STATISTICAL ANALYSIS PLAN

Protocol No.:	SPD405-207
Protocol 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
Sponsor:	Shire Pharmaceutical Development Ltd. (now part of Takeda) Hampshire International Business Park Chineham, Basingstoke Hampshire, RG24 8EP
Version No. and Date	Version 3.0, 14 February 2019

Version No:	Document History Description of Update	Author(s)	Effective Date
Version 0.1	Draft Version	PPD / PPD	16/09/2014
Version 0.2	Updated with SHIRE review comments on V0.1	PPD	8/10/2014
Version 0.3	Updated with SHIRE review comments on V0.2	PPD	31/10/2014
Version 1.0	Updated with SHIRE review comments on V0.3	PPD	12/11/2014
Version 1.0	Updated with SHIRE review comments on V1.0 (12Nov14)	PPD	14/11/2014
Version 1.0	Updated with SHIRE review comments on V1.0 (14Nov14)	PPD	17/11/2014
Version 1.1	Started updates to SAP related to Protocol Version 6.0 (Amendment 5), 18 Oct 2016	PPD	22/5/2017

Version 1.2	Updates based on Team comments throughout the document	PPD	14/6/2017
Version 2.0	Provided clarification of Age Group definitions to be summarized in Section 5: Subject Disposition, Section 7: Demographics and Baseline Characteristics Clarified how and when local laboratory data would be used in the absence of central lab data. Wording was added to clarify subjects who will be considered for inclusion for the PP2, PP1 and SCS analysis sets.	PPD	25/7/2017
Version 3.0	Number of evaluable subjects required updated to 32. Definition of PP1 and PP2 updated for KDOQI targets. Added evaluable subject determination specifications to the appendix. Added a summary of the number of subjects achieving age-specific KDOQI serum phosphorous target by week for both PP2 and FAS. Clarifications added to subject evaluability section. Incorporating further client comments on subject evaluability section.	PPD / PPD	14/02/2019

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ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{0-t}	area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
CC	calcium carbonate
CKD	chronic kidney disease
C_{max}	maximum plasma concentration
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
FAS	Full Analysis Set
FGF-23	fibroblast growth factor 23
GGT	gamma glutamyl transferase
IP	investigational product
KDOQI	Kidney Disease Outcomes Quality Initiative
LC	lanthanum carbonate
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
PK	pharmacokinetic
PP	per-protocol
PTH	parathyroid hormone
SAE	serious adverse event
SOC	system organ class
SAP	statistical analysis plan
TEAE	treatment-emergent adverse event
TRAP	tartrate-resistant acid phosphatase
WHO	World Health Organisation

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy, safety, and pharmacokinetic data as described in the final study protocol version 6.0 dated 18 Oct 2016 incorporating most recent amendment #5. Specifications for tables, figures, and listings are contained in a separate document.

2. STUDY DESIGN

2.1 General Study Design

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

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 Kidney Disease Outcomes Quality Initiative (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: Schedule of Assessments for Part 1, Part 2a (Treatment Periods 1 and 2), and Part 3).

Part 1 is complete and an interim clinical study report interpreting and summarizing the data for the first 10 subjects in Part 1 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 Paediatric 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: Study Design Flow Chart- Part 1, Part 2a (Treatment Periods 1 and 2) and Part 3Figure 1, all subjects were to receive lanthanum carbonate in part 2, period 2 of the crossover and had the option to continue on to Part 3 of the study on the same treatment, ie, lanthanum carbonate for up to 6 months. If needed, there was a washout period for up to 3 weeks between treatment with calcium carbonate (Part 2, Treatment Period 1) and lanthanum carbonate

(Part 2, 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 Protocol Version 6.0 (Amendment 5), Section 4.5.1 [Subject Stopping Criteria] and Section 6.2.1 [Dosing, Hypercalcemia]) for up to 6 additional months.

Following Version 6.0 (Amendment 5), Part 2 is amended to enrol subjects to receive lanthanum carbonate treatment only. The calcium carbonate treatment followed by lanthanum carbonate treatment is referred to as Part 2a in protocol Version 6 (Amendment 5). Subjects to be enrolled under Version 6 (Amendment 5), of protocol will enter/be enrolled directly into Part 2b, which is 8 weeks of lanthanum treatment only.

Part 2b: 8-week lanthanum carbonate treatment

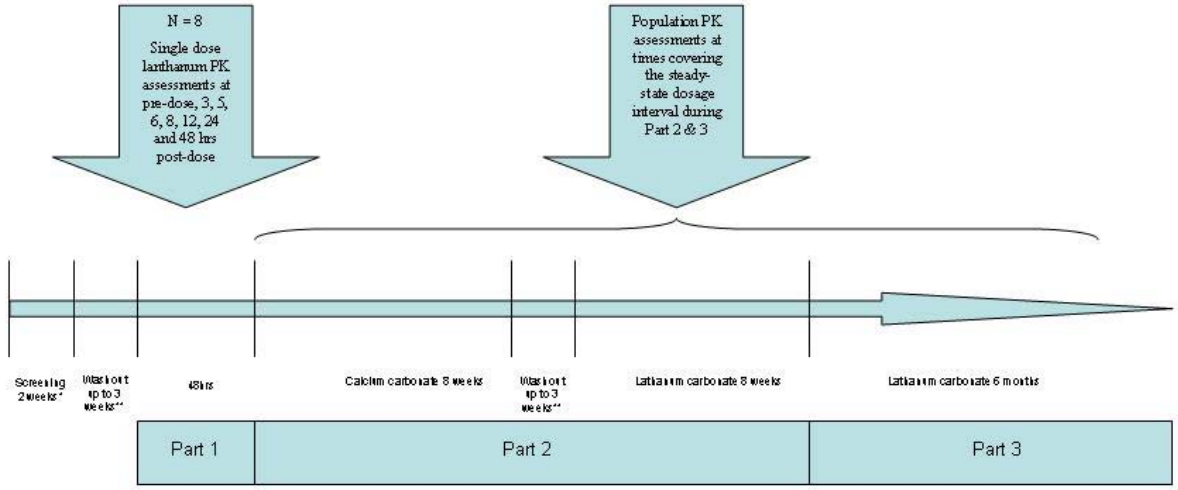
Given the extreme difficulty in recruiting enough subjects to obtain the originally proposed sample size of 50 subjects required for the Per-protocol Set for a cross-over non-inferiority study, the active comparator (calcium carbonate) treatment arm was removed (see Part 2a) in Part 2b; serious consideration 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 32 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 Protocol Version 6.0 (Amendment 5), Section 4.5.1 [Subject Stopping Criteria] 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

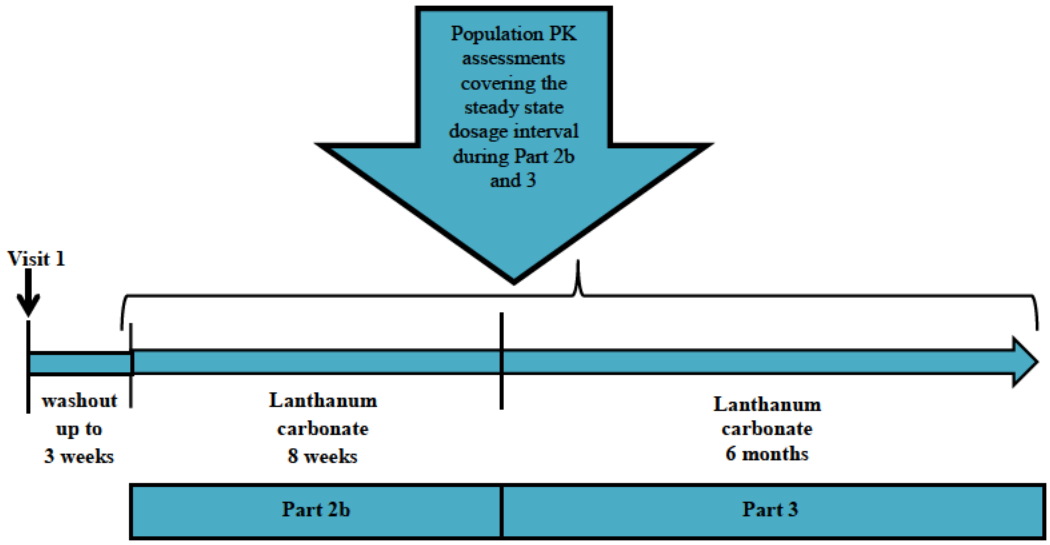


*** Screening is only required once, either at Part 1 for subjects participating, otherwise at Part 2.**

**** 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 (Protocol Version 6, Amendment 5)



***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.**

2.2 Randomization

Not applicable. This is an open-label study.

2.3 Blinding

This is an open-label study; the study includes only 1 sequence in Part 2, (calcium carbonate for the treatment period 1 and lanthanum carbonate for the treatment period 2). Blinding is not applicable.

2.4 Schedule of Assessments

Table 1 below presents a schematic of the study design.

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	✔		✔	✔				✔			✔		✔	
Local laboratory tests[f]		✔		✔	✔	✔	✔		✔	✔		✔		
Central laboratory phosphate		✔			✔				✔					

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]**
confirmation														
Biochemistry	✔			✔				✔			✔		✔	
Hematology	✔			✔									✔	
Biochemical bone markers	✔			✔				✔			✔		✔	
Pregnancy test (where applicable)	✔			✔									✔	
Lanthanum pharmacokinetics			✔							✔[g]		✔[h]		
Investigational product dispensed			✔	✔[e]	✔[e]	✔	✔	✔	✔	✔	✔[i]	✔		
Investigational product collected						✔	✔	✔		✔	✔	✔	✔	
Dose adjustment (as needed) and compliance						✔	✔	✔		✔	✔	✔	✔	
Record adverse events	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Record concomitant medication	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔

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]**
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.

[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.

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]**

[i] For subjects entering Part 3 only.

[j] Only for subjects completing the washout.

[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	✔					✔	

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]**
Biochemical bone markers	✔			✔		✔	
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	✔		✔	✔	✔	✔	

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]**

[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.

[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.

2.5 Determination of Sample Size

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 Kidney Disease Outcome Quality Initiative (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 32 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 paediatric population.

For the investigation of safety profile in hyperphosphatemic children and adolescents with chronic kidney disease (CKD) on dialysis treated with lanthanum carbonate, a sample size of 32 subjects is necessary in order to observe at least one event with a true event rate of 5% at a probability of 80.6%.

2.6 Multiplicity Adjustments for Type I Error Control

There is a single primary objective that specifies summarization of the percentage of subjects achieving age-specific KDOQI targets for serum phosphorus in hyperphosphatemic children and adolescents with CKD who are on dialysis, following 8 weeks of treatment with lanthanum carbonate. Consequently, no adjustment for multiplicity is required.

3. OBJECTIVES

3.1.1 Primary Objectives

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.

3.1.2 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 [Cmax] and area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration [AUC0-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 and weight**.**

4. SUBJECT POPULATION SETS

4.1 Screened Set

The Screened Set is defined as the set of subjects who have signed informed consent.

4.2 Enrolled Set

The Enrolled Set is defined as subjects who have signed informed consent and have begun some study procedures (eg, dispensed investigational product, current drug has been withdrawn).

4.3 Safety Analysis Sets

4.3.1 Safety Analysis Set 1 (SAS1)

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

4.3.2 Safety Analysis Set 2 (SAS2)

Safety Analysis Set 2 is defined as 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 and will include events occurring during calcium carbonate therapy prior to receiving lanthanum carbonate or going off study. Safety assessments from the period when a subject is exposed to lanthanum carbonate will be summarized for lanthanum carbonate treatment.

4.3.3 Safety Completer Set (SCS)

The Safety Completer Set is defined as subjects who receive at least 8 weeks of lanthanum carbonate treatment from either Part 2 or Part 3 of the study.

4.4 Full Analysis Set (FAS)

The Full Analysis Set is defined as 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.

4.5 Per-protocol Set 1 (PP1)

Per-protocol Set 1 is defined as 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 above the age-specific KDOQI targets at study entry and between the calcium carbonate treatment and lanthanum carbonate treatment at Visit 2.4 or the visits during washout will be included in this

set. Further details are described in the Evaluable Subjects Determination Plan which can be found in Section 21.

4.6 Per-protocol Set 2 (PP2)

Per-protocol Set 2 is defined as 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 above the age-specific KDOQI targets prior to the start of lanthanum carbonate treatment will be included in this set. Further details are described in the Evaluable Subjects Determination Plan which can be found in Section 21.

Subjects who experienced hypophosphatemia, that lead to temporary interruption or discontinuation of treatment before the 8-week phosphate assessment, are considered compliant with the 8 week treatment requirement (as treatment dosed per-protocol, Section 6.2.1) and can thus be included in the PP2, PP1, and SCS analysis populations.

In previous versions of the protocol, a Per-protocol (PP) Set, defined as consisting "… of all Subjects in the FAS who complete Part 2 (ie, subjects who have a visit 2.8 serum phosphorus assessment) and do not have any pre-defined major protocol deviations that may affect the primary efficacy variable" was the only analysis set created to summarize efficacy endpoints. Following Protocol Version 6.0 (Amendment 5), two PP sets: PP1 and PP2 were defined.

4.7 Pharmacokinetic Sets (PK Sets)

4.7.1 Pharmacokinetic Set 1

The Pharmacokinetic Set 1 is defined in Section 12.1.

4.7.2 Pharmacokinetic Set 2

The Pharmacokinetic Set 2 is defined in Section 12.1.

5. SUBJECT DISPOSITION

Part 1: A summary table will be produced for all subjects showing the number of subjects screened and enrolled, in addition to the number and proportion of subjects in the Safety Analysis Set 1, subjects who completed Part 1, subjects who prematurely discontinued from Part 1 (also split by reason for withdrawal) and subjects who entered Part 2 (**Table 1.1.1.1)**. This summary table will also be presented by age group (≥ 10 to <12 years, ≥12 to <18 years). (**Table 1.1.1.2)**

Part 2 (2a and 2b):

A summary table will be produced by treatment group, showing the number and proportion of subjects in the Safety Analysis Set 2 (including those who entered the study in Part 2b), subjects who completed Part 2, subjects who prematurely discontinued from Part 2 (also split by reason for withdrawal), subjects who entered Part 3 (prematurely or otherwise), including those who entered Part 3 due to hypercalcaemia during treatment with calcium carbonate in Part 2 (a), subjects in the FAS, PP1, PP2 and subjects in the SCS Set. **(Table 1.1.2.1)** This summary table will also be presented by age group (≥ 10 to <12 years, ≥12 to <18 years). **(Table 1.1.2.2)**

Part 2a (Treatment Period 2), Part 2b and Part 3 Combined (Lanthanum Carbonate only): A summary table will be produced showing the number and proportion of subjects in Safety Analysis Set 2 who completed the study, who entered Part 3 due to hypercalcaemia during treatment with calcium carbonate in Part 2a (Treatment Period 1), subjects in the FAS, PP2, SCS Set and subjects who prematurely discontinued from the study (also split by reason for withdrawal). **(Table 1.1.3.1)** This summary table will also be presented by age group (≥ 10 to <12 years, ≥12 to <18 years). **(Table 1.1.3.2)**

An enrolment summary will be presented by site, and by country, showing the first day of consent, and the last study completion/withdrawal date among all Enrolled Subjects, the duration of enrolment (in days) [calculated as (last date of contact for any subject at that site - the first date of informed consent for any subject at that site + 1)], and the number of subjects enrolled and in each subject population set. The number and proportion of subjects enrolled in total, by site, and by country will be summarised. For individual sites, the site location and primary investigator's name will also be presented. **(Table 1.1.4)**

A listing of all Screen Failures (ie, subjects who gave informed consent and failed to meet the inclusion and/or met at least 1 of the exclusion criteria and were not administered IP(s) as defined by the protocol) will be presented along with reasons for screen fail and details of any adverse events (AEs).

A listing of subject disposition **(Listing 1.1)** will be provided for all Enrolled Subjects, including the date of informed consent/assent, date of first dose and date of last dose for each part of the study (Part 1, Part 2, and Part 3) and each treatment group, accordingly (Part 2a: Calcium Carbonate, Part2a: Lanthanum Carbonate), date of completion/discontinuation, and whether the subject completed the study. Details of early terminations will also be listed for all Enrolled Subjects including the date of informed consent/assent, date of first dose and date of last dose for the part of the study (Part 1, Part 2, or Part 3) and treatment group, accordingly (Part 2a: Calcium

Carbonate, Part 2a: Lanthanum Carbonate or Part 2b: Lanthanum Carbonate) in which the subject withdrew, date of termination, duration of exposure (days), and primary reason for discontinuation as recorded on the termination page in the eCRF. **(Listing 1.2)** A listing of study analysis set classifications will be provided for all Enrolled Subjects specifying whether each subject was part of the defined analysis sets of Section 4, or not. **(Listing 1.3)**

6. PROTOCOL DEVIATIONS

Part 1: A summary of the number (and percentage) of all Safety Analysis Set 1 with any protocol deviations, as well as the categories of deviations, will be provided overall and by site. **(Table 1.5.1)**

Part 2: A summary of the number (and percentage) of subjects in the Safety Analysis Set 2 with any protocol deviations, as well as the categories of deviations, will be provided overall and by site for each treatment group. **(Table 1.5.2)**

Part 2 and 3 combined (Lanthanum Carbonate only): A summary of the number (and percentage) of subjects in the Safety Analysis Set 2 and SCS with any protocol deviations, as well as the categories of deviations, will be provided overall and by site. **(Table 1.5.3, Table 1.5.4)**

Protocol deviation data will be listed for all enrolled subjects. **(Listing 2.1.1)**

Evaluable subjects for the PP1 and PP2 Sets will be listed for the Full Analysis Set. **(Listing 2.1.2)**

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Part 1: Descriptive summaries will be presented for Lanthanum Carbonate for the Safety Analysis Set 1 **(Table 1.2.1.1.1)** and presented by age group (≥ 10 to <12 years, ≥12 to <18 years). (**Table 1.2.1.1.2)**

Part 2: Descriptive summaries will be presented by treatment group for the Safety Analysis Set 2, the FAS, the PP1, the PP2 for lanthanum carbonate treatment only (Part 2a, Treatment Period 2 and Part 2b) additionally presented by age group (≥ 10 to <12 years, ≥12 to <18 years) **(Table 1.2.1.2.1 to Table 1.2.1.4.2 and Table 1.2.1.5.1 and Table 1.2.1.5.2, respectively)**.

Part 2 and 3 Combined (Lanthanum Carbonate only): Descriptive summaries will be presented for Lanthanum Carbonate for the SCS for 8 weeks of lanthanum carbonate treatment only, **(Table 1.2.1.6.1)** additionally presented by age group (≥ 10 to <12 years, ≥12 to <18 years). **(Table 1.2.1.6.2)**

Pharmacokinetic Set 1: Descriptive summaries will be presented for PK Set 1 **(Table 1.2.1.7.1)**, and additionally presented by age group (≥ 10 to <12 years, ≥12 to <18 years). **(Table 1.2.1.7.2)**

Pharmacokinetic Set 2: Descriptive summaries will be presented for PK Set 2 **(Table 1.2.1.7.3)**, and additionally presented by age group (≥ 10 to <12 years, ≥12 to <18 years). **(Table 1.2.1.7.4)**

The following demographic characteristics will be summarised in the following order in the tables: age (years), age group (categorical: <10 years, ≥ 10 to <12 years, ≥12 to <18 years and ≥18 years), sex, ethnicity, race, weight (kg), height (cm) and Body Mass Index (kg/m^2). Continuous variables such as subject age, weight, and height will be summarised using number of observations, mean, standard deviation, median, minimum, and maximum values. Categorical variables such as the subject's sex, ethnicity, and race will be summarised using number of observations and percentages for each category. Please note that age will only be calculated when the date of birth is not partial. Age will be calculated as the difference between date of birth and date of informed consent or assent, which is usually signed at the beginning of the Screening Period.

Renal history will be summarised for each of the Safety Analysis Sets (Safety Analysis Set 1, Safety Analysis Set 2 and the SCS) for each Part of the study **(Table 1.2.2.1 [Part 1], Table 1.2.2.2 [Part 2], Table 1.2.2.3 [Part 2 and 3 combined])**, including the number and proportion of subjects who have each of the primary and secondary renal disease diagnoses stated in the eCRF, subjects who have haemodialysis and peritoneal dialysis and the categorical calcium concentrate (mmol/L) of the dialysate currently used for the subjects. In addition, summary statistics (n, mean, standard deviation, minimum, median, and maximum) for the time since first dialysis (calculated as the difference between date of first dialysis and date of informed consent or assent, truncated to years) will be presented.

A listing of demographic and other baseline characteristics will be provided for all Enrolled Subjects. **(Listing 4.1)**

Renal history and diagnosis information including primary renal disease diagnosis, secondary renal disease diagnosis, date of first dialysis, type of dialysis, and the current calcium concentration of the dialysate the subject is using will also be listed for all Enrolled Subjects. **(Listing 4.2)**

Medical history including verbatim term, date of onset, and date resolved (or whether it was ongoing) will be listed for all Enrolled Subjects. **(Listing 4.3)**

8. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

8.1 Exposure to Investigational Product

Exposure to IP will be summarised in terms of treatment duration for Parts 2 and 3, which is calculated as the number of days from the date of first dose of IP taken to the date of the last dose of IP taken within the respective part of the study, inclusively.

Part 1: Data regarding study drug exposure during Part 1 will be listed for the Safety Analysis Set 1, including treatment start date, treatment start time, and dose per administration (mg). **(Listing 5.1.1)** For the Safety Analysis Set 2, summary statistics (n, mean, standard deviation, minimum, median, and maximum) for the total daily dose (mg/day), and length of exposure (days) will be presented by treatment group where total dose is defined as the sum of the doses within a treatment group and total daily dose is defined as the total dose / total days of dosing. In addition, total exposure (person-years and a summary of the number (and percentage) of subjects who fall within the categories of ≤1 week, >1-2 weeks, >2-3 weeks, >3-4 weeks, >4-5 weeks, >5-6 weeks, >6-7 weeks, >7-8 weeks, and >8 weeks, for the length of exposure will be presented by treatment group. Total exposure (person-years) will be the total number of days of IP (last dose – first dose + 1) summed over all subjects within a treatment group divided by 365.25 days. **(Table 4.1.1; Listing 5.1.2)**

Part 2 and 3 Combined (Lanthanum carbonate only): For the Safety Analysis Set 2 and SCS, summary statistics (n, mean, standard deviation, minimum, median, and maximum) for the total daily dose (mg/day), and length of exposure (days) will be presented. In addition, total exposure (person-years) and a summary of the number (and percentage) of subjects whose length of exposure fall within specified categories (≤1 week, >1-4 weeks, >4-8 weeks, >8-12 weeks, >12-16 weeks, >16-20 weeks, >20-24 weeks, >24-28 weeks, >28-32 weeks, and >32 weeks) will be presented. **(Table 4.1.2 and Table 4.1.3)**

Data regarding study drug exposure during Part 2 and 3 will be listed for the Safety Analysis Set 2 and SCS, including date of first dose, treatment, total daily dose (mg), and date of last dose. In addition the date the IP was returned from the previous visit, the amount of IP returned, the amount of IP taken, as well as the date the IP was dispensed, and the amount of IP dispensed, will also be listed by timepoint. **(Listing 5.1.2 and Listing 5.1.3, respectively)**

8.2 Measurement of Treatment Compliance

Investigational Product dosing compliance for a specified period is defined as the total number of sachets/tablets actually taken by a subject during that period divided by the number of sachets/tablets expected to be taken during the same period multiplied by 100. The total number of sachets/tablets actually taken is calculated by the total number of sachets/tablets dispensed minus the number of sachets/tablets returned. The number of sachets/tablets expected to be taken for a specified period is calculated as the number of days in that period multiplied by the number of sachets/tablets to be taken per day during that period. Within the summary tables of IP exposure, a summary of the number (and percentage) of subjects who fall within the compliance categories of <60%, 60% - 120%, and >120% will be presented. Exposure in Part 2 will be summarized by treatment group for Safety Analysis Set 2 **(Table 4.1.1);** Lanthanum Carbonate

exposure in Part 2 and 3 combined will be summarized for the Safety Analysis Set 2 and SCS **(Table 4.1.2 and Table 4.1.3, respectively).** Subject compliance within Part 1, Part 2 only and within Part 2 and 3 combined will be listed within the IP accountability listing by treatment group**. (Listing 5.1.1, Listing 5.1.2, Listing 5.1.3)**

9. PRIOR AND CONCOMITANT MEDICATION

Presently, version 2013Sep01_DD (Basic) of the World Health Organization (WHO) drug dictionary, is being used to classify prior and concomitant medications by therapeutic class. However, nearer to the conclusion of data collection, a decision will be made as to the most desirable dictionary to use.

Prior medications will be presented for Part 1 **(Table 1.3.1)** and Part 2 **(Table 1.3.2)** and defined as any medication with a start date prior to the date of first IP intake in the relevant Part of the study, irrespective of when they stopped (for more specifics please see Protocol Section 5.1). Concomitant medication usage will be summarised by the number and proportion of subjects receiving each medication within each preferred term for the Safety Analysis Set 1, Safety Analysis Set 2 and the SCS.

Part 1: Concomitant medications in Part 1 are defined as any medication with a start date prior to Part 1 and continuing on to 2 days after the day of IP in Part 1. Concomitant medication usage will be summarised by the number and proportion of subjects receiving each medication within each preferred term for the Safety Analysis Set 1. Multiple medication usage by a subject in the same category will be counted only once. **(Table 1.3.3)**

Part 2: Concomitant medication in Part 2 of the study is defined as any medication with a start date prior to Part 2 and continuing after the first dose of IP in Part 2, or with a start date between the dates of the first and last doses of IP in Part 2, inclusive. **Any medication with a start date after the date of the last dose of IP in Part 2 will not be considered a concomitant medication in Part 2**. In the case of missing or partially missing start or stop dates for concomitant medications, if the information available could only lead to the medication being considered as starting on or after the first dose of IP in Part 2 and on or before the last dose date in Part 2 then it will be considered concomitant in Part 2. Concomitant medications will be listed and summarised by preferred drug name and treatment group. Concomitant medication usage will be summarised by the number and proportion of subjects in each treatment group receiving each medication within each preferred term for the Safety Analysis Set 2. Multiple medication usage by a subject in the same category will be counted only once. **(Table 1.3.4, Table 1.3.5)**

Part 2 and 3 combined (Lanthanum carbonate only): Concomitant medications in Part 2 and 3 combined are defined as any medication with a start date prior to and continuing after the first dose of lanthanum carbonate in Part 2 or 3, or with a start date between the dates of the first and last doses of lanthanum carbonate (inclusive) within Part 2 and 3 combined. Any medication with a start date after the date of the last dose of lanthanum carbonate in Part 2 and 3 combined will not be considered a concomitant medication in Part 2 and 3 combined. In the case of missing or partially missing start or stop medication dates, if with the available information one could only conclude that a medication started on or after the first dose of lanthanum carbonate in Part 2 or 3, and on or before the last dose of lanthanum carbonate in Part 2 and 3 combined, then the medication will be considered concomitant in Part 2 and 3 combined. Concomitant medications will be listed and summarised by preferred drug name. Concomitant medication usage will be summarised by the number and proportion of subjects receiving each medication within each preferred term for the Safety Analysis Set 2 and the SCS. Multiple medication usage by a subject in the same category will be counted only once. **(Tables 1.3.6 and Table 1.3.7)**

All prior and concomitant medications will be listed (Listing 4.4) including medication name, preferred drug name, the total daily dose (and units), route, frequency, indication, start date of medication, stop date of medication (or whether ongoing), classification of prior and concomitant, and if it was a concomitant medication; whether it was a vitamin D therapy, growth hormone, or proton pump inhibitor.

10. EFFICACY ANALYSES

Efficacy analyses will be based on the PP2, PP1and FAS Sets. Generally, Baseline, for all efficacy analyses, is defined as the last assessment prior to the first dose of IP. A detailed description of Baseline, for the study, for treatment groups in Parts 2 and 3, can be found in the TLG shells, Appendix 2.

All confidence intervals will be 2-sided 95% confidence intervals.

10.1 Primary Efficacy Endpoint(s) and Analysis

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 an exact (Clopper-Pearson) 95% confidence interval. PP2 will be the primary analysis population and 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. Please note that serum phosphorous assessments must come from a homogeneous source ie, from either central or local laboratory for baseline and following weeks 8 of lanthanum treatment, respectively, within subject **(Table 3.1.1.1 and Table 3.1.1.2)**. KDOQI Serum Phosphorous Target Achievement will be listed **(Listing 6.1).**

10.2 Key Secondary Efficacy Endpoint(s) and Analysis

Not applicable.

10.3 Other Secondary Efficacy Endpoint(s) and Analysis

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

Secondary variables are:

- The percentage of subjects with serum phosphorus levels at or 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 similarly as for the primary efficacy variable, however, this will be performed for each treatment arm. The PP1 and FAS will be used for this summarization. (Table 3.1.2.1 and Table 3.1.2.2) The KDOQI serum phosphorus targets are defined above.

- 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. The PP2 and FAS will be used for this summarization **(Table 3.1.4.1 to Table 3.1.4.6)** [Part 2 and 3 combined].
- 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**.** The PP1 and FAS Set will be used for this summarization **(Table 3.1.3.1 to Table 3.1.3.6)** [Part 2].
- Change from baseline in serum phosphorus, calcium and calcium-phosphorus product levels at the last visit of 8-week treatment period during Part 2 and monthly during the 6-month extension phase (Part 3). The PP2 and FAS Sets will be used for this summarization **(Table 3.1.4.1 to Table 3.1.4.6)** [Part 2 and 3 combined].
- 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 (**Tables 3.1.5.1 to 3.1.5.14** [Part 2a and 3], **Tables 3.2.5.1 to 3.2.5.14** [Part 2b and 3]) will be summarized for PP1 and FAS and PP2 and FAS, respectively.
- Height and Weight at:
    - Visits 2.0, 2.4, 2.8, and 3.5 (Parts 2a and 3): **(**PP1 and FAS Sets)
    - Visits 1.0, 2.4, and 3.5 (Parts 2b and 3). (PP2 and FAS Sets)

  (**Tables 3.1.6.1 to 3.1.6.4, Tables 3.1.7.1 to 3.1.7.4**, respectively).
- Number and percentage of subjects with serum phosphorus levels at the age-specific KDOQI targets by week of treatment with lanthanum carbonate for PP2 and FAS (**Tables 3.1.8.1 to 3.1.8.2,** respectively).

All secondary variables will be summarised using descriptive statistics as follows:

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

All secondary efficacy endpoints will be summarised using both an appropriate PP Set (for the endpoint) and the FAS. Serum phosphorus, calcium, and calcium-phosphorus product will be summarized for Part 2 by treatment and weeks of administration of treatment, and for Part 2 and 3 combined for lanthanum carbonate only by weeks of treatment with lanthanum carbonate. For summaries by week of treatment, +/-1 week will be used to assign values to a timepoint ie, Week 8 will include 7-9 weeks of exposure. If more than 1 value for a subject falls into one window, then the value closest to the planned visit will be included in the summary, ie, if we have a value on day 51 and a value on day 57, the day 57 value will be used in the Week 8 summary. If two values are equidistance from the timepoint then the higher value will be used for analysis, assuming worst case.

All other secondary endpoints will be summarized by scheduled assessment.

It is stated in the protocol that 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 analysed. However, it should be clarified that in the case of missing central laboratory data, local laboratory data will be used, as appropriate. For example, in the case of the change from baseline to an assessment following 8 weeks of an IP, both assessments (baseline and following 8 weeks of treatment) must be from either the central or the local lab.

Bar charts will be provided for the mean change from baseline in Part 2 by treatment group for serum phosphorus, **(Figure 3.1.3.1)** calcium **(Figure 3.1.3.2,),** and calcium-phosphorus product **(Figure 3.1.3.3)** for the PP1 Set**.**

The mean change from baseline in Part 2 and 3 combined by weeks of treatment with lanthanum carbonate will also be graphically presented, via line graph for serum phosphorus, calcium, and calcium-phosphorus product for the following Analysis Populations: PP2, FAS Sets. **(Figures 3.1.4.1 to 3.1.4.6)**

10.4 Exploratory Efficacy Endpoint(s) and Analyses

Not applicable.

11. SAFETY ANALYSES

For scheduled assessment all safety variables for Part 1 will be summarised using the Safety Analysis Set 1; Safety variables for Parts 2 and 3 will be summarised using the Safety Analysis Set 2 and SCS (where applicable). Safety variables include AEs, clinical laboratory variables, vital signs, and electrocardiogram (ECG) variables. For each safety variable, the last value collected before the first dose of IP will be used as baseline for all analyses of that safety variable. Additionally, a detailed description of Baseline, for treatment groups in Parts 2 and 3, can be found in the TLG shells, Appendix 2.

11.1 Adverse Events

Onset day of an AE is calculated as (start date of the AE - date of the first dose of IP) + 1. AEs will be classified into system organ class (SOC) and preferred term (PT) using Version 16.1, of MedDRA, to be determined closer to the conclusion of data collection.

An AE that occurs during the study will be considered a treatment emergent AE (TEAE) if it has a start date on or after the first dose of IP. TEAEs will be allocated to Part 1, Part 2, or Part 3, based on the onset date of the AE relative to the date and Part of the most recently administered IP. If an AE occurred more than 3 weeks after the date of the most recent IP, it will not be considered a TEAE. In the case of increases in severity, if there is more than 1 reference AE with the same preferred term then the AE with the greatest severity will be used as the benchmark for comparison to the AEs occurring in each Part of the study.

Part 1: An overall summary **(Table 4.2.1.1)** and summary by age group **(Table 4.2.1.2)** of the number of subjects in Safety Analysis Set 1 with TEAEs in Part 1 will be presented, including the number and proportion of subjects with any TEAEs, serious TEAEs, TEAEs related to lanthanum carbonate, TEAEs leading to study withdrawal, and TEAEs leading to death. The number of events, incidence, and percentage of TEAEs will be presented by SOC, and by preferred term **(Table 4.2.2.1);** by SOC, preferred term, and maximum severity **(Table 4.3.1.1);** and by SOC, preferred term, and relationship to lanthanum carbonate **(Table 4.3.2.1).** Similar summaries by SOC and preferred term will be produced for SAEs **(Table 4.4.1.1),** for deaths **(Table 4.4.2.1),** and for TEAEs leading to study withdrawal **(Table 4.4.3.1).** AEs **(Listing 7.1),** SAEs **(Listing 7.2),** AEs related to lanthanum carbonate **(Listing 7.3),** AEs leading to study withdrawal **(Listing 7.4),** and deaths **(Listing 7.5)** will be listed. AEs related to bone disease (preferred terms: adynamic bone disease and long bone fracture) are of special interest and will be summarised by SOC and preferred term **(Tables 4.5.1.1 and 4.5.2.1)** and listed separately **(Listing 7.6)**.

Part 2: An overall summary **(Table 4.2.1.3)** and summary by age group **(Table 4.2.1.4)** of the number of subjects in Safety Analysis Set 2 with TEAEs in Part 2 will be presented, including the number and proportion of subjects with any TEAEs, serious TEAEs, TEAEs related to IP, TEAEs leading to study withdrawal, and TEAEs leading to death. The number of events, incidence, and percentage of TEAEs in each treatment group will be presented by SOC and preferred term **(Table 4.2.2.2)**; by SOC, preferred term, and maximum severity **(Table 4.3.1.2);** and by SOC, preferred term, and relationship to IP **(Table 4.3.2.2).** Similar summaries by SOC and preferred term will be produced for SAEs **(Table 4.4.1.2),** for deaths **(Table 4.4.2.2),** and for

TEAEs leading to study withdrawal **(Table 4.4.3.2).** AEs, AEs related to IP, SAEs, AEs leading to study withdrawal, and deaths will be listed **(Listing 7.1, Listing 7.3, Listing 7.4 and Listing 7.5).** TEAEs related to bone disease (preferred terms: adynamic bone disease and long bone fracture) are of special interest and will be summarised by SOC and preferred term for Part 2 **(Tables 4.5.1.2 and 4.5.2.2)** and listed separately **(Listing 7.6).**

Part 2 and 3 combined (lanthanum carbonate only): An overall summary **(Tables 4.2.1.5 and 4.2.1.7)** and summary by age group **(Tables 4.2.1.6 and 4.2.1.8)** of the number of subjects in Safety Analysis Set 2 and SCS with TEAEs in Part 2 and 3 combined will be presented. The number of events, incidence, and percentage of TEAEs will be presented by SOC by preferred term **(Tables 4.2.2.3 and 4.2.2.4);** by SOC, preferred term, and maximum severity **(Tables 4.3.1.3 and 4.3.1.4);** and by SOC, preferred term, and relationship to lanthanum carbonate **(Tables 4.3.2.3 and 4.3.2.4).** Similar summaries by SOC and preferred term will be produced for SAEs **(Tables 4.4.1.3 and 4.4.1.4),** for deaths **(Tables 4.4.2.3 and 4.4.2.4),** and for TEAEs leading to study withdrawal **(Tables 4.4.3.3 and 4.4.3.4)**. AEs, AEs related to lanthanum carbonate, SAEs, AEs leading to study withdrawal, and deaths will be listed (refer to listings noted above). TEAEs related to bone disease (preferred terms: adynamic bone disease and long bone fracture) are of special interest and will be presented by SOC and preferred term in **Table 4.5.1.3 and Table 4.5.1.4** and **by sex and age group in Table 4.5.2.3 and 4.5.2.4** and will be listed separately. **(Listing 7.6)**

Only Part 2 will be summarised by treatment group (Calcium Carbonate and Lanthanum Carbonate) for the Safety Analysis Set 2 population summary.

11.2 Clinical Laboratory Variables

Clinical laboratory data (biochemistry, haematology, and biochemical bone markers) will be summarised by parameter and visit for Part 1 for the Safety Analysis Set 1 **(Tables 4.6.1.1, 4.6.1.2 and 4.6.1.3,** respectively**)**.

Clinical laboratory data (biochemistry, haematology, and biochemical bone markers) will be summarised by parameter, visit and treatment group for Part 2 and 3 for the Safety Analysis Set 2 (**Tables 4.6.2.1, 4.6.2.2 and 4.6.2.3,** respectively). Additionally, summarization will also be performed by parameter and visit for Lanthanum Carbonate for Parts 2 and 3 for the SCS (**Tables 4.6.2.4, 4.6.2.5 and 4.6.2.6,** respectively).

Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) for clinical laboratory values (in SI units) and changes from baseline at each assessment time point as well as shift tables (in terms of abnormality: low, normal, and high) from baseline to each visit for quantitative variables will be presented for the following clinical laboratory variables for Part 2 and 3 for the Safety Analysis Set 2 (**Tables 4.6.3.1, 4.6.3.2, 4.6.3.3**) and SCS (**Tables 4.6.3.4, 4.6.3.5 and 4.6.3.6**).

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	Alanine aminotransferase (ALT)
Potassium	ALP
Calcium	Gamma glutamyl transferase (GGT)
Urea	Total bilirubin
Creatinine	Magnesium
Albumin	Serum phosphorus
Total protein	25-hydroxy Vitamin D[a]
Aspartate aminotransferase (AST)	

[a] 25-hydroxy Vitamin D will be measured at baseline and End of Study (EOS) only.

Haematology

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

Haemoglobin	Mean corpuscular haemoglobin (MCH)
Haematocrit	Mean corpuscular haemoglobin concentration (MCHC)
Red blood cells	White blood cell count – total and differential
Mean corpuscular volume (MCV)	Platelet count

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:

Tartrate-resistant acid phosphatase	Bone ALP
Osteocalcin	Sclerostin
Fetuin- A	PTH
FGF-23	

Normal ranges for all clinical laboratory data parameters (biochemistry, haematology, and biochemical bone markers) will be listed **(Tables 4.6.5.1, 4.6.5.2 and 4.6.5.3,** respectively**)**.
All clinical laboratory data including serum pregnancy test results will be listed **(Listings 8.1.1** [clinical laboratory sample collection and results for pregnancy]
and Listing 8.1.2 [clinical laboratory test results]**)**.

11.3 Vital Signs

Vital signs data [height (cm), weight (kg), pulse (beats/min), systolic blood pressure (mmHg), and diastolic blood pressure (mmHg)] will be summarised by visit and by timepoint (for Visit 1.1); by Lanthanum Carbonate for Part 1 **(Table 4.7.1),** by treatment group for Part 2 and 3, for Lanthanum Carbonate only for Part 2 and 3 for the Safety Analysis Set **2 (Table 4.7.2 and Table 4.7.3,** respectively) and for Lanthanum Carbonate only for Part 2 and 3 for the SCS **(Table 4.7.4).** Baseline is defined as the last assessment prior to the first dose of IP. A detailed description of Baseline, for the study, for treatment groups in Parts 2 and 3, can be found in the TLG shells, Appendix 2.

Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) for vital sign variables and their changes from baseline at each post-baseline visit will be presented.

All vital signs data will be listed **(Listing 8.2.1).**

11.4 Electrocardiogram (ECG)

ECG interpretation will be summarised by visit for Lanthanum Carbonate only for Parts 2a and 3 combined and Parts 2b and 3 combined for the Safety Analysis Set 2 **(Table 4.8.1 and Table 4.8.2,** respectively) and the SCS (**Table 4.8.3 and Table 4.8.4**, respectively). A shift table (in terms of clinical significance: normal, abnormal not clinically significant, and abnormal clinically significant) from baseline to each visit for qualitative ECG results will be presented for Lanthanum Carbonate only for Parts 2a and 3 combined and Parts 2b and 3 combined for the Safety Analysis Set 2 (**Table 4.8.5 and Table 4.8.6,** respectively) and for the SCS (**Table 4.8.7 and Table 4.8.8,** respectively).
ECG Investigator interpretations will be listed **(Listing 8.3.1)**.

11.5 Other Safety Variables

No other safety assessments/variables are planned for this study.

12. CLINICAL PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

12.1 Pharmacokinetics Population (and Pharmacodynamic Population, if applicable)

Pharmacokinetic Set 1 - Subjects in the Safety Analysis Set 1 who have at least 1 measurable post-dose plasma concentration of Lanthanum Carbonate. Subjects in Part 1 who vomited may be excluded from Pharmacokinetic Set 1.

Pharmacokinetic Set 2 - Subjects in Safety Analysis Sets 1 or 2 who have at least 1 measurable post-dose plasma concentration of Lanthanum Carbonate will be included in Pharmacokinetic Set 2.

12.2 Pharmacokinetic Methods

12.2.1 Concentration Data

Plasma lanthanum concentrations will be measured using Inductively Coupled Plasma Mass Spectrometry.

12.2.2 Handling BLQ Values

The following procedures will be used for plasma concentrations below the lower limit of quantification (LLOQ) (reported as not quantifiable [NQ]):

- Plasma samples that are BLQ are reported as zero on the data listings.
- Samples that are BLQ are treated as zero in the calculation of summary statistics (eg mean, SD, etc.) for the plasma concentrations at individual time points.
- Mean concentrations are reported as zero if all values are BLQ, and no descriptive statistics are reported. If the calculated mean (± SD) concentration is less than the LLOQ, the value will be reported as calculated. The mean values derived using these conventions will be used to create the mean plasma concentration versus time plots.
- For calculation of area under the plasma concentration curve (AUC), BLQ values are set equal to zero in the dataset loaded into WinNonlin for pharmacokinetic analysis. WinNonlin uses the zero values that occur before the first time point with a concentration greater than LLOQ, but WinNonlin excludes the zero values from the AUC calculation for all later time points.

12.2.3 Pharmacokinetic Parameters

Part 1

The PK analysis for Part 1 will be conducted by the Clinical Pharmacology and Pharmacokinetics Department of Shire Pharmaceuticals or its designee using WinNonlin Phoenix version 6.2 or higher (Pharsight Corporation, Mountain View, California, USA).

PK parameters will be determined from the plasma concentration-time data for lanthanum by non-compartmental analysis. All calculations will be based on actual sampling times.

The PK parameters will include, but not be limited to:

- C_{max} Maximum concentration occurring at t_{max}
- t_{max} Time of maximum observed concentration sampled during a dosing interval
- $AUC_{0-\infty}$ Area under the curve extrapolated to infinity, calculated using the observed value of the last non-zero concentration
- AUC_{last} Area under the curve from the time of dosing to the last measurable concentration
- AUC_{0-48} Area under the curve over the interval from dosing to 48 hours post-dose
- $t_{½}$ Terminal half-life
- λ_z First order rate constant associated with the terminal (log-linear) portion of the curve
- CL/F Total body clearance for extravascular administration divided by the fraction of dose absorbed
- Vz/F Volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed.

Parts 2 and 3

The PK analysis for Parts 2 and 3 will be conducted by a vendor that specializes in population PK analysis**.**

Plasma concentration-time data for Part 2 treatment period 2, and Part 3 will be combined with those from Part 1 and subjected to population PK analysis using NONMEM to determine estimates of steady-state systemic exposure ($C_{max,}$ 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.

12.3 Statistical Analysis of Pharmacokinetic Data

All of the PK analyses for Part 1 will be performed using the Pharmacokinetic Set 1. All of the PK analyses for Parts 2 and 3 will be performed using the Pharmacokinetic Set 2.

Summary statistics (number of observations, mean, standard deviation, coefficient of variation, median, maximum, minimum, and geometric mean) will be determined for all pharmacokinetic parameters by age group for Part 1. Plasma concentrations at each nominal sampling time will also be summarized by age group for Part 1 using descriptive statistics (number of observations, mean, standard deviation, coefficient of variation, median, maximum, and minimum).

12.4 Pharmacodynamic Methods

Not Applicable.

12.5 Statistical Analysis of Pharmacodynamic Data (if applicable)

Not Applicable.

12.6 Analyses of Pharmacokinetic/Pharmacodynamic Relationships (If applicable)

Not Applicable.

12.7 Changes in the Pharmacokinetic or Statistical Methods from Those stated in the Protocol

The definition of the Pharmacokinetic Set 1 and Pharmacokinetic Set 2 appears as follows in Protocol Version 6.0 (Amendment 5):

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 PK data are considered sufficient and interpretable will be included in Pharmacokinetic Set 2

The definition of Pharmacokinetic Set 1 and Pharmacokinetic Set 2 appears as the following in the present SAP for simplification and as a result of standardization of these definitions across studies within Shire:

Pharmacokinetic Set 1 - Subjects in the Safety Analysis Set 1 who have at least 1 measurable post-dose plasma concentration of Lanthanum Carbonate. Subjects in Part 1who vomited may be excluded from Pharmacokinetic Set 1.

Pharmacokinetic Set 2 - Subjects in Safety Analysis Sets 1 or 2 who have at least 1 measurable post-dose plasma concentration of Lanthanum Carbonate will be included in Pharmacokinetic Set 2.

12.8 Pharmacokinetic References

Not Applicable.

12.9 Table of Contents for Pharmacokinetic Figures, Tables, and Listings

Formats and numbering of the tables, listings and figures will be finalized prior to the completion of the Clinical Study Report. No revision to this document is required for changes which do not affect the statistical or PK methods, definitions, or rules defined in this document.

In the event that a limited number of samples yield measurable concentrations, the PK tables, listings and figures will be generated as deemed appropriate. No revision of this document will

be required.

TABLES

PK Tables will be provided by Clinical Pharmacology and Pharmacokinetics Department of Shire Pharmaceuticals or its' designee, as overseen by the pharmacology group.

LISTINGS

PK Listings will be provided by Clinical Pharmacology and Pharmacokinetics Department of Shire Pharmaceuticals or its' designee, as overseen by the pharmacology group.

FIGURES

Pharmacokinetic Figures

PK Figures will be provided by Clinical Pharmacology and Pharmacokinetics Department of Shire Pharmaceuticals or its' designee, as overseen by the pharmacology group.

13. OTHER ANALYSES

Not applicable.

14. INTERIM ANALYSIS

No formal interim analysis is planned for this study. However, a descriptive analysis of efficacy and safety data was produced in Q4 2014 to assist with regulatory interactions as recruitment targets had not been met.

15. DATA MONITORING/REVIEW COMMITTEE

Not applicable.

16. COMPUTER METHODS

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).

17. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

The following changes to the analyses as outlined in the Protocol Version 6.0 (Amendment 5), 18 Oct 2016 were as follows:

- Subject Disposition for Part 2 (2a and 2b) was proposed to be presented by Treatment group. However, the presentation will be presented by Parts 2a and 2b.

- The Safety Analysis Set 2 was redefined 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 as a result of and in response to discussions with PDCO.

- An inconsistency in wording exists between the protocol Synopsis (under the Efficacy Analysis section on pages 29 and 30) and protocol Section 9.10.2 (Secondary Variables, page 80). The Synopsis wording states "For the long-term assessment, efficacy and safety variables will be summarized using the FAS and SAS2, respectively…" whereas the wording in Section 9.10.2 states "For the long-term assessment, efficacy and safety variables will be summarized using the Safety Analysis Set 2 for each visit using descriptive statistics…". The wording will no longer appear in the text, but the SAP will more closely follow what appears in the protocol Synopsis and summarize long-term variables using the FAS analysis population.

  The definitions of the FAS and SAS2 are identical except for a subsequent required assessment (ie, at least 1 phosphate assessment or the completion of at least 1 follow-up safety assessment, respectively). It is unlikely that a subject would complete a follow-up safety assessment without also having at least 1 phosphate assessment. As a result, if there is a difference in the size or quality between these 2 analysis populations it would be negligible and hence no impact on the summaries that will be provided.

- The age group categories that will summarized within the Demographic and Baseline Characteristics tables has been updated from 2 categories (ie, <12 years and ≥12 years) to 4 categories (<10 years, ≥ 10 to <12 years, ≥12 to <18 years and ≥ 18 years) to account for the ages of all subjects who participated in the study across various versions of the protocol and age group categories that appear in the most recent and up-to-date CRF.

- The age group categories that will be summarized for the "by Age" summary tables for Subject Disposition, Demographic and Baseline Characteristics and Adverse Events have been clarified and now explicitly align with the age groups upon which the primary and secondary endpoints are analysed (≥ 10 to <12 years and ≥12 to <18 years vs. <12 years and ≥12 years).

- The study will enrol at least 32 (rather than 35) subjects who complete 8 weeks of treatment with lanthanum carbonate and are assessable for the primary endpoint.

- The definitions of PP1 and PP2 will only include subjects who have serum phosphate levels above the age-specific KDOQI target (rather than equal to or above).

18. DATA HANDLING CONVENTIONS

18.1 General Data Reporting Conventions

Continuous variables will be summarised using the following descriptive statistics: n, mean, median, standard deviation, minimum, maximum. Categorical and count variables will be summarised by the number of subjects (n) and the percent of subjects in each category. Percentages will be presented as whole numbers.

See Shire Standards for rules on the number of decimal places to present data and p-values.

18.2 Derived Efficacy Endpoints

Not applicable.

18.3 Repeated or Unscheduled Assessments of Safety Parameters

If a subject has repeated assessments before the start of IP, then the results from the final assessment made prior to the start of IP will be used as baseline. If end of study assessments are repeated or unscheduled, the last post-baseline assessment will be used as the end of study assessment for generating descriptive statistics.

18.4 Missing Date of Investigational Product

When the date of the last dose of IP is missing for a subject in any Part of the study, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last visit date when IP was returned will be used in the calculation of treatment duration.

18.5 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, incomplete (ie, partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

18.5.1 Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing day and month

- If the year of the incomplete start date is the same as the year of the date of the first dose of IP, then the day and month of the date of the first dose of IP will be assigned to the missing fields.
- If the year of the incomplete start date is before the year of the date of the first dose of IP, then December 31 will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the date of the first dose of IP,

then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of IP, then the day of the date of the first dose of IP will be assigned to the missing day
- If either the year is before the year of the date of the first dose of IP or if both years are the same but the month is before the month of the date of the first dose of IP, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the date of the first dose of IP or if both years are the same but the month is after the month of the date of the first dose of IP, then the first day of the month will be assigned to the missing day.

18.5.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of IP is missing, then replace it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the same as the year as of the date of the last dose of IP, then the day and month of the date of the last dose of IP will be assigned to the missing fields
- If the year of the incomplete stop date is before the year of the date of the last dose of IP, then 31 December will be assigned to the missing fields
- If the year of the incomplete stop date is after the year of the date of the last dose of IP, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of IP, then the day of the date of the last dose of IP will be assigned to the missing day
- If either the year is before the year of the date of the last dose of IP or if both years are the same but the month is before the month of the date of the last dose of IP, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the last dose of IP or if both years are the same but the

month is after the month of the date of the last dose of IP, then the first day of the month will be assigned to the missing day.

18.6 Missing Date Information for Adverse Events

For AEs, the default is to only impute incomplete (ie, partially missing) start dates. Incomplete stop dates may also be imputed when calculation of the duration of an AE is required per the protocol. If imputation of an incomplete stop date is required, and both the start date and the stop date are incomplete for a subject, impute the start date first.

18.6.1 Incomplete Start Date

Follow same rules as in Section 18.5.1.

18.6.2 Incomplete Stop Date

When required per the protocol, follow the same rules as in Section 18.5.2.

18.7 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of IP, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of IP, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

18.8 Missing Relationship to Investigation Product for Adverse Events

If the relationship to IP is missing for an AE starting on or after the date of the first dose of IP, a causality of "Related" will be assigned. The imputed values for relationship to double-blind IP will be used for incidence summaries, while the actual values will be presented in data listings.

18.9 Character Values of Clinical Laboratory Variables

If the reported value of a clinical laboratory endpoint cannot be used in a statistical analysis due to, for example, that a character string is reported for a numerical endpoint, the appropriately determined coded value will be used in the statistical analysis. However, the actual values as reported in the database will be presented in data listings. Coding of special character values will be determined before the database lock.

19. REFERENCES

None

20. TABLE OF CONTENTS FOR TABLES, FIGURES AND LISTINGS

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Table	Title	Shire Std
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3.2.5.4	Summary of Change from Baseline in Osteocalcin in Part 2 and 3 Combined for Lanthanum Carbonate (Parts 2b and 3) (Full Analysis Set)	Y

Table	Title	Shire Std
3.2.5.5	Summary of Change from Baseline in Tartrate-Resistant Acid Phosphatase in Part 2 and 3 Combined for Lanthanum Carbonate (Parts 2b and 3) (Per-protocol Set 2)	Y
3.2.5.6	Summary of Change from Baseline in Tartrate-Resistant Acid Phosphatase in Part 2 and 3 Combined for Lanthanum Carbonate (Parts 2b and 3) (Full Analysis Set)	Y
3.2.5.7	Summary of Change from Baseline in Fibroblast Growth Factor-23 in Part 2 and 3 Combined for Lanthanum Carbonate (Parts 2b and 3) (Per-protocol Set 2)	Y
3.2.5.8	Summary of Change from Baseline in Fibroblast Growth Factor-23 in Part 2 and 3 Combined for Lanthanum Carbonate (Parts 2b and 3) (Full Analysis Set)	Y
3.2.5.9	Summary of Change from Baseline in Parathyroid Hormone in Part 2 and 3 Combined for Lanthanum Carbonate (Parts 2b and 3) (Per-protocol Set 2)	Y
3.2.5.10	Summary of Change from Baseline in Parathyroid Hormone in Part 2 and 3 Combined for Lanthanum Carbonate (Parts 2b and 3) (Full Analysis Set)	Y
3.2.5.11	Summary of Change from Baseline in Sclerostin in Part 2 and 3 Combined for Lanthanum Carbonate (Parts 2b and 3) (Per-protocol Set 2)	Y
3.2.5.12	Summary of Change from Baseline in Sclerostin in Part 2 and 3 Combined for Lanthanum Carbonate (Parts 2b and 3) (Full Analysis Set)	Y
3.2.5.13	Summary of Change from Baseline in Fetuin-A in Part 2 and 3 Combined for Lanthanum Carbonate (Parts 2b and 3) (Per-protocol Set 2)	Y
3.2.5.14	Summary of Change from Baseline in Fetuin-A in Part 2 and 3 Combined for Lanthanum Carbonate (Parts 2b and 3) (Full Analysis Set)	Y
3.1.6.1	Summary of Change from Baseline in Height (cm) in Part 2 and 3 Combined by Treatment Group (Parts 2a and 3) (Per-protocol Set 1)	Y
3.1.6.2	Summary of Change from Baseline in Height (cm) in Part 2 and 3 Combined by Treatment Group (Parts 2a and 3) (Full Analysis Set)	Y
3.1.6.3	Summary of Change from Baseline in Weight (kg) in Part 2 and 3 Combined by Treatment Group (Parts 2a and 3) (Per-protocol Set 1)	Y
3.1.6.4	Summary of Change from Baseline in Weight (kg) in Part 2 and 3 Combined by Treatment Group (Parts 2a and 3) (Full Analysis Set)	Y
3.1.7.1	Summary of Change from Baseline in Height (cm) in Part 2 and 3 Combined for Lanthanum Carbonate (Parts 2b and 3) (Per-protocol Set 2)	Y

Table	Title	Shire Std
3.1.7.2	Summary of Change from Baseline in Height (cm) in Part 2 and 3 Combined for Lanthanum Carbonate (Parts 2b and 3) (Full Analysis Set)	Y
3.1.7.3	Summary of Change from Baseline in Weight (kg) in Part 2 and 3 Combined for Lanthanum Carbonate (Parts 2b and 3) (Per-protocol Set 2)	Y
3.1.7.4	Summary of Change from Baseline in Weight (kg) in Part 2 and 3 Combined for Lanthanum Carbonate (Parts 2b and 3) (Full Analysis Set)	Y
3.1.8.1	Summary of Percentage of Subjects achieving Age-specific KDOQI Serum Phosphorous Target by Weeks of Treatment with Lanthanum Carbonate (Per-protocol Set 2)	
3.1.8.2	Summary of Percentage of Subjects achieving Age-specific KDOQI Serum Phosphorous Target by Weeks of Treatment with Lanthanum Carbonate (Full Analysis Set)	
4.1.1	Investigational Product Exposure in Part 2 (Part 2a and Part 2b) by Treatment Group (Safety Analysis Set 2)	Y
4.1.2	Investigational Product Exposure in Part 2 and 3 Combined (Lanthanum Carbonate only) (Safety Analysis Set 2)	Y
4.1.3	Investigational Product Exposure in Part 2 and 3 Combined (Lanthanum Carbonate only) (Safety Completer Set)	Y
4.2.1.1	Overall Treatment-emergent Adverse Events (TEAEs) in Part 1 (Safety Analysis Set 1 – Subjects Taking Lanthanum Carbonate)	Y
4.2.1.2	Overall Treatment-emergent Adverse Events (TEAEs) in Part 1 by Age Group (Safety Analysis Set 1 – Subjects Taking Lanthanum Carbonate)	Y
4.2.1.3	Overall Treatment-emergent Adverse Events (TEAEs) in Part 2 (Part 2a and Part 2b) by Treatment Group (Safety Analysis Set 2)	Y
4.2.1.4	Overall Treatment-emergent Adverse Events (TEAEs) in Part 2 (Part 2a and Part 2b) by Treatment and Age Group (Safety Analysis Set 2)	Y
4.2.1.5	Overall Treatment-emergent Adverse Events (TEAEs) in Part 2 and 3 Combined for Lanthanum Carbonate (Safety Analysis Set 2 – Subjects Taking Lanthanum Carbonate)	Y
4.2.1.6	Overall Treatment-emergent Adverse Events (TEAEs) in Part 2 and 3 Combined by Age Group (Safety Analysis Set 2 – Subjects Taking Lanthanum Carbonate)	Y
4.2.1.7	Overall Treatment-emergent Adverse Events (TEAEs) in Part 2 and 3 Combined (Safety Completer Set – Subjects Taking Lanthanum Carbonate)	Y
4.2.1.8	Overall Treatment-emergent Adverse Events (TEAEs) in Part 2 and 3 Combined by Age Group (Safety Completer Set – Subjects Taking Lanthanum Carbonate)	Y

Table	Title	Shire Std
4.2.2.1	Treatment-emergent Adverse Events by System Organ Class and Preferred Term in Part 1 (Safety Analysis Set 1 – Subjects Taking Lanthanum Carbonate)	Y
4.2.2.2	Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Treatment Group in Part 2 (Part 2a and Part 2b) (Safety Analysis Set 2)	Y
4.2.2.3	Treatment-emergent Adverse Events by System Organ Class and Preferred Term in Part 2 and 3 Combined for Lanthanum Carbonate (Safety Analysis Set 2 – Subjects Taking Lanthanum Carbonate)	Y
4.2.2.4	Treatment-emergent Adverse Events by System Organ Class and Preferred Term in Part 2 and 3 Combined for Lanthanum Carbonate (Safety Completer Set – Subjects Taking Lanthanum Carbonate)	Y
4.3.1.1	Treatment-emergent Adverse Events by Maximum Severity, System Organ Class and Preferred Term in Part 1 (Safety Analysis Set 1 – Subjects Taking Lanthanum Carbonate)	Y
4.3.1.2	Treatment-emergent Adverse Events by Maximum Severity, System Organ Class, Preferred Term and Treatment Group in Part 2 (Part 2a and Part 2b) (Safety Analysis Set 2)	Y
4.3.1.3	Treatment-emergent Adverse Events by Maximum Severity, System Organ Class and Preferred Term in Part 2 and 3 Combined for Lanthanum Carbonate (Safety Analysis Set 2 – Subjects Taking Lanthanum Carbonate))	Y
4.3.1.4	Treatment-emergent Adverse Events by Maximum Severity, System Organ Class and Preferred Term in Part 2 and 3 Combined for Lanthanum Carbonate (Safety Completer Set – Subjects Taking Lanthanum Carbonate)	Y
4.3.2.1	Treatment-emergent Adverse Events Considered Related to Investigational Product by System Organ Class and Preferred Term in Part 1 (Safety Analysis Set 1 – Subjects Taking Lanthanum Carbonate)	Y
4.3.2.2	Treatment-emergent Adverse Events Considered Related to Investigational Product by System Organ Class, Preferred Term and Treatment Group in Part 2 (Part 2a and Part 2b) (Safety Analysis Set 2)	Y
4.3.2.3	Treatment-emergent Adverse Events Considered Related to Investigational Product by System Organ Class and Preferred Term in Part 2 and 3 Combined for Lanthanum Carbonate (Safety Analysis Set 2 – Subjects Taking Lanthanum Carbonate)	Y
4.3.2.4	Treatment-emergent Adverse Events Considered Related to Investigational Product by System Organ Class and Preferred Term in Part 2 and 3 Combined for Lanthanum Carbonate (Safety Completer Set – Subjects Taking Lanthanum Carbonate)	Y

Table	Title	Shire Std
4.4.1.1	Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term in Part 1 (Safety Analysis Set 1 – Subjects Taking Lanthanum Carbonate)	Y
4.4.1.2	Treatment-emergent Serious Adverse Events by System Organ Class, Preferred Term and Treatment Group in Part 2 (Part 2a and Part 2b) (Safety Analysis Set 2)	Y
4.4.1.3	Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term in Part 2 and 3 Combined for Lanthanum Carbonate (Safety Analysis Set 2 – Subjects Taking Lanthanum Carbonate)	Y
4.4.1.4	Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term in Part 2 and 3 Combined for Lanthanum Carbonate (Safety Completer Set – Subjects Taking Lanthanum Carbonate)	Y
4.4.2.1	Deaths by System Organ Class and Preferred Term in Part 1 (Safety Analysis Set 1 – Subjects Taking Lanthanum Carbonate)	Y
4.4.2.2	Deaths by System Organ Class, Preferred Term and Treatment Group in Part 2 (Part 2a and Part 2b) (Safety Analysis Set 2)	Y
4.4.2.3	Deaths by System Organ Class and Preferred Term in Part 2 and 3 Combined for Lanthanum Carbonate (Safety Analysis Set 2 – Subjects Taking Lanthanum Carbonate)	Y
4.4.2.4	Deaths by System Organ Class and Preferred Term in Part 2 and 3 Combined for Lanthanum Carbonate (Safety Completer Set – Subjects Taking Lanthanum Carbonate)	Y
4.4.3.1	Treatment-emergent Adverse Events leading to study withdrawal by System Organ Class and Preferred Term in Part 1 (Safety Analysis Set 1 – Subjects Taking Lanthanum Carbonate)	Y
4.4.3.2	Treatment-emergent Adverse Events leading to study withdrawal by System Organ Class, Preferred Term and Treatment Group in Part 2 (Part 2a and Part 2b) (Safety Analysis Set 2)	Y
4.4.3.3	Treatment-emergent Adverse Events leading to study withdrawal by System Organ Class and Preferred Term in Part 2 and 3 Combined for Lanthanum Carbonate (Safety Analysis Set 2 – Subjects Taking Lanthanum Carbonate)	Y
4.4.3.4	Treatment-emergent Adverse Events leading to study withdrawal by System Organ Class and Preferred Term in Part 2 and 3 Combined for Lanthanum Carbonate (Safety Completer Set – Subjects Taking Lanthanum Carbonate)	Y
4.5.1.1	Treatment-emergent Bone Disease Adverse Events of Special Interest by System Organ Class and Preferred Term in Part 1 (Safety Analysis Set 1 – Subjects Taking Lanthanum Carbonate)	Y
4.5.1.2	Treatment-emergent Bone Disease Adverse Events of Special Interest by System Organ Class, Preferred Term and Treatment Group in Part 2 (Part 2a and Part 2b) (Safety Analysis Set 2)	Y

Table	Title	Shire Std
4.5.1.3	Treatment-emergent Bone Disease Adverse Events of Special Interest by System Organ Class, Preferred Term in Part 2 and 3 Combined for Lanthanum Carbonate (Safety Analysis Set 2 – Subjects Taking Lanthanum Carbonate)	Y
4.5.1.4	Treatment-emergent Bone Disease Adverse Events of Special Interest by System Organ Class, Preferred Term in Part 2 and 3 Combined for Lanthanum Carbonate (Safety Completer Set – Subjects Taking Lanthanum Carbonate)	Y
4.5.2.1	Treatment-emergent Bone Disease Adverse Events of Special Interest by Sex and Age Group in Part 1 (Safety Analysis Set 1)	Y
4.5.2.2	Treatment-emergent Bone Disease Adverse Events of Special Interest by Sex and Age Group and Treatment Group in Part 2 (Part 2a and Part 2b) (Safety Analysis Set 2)	Y
4.5.2.3	Treatment-emergent Bone Disease Adverse Events of Special Interest by Sex and Age Group in Part 2 and 3 Combined for Lanthanum Carbonate (Safety Analysis Set 2 – Subjects Taking Lanthanum Carbonate)	Y
4.5.2.4	Treatment-emergent Bone Disease Adverse Events of Special Interest by Sex and Age Group in Part 2 and 3 Combined for Lanthanum Carbonate (Safety Completer Set – Subjects Taking Lanthanum Carbonate)	Y
4.6.1.1	Quantitative Clinical Laboratory Results in Part 1: Biochemistry (Safety Analysis Set 1 – Subjects Taking Lanthanum Carbonate)	Y
4.6.1.2	Quantitative Clinical Laboratory Results in Part 1: Haematology (Safety Analysis Set 1 – Subjects Taking Lanthanum Carbonate)	Y
4.6.1.3	Quantitative Clinical Laboratory Results in Part 1: Biochemical Bone Markers (Safety Analysis Set 1 – Subjects Taking Lanthanum Carbonate)	Y
4.6.2.1	Quantitative Clinical Laboratory Results in Part 2 and 3 Combined by Treatment Group: Biochemistry (Safety Analysis Set 2)	Y
4.6.2.2	Quantitative Clinical Laboratory Results in Part 2 and 3 Combined by Treatment Group: Haematology (Safety Analysis Set 2)	Y
4.6.2.3	Quantitative Clinical Laboratory Results in Part 2 and 3 Combined by Treatment Group: Biochemical Bone Markers (Safety Analysis Set 2)	Y
4.6.2.4	Quantitative Clinical Laboratory Results in Part 2 and 3 Combined by Treatment Group for Lanthanum Carbonate: Biochemistry (Safety Completer Set – Subjects Taking Lanthanum Carbonate)	Y
4.6.2.5	Quantitative Clinical Laboratory Results in Part 2 and 3 Combined by Treatment Group for Lanthanum Carbonate: Haematology (Safety Completer Set – Subjects Taking Lanthanum Carbonate)	Y

Table	Title	Shire Std
4.6.2.6	Quantitative Clinical Laboratory Results in Part 2 and 3 Combined by Treatment Group for Lanthanum Carbonate: Biochemical Bone Markers (Safety Completer Set – Subjects Taking Lanthanum Carbonate)	Y
4.6.3.1	Shift from Baseline in Clinical Laboratory Results in Part 2 and 3 Combined by Treatment Group: Biochemistry (Safety Analysis Set 2)	Y
4.6.3.2	Shift from Baseline in Clinical Laboratory Results in Part 2 and 3 Combined by Treatment Group: Haematology (Safety Analysis Set 2)	Y
4.6.3.3	Shift from Baseline in Clinical Laboratory Results in Part 2 and 3 Combined by Treatment Group: Biochemical Bone Markers (Safety Analysis Set 2)	Y
4.6.4.1	Normal Ranges: Biochemistry	Y
4.6.4.2	Normal Ranges: Haematology	Y
4.6.4.3	Normal Ranges: Biochemical Bone Markers	Y
4.7.1	Actual Values and Change from Baseline in Vital Signs in Part 1 (Safety Analysis Set 1 – Subjects Taking Lanthanum Carbonate)	Y
4.7.2	Actual Values and Change from Baseline in Vital Signs in Part 2 and 3 Combined by Treatment Group (Safety Analysis Set 2)	Y
4.7.3	Actual Values and Change from Baseline in Vital Signs in Part 2 and 3 Combined for Lanthanum Carbonate (Safety Analysis Set 2 – Subjects Taking Lanthanum Carbonate)	Y
4.7.4	Actual Values and Change from Baseline in Vital Signs in Part 2 and 3 Combined for Lanthanum Carbonate (Safety Completer Set – Subjects Taking Lanthanum Carbonate)	Y
4.8.1	ECG Interpretation in Part 2 and 3 Combined by Timepoint for Lanthanum Carbonate only (Parts 2a and 3) (Safety Analysis Set 2)	Y
4.8.2	ECG Interpretation in Part 2 and 3 Combined by Timepoint for Lanthanum Carbonate only (Parts 2b and 3) (Safety Analysis Set 2)	Y
4.8.3	ECG Interpretation in Part 2 and 3 Combined by Timepoint for Lanthanum Carbonate only (Parts 2a and 3) (Safety Completer Set)	Y
4.8.4	ECG Interpretation in Part 2 and 3 Combined by Timepoint for Lanthanum Carbonate only (Parts 2b and 3) (Safety Completer Set)	Y
4.8.5	Shift from Baseline to Post-Baseline Timepoint in Qualitative ECG Results in Part 2 and 3 Combined for Lanthanum Carbonate only (Parts 2a and 3) (Safety Analysis Set 2)	Y
4.8.6	Shift from Baseline to Post-Baseline Timepoint in Qualitative ECG Results in Part 2 and 3 Combined for Lanthanum Carbonate only (Parts 2b and 3) (Safety Analysis Set 2)	Y

Table	Title	Shire Std
4.8.7	Shift from Baseline to Post-Baseline Timepoint in Qualitative ECG Results in Part 2 and 3 Combined for Lanthanum Carbonate only (Parts 2a and 3) (Safety Completer Set)	Y
4.8.8	Shift from Baseline to Post-Baseline Timepoint in Qualitative ECG Results in Part 2 and 3 Combined for Lanthanum Carbonate only (Parts 2b and 3) (Safety Completer Set)	Y

Figure	Title	Shire Std
3.1.3.1	Bar Chart of Mean Change from Baseline and 95% CI for Serum Phosphorous after 8-weeks of Treatment in Part 2 (Part 2a and Part 2b) by Treatment Group (Per-protocol Set 1)	
3.1.3.2	Bar Chart of Mean Change from Baseline and 95% CI for Calcium after 8-weeks of Treatment in Part 2 (Part 2a and Part 2b) by Treatment Group (Per-protocol Set 1)	
3.1.3.3	Bar Chart of Mean Change from Baseline and 95% CI for Calcium-Phosphorous Product after 8-weeks of Treatment in Part 2 (Part 2a and Part 2b) by Treatment Group (Per-protocol Set 1)	
3.1.4.1	Line Graph of Mean Change from Baseline and 95% CI in Serum Phosphorous in Part 2 and 3 Combined by Weeks of Treatment with Lanthanum Carbonate (Per-protocol Set 2)	
3.1.4.2	Line Graph of Mean Change from Baseline and 95% CI in Serum Phosphorous in Part 2 and 3 Combined by Weeks of Treatment with Lanthanum Carbonate (Full Analysis Set)	
3.1.4.3	Line Graph of Mean Change from Baseline and 95% CI in Calcium in Part 2 and 3 Combined by Weeks of Treatment with Lanthanum Carbonate (Per-protocol Set 2)	
3.1.4.4	Line Graph of Mean Change from Baseline and 95% CI in Calcium in Part 2 and 3 Combined by Weeks of Treatment with Lanthanum Carbonate (Full Analysis Set)	
3.1.4.5	Line Graph of Mean Change from Baseline and 95% CI in Calcium-Phosphorous Product in Part 2 and 3 Combined by Weeks of Treatment with Lanthanum Carbonate (Per-protocol Set 2)	
3.1.4.6	Line Graph of Mean Change from Baseline and 95% CI in Calcium-Phosphorous Product in Part 2 and 3 Combined by Weeks of Treatment with Lanthanum Carbonate (Full Analysis Set)	

Listing	Title	Shire Std
	Listing of Subject Data for Screen Failures	Y
1.1	Subject Disposition (Enrolled Set)	Y
1.2	Subjects Who Terminated from the Study (Enrolled Set)	Y

Listing	Title	Shire Std
1.3	Study Analysis Set Classification (Enrolled Set)	Y
2.1.1	Listing of Protocol Deviations (Enrolled Set)	Y
2.1.2	Listing of Evaluable Subjects (Full Analysis Set)	
4.1	Subject Demographic and Baseline Characteristics (Enrolled Subjects)	Y
4.2	Renal History (Enrolled Subjects)	Y
4.3	Medical History (Enrolled Set)	Y
4.4	Prior and Concomitant Medications (Enrolled Set)	Y
5.1.1	Investigational Product Accountability in Part 1 (Safety Analysis Set 1)	Y
5.1.2	Investigational Product Accountability in Part 2 and 3 Combined (Safety Analysis Set 2)	Y
5.1.3	Investigational Product Exposure in Part 2 and 3 Combined (Safety Completer Set)	Y
5.2	Pharmacokinetic Blood Draw Times (Enrolled Set)	Y
6.1	KDOQI Serum Phosphorous Target Achievement (Enrolled Set)	Y
7.1	Adverse Events (Enrolled Set)	Y
7.2	Serious Adverse Events (Enrolled Set)	Y
7.3	Adverse Events Related to Investigational Product (Enrolled Set)	Y
7.4	Adverse Events Leading to Study Withdrawal (Enrolled Set)	Y
7.5	Adverse Events Leading to Death (Enrolled Set)	Y
7.6	Subjects Reporting Bone Disease Treatment-emergent Adverse Events (Enrolled Set)	Y
8.1.1	Clinical Laboratory Sample Collection and Results for Pregnancy (Enrolled Set)	Y
8.1.2	Clinical Laboratory Test Results (Enrolled Set)	Y
8.2.1	Vital Signs (Enrolled Set)	Y
8.3.1	12-lead ECG Investigator’s Interpretation (Enrolled Set)	Y

21. APPENDIX

21.1 Evaluable Subject Determination Plan

1. Definition of Evaluable Subject in Per-Protocol Analysis Set 2 for Primary Endpoint Assessment

For the purposes of the primary endpoint assessment, at least 32 subjects, who complete 8 weeks of treatment with lanthanum carbonate and are assessable for baseline and 8 weeks serum phosphate level, will be required. Approximately 65 subjects may be enrolled to acquire at least 32 evaluable subjects. In order to prevent over enrolment, subjects' evaluability status will be assessed and confirmation of achieving at least 32 evaluable subjects will be performed.

The criteria that subjects must meet to determine eligibility include:

- Aged 10 years to <18 years of age at the time of consent
- Confirmed serum phosphorus level drawn prior to commencing Lanthanum therapy in Part 2 or Part 3 of the clinical trial (Baseline Phosphorus)
    - Subjects who participated in Part 2a and received calcium carbonate, baseline serum phosphorus must be drawn after a washout period of up to 3 weeks
- Baseline serum phosphorus levels above KDOQI recommendations:
    - Age <12 years: Serum phosphorus >6.0mg/dL (1.94mmol/L)
    - Age ≥12 years and older: Serum phosphorus >5.5mg/dL (1.78mmol/L)
- Demonstration of 8 weeks of Lanthanum therapy
- Confirmed serum phosphorus level after 8 weeks of Lanthanum therapy
- Both baseline and 8 weeks serum phosphorus levels are assessed at the same lab (central or local lab)
- Subjects, who received lanthanum carbonate therapy in part 2 or part 3 but did not receive 8 weeks of continuous treatment because of temporary dose interruption due to hypophosphatemia (protocol Appendix 2: guidelines for phosphorus and calcium levels), will be considered evaluable, if they satisfy other criteria mentioned above (eg baseline phosphate > KDOQI target).

1.1 Data Variable Requirements

I. Subject Age

Age is calculated using Informed Consent Date minus Birth date. However, birth date may not be available in all cases (due to subject privacy concerns). When instead of birth date only birth year is entered in the clinical database, age will be imputed using June 30th of the year of birth. However, if the age falls below 10 years old or over 18 years old and inclusion criteria number 01 is met, we will consider the age-categories to confirm whether the age-criterion was met. KDOQI Target: Created based on age condition:

- If DM.AGE <12 years, then KDOQI Target = 1.94mmol/L
- If DM.AGE ≥12 years, then KDOQI Target = 1.78mmol/L

II. First Lanthanum Carbonate Medication

Time of First Exposure to Treatment (Lanthanum Carbonate) in either Part 2 or Part 3 of the study.

III. Baseline Phosphate Level:

Procedural Steps:

i) Obtain the baseline lab visit (from central lab) for each individual subject and choose the lab visit that is closest to the first lanthanum carbonate administration date; and
ii) Obtain the baseline lab visit (from local lab, whenever available) for each individual subject and choose the lab visit that is closest to the first lanthanum carbonate administration date. This data will be used further when there is no central lab baseline Phosphate result (see below)l lab result.

IV. Post 8-week Phosphate Level:

i) Subset week 8 central lab data from Part 2 or Part 3 central lab data, selecting the on-treatment record closest to target day 56/week 8 (with +/-7 days window). Target day is created using the first dose of Lanthanum in Part 2 or Part 3 (if Part 2 first Lanthanum dose is missing).
ii) Subset week 8 local lab data from Part 2 or Part 3 local lab data, select the on-treatment record closest to target day 56/week 8 (with +/-7 days window). Target day is created using the first dose of Lanthanum in Part 2 or Part 3 (if Part 2 first Lanthanum dose is missing).
iii) For subjects who experienced hypophosphatemia, that lead to temporary interruption or discontinuation of treatment before the 8 weeks phosphate assessment they will be considered compliant with the 8 weeks treatment requirement.

In the case of missing central lab data, local lab data will be used. Serum phosphorous assessments must come from a homogeneous source ie, from either central or local lab for baseline and following weeks 8 of lanthanum treatment, respectively, within subject.

If baseline phosphorus value from central lab is available and above the KDOQI criteria, but the central lab 8-week value is missing, then local lab data (baseline and day 56/week 8 phosphorus results) can be used.
NB. Both the baseline and day 56/week 8 phosphorus results must come from a single source (both central or both local).

If baseline phosphorus value from central lab is available and not above the KDOQI criteria, then the subject is not evaluable even if the subject has local lab values for both baseline and 8-week and the baseline value satisfies KDOQI criteria. Evaluability based on local lab is assessed only if central laboratory data is missing.

1.2 Data Sources for Assessment of Evaluability

Evaluability Assessment will be performed on the subject level analysis data set (one record per subject) created through the steps described in section V.

Evaluability is determined if the following conditions are met

1. If subject is not a screen failure
2. Baseline Phosphate data is not missing, and baseline phosphate is ≥ KDOQI Target
3. Week 8 Phosphate data is not missing

OR

Phosphate value missing at Week 8, but early termination shows hypophosphatemia (Protocol Appendix 2: guidelines for phosphorus and calcium levels).

2. Definition of Evaluable Subjects in Per-Protocol Analysis Set 1 for Primary Endpoint Assessment

Evaluable subjects in per-protocol 1 population will be defined similar to evaluable subject in per-protocol 2 population, see above, with subjects meeting the following criteria to be deemed eligible for the per-protocol 1 population:

- Aged 10 years to <18 years of age at the time of consent
- Confirmed serum phosphorus level at study entry and between the calcium carbonate treatment and lanthanum carbonate treatment at Visit 2.4 or unscheduled visits in part 2 (Baseline Phosphorus)
    - Subjects who participated in Part 2a and received calcium carbonate, baseline serum phosphorus must be drawn after a washout period of up to 3 weeks
- Baseline serum phosphorus levels above KDOQI recommendations:
    - Age <12 years: Serum phosphorus >6.0mg/dL (1.94mmol/L)
    - Age ≥12 years and older: Serum phosphorus >5.5mg/dL (1.78mmol/L)
- Demonstration of 8 weeks of Calcium Carbonate therapy followed by 8 weeks of Lanthanum therapy
- Confirmed serum phosphorus level after 8 weeks of Calcium Carbonate therapy followed by 8 weeks of Lanthanum therapy
- Both baseline and 8 weeks serum phosphorus levels are assessed at the same lab (central or local lab)

- Subjects, who received Calcium Carbonate and Lanthanum Carbonate therapy in part 2 or part 3 but did not receive 8 weeks of continuous treatment because of temporary dose interruption due to hypophosphatemia (protocol Appendix 2: guidelines for phosphorus and calcium levels), will be considered evaluable, if they qualify other criteria mentioned above (eg baseline phosphate > KDOQI target).