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Sponsor: Sanofi **Drug substance(s):** GZ419831	**Study Identifiers:** U1111-1160-6394, NCT02332811 **Study code:** SVCARB10012
Title of the study: An open label, dose titration study of sevelamer carbonate tablets and powder in hyperphosphatemic chronic kidney disease patients (TOSCANA)	
Study centers: The study was carried out in 4 clinical sites in Russia	
Study period: Date first patient enrolled: 03/Oct/2013 Date last patient completed: 17/Jul/2014	
Phase of development: Phase III	
Objectives: **Primary objective:** To evaluate the reduction in serum phosphorus from baseline to end of study with sevelamer carbonate tablets 800 mg and sevelamer carbonate powder 2.4 g in chronic kidney disease (CKD) patients both on haemodialysis and not on dialysis. **Secondary objective(s):** To evaluate the safety on the basis of adverse events, changes in laboratory values and vital signs from baseline (Day 0) to Day 56 (End of treatment/End of Study).	
Methodology: This study was a prospective, open-label, parallel-group, non-comparative, local, multicenter, dose titration. The study consisted of 3 periods: a 2-week screening period, a 2-week washout period, an 8-week treatment period. For eligible patients who were not on phosphate binders at study entry, 5 visits (instead of 6 visits determined) were planned: screening and randomization visits could be combined in this case. Eligible patients were allocated into the treatment groups for 8-week treatment period and received sevelamer carbonate 800 mg tablets or 2,4 g powder. Starting dose of the sevelamer carbonate was defined based on initial serum phosphorus level: 2,4 g per day for patients with serum phosphorus level from 1.78 to 2.42 mmol/L (5.5 – 7.5 mg/dL) and 4,8 g per day for patients with serum phosphorus level > 2.42 mmol/L (> 7.5 mg/dL). During the treatment period, the sevelamer daily dose was to be increased by 2,4 g (by 3 tablets per day or one sachet per day depending on treatment group) at each of the planned visits (Day 14, Day 28, and Day 42) if the subject's serum phosphorous measurement was >5,5 mg/dL (1,78 mmol/L). At Day 56, final serum phosphorus samples were taken and study medication was stopped (End of treatment), and patients were returned to their pre-treatment phosphorus binders, if required. Adverse events (AEs) were assessed in all patients who received at least one dose of the study drug. Any serious adverse event (SAE) occurring within 30 days of study completion or termination was also reported.	
Number of patients: Planned: 96 patients Randomized: 96 patients Treated: 96 patients **Evaluated:** Efficacy: 88 Safety: 96	

Diagnosis and criteria for inclusion:

Men or women 18 years of age or older with CKD not on dialysis or on a stable haemodialysis regimen who were not currently on phosphate binder(s) or were willing to stop discontinue and enter a 2 week washout period, with the following laboratory measurements:

- Intact parathyroid hormone (iPTH) ≤ 1000 pg/mL at screening (including results obtained within 60 days prior to screening).
- If not taking a phosphate binder, a serum phosphorus measurement >5.5 mg/dL (1.78 mmol/L) at Screening (Visit 1).
- If taking a phosphate binder at screening, a serum phosphorus measurement > 5.5 mg/dL (1.78 mmol/L) after the two-week washout period at Visit 2 (Day 0).

Study treatments

Investigational medicinal product(s):

Sevelamer carbonate 2,4 g powder

Formulation: Powder

Route(s) of administration: Oral administration

Dose regimen: 3 times per day

Sevelamer carbonate 800 mg tablets

Formulation: Tablets

Dose regimen: 3 times per day

Duration of treatment: 8 weeks

Duration of observation: 8 weeks

Criteria for evaluation:

Efficacy:

Primary efficacy criterion: the change in serum phosphorus from baseline (Day 0) to Day 56 (end-of-treatment).

Safety: Safety was evaluated on the basis of adverse events, changes in laboratory values, and vital signs from baseline (Day 0) to Day 56 (End of treatment/End of Study).

Statistical methods:

To summarize continuous variables, the number of patients, mean standard deviation, minimum, maximum values and median have been calculated. To summarize categorical variables, number and percentage for each treatment have been calculated.

Values of descriptive statistics are presented for:

- Demographic data and baseline characteristics for all patients and every treatment group.
- Safety values including adverse events, laboratory values, blood pressure and vital signs.

The change in mean phosphorus level from baseline to Day 56 (Visit 5) will be analyzed and summarized as continuous variables.

Summary results:

Local randomized study was conducted for examination of efficacy and safety of sevelamer carbonate tablets and powder. Ninety-six (96) hyperphosphatemic chronic kidney disease patients both on haemodialysis and not on dialysis were included.

Demographics:

Ninety-six hyperphosphatemic chronic kidney disease (CKD) patients (48 patients on haemodialysis and 48 patients not on haemodialysis) were enrolled into the study, among which 48 (50%) were female. At the enrollment of the study mean serum phosphorus level was 2,33 ± 0,497 mmol/L, the mean age was 55,6± 13,41 years, BMI – 26,9 ± 5,54 kg/m^2.

The following table provides cumulative demographic data of the test population:

		Patients on haemodialysis (n=48)	Patients not on haemodialysis (n=48)	All patients (n=96)
Age (years)	Mean	58,0	53,2	55,6
	SD	11,41	14,87	13,41
	Range	25,0 - 76,0	18,0 – 81,0	18,0 – 81,0
Sex (female)	n (%)	26 (54,2%)	22 (45,8%)	48 (50%)
Sex (male)	n (%)	22 (45,8%)	26 (54,2%)	48 (50%)
Weight (kg)	Mean	77,8	76,3	77,1
	SD	16,94	14,57	15,73
	Range	48,5 – 127,0	48,0 – 108,0	48,0 – 127,0
Height (cm)	Mean	167,1	171,5	169,3
	SD	9,29	6,92	8,45
	Range	149,0 – 182,0	155,0 – 183,0	149,0 – 183,0
BMI (kg/m^2)	Mean	28,0	25,9	26,9
	SD	6,32	4,45	5,54
	Range	17,3 – 46,1	19,2 – 36,6	17,3 – 46,1
Phosphorus level (mmol/L)	Mean	2,55	2,10	2,33
	SD	0,536	0,326	0,497
	Range	1.83 – 3,88	1,79 – 3,65	1,79 – 3,88

According to protocol requirements, 48 (50%) out of 96 patients were allocated to treatment with sevelamer carbonate 800 mg tablets and 48 (50%) to treatment with sevelamer carbonate 2,4 g powder with the following treatment groups:

CKD patients not on dialysis

- 24 patients- 800 mg. tablets group
- 24 patients– 2.4 g. powder group

CKD patients on haemodialysis

- 24 patients- 800 mg. tablets group
- 24 patients– 2.4 g. powder group

As per protocol the starting dose of sevelamer carbonate was either 2,4 g or 4,8 g per day based on serum phosphorus level:

Serum phosphorus level in patients	Total daily dose of sevelamer carbonate to be taken over 3 meals per day
1.78 – 2.42 mmol/L (5.5 – 7.5 mg/dL)	2.4 g
> 2.42 mmol/L (> 7.5 mg/dL)	4.8 g

At Visit1/Visit 2 based on serum phosphorus level, initial treatment with 2,4 g daily dose was administered to 25 (52,1%) patients in the dialysis group and in 42 (87,5%) patients in the non-dialysis group. Administration of 4,8 g daily dose was required in 23 (47,9%) of dialysis patients and 6 (12,5%) of non-dialysis patients. A total of 67 (69,8%) patients started treatment with 2,4 g daily dose of sevelamer carbonate and 29 (30,2%) patients – with 4,8 g daily.

The following table provides the overview of administered treatments at Visit 1/Visit 2.

Visit	Treatment group	Daily dose administered	Patients on haemodialysis (n=48)	Patients not on haemodialysis (n=48)	All patients (n=96)
Visit 1/ Visit 2	Sevelamer carbonate 2,4 g powder	2,4 g daily	12 (25%)	22 (45,8%)	34 (35,4%)
		4,8 g daily	12 (25%)	2 (4,2%)	14 (14,6%)
	Sevelamer carbonate 800 mg tablets	2,4 g daily	13 (27,1%)	20 (41,7%)	33 (34,4%)
		4,8 g daily	11 (22,9%)	4 (8,3%)	15 (15,6%)

Based on serum phosphorus level, 34 (35,4%) of patients at Visit 3 continued the 2,4 g daily dose regimen; 34 (35,4%) of the patients where administered the 4,8g daily dose, while 24 (25%) of patients continued at a daily dose of 7,2 g.

Detailed treatment distribution at Visit 3 is provided in the table below.

Visit	Treatment group	Daily dose administered	Patients on haemodialysis (n=48)	Patients not on haemodialysis (n=48)	All patients (n=96)
Visit 3	Sevelamer carbonate 2,4 g powder	2,4 g daily	5 (10,4 %)	13 (27,1%)	18 (18,7%)
		4,8 g daily	9 (18,8%)	9 (18,7%)	18 (18,7%)
		7,2 g daily	10 (20,8%)	1 (2,1%)	11 (11,5%)
	Sevelamer carbonate 800 mg tablets	2,4 g daily	4 (8,3%)	12 (25,0%)	16 (16,7%)
		4,8 g daily	8 (16,7%)	8 (16,7%)	16 (16,7%)
		7,2 g daily	10 (20,8%)	3 (6,2%)	13 (13,5%)
Discontinued patients			**2 (4,2%)**	**2 (4,2%)**	**4 (4,2%)**

At Visit 4 based on serum phosphorus level, the 2,4 g daily dose regimen was continued in 26 (27,1%) patients, 4,8g daily dose was administered to 22 (22,9%) patients, 7,2 g daily intake of sevelamer carbonate was required in 22 (22,9%) patients while 18 (18,7%) patients continued at the daily dose of 9,6 g.

Detailed treatment distribution at Visit 4 is provided in the table below.

Visit	Treatment group	Daily dose administered	Patients on haemodialysis (n=48)	Patients not on haemodialysis (n=48)	All patients (n=96)
Visit 4	Sevelamer carbonate 2,4 g powder	2,4 g daily	1 (2,1%)	13 (27,1%)	14 (14,6%)
		4,8 g daily	5 (10,4%)	6 (12,5%)	11 (11,5%)
		7,2 g daily	10 (20,8%)	4 (8,3%)	14 (14,6)
		9,6 g daily	7 (14,6%)	0 (0%)	7 (7,3%)
	Sevelamer carbonate 800 mg tablets	2,4 g daily	2 (4,2%)	10 (20,8%)	12 (12,5%)
		4,8 g daily	5 (10,4%)	6 (12,5%)	11 (11.4%)
		7,2 g daily	4 (8,3%)	4 (8,3%)	8 (8,3%)
		9,6 g daily	9 (18,8)	2 (4,2%)	11 (11,5)
Discontinued patients			**4 (8,3%)**	**3 (6,3%)**	**7 (7,3%)**

Eighteen (18,7%) patients at Visit 5 continued 2,4 g daily dose regimen, 23 (24,0%) patients required 4,8g daily dose was administered to 23 (24,0%) patients, 7,2 g daily intake of sevelamer carbonate required 15 (39,6%) patients, daily dose 9,6 g per day was administered to 20 (20,8%) patients while 10 (10,4%) of patients were up-titrated to 12,0 g daily.

Detailed treatment distribution at Visit 5 is provided in the table below.

Visit	Treatment group	Daily dose administered	Patients on haemodialysis (n=48)	Patients not on haemodialysis (n=48)	All patients (n=96)
Visit 5	Sevelamer carbonate 2,4 g powder	2,4 g daily	0 (0%)	11 (22,9%)	11 (11,5%)
		4,8 g daily	4 (8,3%)	8 (16,7%)	12 (12,5%)
		7,2 g daily	6 (12,5%)	2 (4,2%)	8 (8,3%)
		9,6 g daily	8 (16,7%)	2 (4,2%)	10 (10,4%)
		12 g daily	5 (10,4%)	0 (0%)	5 (5,2%)
	Sevelamer carbonate 800 mg tablets	2,4 g daily	0 (0%)	9 (18,7%)	9 (9,4%)
		4,8 g daily	5 (10,4%)	6 (12,5%)	11 (11,5%)
		7,2 g daily	4 (8,3%)	3 (6,2%)	7 (7,3%)
		9,6 g daily	8 (16,7%)	2 (4,2%)	10 (10,4%)
		12 g daily	3 (6,3%)	2 (4,2%)	5 (5,2%)
	Discontinued patients		4 (8,3%)	3 (6,3%)	7 (7,3%)
	Deaths		1 (2,1%)		1 (1,04%)

In total, 7 patients (7,3%) refused to participate and 1 patient died. The fatal outcome was the result of 5 SAEs in 1 dialysis patient.

Efficacy results:

The primary objective of this study was to assess the change in serum phosphorus from baseline (Day 0) to Day56 (End of treatment). Out of 96 randomized patients, 88 (91,7%) completed the study.

Serum phosphorus level progressively decreased in all patients from 2,33 ± 0,50 mmol/L at Visit 1/ 2 to 1,83 ± 0,47 mmol/L at Visit 6. Mean serum phosphorus level decreased from 2,55 ± 0,54 mmol/L at Visit 1/Visit 2 to 1,92 ± 0,48 mmol/L at Visit 6 ($p<0,0001$) in dialysis patients and from 2,10 ± 0,35 to 1,72 ± 0,44 mmol/L in not dialysis patients ($p<0,0001$).

Detailed serum phosphorus data over time are presented in the table below.

		Visit 1/2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 1-2/Visit 6 p
Patients on dialysis	N	48	46	43	43	43	<0,0001
	Mean	2,55	2,10	2,14	2,00	1,92	
	SD	0,54	0,46	0,50	0,63	0,48	
	Range	1,83-3,88	1,25-3,41	1,34-3,49	1,07-3,78	1,04-3,14	
Patients not on dialysis	N	48	46	45	45	45	<0,0001
	Mean	2,10	1,74	1,66	1,66	1,72	
	SD	0,33	0,32	0,46	0,50	0,44	
	Range	1,79-3,65	0,97-2,40	0,90-2,76	0,99-3,89	0,93-3,04	
All patients	N	96	92	88	88	88	<0,0001
	Mean	2,33	1.92	1,89	1,83	1,83	
	SD	0,50	0,43	0,52	0,59	0,47	
	Range	1,79-3,88	0,97-3,41	0,90=3,49	0,99-3,89	0,93-3,14	

The primary efficacy endpoint was met as demonstrated by a statistically significant reduction of serum phosphorus level in both CKD patients on haemodialysis as well as in CKD patients not requiring haemodialysis.

Safety Results:

The mean ± SD days on sevelamer carbonate was 63,5 days (53 – 77 days). Out of 88 completed the study patients 87 (98,9%) had good compliance (from 80% to 120%) and in 1 (1,1%) patient compliance was assessed as medium (73,2%).

Safety analysis included 96 patients who received at least one dose of sevelamer carbonate.

Of the 96 patients in the safety analysis, 17 treatment emergent adverse events were reported in 10 patients (10,4%) including 10 serious adverse events in 5 (5,2%) patients and 7 non-serious AEs reported in 6 (6,25%) patients.

Seven (7,3%) patients experienced 1 adverse event, 1 (1,04%) patient – 3 adverse events, 1 (1,04%) patient – 2 adverse events, and 1 (1,04%) patient – 5 adverse events. The most frequently reported adverse events were gastro-intestinal: constipation (3 events reported in 2 [2,1%] patients). Other events were reported as a single event in a single patient.

There were 10 treatment emergent SAEs reported in 5 (5,2%) patients. All SAEs were assessed as not related to sevelamer carbonate. SAE disposition is presented below.

Treatment Emergent Serious Adverse Events (Safety Set)

AE Term	Sevelamer Carbonate (n=96)	
System Organ Class preferred term	Patient n (%)	Event n
All	5 (5,2%)	10
Respiratory system:	1 (1,04%)	4
Pneumonia	1 (1,04%)	1
Double-sided hydrothorax	1 (1,04%)	1
Pulmonary edema	1 (1,04%)	1
Respiratory failure	1 (1,04%)	1
Cardiovascular system	2 (2,1%)	3
Acute myocardial infarction	1 (1,04%)	1
Unstable angina	1 (1,04%)	1
Congestive heart failure worsening	1 (1,04%)	1
Renal and urogenital system	2 (2,1%)	2
Chronic kidney disease worsening	2 (2,1%)	2
Infections and Infestations	1 (1,04%)	1
Sepsis	1 (1,04%)	1

One (1,04%) patient experienced 5 SAEs with fatal outcome. A patient was hospitalized with pneumonia, double-sided hydrothorax, pulmonary edema, and respiratory failure. After 1 week of in-hospital stay, sepsis was diagnosed and the next day, the patient died. The fatal case was reported according to local regulation.

Another 2 patients experienced 3 cardiovascular SAEs. Another patient experienced acute myocardial infarction assessed as moderate. One patient experienced unstable angina and congestive heart failure worsening assessed as severe. Both patients refused to further participate and were withdrawn from the study.

Another 2 (2,1%) patients experienced worsening of chronic kidney disease. Both cases were assessed by the investigator as moderate. In 1 patient, there were no actions with regard to the study drug intake. The SAE resolved, and the patient completed the study. Another patient refused to further participate; the study drug was permanently discontinued and the patient was withdrawn from the study.

Four non-serious adverse events in 3 (3,1%) patients were assessed as related to sevelamer carbonate intake. One patient reported 2 events of constipation. The first episode was mild with no actions taken with regard to study drug. After the second episode, assessed as moderate, the patient refused to further participate in the study due to adverse event and was withdrawn. Another patient reported moderate constipation and refused to further participate in the study due to this adverse event. Another patient reported nausea assessed as moderate and refused to continue participation.

There were a total of 6 patients who refused to participate due to adverse events:

Preferred term(s)	Severity	Causal relationship to Sevelamer Carbonate	Outcome
Arterial blood pressure increase	Severe	Not related	Recovered
Unstable angina	Moderate	Not related	Recovered
Congestive heart failure worsening	Severe	Not related	Recovered
Acute myocardial infarction	Moderate	Not related	Recovered
Chronic kidney disease worsening	Moderate	Not related	Recovered with sequel
Constipation	Moderate	Related	Recovered
Nausea	Moderate	Related	Recovered
Nausea	Moderate	Related	Recovered

Another patient refused to participate without any reason provided.

All cases of discontinuations were the result of patient decision to stop participation in the study but not due to investigator medical decision and not due to safety reasons.

No other clinically significant changes in general health and laboratory values planned per protocol were reported.

In general, the safety profile of sevelamer carbonate observed during this study in CKD patient on dialysis and not on dialysis was similar to previously reported in other studies (SVCARB00105, SVCARB00205). All adverse events considered related to study drug (treatment emergent AEs) were gastrointestinal disorders, including nausea and constipation, and were consistent with the safety profile.

SAEs were consistent with patients' underlying diseases.

Basing on the available information sevelamer carbonate powder and tablets in patients with CKD both on dialysis and not on dialysis can be considered as safe and well tolerated.

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