Final Report

according to § 13 Subsection 9 GCP-V

Study to investigate the therapeutic equivalence of OsvaRen® tablets and OsvaRen® granules

Study Code:	RP-OSV-02-D
Study Design:	Open, controlled, randomized, cross-over study with two groups
Report Status:	Final
Date:	2016-04-04

Confidential

Clinical Research

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This report is a summary report, compiled according to § 13 subsection 9 GCP-V.
It follows the guideline „Structure and Content of Clinical Study Reports“ (CPMP/ICH/137/95).

The report represents essentially chapter 2 of the study report that was compiled in accordance with section 42b sub-section 1 AMG (German Medicinal Products Act).

The report comprises 12 pages. Page 10 is followed by the signature pages “109” and”110” taken from the comprehensive report following section 42b sub-section 1 AMG.

TITLE PAGE

STUDY TITLE:	Study to investigate the therapeutic equivalence of OsvaRen® tablets and OsvaRen® granules
TEST DRUG:	Control drug: OsvaRen® tablets (Treatment A) Investigational drug: OsvaRen® granules (Treatment B)
INDICATION:	Hyperphosphataemia in the setting of dialysis dependent renal failure
DESIGN:	Open, controlled, randomised, cross-over study with two groups
SPONSOR:	Fresenius Medical Care Deutschland GmbH Clinical Research Else-Kröner-Str. 1 61352 Bad Homburg, Germany
PROTOCOL CODE:	RP-OSV-02-D
INITIATION DATE (FPI):	2014-01-02
COMPLETION DATE (LPO):	2015-04-30 The study was completed according to protocol amendment 03.
COORDINATING INVESTIGATOR:	Prof. Dr. med. Jürgen Floege Director of Division of Nephrology and Clinical Immunology RWTH University Hospital Aachen Aachen, Germany
PROJECT MANAGER:	Dr. Frank Laukhuf Fresenius Medical Care Deutschland GmbH Clinical Research Bad Homburg, Germany
BIOSTATISTICIAN:	Volker Schoder Fresenius Medical Care Deutschland GmbH Clinical Research Bad Homburg, Germany
CLINICAL SAFETY OFFICER	Dr. Justyna Kozik-Jaromin Fresenius Medical Care Deutschland GmbH Clinical Research Bad Homburg, Germany
GCP STATEMENT:	This study was performed in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments) and local legal and regulatory requirements.
DATE OF REPORT:	2016-04-04

AUTHORS

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REPORT

Name of Sponsor/Company: Fresenius Medical Care Deutschland GmbH	**(For National Authority Use only)**
Name of Finished Product: Treatment A: OsvaRen® tablets Treatment B: OsvaRen® granules	
Name of Active Ingredient: Calcium acetate / magnesium carbonate	

Title of Study:

Study to investigate the therapeutic equivalence of OsvaRen® tablets and OsvaRen® granules

Investigators:

Dr. med. W. Ries & Dr. med. S. Schmiedel, Flensburg, Germany
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Dr. med. Ute Domröse & Dr. med. M. Nielebock, Magdeburg, Germany
Prof. Dr. med. J. Radermacher & Dr. med. U. Schmitz, Minden, Germany
Dr. med. M. Schmitz & Prof. Dr. med. P. Heering, Solingen, Germany
Prof. Dr. med. M. Koch & Dr. med. S. Aker, Velbert, Germany
Dr. med. Kai Toussaint & Dr. med. Rolf Schneidenbach, Hamburg, Germany
Dr. med. Christoph Haufe & Dr. med. Ines Solf, Erfurt, Germany
Dr. med. Stephan Wagner & Dr. med. Sebastian Zschätzsch, Gießen, Germany

Study centres:

Germany:
- Ev. Luth. Diakonissenanstalt Flensburg, Medizinische Klinik, Flensburg
- Zentrum für Nieren-, Hochdruck und Stoffwechselerkrankungen, Hannover
- PHV-Dialysezentrum Kiel, Kiel
- Dialysezentrum Diamant Magdeburg, Magdeburg
- Zentrum Innere Medizin – Nephrologie, Minden
- Klinikum Solingen, Klinik für Nephrologie und Allgemeine Innere Medizin, Solingen
- Nephrologisches Zentrum Velbert am Klinikum Niederberg, Velbert
- Nephrocare Hamburg-Barmbek GmbH, Medizinisches Versorgungszentrum, Hamburg
- KfH-Nierenzentrum am Georg-Haas-Zentrum, Erfurt
- Nephrologische Gemeinschaftspraxis Georg-Haas-Dialysezentrum der PHV, Gießen

Publication:

This study has not yet been published.

First Date of Enrolment: 2014-01-02 **Date of Last Completed:** 2015-04-30	**Phase of Development:** 2/3

Objectives:

Primary objective
- Therapeutic equivalence of both products, i.e. granules versus tablets

Secondary objective
- Comparison of the number of patients reaching serum phosphate levels <1.76 mmol/L and the difference in serum phosphate levels between the first and last visit under each treatment in both treatment sequences
- Safety profile of OsvaRen® granules in comparison to OsvaRen® tablets, especially regarding serum calcium, magnesium, and PTH

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Further assessments
- Serum calcium
- Serum magnesium
- Serum potassium
- Serum sodium
- Serum standard bicarbonate
- Full blood count
- iPTH
- Lipids
- Liver parameters
- Alkaline phosphatase
- High sensitivity C-reactive protein (hs-CRP)
- Serum creatinine, serum urea
- Serum total protein
- Serum albumin
- Single pool Kt/V and other dialysis related parameters in order to determine that dialysis prescription, modality, and dialysate composition have not been changed during the study

Methodology:

The study was designed as an open, controlled, randomised, cross-over study.

Number of Patients:

Planned/enclosed: 60 (planned) / 61 (enclosed)
Analysed: 55 (ITT) / 26 (PP)

Diagnosis and Main Criteria for Inclusion:

Inclusion:
- Signed written informed consent form was obtained prior to starting the screening visit
- Male and female patients 18–80 years of age with dialysis dependent renal failure (CKD 5D)
- Patients received 3x/week in-centre renal replacement therapy for at least 2 months on either low-flux or high-flux HD or oHDF
- Prescribed haemodialysis session duration was ≥4 hours
- spKt/V ≥1.20 according to last in-centre measurement prior the study enrolment
- Patients received OsvaRen® tablets for at least 12 weeks as sole phosphate binder and the titration phase had been completed according to physician's discretion
- Patients were able to take the study medication as prescribed, particularly OsvaRen® stickpacks
- Patients were willing to stop any calcium, magnesium or vitamin D containing supplements
- Patients were willing to maintain their typical diet with regards to phosphate uptake for the time of the study
- Patients were willing to comply with the study protocol

Exclusion:
- Pregnant women (by blood ß-hCG pregnancy test) or women breast-feeding or unwilling to use contraceptive measures during the entire course of the study or
- Patients with a life expectancy shorter than the planned duration of the study or
- Patients with any acute or chronic severe disease potentially interfering with study outcomes or
- Patients with PTH levels > 800 ng/L or
- Patients who participated in an interventional clinical study during the preceding 30 days or
- Patients suffering from any other, not mentioned condition which could interfere with the patient's ability to comply with the study or
- Patients who previously participated in the same study

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Name of Finished Product: Treatment A: OsvaRen® tablets Treatment B: OsvaRen® granules	
Name of Active Ingredient: Calcium acetate / magnesium carbonate	

Test Product, Dose and Mode of Administration, Batch Number:

Each stick-pack of OsvaRen® granules contains as active ingredients:
- Calcium acetate: 435.00 mg (corresponding to 110 mg elemental calcium)
- Magnesium carbonate (basic, heavy): 235.00 mg (corresponding to 60 mg elemental magnesium)

OsvaRen® granules were administered orally according to the investigator's pre-study prescription which had to be kept constant during the entire study period (one stickpack of granules is comparable in the content of active ingredients and therefore equivalent to the dosage of one tablet).

Batch number: ULN18G500 to ULN18G999

Duration of Treatment:

Treatment duration was 4 weeks for each formulation

Reference Therapy:

Each film-coated tablet of OsvaRen® contains as active ingredients:
- Calcium acetate: 435.00 mg (corresponding to 110 mg elemental calcium)
- Magnesium carbonate (basic, heavy): 235.00 mg (corresponding to 60 mg elemental magnesium)

OsvaRen® tablets were administered orally according to the investigator's pre-study prescription which had to be kept constant during the entire study period.

Batch number: ULN18G001 to ULN18G499

Criteria for Evaluation:

Efficacy:

Primary parameters
- Serum phosphate

Secondary parameter
- Number of patients with serum phosphate levels <1.76 mmol/L
- Difference in serum phosphate levels between the first and last visit of each pharmaceutical form

Further parameters
- Calcium, magnesium, potassium, sodium
- Standard bicarbonate
- Full blood count
- iPTH
- Lipids (total cholesterol, high-density lipoprotein, cholesterol, triglycerides, calculated low-density lipoprotein)
- Liver parameters (aspartate transaminase, alanine transaminase, gamma-glutamyl transpeptidase)
- Alkaline phosphatase
- High sensitivity C reactive protein
- Creatinine, urea
- Total protein, albumin

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Safety:

- Adverse events

Statistical Methods:

For confirmatory analysis of the primary variable, assessed at visits 6 and 8, a linear mixed model, including treatment, period and sequence as fixed factors and patient as random factor, was applied.

For secondary variables, descriptive measures and p-values were determined as follows: for the proportion of patients with phosphate < 1.76mmol/l, Prescott's test for analysis of dichotomous variables in cross-over design was used. For the analysis of difference in phosphate levels from first to last visit, the linear mixed model described above was used with baseline value as additional covariate.

Concerning safety variables, Poisson regression was used to compare the frequencies of adverse events between treatments. In addition, descriptive statistics for (S)AEs per patient year, calcium, magnesium, and PTH are given.

All statistical analyses were performed using SAS V9.4.

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Results

The study sample was characterised as follows: ITT population: 55, PP population: 26, Safety population: 61. The study was terminated as planned in 51 patients. Reasons for drop out were adverse event (n=4), intolerable taste of study drug (n=2), death, phosphate level too high in run-in phase, serum phosphate level too unstable in run-in phase, and withdrawal of consent.

Patients of the ITT population (76.4% male, 23.6% female) were 33 to 80 years of age (mean age ± SD: 66.7 ± 10.6 years). The most frequently documented underlying diseases were glomerulonephritis and diabetes. Among the concomitant diseases, cardiovascular diseases and metabolic / endocrine diseases were named most frequently. The dialysis vintage ranged from 2.0 to 455.4 months, with a median of 33.7 months for the ITT population. Patients received either oHDF (56.4%) or HD (43.6%). At study start, the majority of patients from the SP population received vitamin D analogues (86.9%), diuretics (70.5%), and drugs for acid related disorders (63.9%) concomitantly. Mean drug adherence, defined as percentage of drug taken, in the ITT population was 94.7% for tablets and 95.4% for granules.

Efficacy Results:

Primary variables

Serum phosphate levels could be maintained with both formulations during the study period. There was no major change in serum phosphate from pre-randomisation levels with either treatment. A phosphate ratio between both study sequences of 0.94 and 0.97 was achieved for the PP and ITT population, respectively. As the 95% confidence interval falls completely within the pre-defined range of 0.8 and 1.25, equivalence can be concluded.

Secondary variables

After 2 weeks, a phosphate ratio of 0.98 and 0.96 between both study periods was achieved for the PP and ITT population, respectively. As the 95% confidence interval falls completely within the pre-defined range of 0.8 and 1.25, equivalence can be concluded also for the 2-week treatment period. The majority of patients reached the target serum phosphorus level of ≤1.76 mmol/L. A difference in the proportions between treatment regimens could not be confirmed (p=0.770 and p=0.987 for PP and ITT population, respectively).

The urea reduction rate remained constant through all treatment periods and no significant differences between tablets and granules were observed in the Kt/V.

Safety Results:

In total, 230 adverse events were documented in 52 patients. Of those, 212 AEs were not related to the study drug. Causal relationship was assessed as unlikely for 10 AEs, likely for 3 AEs, and definite for 5 AEs. Gastrointestinal disorders were reported most frequently, followed by vascular disorders, injury, poisoning and procedural complications, and respiratory, thoracic and mediastinal disorders. The incidence of adverse events was slightly higher during the granules phase (AE ratio tablets/granules 0.882, 95% CI 0.124-6.259), however, the difference was not statistically significant (p=0.6263). In total, 14 SAEs occurred in 12 patients. Only one patient experienced an SAE during the granules phase. None of the SAEs was related to either OsvaRen® formulation. One patient died during the study. The event was documented as sudden death due to ischaemic cardiac event. There was no relation to OsvaRen®. There were three patients with observations of mild hypercalcaemia and 31 patients with mild hypermagnesaemia. Differences according to treatment group were not observed.

Conclusion:

Confirming the study hypothesis, OsvaRen® tablets and granules were therapeutically equivalent. Both formulations are comparably well tolerated without clear evidence for safety signals.

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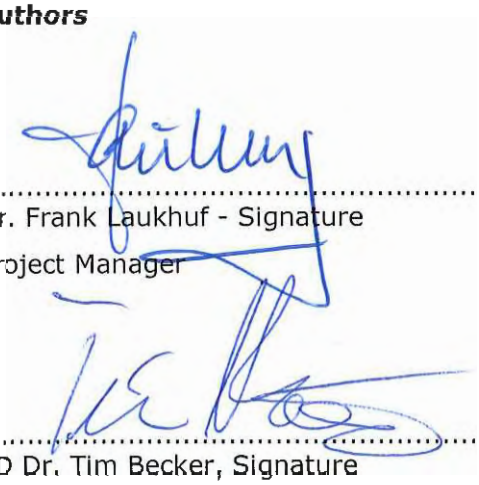
Date of the Report: 2016.04.04	

16.1.6 Signatures

Study Title: Study to investigate the therapeutic equivalence of OsvaRen® tablets and OsvaRen® granules

Study Code: RP-OSV-02-D

Authors



Dr. Frank Laukhuf - Signature
Project Manager

HG, 6.4.2016
Place, Date

PD Dr. Tim Becker, Signature
Biostatistician

HG, 6.4.2016
Place, Date

Dr. Justyna Kozik-Jaromin, Signature
Clinical Safety Officer

HG, 07.04.2016
Place, Date

Approved

Dr. Adelheid Gauly, Signature
Vice President Clinical & Epidemiological Research

HG, 6.4.2016
Place, Date

16.1.6 Signatures (continuation)

Study Title: Study to investigate the therapeutic equivalence of OsvaRen® tablets and OsvaRen® granules

Study Code: RP-OSV-02-D

Principal Investigator

Name: Prof. Dr. med. Jürgen Floege

Centre: Division of Nephrology and Clinical Immunology

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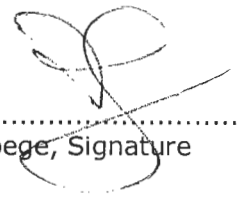

..... Prof. Floege, Signature

Aachen 7.4.16

..... Place, Date