Clinical trial results:
A multicenter, randomized, double-blind, multiple dose, crossover study to evaluate the safety and equivalence of serum phosphate control of a new sevelamer carbonate tablet formulation in comparison with Renvela® in chronic kidney disease patients on hemodialysis

Summary

EudraCT number	2011-006320-20
Trial protocol	BG
Global end of trial date	03 January 2013

Results information

Result version number	v1 (current)
This version publication date	10 June 2016
First version publication date	10 June 2016

Trial information

Trial identification

Sponsor protocol code	CT.SVL.PD.10.001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Synthon B.V.
Sponsor organisation address	Microweg 22, Nijmegen , Netherlands,
Public contact	clinical pharmacology , Synthon BV, +31 243727700, clinicalpharmacology@synthon.com
Scientific contact	clinical pharmacology , Synthon BV, +31 243727700, clinicalpharmacology@synthon.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 February 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 January 2013
Global end of trial reached?	Yes
Global end of trial date	03 January 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of Synthon sevelamer carbonate (SVL) compared to Renvela® (Genzyme) tablets in patients with CKD on hemodialysis based on the evaluation of the incidence of adverse events and serious adverse events as well as compliance.

Protection of trial subjects:

The following parameters were defined as safety parameters in the trial:
- general medical examination
- vital signs (blood pressure, heart rate, body temperature)
- 12 lead ECG
- routine clinical laboratory tests
- HIV and serum pregnancy test
- adverse events monitoring

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 April 2012
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	Bulgaria: 93
Worldwide total number of subjects	93
EEA total number of subjects	93

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	81

From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Planned for screening: 150, Screened: 124, Randomized: 93, Evaluated: 90

Pre-assignment

Screening details:

Planned for screening: 150, Screened: 124, Randomized: 93, Evaluated: 90

Period 1

Period 1 title	Period 1 - Run-in
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

During the run-in period, the patient and the investigator were not blinded to the medication. All the patients received the reference product only in the period. This was to get familiar with the large size of the capsules. Besides this, this period was used to get the patients on a stable Sevelemer dosis.

Arms

Arm title	Reference
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Renvela 800 mg film-coated tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received 1 to 5 800 mg tablets three times daily. The tablets had to be taken with meals and swallowed whole.

All tablets were overencapsulated.

Number of subjects in period 1	Reference
Started	93
Completed	93

Period 2

Period 2 title	Period 2- Double blind treatment phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Test

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Sevelamer carbonate 800 mg film-coated tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received 1 to 5 800 mg tablets three times daily. The tablets had to be taken with meals and swallowed whole.

All tablets were overencapsulated.

Arm title	Reference

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Renvela 800 mg film-coated tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received 1 to 5 800 mg tablets three times daily. The tablets had to be taken with meals and swallowed whole.

All tablets were overencapsulated.

Number of subjects in period 2	Test	Reference
Started	46	47
Completed	45	46
Not completed	1	1
Adverse event, non-fatal	1	1

Period 3

Period 3 title	Period 3- Double blind treatment phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Test

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Sevelamer carbonate 800 mg film-coated tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received 1 to 5 800 mg tablets three times daily. The tablets had to be taken with meals and swallowed whole.

All tablets were overencapsulated.

Arm title	Reference

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Renvela 800 mg film-coated tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received 1 to 5 800 mg tablets three times daily. The tablets had to be taken with meals and swallowed whole.

All tablets were overencapsulated.

Number of subjects in period 3	Test	Reference
Started	46	45
Completed	46	45

Baseline characteristics

Reporting groups	
Reporting group title	Reference

Reporting group description: -

Reporting group values	Reference	Total	
Number of subjects	93	93	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	81	81	
From 65-84 years	12	12	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	29	29	
Male	64	64	

End points

End points reporting groups

Reporting group title	Reference
Reporting group description: -	
Reporting group title	Test
Reporting group description: -	
Reporting group title	Reference
Reporting group description: -	
Reporting group title	Test
Reporting group description: -	
Reporting group title	Reference
Reporting group description: -	

Primary: Evaluation safety and tolerability of sevelamer carbonate

End point title	Evaluation safety and tolerability of sevelamer carbonate

End point description:

End point type	Primary

End point timeframe:

Entire study, so period 1 run-in phase and period 2 and 3 of the double blind treatment period

End point values	Reference	Test	Reference	Test
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	93	46	47	46
Units: incidence of AEs and SAEs	93	45	46	46

End point values	Reference			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: incidence of AEs and SAEs	45			

Statistical analyses

Statistical analysis title	Primary endpoint Safety

Statistical analysis description:

Summary statistics on incidence of treatment emergent adverse events and percentage of subjects who withdrew due to adverse events.

Values entered at "Parameter estimate" should not be taken in consideration. Only summary statistics were used for primary endpoint as described above.

Comparison groups	Test v Reference v Test v Reference
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Incidence of AEs
Point estimate	1.1
Confidence interval	
level	Other: 0 %
sides	2-sided
lower limit	1.1
upper limit	1.1
Variability estimate	Standard error of the mean

Notes:

[1] - A total number of 26 AEs occurred during the double-blind phase: 12 AEs were reported under treatment with the test
product and 14 AEs under treatment with ref. 5 AEs in 4 patients were reported as serious, all under treatment with the ref product. No AE was judged as related to study medication. One SAE (transplant) lead to a permanent withdraw of the study drug. In total, 2 patients were withdrawn due to an AE: The %of subjects withdrawn due to AEs is 1.1% for the test and 1.1% for Ref.

Secondary: Bioequivalence Test and Reference

End point title	Bioequivalence Test and Reference

End point description:

End point type	Secondary

End point timeframe:

During period 2 and 3 (Double-blind treatment periods)

End point values	Reference	Test	Reference	Test
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	93	46	47	46
Units: Mean serum concentration	93	45	47	46

End point values	Reference			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Mean serum concentration	45			

Statistical analyses

Statistical analysis title	T/R ratio for mean serum phosphorus concentration
Comparison groups	Test v Reference v Test v Reference

Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	equivalence[2]
Parameter estimate	T/R ratio serum concentration
Point estimate	98.36
Confidence interval	
level	90 %
sides	2-sided
lower limit	95.22
upper limit	101.61
Variability estimate	Standard error of the mean

Notes:

[2] - The number of subjects specified for this analysis is incorrect. It should state 90 instead of 184. Since this is a 2-way crossover bioequivalence study all 93 subjects have received test and reference and all the data was taken into account for the statistical analysis.

3 subjects were excluded from analysis. 93-3=90

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Throughout the entire study period	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	unknown

Reporting groups	
Reporting group title	Test
Reporting group description: -	
Reporting group title	Reference
Reporting group description: -	

Serious adverse events	Test	Reference	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 93 (0.00%)	4 / 93 (4.30%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
neutrophilia			
subjects affected / exposed	0 / 93 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
coronary artery disease			
subjects affected / exposed	0 / 93 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Immune system disorders			
Transplant			
subjects affected / exposed	0 / 93 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure chronic			

subjects affected / exposed	0 / 93 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
arthropathy			
subjects affected / exposed	0 / 93 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Test	Reference	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 93 (8.60%)	12 / 93 (12.90%)	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 93 (0.00%)	1 / 93 (1.08%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Neutrophilia			
subjects affected / exposed	0 / 93 (0.00%)	1 / 93 (1.08%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 93 (0.00%)	1 / 93 (1.08%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
constipation			
subjects affected / exposed	0 / 93 (0.00%)	2 / 93 (2.15%)	
occurrences (all)	0	3	
nausea			
subjects affected / exposed	0 / 93 (0.00%)	2 / 93 (2.15%)	
occurrences (all)	0	3	
vomitting			

subjects affected / exposed	1 / 93 (1.08%)	2 / 93 (2.15%)	
occurrences (all)	2	3	
abdominal discomfort			
subjects affected / exposed	1 / 93 (1.08%)	0 / 93 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	1 / 93 (1.08%)	0 / 93 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 93 (1.08%)	1 / 93 (1.08%)	
occurrences (all)	1	1	
Endocrine disorders			
Hyperparathyroidism secondary			
subjects affected / exposed	1 / 93 (1.08%)	0 / 93 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 93 (0.00%)	1 / 93 (1.08%)	
occurrences (all)	0	1	
Infections and infestations			
cytomegalovirus infection			
subjects affected / exposed	0 / 93 (0.00%)	1 / 93 (1.08%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 93 (0.00%)	2 / 93 (2.15%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
hypoproteinamia			
subjects affected / exposed	0 / 93 (0.00%)	1 / 93 (1.08%)	
occurrences (all)	0	1	
Decreased appetite			
subjects affected / exposed	3 / 93 (3.23%)	0 / 93 (0.00%)	
occurrences (all)	4	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported