement to confirm acceptance and willingness to comply with the study protocol.

If the Investigator suspends or terminates the study at their site, the Investigator will promptly inform the Sponsor and the IRB/IEC and provide them with a detailed written explanation. The Investigator will also return all investigational product, containers, and other study materials to the Sponsor. Upon study completion, the Investigator will provide the Sponsor, IRB/IEC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/IECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the Sponsor, applicable CRO, Investigator, or for multi-site studies, the Coordinating Principle Investigator according to national provisions and will be documented in the Investigator Agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

Case Report Forms are supplied by the CRO and should be handled in accordance with instructions from the Sponsor.

The Investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case Report Forms must be completed by the Investigator or designee as stated in the site delegation log.

All data will have separate source documentation; no data will be recorded directly onto the CRF.

All data sent to the Sponsor must be endorsed by the Investigator.

The Clinical Research Associate/Study Monitor will verify the contents against the source data per the Monitoring Plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file and original clinical laboratory reports, and histology reports. All key data must be recorded in the subject's medical records.

All key data must be recorded in the subject's medical records.

The Investigator must permit authorized representatives of the Sponsor, the respective national, local, or foreign regulatory authorities, the IRB/IEC, and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The Clinical Research Associate/Study Monitor (and auditors, IRB/IEC or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the Sponsor or its representatives, national or local regulatory authorities, or the IRB/IEC having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays etc). Non-study site personnel will not disclose any personal information or personal medical information.

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the United States Food and Drug Administration, European Medicines Agency, UK Medicines and Healthcare products Regulatory Agency) or an auditor).

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the Sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the United States Food and Drug Administration (as well as other United States national and local regulatory authorities), the European Medicines Agency, the Medicines and Healthcare Products Regulatory Agency, other regulatory authorities, the Sponsor or its representatives, and the IRB/IEC for each site.

10.2.3.4 Financial Disclosure

The Investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the value of the compensation for conducting the study could be influenced by the outcome of the study. The following information is collected: any significant payments from the Sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the Sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

In consideration of participation in the study, the Sponsor pays the Investigator or nominated payee the sums set out in the payment schedule attached to the Investigator agreement.

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the Investigator to obtain written informed consent, and assent where applicable, from all study subjects prior to any study-related procedures including screening assessments. All consent and assent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's LAR as applicable is requested to sign the Subject Informed Consent Form or a certified translation, if applicable after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent and assent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's LAR as applicable. If applicable, it is provided in a certified translation of the local language. Signed consent/assent forms must remain in each subject's study file and must be available for verification at any time.

Site personnel should document parent/LAR/caregiver teaching and understanding within the source documents for safe, responsible storage and administration of investigational product to the study subject.

The Principal Investigator provides the Sponsor with a copy of the consent form (and assent form where applicable) which was reviewed by the IRB/IEC and which received their favourable opinion/approval. A copy of the IRB/IEC's written favourable opinion/approval of these documents must be provided to the Sponsor, prior to the start of the study unless it is agreed to

and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, Sponsor or Coordinating Principal Investigator) is responsible for this action. Additionally, if the IRB/IEC requires modification of the sample Subject Information and Consent document provided by the Sponsor, the documentation supporting this requirement must be provided to the Sponsor.

10.3.2 Institutional Review Board or Independent Ethics Committee

For sites outside the EU, it is the responsibility of the Investigator to submit this protocol, the informed consent document (approved by the Sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/IEC for review, and all must be approved prior to site initiation.

For sites within the EU, the applicant for an IEC opinion can be the Sponsor, the Investigator, or for multi-site studies the Coordinating Principal Investigator or Sponsor, according to national provisions.

Responsibility for coordinating with IRBs/IECs is defined in the Investigator Agreement.

Prior to implementing changes in the study, the Sponsor and the IRB/IEC must approve any revisions of any revised informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the Sponsor has received written IRB/IEC approval of and copies of revised documents.

For sites outside the EU, the Investigator is responsible for keeping the IRB/IEC appraised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; for sites within the EU, this can be done by the Sponsor, the Investigator or for multi-site studies the Coordinating Principal Investigator, according to national provisions. The Investigator must also keep the local IRB/IEC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the Sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the Sponsor; third parties with whom the Sponsor may develop, register, or market lanthanum carbonate; national or local regulatory authorities; and the IRB(s)/IEC(s) which gave approval for the study to proceed. The Sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number. However, their initials and date of birth may also be collected and used to assist the Sponsor to verify the accuracy of the data, for example, to confirm that laboratory results have been assigned to the correct subject.

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2-4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish, and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

11. REFERENCES

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12. APPENDICES

APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol (V 1.0)	11 Apr 2012	Global
Amendment 1.0 (V 2.0)	13 Jul 2012	Global
Amendment 1.0 GER	09 Oct 2012	Country-specific
Amendment 1.0 RUS	25 Apr 2013	Country-specific
Amendment 2.0 (V 3.0)	24 Sep 2012	Global
Amendment 2.0 RUS	28 July 2014	Country-specific
Amendment 3.0 (V 4.0)	17 Apr 2014	Global
Amendment 4.0 (V 5.0)	02 Mar 2015	Global
Amendment 5.0 (V 6.0)	18 Oct 2016	Global

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number: 4.0	**Amendment Date:** 02 Mar 2015	**Global/Country/Site-Specific:** Global
Description of Change		**Section(s) Affected by Change**
Protocol revised to match updated SAP: Redefined Full Analysis Set. Redefined Safety Analysis Set 3. Described subject disposition for all study parts. Described summarization methods for demographic and baseline characteristics (updated to align with finalized SAP). Described intent for listing and analyzing investigational product exposure. Described methods for listing prior and concomitant medication. Described safety analyses.		Study Synopsis; Section 9.5; Section 9.6; Section 9.7; Section 9.8; Section 9.9; Section 9.11
Changed coordinating principal investigator to PPD, MD, PhD.		Title page; Study Synopsis
Updated study duration to 44 months (extended to 2016).		Study Synopsis
Protocol updated to include collection and analysis of local laboratory values for serum calcium, serum phosphorus, and calcium phosphorus product for Visits 3.0 through 3.4.		Table 1; Section 7.1.2.7; Section 9.10.2
Clarification of characterization of lab parameters.		Section 7.2.3.5

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number: **3.0**	**Amendment Date:** **17 Apr 2014**	**Global/Country/Site-Specific:** **Global**
Description of Change		**Section(s) Affected by Change**
Age range amended from 6 months to <18 years to 10 years to <18 years		Protocol Title; Sections 2.2.2, 3.2, 4.1, 6.2.1, 7.1.2, 7.2.2, 9.10.1; Study Synopsis
Part 3 reduced from 10 months to 6 months and overall exposure to lanthanum reduced from 12 months to 8 months		Protocol Title; Table 1; Sections 2.2.2, 3.1 (Figure 1), 6.2.1, 7.1.2.7, 7.2.2, 7.2.3.6, 7.2.3.7, 9.10.2; Study Synopsis
Study Physician changed to PPD		Protocol Signature page
SAE and pregnancy notification changed from 1 business day to 24 hours		Emergency Contact Information; Product Quality Complaints; Sections 6.4, 8.1.6, 8.1.7, 8.2.2, 8.2.4
Emergency contact information outside of normal office hours updated		Emergency Contact Information
Removal of length, head circumference and Tanner staging from physical assessments, as these are no longer required due to the age range change		Table 1; Sections 7.1.1.1, 7.1.1.2, 7.1.2.3, 7.1.2.6, 7.1.2.8, 7.2.1, 7.2.3.2, 7.2.3.4, 9.7, 9.10.2; Study Synopsis
Visit windows detailed for each Part of the study		Table 1; Sections 7.1.2.1, 7.1.2.2, 7.1.2.3, 7.1.2.5
Safety follow-up period extended from 7 days after last visit to 7-14 days from last dose of investigational period, except for subjects who undergo kidney transplantation, whose follow-up call will be 30±7 days after the last dose.		Table 1; Section 7.1.3; Study Synopsis
Screening Visit Part 1 amended to Week -5		Table 1; Section 7.1.1.1; Study Synopsis
An ECG is no longer required at Visits 1.1 and 2.4		Table 1, Table 2; Sections 7.1.2.1, 7.1.2.3 , 7.2.3.7
Clarification that assessments scheduled for Visit 3.5 are not required for subjects who discontinue early due to having a kidney transplant, but that they need a safety follow-up call at 30±7 days following the last dose of investigational product		Table 1; Sections 4.5.1, 7.1.3; Study Synopsis
Clarified dispensing timings of investigational product in relation to washout		Table 1; Section 6.2.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number: 3.0	**Amendment Date: 17 Apr 2014**	**Global/Country/Site-Specific: Global**
Description of Change		**Section(s) Affected by Change**
Added that calcium levels, in addition to phosphate levels, should be measured locally for titration purposes during the first treatment period of Part 2		Table 1; Section 7.1.2.2
Footnote (c) added to clarify timings of pharmacokinetic sampling, for consistency with Section 7.2.4.1		Table 2
Subject numbers reduced to reflect narrower age range		Sections 3.1 (Figure 1), 3.2, 4.5, 9.13; Study Synopsis
The dose of calcium carbonate given in period 1 of Part 2 will be based on standard clinical practice, and not to any fixed regimen		Section 3.3, 6.2.1, 7.1.1.3; Study Synopsis
Number of sites updated; no sites in Asia or South Africa will now participate in the study but the Russian Federation has been included		Section 3.4; Study Synopsis
Inclusion criterion of a solid food diet has been removed due to amended age range		Section 4.1; Study Synopsis
Due to the amended age range, all females will now be of child-bearing potential. Consequently, contraceptive requirements and pregnancy tests are now applicable to all female subjects		Sections 4.1, 4.3, 5.2, 7.1.1.1, 7.1.1.2, 7.1.2.8, 7.2.3.6, 7.2.5 (Table 4); Study Synopsis
Exclusion criterion relating to serum calcium level removed		Section 4.2; Study Synopsis
Subject stopping criteria amended		Section 4.5.1
Reasons for automatic discontinuation amended; some subjects may now continue in the study subject to agreement between Sponsor and Investigator		Section 4.5.2
Concomitant treatment restrictions updated		Section 5.2
Details of investigational product providers removed		Section 6.1
Starting dose of lanthanum carbonate in the second treatment period of Part 2 amended to reflect the change in age range of subjects. All subjects will now be given a 1500mg starting dose		Sections 6.2.1, 7.1.2.3, 7.1.2.4, 7.1.2.5; Study Synopsis
Clarified that participation in Part 3 is subject to country regulations		Section 6.2.1; Study Synopsis
Clarified that the lanthanum carbonate given in Parts 2 and 3 should be mixed with food and divided equally between all meals		Section 6.2.1 Study Synopsis
Clarified that some subjects may not require a washout		Sections 6.2.1, 7.1.1.2; Study Synopsis
Clarified that titration should continue until serum phosphorus levels meet KDOQI age guidelines		Section 6.2.1; Study Synopsis
Dosing adjustments for subjects who develop hypercalcaemia have been updated and clarified		Section 6.2.1
Drug accountability and return of investigational product clarified		Sections 6.6, 7.1.2.2, 7.1.2.5

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number: **3.0**	**Amendment Date:** **17 Apr 2014**	**Global/Country/Site-Specific:** **Global**
Description of Change		**Section(s) Affected by Change**
Text amended to clarify that meeting the phosphate level criterion at Visit 1 is not critical; providing all other criteria are met, subjects should still enter the washout period for Part 1		Section 7.1.1.1
Clarification that eligibility can also be confirmed based on local laboratory results but the central laboratory result must also be obtained. Subjects will be allowed to continue in the study even if the central laboratory results do not agree with local results		Sections 7.1.1.2, 7.1.1.3, 7.1.2.3, 7.1.2.4
Correction made to age range of subjects with phosphate level >6.0mg/dL		Section 7.1.1.3
Simplified text relating to phosphate levels and washout		Section 7.1.1.3
Clarified that if phosphate levels do not reach the required levels at Visit 2.4, then the subject should enter a washout period of 3 weeks or until the targeted levels are reached, whichever is earliest		Sections 7.1.2.3, 7.1.2.4; Study Synopsis
For additional care of subjects, lanthanum may be provided at the end of the study		Section 7.1.4
Clarified acceptable dose levels in Part 3		Section 7.1.2.4
Clarified that study physician can assess ECGs, providing that they are suitably trained		Section 7.2.3.7
Due to the change in age range of the subjects recruited, data will be summarized on the overall population only, and not by age group		Sections 9.3, 9.11 Study Synopsis
Clarified how the Per-protocol Set will be determined		Section 9.5; Study Synopsis
Summary statistics by visit will no longer be presented for Part 2 or Part 3		Sections 9.8 9.11
Non-inferiority margin changed from 15% to 18%		Sections 9.10.1, 9.13; Study Synopsis
Sample size justification added		Section 9.13; Study Synopsis
Study period extended to Dec 2015		Study Synopsis
Deleted Contacts from appendices and added Guidelines for Phosphorus, Calcium and Parathyroid Hormone as Appendix 2		Appendices; Sections 4.5.1, 6.2.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number: 2.0	**Amendment Date:** 24 Sep 2012	**Global/Country/Site-Specific:** Global
Description of Change		**Section(s) Affected by Change**
Study physician changed to PPD		Protocol Signature Page
Addition of Visit 3.9 to ensure 12 months of treatment with lanthanum carbonate		Study Synopsis Table 1 7.1.2.8 7.1.2.9 7.1.3 7.2.2 7.2.3.6 7.2.3.7 9.10.2
The following assessments are no longer required at Visit 2.5: ECG, vital signs, tanner stage, height or length, weight, head circumference or blood samples for biochemistry, and bone markers		Study Synopsis Table 1 7.1.2.6 7.2.2 7.2.3.7 7.2.5 9.10.2
Clarification of when investigational product will be dispensed for subjects entering the washout periods in Part 2		Table 1
Correction that Inclusion and Exclusion Criteria will be checked during the washout for subjects who enter the first washout in Part 2 prior to having investigational product dispensed (W1)		Table 1
Clarification that the calcium carbonate dose may be adjusted as required in Visits 2.1 and 2.2-2.3		Table 1
Table of Assessments updated to reflect that investigational product will be collected at Visit 2.1		Table 1
Addition of the confirmation of dialysis adequacy and dietary advice will be made at Visit 1.0		Table 1 7.1.1.1
Naming of washout periods to allow identification of phosphate values (W1, W2)		Table 1 7.1.1.3 7.1.2.1 7.1.2.5
Addition of confirmatory phosphate value to washout period visits W1 and W2		Table 1 7.1.2.1 7.1.2.5
Clarification that local laboratory tests may be taken at all visits between Visits 2.5-2.7		Table 1 7.1.2.6
Deleted Section 7.1.2.2 Part 2: Visit 2.1 (Week 2) and combined it with Section 7.1.2.3 Part 2: Visits 2.2-2.3 (Weeks 4 and 6; ±1 day)		7.1.2.2
Clarification that subjects may start lanthanum carbonate treatment at Visit		7.1.2.4

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number: **2.0**	**Amendment Date:** **24 Sep 2012**	**Global/Country/Site-Specific:** **Global**
Description of Change		**Section(s) Affected by Change**
2.4 if phosphate criteria are met		
Confirmation that subjects will not be withdrawn from the study if they do not meet phosphate criteria following Visit 2.4 but will start lanthanum carbonate therapy and be assessed for Part 3. These subjects cannot be included in the Per-protocol (PP) Set		7.1.2.5 9.5
Correction that lanthanum carbonate is taken with meals		7.1.2.6
Clarification of which visits height or length, head circumference, and weight secondary variables are being carried out		9.10.2
Insertion of new publication policy text		10.5
Deleted Biosciences appendix and added Protocol History appendix		Appendix 2

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number: **2 RUS**	**Amendment Date:** **28 July 2014**	**Global/Country/Site-Specific:** **Country-specific**
Description of Change		**Section(s) Affected by Change**
Age range amended from 6 months to <18 years to 10 years to <18 years		Protocol Title; Sections 2.2.2, 3.2, 4.1, 6.2.1, 7.1.2, 7.2.2, 9.10.1; Study Synopsis
Duration of enrollment changed from 18 months to 30 months		Study Synopsis
Part 3 reduced from 10 months to 6 months and overall exposure to lanthanum reduced from 12 months to 8 months		Title Page; Protocol Signature Page; Study Synopsis ; Table 1; Sections 2.2.2, 3.1 (Figure 1), 6.2.1, 7.1.2.7, , 9.10.2;
Study Physician changed to PPD		Protocol Signature Page
SAE and pregnancy notification changed from 1 business day to 24 hours		Emergency Contact Information; Product Quality Complaints; Sections 6.4, 8.1.6, 8.1.7, 8.2.2, 8.2.4
Emergency contact information outside of normal office hours updated		Emergency Contact Information
Removal of length, head circumference and Tanner staging from physical assessments, as these are no longer required due to the age range change		Study Synopsis; Table 1; Sections 7.1.1.1, 7.1.1.2, 7.1.2.3, 7.1.2.6, 7.1.2.8, 7.2.1, 7.2.3.2, 7.2.3.4, 9.7, 9.10.2;
Visit windows detailed for each Part of the study		Table 1; Sections 7.1.2.1, 7.1.2.2, 7.1.2.3, 7.1.2.5, 7.1.2.6, 7.1.2.7, 7.1.2.8
Safety follow-up period extended from 7 days after last visit to 7-14 days from last dose of investigational period, except for subjects who undergo kidney transplantation, whose follow-up call will be 30±7 days after the last dose.		Study Synopsis; Table 1; Sections 4.5.1, 7.1.3;
Screening Visit Part 1 amended to Week -5		Study Synopsis; Table 1; Sections 7.1.1.1, 7.1.2.1;
An ECG is no longer required at Visits 1.1 and 2.4		Table 1, Table 2; Sections 7.1.2.1, 7.1.2.3 , 7.2.3.7
Clarification that assessments scheduled for Visit 3.5 are not required for subjects who discontinue early due to having a kidney transplant, but that they need a safety follow-up call at 30±7 days following the last dose of investigational product		Study Synopsis; Table 1; Sections 4.5.1, 7.1.3;
Clarified dispensing timings of investigational product in relation to washout		Table 1; Section 6.2.1
Added that calcium levels, in addition to phosphate levels, should be measured locally for titration purposes during the first treatment period		Table 1; Section 7.1.2.2

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number: **2 RUS**	**Amendment Date:** **28 July 2014**	**Global/Country/Site-Specific:** **Country-specific**
Description of Change		**Section(s) Affected by Change**
of Part 2		
Footnote (c) added to clarify timings of pharmacokinetic sampling, for consistency with Section 7.2.4.1		Table 2
Subject numbers reduced to reflect narrower age range		Study Synopsis; Sections 3.1 (Figure 1), 3.2, 4.5, 9.13;
The dose of calcium carbonate given in period 1 of Part 2 will be based on standard clinical practice, and not to any fixed regimen		Study Synopsis ; Section 3.3, 6.2.1, 7.1.1.3;
Number of sites updated; no sites in Asia or South Africa will now participate in the study but the Russian Federation has been included		Study Synopsis; Section 3.4;
Inclusion criterion of a solid food diet has been removed due to amended age range		Study Synopsis; Section 4.1;
Due to the amended age range, all females will now be of child-bearing potential. Consequently, contraceptive requirements and pregnancy tests are now applicable to all female subjects		Study Synopsis; Sections 4.1, 4.3, 5.2, 7.1.1.1, 7.1.1.2, 7.1.2.8, 7.2.3.6, 7.2.5 (Table 4);
Exclusion criterion relating to serum calcium level removed		Study Synopsis; Section 4.2;
Subject stopping criteria amended		Section 4.5.1
Reasons for automatic discontinuation amended; some subjects may now continue in the study subject to agreement between Sponsor and Investigator		Section 4.5.2
Concomitant treatment restrictions updated		Section 5.2
Details of investigational product providers removed		Section 6.1
Starting dose of lanthanum carbonate in the second treatment period of Part 2 amended to reflect the change in age range of subjects. All subjects will now be given a 1500mg starting dose		Study Synopsis; Sections 6.2.1, 7.1.2.4,
Clarified the administration of the lanthanum carbonate given in Parts 2 and 3		Study Synopsis; Section 6.2.1
Clarified that some subjects may not require a washout		Study Synopsis; Sections 6.2.1, 7.1.1.2;
Clarified that titration should continue until serum phosphorus levels meet KDOQI age guidelines		Study Synopsis; Section 6.2.1;
Dosing adjustments for subjects who develop hypercalcaemia have been updated and clarified		Sections 5.2, 6.2.1
Drug accountability and return of investigational product clarified		Sections 6.6, 7.1.2.2, 7.1.2.3, 7.1.2.5
Text amended to clarify that meeting the phosphate level criterion at Visit 1 is not critical; providing all other criteria are met, subjects should still enter the washout period for Part 1		Section 7.1.1.1
Clarification that eligibility can also be confirmed based on local		Sections 7.1.1.2, 7.1.1.3, 7.1.2.3,

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number: 2 RUS	**Amendment Date: 28 July 2014**	**Global/Country/Site-Specific: Country-specific**
Description of Change		**Section(s) Affected by Change**
laboratory results but the central laboratory result must also be obtained. Subjects will be allowed to continue in the study even if the central laboratory results do not agree with local results		7.1.2.4
Correction made to age range of subjects with phosphate level >6.0mg/dL		Section 7.1.1.3
Simplified text relating to phosphate levels and washout		Section 7.1.1.3
Clarified that if phosphate levels do not reach the required levels at Visit 2.4, then the subject should enter a washout period of 3 weeks or until the targeted levels are reached, whichever is earliest		Study Synopsis; Sections 7.1.2.3, 7.1.2.4;
(Pg. 50) If subject does not reach required phosphate levels post-washout, subject cannot enter second treatment period (but may proceed to third treatment period)		7.1.2.4
For additional care of subjects, lanthanum may be provided at the end of the study		Section 7.1.4
Clarified acceptable dose levels in Part 3		Section 7.1.2.4
Clarified that study physician can assess ECGs, providing that they are suitably trained		Section 7.2.3.7
Due to the change in age range of the subjects recruited, data will be summarized on the overall population only, and not by age group		Study Synopsis; Sections 9.3, 9.11
Clarified how the Per-protocol Set will be determined		Study Synopsis; Section 9.5;
Summary statistics by visit will no longer be presented for Part 2 or Part 3		Sections 9.8, 9.11
Non-inferiority margin changed from 15% to 18%		Study Synopsis; Sections 9.10.1, 9.13;
Percent assurances and confidence intervals updated		Section 9.13
Sample size justification added		Study Synopsis; Section 9.13;
Study period extended to Dec 2015		Study Synopsis
Added Guidelines for Phosphorus, Calcium and Parathyroid Hormone as Appendix 3		Appendices; Sections 4.5.1, 6.2.1
Deleted Contacts from Appendix 1		Appendices

Protocol Amendments		
Amendment Number: 1.0	**Amendment Date:** 13 Jul 2012	**Global/Country/Site-Specific:** Global
Description of Change		**Section(s) Affected by Change**
The addition of sclerostin and fetuin-A parameters to the assay for bone markers		Synopsis Section 2.2.2, Secondary Objectives Section 7.2.2, Efficacy Section 7.2.3.5 Clinical Laboratory Evaluations Section 9.10.2, Secondary Variables
Error in dosing regimen in Parts 1 and 2 has been corrected.		Synopsis
South Africa has been added to participating countries.		Synopsis Section 3.4, Sites and Regions
Number of samples for hematology analysis has been reduced. Requirement for biochemistry and hematology sampling at Visit 1.1 has been removed.		Table 1, Schedule of Assessments Subsections 7.1.2.4, 7.1.2.6, and 7.1.2.7 within Section 7, Study Procedures Table 2, Detailed Schedule of Assessments for Visit 1.1 Section 7.1.2.1, Part 1: Visit 1.1
Clarification and correction of washout periods, and assessments required therein. For subjects enrolling directly into Part 2, there will be a washout period of up to 3 weeks prior to the 8-week calcium carbonate treatment. There will be an additional washout period in Part 2 following calcium carbonate treatment, prior to the 8-week lanthanum carbonate treatment period. For subjects who have already completed Part 1 of the study, the first washout in Part 2 is not required.		Table 1, Schedule of Assessments Section 3.1, Study Design Flow Chart Section 6.2.1, Dosing Section 7.1.1.3, Washout Between Parts 1 and 2 Section 7.1.2.5, Washout Between Visits 2.4 and 2.5
Addition of column describing Visit 2.1 to Study Schedule		Table 1, Schedule of Assessments
Addition of footnote 'd' to Visits 2.1, 2.2-2.3 and 2.4, to explain variable duration		Table 1, Schedule of Assessments
The assessment of inclusion and exclusion criteria at Visit 2.1 for subjects completing the washout has been added		Table 1, Schedule of Assessments
The assessment of lanthanum pharmacokinetics at Visit 3.8 has been deleted		Table 1, Schedule of Assessments
Serum calcium >10.2mg/dL (2.54mmol/L) added as an exclusion criterion		Synopsis Section 4.2, Exclusion Criteria
Subject weight and age in relation to blood sample volume, added as an exclusion criterion		Synopsis Section 4.2, Exclusion Criteria
In addition to mg/dL values, the corresponding values expressed as mmol/L have been presented for phosphate and calcium levels.		Section 4.5.1, Subject Stopping Criteria

Protocol Amendments		
Amendment Number: 1.0	**Amendment Date:** 13 Jul 2012	**Global/Country/Site-Specific:** Global
Description of Change		**Section(s) Affected by Change**
Addition of guidance language in relation to dosing in case of hypophosphatemia, hypocalcemia during Parts 2 and 3, or hypercalcemia whilst taking calcium carbonate in Part 2		Section 6.2.1, Dosing
Addition of the Tanner stage to the Study Assessments		Table 1, Schedule of Assessments Subsections 7.1.1.1, 7.1.1.2, 7.1.2.4, 7.1.2.6, 7.1.2 7, and 7.1.2.9 within Section 7, Study Procedures Section 7.2.1, Demographic and Other Baseline Characteristics Section 7.2.3.2 Physical Examination
Clarification of local laboratory samples and central laboratory samples in the visit schedule, and analyses		Table 1, Schedule of Assessments Subsections 7.1.1.2, 7.1.1.3, 7.1.2.2, 7.1.2.3, 7.1.2.5, and 7.1.2.6 within Section 7, Study Procedures Section 9.10.1, Primary Efficacy Variable Section 9.10.2, Secondary Efficacy Variables
A blood sample for bone markers is no longer required at Visit 2.0 for subjects who have already completed Part 1 of the study.		Table 1, Schedule of Assessments Section 7.1.1.2, Screening Visit Part 2
Confirmation of the adequacy of current dialysis, and dietary advice have been added to the Study Assessments		Table 1, Schedule of Assessments Section 7, Study Procedures
New section added to specify the individual assessments to be carried out at Visit 2.1		Section 7.1.2.2, Part 2: Visit 2.1 (Week 2)
Vitamin D levels, and type of dialysis have been added to the baseline data to be collected		Section 7.2.1 Demographic and Other Baseline Characteristics
Biochemistry parameters amended to include Vitamin D at baseline and end of study, which will be measured as part of the bone markers panel. Magnesium added to biochemistry panel. Glucose will no longer be measured.		Section 7.2.3.5 Clinical Laboratory Evaluations
PTH has been designated as a bone marker, but will be analysed as part of the routine biochemistry panel		Synopsis Section 2.2.2 Secondary Objectives Section 9.10.2 Secondary Variables Section 7.2.3.5 Clinical Laboratory Evaluations

Protocol Amendments		
Amendment Number: 1.0	**Amendment Date:** 13 Jul 2012	**Global/Country/Site-Specific:** Global
Description of Change		**Section(s) Affected by Change**
The correction of blood sample volumes for all laboratory and pharmacokinetic samples		Section 7.2.3.5 Clinical Laboratory Evaluations Section 7.2.4.1 Clinical Pharmacology Assessments Section 7.2.5 Volume of Blood to be Drawn From Each Subject
Advice on the use of a catheter for blood sampling has been deleted		Section 7.2.5 Table 4 Volume of Blood to be Drawn From Each Subject

Protocol Amendments		
Amendment Number: 1.0 GER	**Amendment Date:** 09 Oct 2012	**Global/Country/Site-Specific:** Country specific
Description of Change		**Section(s) Affected by Change**
Study physician changed to PPD		Protocol Signature Page
Actions to be taken to minimize discomfort to subjects added		7.0
Restrictions on the maximum amount of blood that can be drawn from subjects during a 4-week period has been included		7.2.5
The publication policy has been updated to state that: • The results of the study will be published regardless of whether the study results are positive, neutral, or negative • A publication steering committee will be created to act as a non-commercial body that advises or decides on dissemination of scientific study data • The principal investigator will own (or share with other authors) the copyright on his/her publications • The definition of publication is clarified • The results corresponding to the multicenter study should be published first • Authorship will comply with the current International Committee of Medical Journal Editors standards		10.5
The risk benefit assessment has been added		Appendix 2

Protocol Amendments		
Amendment Number: 1.0 RUS	**Amendment Date:** 25 Apr 2013	**Global/Country/Site-Specific:** Country-specific
Description of Change		**Section(s) Affected by Change**
Changed subject age requirement to children aged ≥12 years to <18 years at the time of consent (formerly children and adolescents aged >6 months to <18 years) and revised text as applicable throughout to comply with a regulatory authority request.		Study Synopsis, 2.2.2, 3.2, and 4.1
Added the statement, "Subjects aged 6 months to <12 years at the time of consent will be recruited from other participating countries."		Study Synopsis, 4.5, 9.3, 9.11, and 9.13
Revised text to give the correct phosphate levels for children aged ≥12 years to <18 years as >5.5mg/dL (1.78mmol/L); formerly stated 'children aged <12 years: serum phosphate >6.0mg/dL (1.94mmol/L).		4.1, Table 3, 6.2.1, 7.1.1.2, 7.1.1.3, 7.1.2.3, 7.1.2.4, 7.2.2, and 9.10.1
Deleted text regarding head circumference measurement for subjects aged up to 36 months		Study Synopsis, Table 1, 7.1.1.1, 7.1.1.2, 7.1.2.3, 7.1.2.6, 7.1.2.8, 7.2.1, 7.2.3.4, 9.10.2, 9.11, and 9.13
Deleted "length" as it pertained to measurement of height for infants		Study Synopsis, Table 1, 5.2, 7.1.1.1, 7.1.1.2, 7.1.2.3, 7.1.2.6, 7.1.2.8, 7.2.1, 7.2.3.4, 9.7, 9.10.2
• Deleted "children and adolescents" when describing female subjects • Revised text to indicate that 'female subjects should be premenarchal' (formerly 'female subjects should be premenarchal or aged <9 years')		4.3
Revised text to ensure that references to dosing are for children aged ≥12 years to <18 years only (formerly also referenced subjects aged <2 years and aged 2-12 years).		Study Synopsis, 6.2.1, 7.1.2.1, 7.1.2.3, 7.1.2.4, 7.1.2.5,
Hypophosphataemia criteria measurements corrected to cover children aged ≥12 years to <18 years only.		6.2.1
Revised the number of evaluable subjects to 8 (formerly 16) for Part 1 and to 44 (formerly 100) for Part 2 for the pharmacokinetic assessments.		Study Synopsis, Figure 1, and 9.13
Text added to indicate that Investigator name/contact information is provided under separate cover		Appendix 1
Text added indicating that Investigator contact information is provided under separate cover.		Appendix 2

APPENDIX 2 GUIDELINES FOR PHOSPHORUS AND CALCIUM

The following guidelines summarize the requirements for each parameter during the study.

Parameter	Value	Age Range (Years)	Action
Phosphate	<4.0mg/dL (1.29mmol/L)	12 to <18	Monitor phosphate levels carefully and consider reducing the binder dose by 25% depending on the rate at which phosphate is falling.
	<4.5mg/dL (1.45mmol/L)	10 to <12	
Phosphate	<3.5mg/dL (1.13mmol/L)	12 to <18	Binder should be stopped and phosphate levels monitored closely. The binder should be resumed at 50% of the prior dose when phosphate levels are >4.0mg/dL (1.29mmol/L).
Phosphate	<4.0mg/dL (1.29mmol/L)	10 to <12	Binder should be stopped and phosphate levels monitored closely. The binder should be resumed at 50% of the prior dose when phosphate levels are >4.5mg/dL (1.45mmol/L).
Phosphate	>10.0mg/dL (3.23mmol/L) except during washout periods	10 to <18	Discontinue subject.
Calcium	<8.8mg/dL (2.20mmol/L)	10 to <18	Subject should receive therapy to increase calcium levels.
Calcium	>10.2mg/dL (2.54mmol/L) during Part 2 Treatment Period 1	10 to <18	Active vitamin D sterols should be decreased by 50%, calcium carbonate decreased by 25% and the subjects should be monitored. If after 2 weeks hypercalcaemia persists, active vitamin D sterols should be stopped. If after another 2 weeks it persists the subject should be withdrawn from Part 2 and may continue to Part 3.
Calcium	>10.2mg/dL	10 to <18	Active vitamin D sterols

Parameter	Value	Age Range (Years)	Action
	(2.54mmol/L) during lanthanum carbonate treatment		should be decreased by 50%, calcium carbonate decreased by 25% and the subjects should be monitored. If after 2 weeks hypercalcaemia persists, active vitamin D sterols should be stopped.
Calcium	>11.5mg/dL (2.88mmol/L) during first treatment period of Part 2	10 to <18	Discontinue subject from Part 2, and proceed to Part 3.