



## 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,<br>clinicalpharmacology@synthon.com |
| Scientific contact           | clinical pharmacology , Synthon BV, +31 243727700,<br>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 Synthron 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

|  |                                    |
|--|------------------------------------|
| <b>Arm title</b>                       | 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.

|                                       |           |
|---------------------------------------|-----------|
| <b>Number of subjects in period 1</b> | 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 |
|------------------------------|-----|

|                  |      |
|------------------|------|
| <b>Arm title</b> | 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.

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 2</b> | 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 |
|------------------------------|-----|

|                  |      |
|------------------|------|
| <b>Arm title</b> | 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.

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 3</b> | 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<br>(gestational age < 37 wks) | 0         | 0     |  |
| Newborns (0-27 days)                                  | 0         | 0     |  |
| Infants and toddlers (28 days-23<br>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 <sup>[1]</sup>                |
| 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 <sup>[2]</sup>    |
| 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 %

| <b>Non-serious adverse events</b>                     | 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<br>occurrences (all)  | 1 / 93 (1.08%)<br>2                            | 2 / 93 (2.15%)<br>3                            |  |
| abdominal discomfort<br>subjects affected / exposed<br>occurrences (all)  | 1 / 93 (1.08%)<br>1                            | 0 / 93 (0.00%)<br>0                            |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)   | 1 / 93 (1.08%)<br>2                            | 0 / 93 (0.00%)<br>0                            |  |
| Skin and subcutaneous tissue disorders<br>Pruritus<br>subjects affected / exposed<br>occurrences (all)  | 1 / 93 (1.08%)<br>1                            | 1 / 93 (1.08%)<br>1                            |  |
| Endocrine disorders<br>Hyperparathyroidism secondary<br>subjects affected / exposed<br>occurrences (all)  | 1 / 93 (1.08%)<br>1                            | 0 / 93 (0.00%)<br>0                            |  |
| Musculoskeletal and connective tissue disorders<br>Pain in extremity<br>subjects affected / exposed<br>occurrences (all)  | 0 / 93 (0.00%)<br>0                            | 1 / 93 (1.08%)<br>1                            |  |
| Infections and infestations<br>cytomegalovirus infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | 0 / 93 (0.00%)<br>0<br><br>0 / 93 (0.00%)<br>0 | 1 / 93 (1.08%)<br>1<br><br>2 / 93 (2.15%)<br>2 |  |
| Metabolism and nutrition disorders<br>hypoproteinemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 0 / 93 (0.00%)<br>0<br><br>3 / 93 (3.23%)<br>4 | 1 / 93 (1.08%)<br>1<br><br>0 / 93 (0.00%)<br>0 |  |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported