

**Clinical trial results:**

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

Summary

EudraCT number	2012-000171-17
Trial protocol	HU DE PL Outside EU/EEA CZ RO
Global end of trial date	16 November 2018

Results information

Result version number	v1 (current)
This version publication date	31 May 2019
First version publication date	31 May 2019

Trial information**Trial identification**

Sponsor protocol code	SPD405-207
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01696279
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire
Sponsor organisation address	300 Shire Way, Lexington, United States, MA 02421
Public contact	Study Contact, Shire, 1 866-8425335, ClinicalTransparency@shire.com
Scientific contact	Study Contact, Shire, 1 866-8425335, ClinicalTransparency@shire.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000637-PIP01-09
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 November 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	16 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was 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 were on dialysis, following 8 weeks of treatment with lanthanum carbonate.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation of Good Clinical Practice, the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 February 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Chile: 5
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Russian Federation: 15
Country: Number of subjects enrolled	Turkey: 8
Worldwide total number of subjects	63
EEA total number of subjects	35

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	14
Adolescents (12-17 years)	49
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 23 study centers between 15 February 2013 (first subject first visit) and 16 November 2018 (last subject last visit).

Pre-assignment

Screening details:

It is a 3 part study (Part 1: Pharmacokinetic assessment, Part 2: (Part 2a-calcium carbonate and lanthanum carbonate [crossover comparison] + Part 2b-lanthanum carbonate), Part 3: lanthanum carbonate treatment for 6 months).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Overall Study
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Arm description:

Study was conducted in 3 parts, subjects aged 10 to 12 years received 500 milligram (mg) and greater than (>) 12 years received 1000 milligram single dose of lanthanum carbonate oral powder respectively during part 1. Followed by part 2 during when subjects received calcium carbonate tablet for 8 weeks until a maximum daily dose of 6500 mg was reached (part 2a-Treatment period 1) and then received lanthanum carbonate oral powder for 8 weeks at a daily dose of 1500 mg was reached (part 2a-Treatment period 2). Eligible subjects received lanthanum carbonate oral powder for 8 weeks at a daily dose of 1500 mg, which was titrated bi-weekly until a daily dose of 3000 mg was achieved (part 2b). Subjects who completed part 2 continued the same treatment for additional 6 months during the part 3.

Arm type	Experimental
Investigational medicinal product name	Lanthanum carbonate
Investigational medicinal product code	SPD405
Other name	Fosrenol
Pharmaceutical forms	Powder for oral solution in sachet
Routes of administration	Oral use

Dosage and administration details:

Subjects aged 10 to 12 years received 500 mg and >12 years received 1000 milligram single dose of lanthanum carbonate oral powder during Part 1 and at a daily dose of 1500 mg in part 2 and 3000 mg in part 3.

Investigational medicinal product name	Calcium carbonate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received calcium carbonate until the target serum phosphorus level achieved or until a maximum daily dose of 6500 mg was reached, once the serum phosphorus control was achieved the dose was maintained until the end of 8 week treatment period (Part 2a: treatment period 1).

Number of subjects in period 1	Overall Study
Started	63
Subjects started Part 1	20 ^[1]
Subjects entered Part 2	53
Subjects entered Part 3	42
Completed	34
Not completed	29
Consent withdrawn by subject	1
Adverse Event	5
Kidney Transplant	15
Non-Compliance with study drug	2
Unspecified	4
Protocol Violation	1
Missing	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Milestone is added here to provide more clarity about the subject movement within the study.

Baseline characteristics

Reporting groups

Reporting group title	Overall Study
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Reporting group description:

Study was conducted in 3 parts, subjects aged 10 to 12 years received 500 milligram (mg) and greater than (>) 12 years received 1000 milligram single dose of lanthanum carbonate oral powder respectively during part 1. Followed by part 2 during when subjects received calcium carbonate tablet for 8 weeks until a maximum daily dose of 6500 mg was reached (part 2a-Treatment period 1) and then received lanthanum carbonate oral powder for 8 weeks at a daily dose of 1500 mg was reached (part 2a-Treatment period 2). Eligible subjects received lanthanum carbonate oral powder for 8 weeks at a daily dose of 1500 mg, which was titrated bi-weekly until a daily dose of 3000 mg was achieved (part 2b). Subjects who completed part 2 continued the same treatment for additional 6 months during the part 3.

Reporting group values	Overall Study	Total	
Number of subjects	63	63	
Age categorical			
Units: Subjects			
Age group: < 10 years	3	3	
Age group: ≥10 to <12 years	11	11	
Age group: ≥12 to <18 years	49	49	
Age group: ≥18 years	0	0	
Age continuous			
Units: years			
arithmetic mean	13.41		
standard deviation	± 2.67	-	
Gender categorical			
Units: Subjects			
Female	27	27	
Male	36	36	
Race/Ethnicity, Customized			
Units: Subjects			
White	61	61	
Black or African American	0	0	
Native Hawaiian or other Pacific Islander	0	0	
Asian	0	0	
American Indian or Alaska Native	0	0	
Multiple	2	2	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	5	5	
Not Hispanic or Latino	58	58	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Overall Study
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Reporting group description:

Study was conducted in 3 parts, subjects aged 10 to 12 years received 500 milligram (mg) and greater than (>) 12 years received 1000 milligram single dose of lanthanum carbonate oral powder respectively during part 1. Followed by part 2 during when subjects received calcium carbonate tablet for 8 weeks until a maximum daily dose of 6500 mg was reached (part 2a-Treatment period 1) and then received lanthanum carbonate oral powder for 8 weeks at a daily dose of 1500 mg was reached (part 2a-Treatment period 2). Eligible subjects received lanthanum carbonate oral powder for 8 weeks at a daily dose of 1500 mg, which was titrated bi-weekly until a daily dose of 3000 mg was achieved (part 2b). Subjects who completed part 2 continued the same treatment for additional 6 months during the part 3.

Subject analysis set title	Part 1: Lanthanum Carbonate
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Subjects aged 10 to 12 years received 500 mg and greater than (>) 12 years received 1000 mg single dose of lanthanum carbonate oral powder.

Subject analysis set title	Part 2: Calcium Carbonate
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Subjects received calcium carbonate oral tablet until the target serum phosphorus level achieved or until a maximum daily dose of 6500 mg was reached and once serum phosphorus control was achieved the dose was maintained until the end of 8 weeks (Part 2a: treatment period 1)

Subject analysis set title	Part 2: Lanthanum Carbonate
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Subjects received lanthanum carbonate powder orally at a daily dose of 1500 mg mixed into meals and given three times a day or twice daily with a single dose not exceeding 1000 mg, once the serum phosphorus control was achieved the dose was maintained until the end of 8 week (Part 2a: treatment period 2), also subjects received lanthanum carbonate powder orally at a daily dose of 1500 mg mixed into meals and given three times a day or twice daily with a single dose not exceeding 1000 mg, total daily dose was titrated bi-weekly until a maximum dose of 3000 mg was reached and once the serum phosphorus control was achieved the dose was maintained until the end of 8 week (Part 2b).

Subject analysis set title	Part 2 + Part 3: Lanthanum Carbonate
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Subjects received lanthanum carbonate powder at a daily dose of 1500 mg mixed into meals and given three times a day or twice daily with a single dose not exceeding 1000 mg, total daily dose was titrated bi-weekly until a maximum dose of 3000 mg was reached and once the serum phosphorus control was achieved the dose was maintained until the end of 8 week treatment period (Part 2a and Part 2b) and continue to receive lanthanum carbonate for additional 6 months (Part 3).

Primary: Percentage of Subjects Achieving Age-Specific Kidney Disease Outcomes Quality Initiative (KDOQI) Targets for Serum Phosphate Level Following 8 Weeks of Lanthanum Carbonate Administration (Part 2 + Part 3)

End point title	Percentage of Subjects Achieving Age-Specific Kidney Disease Outcomes Quality Initiative (KDOQI) Targets for Serum Phosphate Level Following 8 Weeks of Lanthanum Carbonate Administration (Part 2 + Part 3) ^[1]
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End point description:

KDOQI serum phosphorus targets were defined for: Adolescents aged greater than or equal to ($\geq$) 12 to less than ($<$) 18 years to be less than or equal to ($\leq$) 5.5 milligrams per deciliter (mg/dL) (1.78 millimoles per liter [mmol/L]); Children aged ≥ 10 years to < 12 years to be ≤ 6.0 mg/dL (1.94 mmol/L). Percentage of subjects achieving age-specific KDOQI targets for serum phosphate level was reported only for the subjects who have received lanthanum carbonate during part 2 or part 3. Per-protocol set 2 (PP2) included subjects who had taken at least 1 dose of investigational product and complete 8 weeks of treatment with lanthanum carbonate and who have serum phosphate assessment data available during Part 2 or Part 3 to

allow summarizing the percentage of subjects achieving age-specific KDOQI target.

End point type	Primary
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End point timeframe:

After 8 weeks of lanthanum carbonate administration

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not performed for this single arm analysis.

End point values	Part 2 + Part 3: Lanthanum Carbonate			
Subject group type	Subject analysis set			
Number of subjects analysed	34			
Units: percentage of subjects				
number (not applicable)	50			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving Age-Specific Kidney Disease Outcomes Quality Initiative (KDOQI) Targets for Serum Phosphate Level During Part 2

End point title	Percentage of Subjects Achieving Age-Specific Kidney Disease Outcomes Quality Initiative (KDOQI) Targets for Serum Phosphate Level During Part 2
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End point description:

KDOQI serum phosphorus targets was defined for: Adolescents aged $\geq 12 < 18$ years to be ≤ 5.5 mg/dL (1.78 [mmol/L]); Children aged ≥ 10 years to < 12 years to be ≤ 6.0 mg/dL (1.94 mmol/L). Percentage of subjects achieving age-specific KDOQI targets for serum phosphate level were reported only for the subjects who have received calcium carbonate followed by 8 weeks of treatment with lanthanum carbonate in Part 2. Per Protocol Set 1 (PP1) included subjects who had taken at least 1 dose of investigational product and complete 8 weeks of calcium carbonate followed by 8 weeks of lanthanum carbonate and who have serum phosphate assessment data available during Part 2 to allow summarizing the percentage of subjects achieving age-specific KDOQI target.

End point type	Secondary
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End point timeframe:

Up to 19 weeks

End point values	Part 2: Calcium Carbonate	Part 2: Lanthanum Carbonate		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	17		
Units: percentage of subjects				
number (not applicable)	58.8	70.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Phosphorus Levels Following Treatment With Lanthanum Carbonate After 8 Weeks

End point title	Change From Baseline in Serum Phosphorus Levels Following Treatment With Lanthanum Carbonate After 8 Weeks
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End point description:

Changes from baseline in serum phosphorus levels in hyperphosphatemic children and adolescents with chronic kidney disease (CKD) who are on dialysis, following treatment with lanthanum carbonate for 8 weeks were combined and reported baseline was defined as the last assessment prior to the first dose of investigational product. PP2 included subjects who had taken at least 1 dose of investigational product and complete 8 weeks of treatment with lanthanum carbonate and who have serum phosphate assessment data available during Part 2 or Part 3 to allow summarizing the percentage of subjects achieving age-specific KDOQI target.

End point type	Secondary
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End point timeframe:

Baseline, Week 8

End point values	Part 2 + Part 3: Lanthanum Carbonate			
Subject group type	Subject analysis set			
Number of subjects analysed	34			
Units: millimole per liter (mmol/L)				
arithmetic mean (standard error)	-0.334 ($\pm$ 0.1035)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Calcium Levels Following Treatment With Lanthanum Carbonate After Week 8

End point title	Change From Baseline in Calcium Levels Following Treatment With Lanthanum Carbonate After Week 8
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End point description:

Changes from baseline in calcium levels in hyperphosphatemic children and adolescents with CKD who are on dialysis, following treatment with lanthanum carbonate for 8 weeks were reported were combined and reported baseline was defined as the last assessment prior to the first dose of investigational product. PP2 included subjects who had taken at least 1 dose of investigational product and complete 8 weeks of treatment with lanthanum carbonate and who have serum phosphate assessment data available during Part 2 or Part 3 to allow summarizing the percentage of subjects achieving age-specific KDOQI target.

End point type	Secondary
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End point timeframe:

Baseline, Week 8

End point values	Part 2 + Part 3: Lanthanum Carbonate			
Subject group type	Subject analysis set			
Number of subjects analysed	34			
Units: millimole per liter (mmol/L)				
arithmetic mean (standard error)	-0.001 ($\pm$ 0.0363)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Calcium-Phosphorus Product Levels Following Treatment With Lanthanum Carbonate After Week 8

End point title	Change From Baseline in Calcium-Phosphorus Product Levels Following Treatment With Lanthanum Carbonate After Week 8
End point description:	
Changes from baseline in calcium-phosphorus product levels in hyperphosphatemic children and adolescents with CKD who are on dialysis, following treatment with lanthanum carbonate for 8 weeks were reported were combined and reported baseline was defined as the last assessment prior to the first dose of investigational product. PP2 included subjects who had taken at least 1 dose of investigational product and complete 8 weeks of treatment with lanthanum carbonate and who have serum phosphate assessment data available during Part 2 or Part 3 to allow summarizing the percentage of subjects achieving age-specific KDOQI target. millimole square per square liter (mmol^2/L^2)	
End point type	Secondary
End point timeframe:	
Baseline, Week 8	

End point values	Part 2 + Part 3: Lanthanum Carbonate			
Subject group type	Subject analysis set			
Number of subjects analysed	34			
Units: mmol^2/L^2				
arithmetic mean (standard error)	-0.577 ($\pm$ 0.2464)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Phosphorus Levels Following Treatment With Calcium Carbonate After 8 Weeks and Lanthanum Carbonate After 8 Weeks During Part 2

End point title	Change From Baseline in Serum Phosphorus Levels Following Treatment With Calcium Carbonate After 8 Weeks and Lanthanum Carbonate After 8 Weeks During Part 2			
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End point description:

Changes from baseline in serum phosphorus levels in hyperphosphatemic children and adolescents with CKD who are on dialysis, following treatment with calcium carbonate after 8 weeks and lanthanum carbonate after 8 weeks were combined and reported. Baseline was defined as the last assessment prior to the first dose of investigational product. PP1 included subjects who had taken at least 1 dose of investigational product and complete 8 weeks of calcium carbonate followed by 8 weeks of lanthanum carbonate and who have serum phosphate assessment data available during Part 2 to allow summarizing the percentage of subjects achieving age-specific KDOQI target.

End point type	Secondary
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End point timeframe:

Baseline, Week 8

End point values	Part 2: Calcium Carbonate	Part 2: Lanthanum Carbonate		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	17		
Units: millimole per liter (mmol/L)				
arithmetic mean (standard error)	-0.520 (± 0.1786)	-0.467 (± 0.1312)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Calcium Levels Following Treatment With Calcium Carbonate After 8 Weeks and Lanthanum Carbonate After 8 Weeks During Part 2

End point title	Change From Baseline in Calcium Levels Following Treatment With Calcium Carbonate After 8 Weeks and Lanthanum Carbonate After 8 Weeks During Part 2
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End point description:

Changes from baseline in calcium levels in hyperphosphatemic children and adolescents with CKD who are on dialysis, following treatment with calcium carbonate after 8 weeks and lanthanum carbonate after 8 weeks were combined and reported. Baseline was defined as the last assessment prior to the first dose of investigational product. PP1 included subjects who had taken at least 1 dose of investigational product and complete 8 weeks of calcium carbonate followed by 8 weeks of lanthanum carbonate and who have serum phosphate assessment data available during Part 2 to allow summarizing the percentage of subjects achieving age-specific KDOQI target.

End point type	Secondary
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End point timeframe:

Baseline, Week 8

End point values	Part 2: Calcium Carbonate	Part 2: Lanthanum Carbonate		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	17		
Units: millimole per liter (mmol/L)				
arithmetic mean (standard error)	0.058 (± 0.0554)	-0.009 (± 0.0574)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Calcium-Phosphorus Product Levels Following Treatment With Calcium Carbonate After 8 Weeks and Lanthanum Carbonate After 8 Weeks During Part 2

End point title	Change From Baseline in Calcium-Phosphorus Product Levels Following Treatment With Calcium Carbonate After 8 Weeks and Lanthanum Carbonate After 8 Weeks During Part 2
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End point description:

Changes from baseline in calcium-phosphorus product levels in hyperphosphatemic children and adolescents with CKD who are on dialysis, following treatment with calcium carbonate after 8 weeks and lanthanum carbonate after 8 weeks were combined and reported. Baseline was defined as the last assessment prior to the first dose of investigational product. PP1 included subjects who had taken at least 1 dose of investigational product and complete 8 weeks of calcium carbonate followed by 8 weeks of lanthanum carbonate and who have serum phosphate assessment data available during Part 2 to allow summarizing the percentage of subjects achieving age-specific KDOQI target.

End point type	Secondary
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End point timeframe:

Baseline, Week 8

End point values	Part 2: Calcium Carbonate	Part 2: Lanthanum Carbonate		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	17		
Units: mmol ² /L ²				
arithmetic mean (standard error)	-0.966 (± 0.4084)	-0.669 (± 0.3834)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Phosphorus Levels at the Last Visit of 8-Week Treatment Period in Part 2 and Monthly During 6-Month Extension Phase of Part 3

End point title	Change From Baseline in Serum Phosphorus Levels at the Last Visit of 8-Week Treatment Period in Part 2 and Monthly During
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End point description:

Change from baseline in serum phosphorus levels at the last visit of each 8-week treatment period during Part 2 and monthly during the 6-month extension phase (Part 3) were reported. Baseline was defined as the last assessment prior to the first dose of investigational product. PP2 included subjects who had taken at least 1 dose of investigational product and complete 8 weeks of treatment with lanthanum carbonate and who have serum phosphate assessment data available during Part 2 or Part 3 to allow summarizing the percentage of subjects achieving age-specific KDOQI target. Here, n = number of subjects evaluable at the specific category time points.

End point type	Secondary
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End point timeframe:

Baseline, Week 8, 12, 16, 20, 24, 28 and Week 32
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End point values	Part 2 + Part 3: Lanthanum Carbonate			
Subject group type	Subject analysis set			
Number of subjects analysed	34			
Units: millimole per liter (mmol/L)				
arithmetic mean (standard deviation)				
Change at Week 8 (n = 34)	-0.334 (± 0.1035)			
Change at Week 12 (n = 30)	-0.416 (± 0.0912)			
Change at Week 16 (n = 27)	-0.314 (± 0.1278)			
Change at Week 20 (n = 25)	-0.316 (± 0.1055)			
Change at Week 24 (n = 23)	-0.322 (± 0.1356)			
Change at Week 28 (n = 20)	-0.236 (± 0.1491)			
Change at Week 32 (n = 13)	-0.143 (± 0.1558)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Calcium Levels at the Last Visit of 8-Week Treatment Period in Part 2 and Monthly During 6-Month Extension Phase of Part 3

End point title	Change From Baseline in Calcium Levels at the Last Visit of 8-Week Treatment Period in Part 2 and Monthly During 6-Month Extension Phase of Part 3
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End point description:

Change from baseline in calcium levels at the last visit of each 8-week treatment period during Part 2 and monthly during the 6-month extension phase (Part 3) were reported. Baseline was defined as the last assessment prior to the first dose of investigational product. PP2 included subjects who had taken at least 1 dose of investigational product and complete 8 weeks of treatment with lanthanum carbonate and who have serum phosphate assessment data available during Part 2 or Part 3 to allow summarizing the percentage of subjects achieving age-specific KDOQI target. Here, n = number of subjects evaluable at the specific category time points.

End point type	Secondary
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End point timeframe:

Baseline, Week 8, 12, 16, 20, 24, 28 and Week 32

End point values	Part 2 + Part 3: Lanthanum Carbonate			
Subject group type	Subject analysis set			
Number of subjects analysed	34			
Units: millimole per liter (mmol/L)				
arithmetic mean (standard error)				
Change at Week 8 (n = 34)	-0.001 (± 0.0363)			
Change at Week 12 (n = 28)	-0.045 (± 0.0475)			
Change at Week 16 (n = 26)	-0.034 (± 0.0534)			
Change at Week 20 (n = 22)	0.003 (± 0.0511)			
Change at Week 24 (n = 22)	-0.010 (± 0.0450)			
Change at Week 28 (n = 20)	0.049 (± 0.0623)			
Change at Week 32 (n = 13)	-0.127 (± 0.0773)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Calcium-Phosphorus Product Levels at the Last Visit of 8-Week Treatment Period in Part 2 and Monthly During 6-Month Extension Phase of Part 3

End point title	Change From Baseline in Calcium-Phosphorus Product Levels at the Last Visit of 8-Week Treatment Period in Part 2 and Monthly During 6-Month Extension Phase of Part 3
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End point description:

Change from baseline in calcium-phosphorus product levels at the last visit of each 8-week treatment period during Part 2 and monthly during the 6-month extension phase (Part 3) were reported. Baseline was defined as the last assessment prior to the first dose of investigational product. PP2 included subjects who had taken at least 1 dose of investigational product and complete 8 weeks of treatment with lanthanum carbonate and who have serum phosphate assessment data available during Part 2 or Part 3 to allow summarizing the percentage of subjects achieving age-specific KDOQI target. Here, n = number of subjects evaluable at the specific category time points.

End point type	Secondary
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End point timeframe:

Baseline, Week 8, 12, 16, 20, 24, 28 and Week 32

End point values	Part 2 + Part 3: Lanthanum Carbonate			
Subject group type	Subject analysis set			
Number of subjects analysed	34			
Units: mmol ² /L ²				
arithmetic mean (standard error)				
Change at Week 8 (n = 34)	-0.577 (± 0.2464)			
Change at Week 12 (n = 28)	-0.783 (± 0.2535)			
Change at Week 16 (n = 26)	-0.575 (± 0.3023)			
Change at Week 20 (n = 22)	-0.362 (± 0.2711)			
Change at Week 24 (n = 22)	-0.578 (± 0.3459)			
Change at Week 28 (n = 20)	-0.326 (± 0.3767)			
Change at Week 32 (n = 13)	-0.570 (± 0.3624)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Biochemical Bone Markers

End point title	Change From Baseline in Biochemical Bone Markers
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End point description:

Change from baseline in bone turnover markers including bone alkaline phosphatase (ALP), osteocalcin, and sclerostin was reported for combined Part 2 and 3. PP1 included subjects who had taken at least 1 dose of investigational product and complete 8 weeks of calcium carbonate followed by 8 weeks of lanthanum carbonate and who have serum phosphate assessment data available during Part 2 to allow summarizing the percentage of subjects achieving age-specific KDOQI target. End of study is the completion if the subjects has benefited from and desires to continue dosing with lanthanum. Here, '99999' in the reported data indicate that the respective subject analysis set was not applicable to the category and n = number of subjects evaluable for each subject analysis set at the specific category time points.

End point type	Secondary
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End point timeframe:

Baseline, Week 8, Week 16 and EOS

End point values	Part 2: Calcium Carbonate	Part 2 + Part 3: Lanthanum Carbonate		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	17		
Units: microgram per liter (ug/L)				
arithmetic mean (standard error)				
ALP: Change at Week 8 (n = 16, 0)	-0.78 (± 8.503)	99999 (± 99999)		
ALP: Change at Week 16 (n = 0, 15)	99999 (± 99999)	31.86 (± 16.334)		

ALP: Change at EOS (n = 0, 13)	99999 (± 99999)	59.12 (± 20.822)		
Osteocalcin: Change at Week 8 (n = 16, 0)	8.2 (± 20.24)	99999 (± 99999)		
Osteocalcin: Change at Week 16 (n = 0, 15)	99999 (± 99999)	10.3 (± 21.57)		
Osteocalcin: Change at EOS (n = 0, 13)	99999 (± 99999)	94.0 (± 32.60)		
Sclerostin: Change at Week 8 (n = 12, 0)	0.146 (± 0.1380)	99999 (± 99999)		
Sclerostin: Change at Week 16 (n = 0, 13)	99999 (± 99999)	-0.062 (± 0.0946)		
Sclerostin: Change at EOS (n = 0, 11)	99999 (± 99999)	-0.051 (± 0.1037)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Biochemical Bone Markers for Tartrate-Resistant Acid Phosphatase (TRAP)

End point title	Change From Baseline in Biochemical Bone Markers for Tartrate-Resistant Acid Phosphatase (TRAP)
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End point description:

Change from baseline in bone turnover markers for, tartrate-resistant acid phosphatase (TRAP) was reported for combined Part 2 and 3. PP1 included subjects who had taken at least 1 dose of investigational product and complete 8 weeks of calcium carbonate followed by 8 weeks of lanthanum carbonate and who have serum phosphate assessment data available during Part 2 to allow summarizing the percentage of subjects achieving age-specific KDOQI target. Here, '99999' in the reported data indicate that the respective subject analysis set was not applicable to the category and n = number of subjects evaluable for each subject analysis set at the specific category time points.

End point type	Secondary
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End point timeframe:

Baseline, Week 8, Week 16 and EOS

End point values	Part 2: Calcium Carbonate	Part 2 + Part 3: Lanthanum Carbonate		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	17		
Units: Unit per liter (U/L)				
arithmetic mean (standard error)				
Change at Week 8 (n = 16, 0)	-1.71 (± 1.141)	99999 (± 99999)		
Change at Week 16 (n = 0, 15)	99999 (± 99999)	1.95 (± 1.173)		
Change at EOS (n = 0, 13)	99999 (± 99999)	4.65 (± 1.934)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Biochemical Bone Markers for Fibroblast Growth Factor 23 (FGF-23)

End point title	Change From Baseline in Biochemical Bone Markers for Fibroblast Growth Factor 23 (FGF-23)
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End point description:

Change from baseline in bone turnover markers including fibroblast growth factor 23 (FGF-23) was reported for combined Part 2 and 3. PP1 included subjects who had taken at least 1 dose of investigational product and complete 8 weeks of calcium carbonate followed by 8 weeks of lanthanum carbonate and who have serum phosphate assessment data available during Part 2 to allow summarizing the percentage of subjects achieving age-specific KDOQI target. Here, '99999' in the reported data indicate that the respective subject analysis set was not applicable to the category and n = number of subjects evaluable for each subject analysis set at the specific category time points.

End point type	Secondary
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End point timeframe:

Baseline, Week 8, Week 16 and EOS

End point values	Part 2: Calcium Carbonate	Part 2 + Part 3: Lanthanum Carbonate		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	17		
Units: relative unit per milliliter (RU/ml)				
arithmetic mean (standard error)				
Change at Week 8 (n = 16, 0)	5130.3 (± 5232.21)	99999 (± 99999)		
Change at Week 16 (n = 0, 15)	99999 (± 99999)	-8162.4 (± 5274.60)		
Change at EOS (n = 0, 13)	99999 (± 99999)	-251.1 (± 1736.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Biochemical Bone Markers for Parathyroid Hormone (PTH)

End point title	Change From Baseline in Biochemical Bone Markers for Parathyroid Hormone (PTH)
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End point description:

Change from baseline in bone turnover markers for parathyroid hormone was reported for combined Part 2 and 3. PP1 included subjects who had taken at least 1 dose of investigational product and complete 8 weeks of calcium carbonate followed by 8 weeks of lanthanum carbonate and who have serum phosphate assessment data available during Part 2 to allow summarizing the percentage of subjects achieving age-specific KDOQI target. Here, '99999' in the reported data indicate that the respective subject analysis set was not applicable to the category and n = number of subjects evaluable for each subject analysis set at the specific category time points.

End point type	Secondary
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End point timeframe:

Baseline, Week 8, Week 16 and EOS

End point values	Part 2: Calcium Carbonate	Part 2 + Part 3: Lanthanum Carbonate		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	17		
Units: picomole per liter (pmol/L)				
arithmetic mean (standard error)				
Change at Week 8 (n = 16, 0)	-7.132 (± 9.7669)	99999 (± 99999)		
Change at Week 16 (n = 0, 15)	99999 (± 99999)	16.273 (± 12.5441)		
Change at EOS (n = 0, 13)	99999 (± 99999)	59.801 (± 16.3097)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Biochemical Bone Markers for fetuin-A

End point title	Change From Baseline in Biochemical Bone Markers for fetuin-A
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End point description:

Change from baseline in bone turnover markers for fetuin-A was reported for combined Part 2 and 3. PP1 included subjects who had taken at least 1 dose of investigational product and complete 8 weeks of calcium carbonate followed by 8 weeks of lanthanum carbonate and who have serum phosphate assessment data available during Part 2 to allow summarizing the percentage of subjects achieving age-specific KDOQI target. Here, '99999' in the reported data indicate that the respective subject analysis set was not applicable to the category and n = number of subjects evaluable for each subject analysis set at the specific category time points.

End point type	Secondary
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End point timeframe:

Baseline, Week 8, Week 16 and EOS

End point values	Part 2: Calcium Carbonate	Part 2 + Part 3: Lanthanum Carbonate		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	17		
Units: gram per liter (g/L)				
arithmetic mean (standard error)				
Change at Week 8 (n = 12, 0)	-0.006 (± 0.0301)	99999 (± 99999)		
Change at Week 16 (n = 0, 13)	99999 (± 99999)	0.037 (± 0.0360)		
Change at EOS (n = 0, 11)	99999 (± 99999)	0.039 (± 0.0273)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Height

End point title	Change From Baseline in Height
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End point description:

Change from baseline in height for combined Part 2 and Part 3 for each drug at Week 8, 16 and end of study was reported. PP1 included subjects who had taken at least 1 dose of investigational product and complete 8 weeks of calcium carbonate followed by 8 weeks of lanthanum carbonate and who have serum phosphate assessment data available during Part 2 to allow summarizing the percentage of subjects achieving age-specific KDOQI target. Here, '99999' in the reported data indicate that the respective subject analysis set was not applicable to the category and n = number of subjects evaluable for each subject analysis set at the specific category time points.

End point type	Secondary
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End point timeframe:

Baseline, Week 8, Week 16, and EOS

End point values	Part 2: Calcium Carbonate	Part 2 + Part 3: Lanthanum Carbonate		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	17		
Units: centimeter (cm)				
arithmetic mean (standard error)				
Change at Week 8 (n = 17, 0)	0.7 (± 0.39)	99999 (± 99999)		
Change at Week 16 (n = 0, 17)	99999 (± 99999)	0.6 (± 0.25)		
Change at EOS (n = 0, 13)	99999 (± 99999)	1.3 (± 0.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Weight

End point title	Change From Baseline in Weight
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End point description:

Change from baseline in weight for combined Part 2 and Part 3 for each drug at Week 8, 16 and end of study (EOS) was reported. PP1 included subjects who had taken at least 1 dose of investigational product and complete 8 weeks of calcium carbonate followed by 8 weeks of lanthanum carbonate and who have serum phosphate assessment data available during Part 2 to allow summarizing the percentage of subjects achieving age-specific KDOQI targets. Here, '99999' in the reported data indicate

that the respective subject analysis set was not applicable to the category and n = number of subjects evaluable for each subject analysis set at the specific category time points.

End point type	Secondary
End point timeframe:	
Baseline, Week 8, Week 16, and EOS	

End point values	Part 2: Calcium Carbonate	Part 2 + Part 3: Lanthanum Carbonate		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	17		
Units: kilogram (Kg)				
arithmetic mean (standard error)				
Change at Week 8 (n = 17, 0)	1.18 (± 0.524)	99999 (± 99999)		
Change at Week 16 (n = 0, 17)	99999 (± 99999)	1.09 (± 0.358)		
Change at EOS (n = 0, 13)	99999 (± 99999)	2.86 (± 0.606)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration up to follow-up (up to Week 42)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	Part 1: Lanthanum Carbonate
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Reporting group description:

Subjects aged 10 to 12 years received 500 mg and >12 years received 1000 mg single dose of lanthanum carbonate oral powder.

Reporting group title	Part 2 + Part 3: Lanthanum Carbonate
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Reporting group description:

Subjects received lanthanum carbonate powder at a daily dose of 1500 mg mixed into meals and given three times a day or twice daily with a single dose not exceeding 1000 mg, total daily dose was titrated bi-weekly until a maximum dose of 3000 mg was reached and once the serum phosphorus control was achieved the dose was maintained until the end of 8 week treatment period (Part 2a and Part 2b) and continue to receive lanthanum carbonate for additional 6 months (Part 3).

Reporting group title	Part 2: Calcium Carbonate
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Reporting group description:

Subjects received calcium carbonate oral tablet until the target serum phosphorus level achieved or until a maximum daily dose of 6500 mg was reached and once serum phosphorus control was achieved the dose was maintained until the end of 8 weeks.

Serious adverse events	Part 1: Lanthanum Carbonate	Part 2 + Part 3: Lanthanum Carbonate	Part 2: Calcium Carbonate
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	19 / 52 (36.54%)	9 / 53 (16.98%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood phosphorus			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Arteriovenous fistula thrombosis subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Graft haemorrhage subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders Hypertension subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	2 / 53 (3.77%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders Arrhythmia subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions Device occlusion subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis in device subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders Abdominal pain			

subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis acute			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Osteochondrosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis perforated			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 20 (0.00%)	2 / 52 (3.85%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 20 (0.00%)	5 / 52 (9.62%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Fluid overload			

subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic disorder			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Part 1: Lanthanum Carbonate	Part 2 + Part 3: Lanthanum Carbonate	Part 2: Calcium Carbonate
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 20 (10.00%)	32 / 52 (61.54%)	25 / 53 (47.17%)
Nervous system disorders			
Somnolence			
subjects affected / exposed	1 / 20 (5.00%)	0 / 52 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	2 / 53 (3.77%)
occurrences (all)	0	0	3
Nausea			
subjects affected / exposed	1 / 20 (5.00%)	3 / 52 (5.77%)	2 / 53 (3.77%)
occurrences (all)	1	5	2
Vomiting			
subjects affected / exposed	1 / 20 (5.00%)	5 / 52 (9.62%)	1 / 53 (1.89%)
occurrences (all)	1	6	2
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 20 (0.00%)	1 / 52 (1.92%)	2 / 53 (3.77%)
occurrences (all)	0	1	2
Nasopharyngitis			
subjects affected / exposed	0 / 20 (0.00%)	2 / 52 (3.85%)	2 / 53 (3.77%)
occurrences (all)	0	3	2
Respiratory tract infection			

subjects affected / exposed	0 / 20 (0.00%)	2 / 52 (3.85%)	3 / 53 (5.66%)
occurrences (all)	0	2	4
Upper respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)	5 / 52 (9.62%)	0 / 53 (0.00%)
occurrences (all)	0	5	0
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 20 (0.00%)	5 / 52 (9.62%)	9 / 53 (16.98%)
occurrences (all)	0	9	9
Hyperphosphataemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 52 (0.00%)	2 / 53 (3.77%)
occurrences (all)	0	0	2
Hypocalcaemia			
subjects affected / exposed	0 / 20 (0.00%)	3 / 52 (5.77%)	3 / 53 (5.66%)
occurrences (all)	0	6	3
Hypophosphataemia			
subjects affected / exposed	0 / 20 (0.00%)	6 / 52 (11.54%)	3 / 53 (5.66%)
occurrences (all)	0	10	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 July 2012	Amendment 1 included the following changes - Addition of sclerostin and fetuin-A parameters to the assay for biochemical bone markers. Correction of error in dosing regimen in Parts 1 and 2. Clarification and correction of washout periods, and assessments required. Addition of guidance language in relation to dosing in case of hypophosphatemia and/or hypocalcemia during Parts 2 and 3 or hypercalcemia while taking calcium carbonate in Part 2. PTH designated as a biochemical bone marker but was to be analyzed as part of the routine biochemistry panel. Biochemistry parameters amended to include vitamin D at baseline and end of study.
24 September 2012	Amendment 2 included the following changes - Addition of confirmatory phosphorus value to washout period visits W1 and W2. Clarification that subjects may start lanthanum carbonate treatment at Visit 2.4 if phosphorus criterion is met. Confirmation that subjects will not be withdrawn from the study if they do not meet phosphorus criteria after Visit 2.4 but will start lanthanum carbonate therapy and be assessed for Part 3. These subjects cannot be included in the per-protocol set. Correction that lanthanum carbonate is taken with meals. Clarification of which secondary endpoints (height or length, head circumference, and weight) are to be measured at subject visits.
17 April 2014	Amendment 3 included the following changes - Age range amended from 6 months to <18 years to 10 years to <18 years. Reduction in Part 3 from 10 months to 6 months and overall exposure to lanthanum reduced from 12 months to 8 months. Change in serious adverse events and pregnancy notification from 1 business day to 24 hours. Extension in safety follow-up period from 7 days after last visit to 7-14 days from the last dose of investigational product, except for subjects who undergo kidney transplant, whose follow-up telephone call will be 30+/-7 days after the last dose of investigational product. Added that calcium levels, in addition to phosphorus levels, should be measured locally for titration purposes during the first treatment period of Part 2. Removal of exclusion criterion relating to serum calcium level. Starting dose of lanthanum carbonate in the second treatment period of Part 2 amended to reflect the change in age range of subjects. All subjects to be given a 1500 mg starting dose. Clarification that the lanthanum carbonate given in Parts 2 and 3 should be mixed with food and divided equally between all meals. Clarification that titration should continue until serum phosphorus levels meet KDOQI age guidelines. Correction made to age range of subjects with phosphorus level >6.0 mg/dL. Clarified acceptable dose levels in Part 3. Clarified how the per-protocol set will be determined. Sample size justification added. Study period extended to December 2015.
02 March 2015	Amendment 4 included the following changes - Protocol revised to match updated SAP (Redefined full analysis set, Redefined Safety Analysis Set 3, Described subject disposition for all study parts, Described summarization methods for demographic and baseline characteristics (updated to align with finalized SAP), Described intent for listing and analyzing investigational product exposure, Described methods for listing prior and concomitant medication, Described safety analyses). Updated study duration to 44 months (extended to 2016).

18 October 2016	Amendment 5 included the following changes - Removed the active comparator (calcium carbonate) treatment arm given the extreme difficulty in recruiting enough subjects to obtain the originally proposed sample size of at least 50 subjects required for the per-protocol set for a crossover non-inferiority study. The original design of Part 2 of Study SPD405-207 was crossover non-inferiority to allow a formal comparison of the efficacy of lanthanum carbonate with calcium carbonate (Part 2a). Under the modified study design, Part 2a has been removed and subjects will only be treated with 8 weeks of lanthanum carbonate in Part 2b of the study for short-term efficacy and safety assessment. Adjusted planned sample size from 72 to 65, with the target to enroll at least 35 subjects (instead of at least 50) who complete 8 weeks of treatment with lanthanum carbonate and are assessable for the primary endpoint, due to low replenishment of eligible subjects and the discontinuation of subjects enrolled in the study, in agreement with Paediatric Committee of the European Medicine Agency. Added that Part 1, single dose, pharmacokinetic assessment of lanthanum carbonate, is complete and the interim clinical study report interpreting and summarizing the data is available. Added or modified the primary and secondary objectives. As a result of the change in the study design, it is no longer necessary to replace subjects who discontinue Part 2 to ensure that 35 subjects enter Part 3 of the study. Updated study duration to 64 months (extended to 2018). Modified or redefined analysis populations. Clarified that the full analysis set and PP2 will be used for the primary endpoint analyses, while the FAS, PP1, and PP2 will be used for the secondary efficacy endpoint analyses. Updated primary and secondary variables to align with the changes made to the primary and secondary objectives and to the definition of analysis populations. Adjusted the planned sample size.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported