Sponsor

Novartis

Generic Drug Name

SBR759

Therapeutic Area of Trial

Chronic kidney disease (CKD)

Approved Indication

Investigational

Study Number

CSBR759A2201 (12-month study including extension phase)

Title

A 12-week, open label, multicenter, titration study, with a 9-month maintenance treatment extension, to demonstrate efficacy of SBR759 compared to sevelamer-HCl in lowering serum phosphate levels in Chronic Kidney Disease patients on hemodialysis

Phase of Development

Phase II

Study Start/End Dates

Study initiation date: 28-Jul-2008 (first patient first visit)

Study completion date: 27-Aug-2010 (last patient last visit)

The study was to be considered complete once all enrolled patients had either completed the 12-month treatment phase or prematurely discontinued the study. The sample size which was planned for this extension phase aimed to allow long term exposure to SBR759 for up to 378 patients. However, Novartis decided to prematurely terminate this CSBR759A2201 extension phase of the study, since the results from the 12-week core phase of this study (CSBR759A2201) failed to confirm the primary objective.

Study Design/Methodology

The 12 week core study had an open-label, randomized, parallel group design with 4 treatment arms. Screened patients with CKD on maintenance renal replacement therapy (i.e. hemodialysis, hemofiltration or hemodiafiltration) meeting inclusion / exclusion criteria, discontinued all phosphate binder(s) and entered a 2-week wash-out/equilibration period. Patients were stratified according to serum phosphate levels (< or ≥ 7.5 mg/dL, i.e. 2.4 mmol/L), obtained from the 72-hr post-dialysis interval prior to baseline visit and confirming their eligibility. At the baseline visit, patients whose pre-dialysis serum phosphate level was ≥ 6.0 mg/dL (1.9 mmol/L) were stratified,

and randomized to receive either SBR759 or sevelamer-HCl treatment in a 2:1 ratio. Patients newly diagnosed with hyperphosphatemia or who had not received a phosphate binder therapy for at least 4 weeks entered directly in the study treatment phase, if all inclusion/exclusion criteria were met. Patients initiated their study treatment with a 12-week titration period, during which their treatment dose was increased every 2 weeks until their serum phosphate level fell below or equal to the target of 5.5 mg/dL (i.e.1.78 mmol/L).

On completing the 12-week treatment period, patients entered an extension period to receive their study treatment for 9 additional months at the dose required to maintain their serum phosphate levels within the same target. Patients with serum phosphate levels above the target of 5.5 mg/dL (i.e.1.78 mmol/L) at the end of the 12-week period were still eligible to participate in the extension. At the end of the extension treatment period, patients were randomly allocated to either a 2-week additional study treatment period or a 2-week treatment withdrawal period.

Centres

102 centers in 18 countries: Australia (5 centers), Belgium (9 centers), Canada (2 centers), Estonia (2 centers), Finland (4 centers), France (7 centers), Germany (8 centers), Italy (6 centers), Latvia (2 centers), Lithuania (2 centers), Norway (4 centers), Romania (4 centers), Russia (6 centers), Spain (1 center), Sweden (7 centers), Switzerland (4 centers), United Kingdom (6 centers), and USA (23 centers)

Publication

None.

Objectives

Primary objectives

To evaluate safety and tolerability of SBR759 compared to sevelamer-HCl over a 12-month period.

Secondary objectives

- To evaluate whether SBR759 has a superior efficacy compared to sevelamer-HCl, as measured by the number of patients with a serum phosphate level below or equal to 5.5 mg/dl (i.e. 1.78 mmol/L) at 12 months.
- To evaluate whether SBR759 has a superior efficacy compared to sevelamer-HCl, as measured by the number of patients with a serum calcium-phosphate product levels below or equal to 55 mg^2/dL^2 at 12 months.
- To evaluate whether SBR759 and/or sevelamer-HCl maintain efficacy after a 1-year treatment, as measured by the number of patients with a serum phosphate level below or equal to 5.5 mg/dL (i.e. 1.78 mmol/L) after a 2-week random treatment withdrawal period, compared to patients maintained under study treatment.
- To evaluate whether SBR759 is associated with less increase in serum iPTH levels compared to sevelamer-HCl at 12 months.
- To evaluate whether SBR759 has an equivalent rate of hypercalcemia events at 12 months compared to sevelamer-HCl, as measured by serum calcium levels.
- To evaluate whether SBR759 has the potential for a protective effect on selected biomarkers for cardiovascular risk and bone metabolism disorders over a 12-month period.
- To evaluate whether changes in scores for treatment experience and satisfaction with treatment at 12 months demonstrate a superior preference for SBR759 compared to sevelamer-HCl.
- To evaluate changes in patient-reported gastrointestinal symptom burden, using gastrointestinal symptom rating scale (GSRS) total and subscales scores, in patients treated with SBR759 compared to patients treated with sevelamer-HCl.

Test Product (s), Dose(s), and Mode(s) of Administration

SBR759 was provided as a brown powder in sachets containing single dose strengths of 1 g, 1.5 g or 3 g. The dose was adjusted every 2 weeks, during the second or third dialysis of the week (i.e. at a 48-hr post-dialysis interval), based on the most recent 72-hr post-dialysis interval results for serum phosphate levels, by increments of 1 g t.i.d.

Dose escalation was pursued until patient serum phosphate levels fell below or equal to the target value of 5.5 mg/dL (1.78 mmol/L). Thereafter, the study drug dose was adjusted, if required, to maintain this target throughout the study.

SBR759 was taken orally by one of the following 3 methods:

- Suspend the dose (all sachets) in a minimal amount of water (or another non-carbonated liquid at drinking temperature).
- Take the contents of the sachet(s) with the first bites of food. If the drug was sprinkled over food, the contents of the sachet could be applied only to foods which could be fully consumed with reasonable assurance and were not too hot. The food could not be re-cooked after study drug was sprinkled on it.
- Pour the content of the sachet(s) directly in the mouth.

Reference Product(s), Dose(s), and Mode(s) of Administration

Sevelamer-HCl was supplied as tablets of 0.8 g strength and was taken during each meal of the day as per the package insert. The dose was adjusted every 2 weeks, during the second or third dialysis of the week (i.e. at a 48-hr post-dialysis interval), based on the most recent 72-hr post-dialysis interval results for serum phosphate levels, by increments of 0.8 g t.i.d.

Dose escalation was pursued until patient serum phosphate levels fell below or equal to the target value of 5.5 mg/dL (1.78 mmol/L). Thereafter, the study drug dose was adjusted, if required, to maintain this target throughout the study.

Criteria for Evaluation

Efficacy variables (secondary objectives)

The secondary efficacy variables for the extension phase were:

- Number (%) of patients with 72-hr serum phosphate level ≤ 1.78 mmol/L (i.e. 5.5 mg/dL) (phosphate responder) by visit.
- Mean 72-hr serum phosphate levels by visit.
- Change from baseline in 72-hr serum phosphate levels by visit.
- Mean iPTH levels by visit.
- Number (%) of patients with 72-hr serum calcium-phosphate product ≤ 4.44 $mmol^2/L^2$ (55 mg^2/dL^2) by visit.
- Mean 72-hr serum calcium-phosphate product (CaXP) levels by visit.

Safety and tolerability assessments (primary objective)

Safety assessments consisted of collecting all Adverse Events (AEs), Serious Adverse Events (SAEs), with their severity and relationship to study drug, and pregnancies. There was regular monitoring of hematology, blood chemistry and urine performed at a central laboratory and regular assessments of vital signs, physical condition and body weight. In addition, electrocardiograms (ECGs) and a number of special laboratory parameters and health-related quality of life assessments were performed. These included measurement of dialysis adequacy (URR), blood coagulation (PT, PTT and INR), blood glucose, iron saturation, iron concentration, iron-binding capacity, transferrin saturation (TSAT), ferritin, 25-OH vitamin D and 1, 25 di-hydroxy vitamin D, intact parathyroid hormone (iPTH), immune Fecal Occult Blood Test (iFOBT), Thyroid Stimulating Hormone (TSH) and thyroxin (free T4), HbA1c, blood gas analysis, GSRS and Treatment Satisfaction with Medication Questionnaire (TSQM).

Pharmacology

None.

Other

None

Statistical Methods

Data were analyzed using SAS version 8.2. The statistical analysis plan was finalized before data from the core period were locked, and while the clinical trial team was still blinded to the treatment codes. The primary objective of this study was to evaluate safety and tolerability of SBR759 compared to sevelamer-HCl over a 12-month period. Summary tables were provided for all efficacy variables using all data from both the core and extension phases. The modified full analysis population (modified FAS) was used to separately evaluate patients eligible to complete the extension phase of the study. The modified FAS population consists of all patients in the FAS population who were randomized before 16 August 2009.

The assessment of safety was based mainly on the frequency of adverse events and on the number of laboratory values that fell outside of pre-determined ranges. Other safety data, including vital signs and electrocardiogram data were also evaluated. All safety summaries were presented within each baseline phosphate stratum by treatment group as well as for the total within a treatment group (i.e. pooled strata). All safety data was listed for all patients and summarized by treatment arm for the safety population.

The following planned analyses were not conducted due to the early termination of the study:

1. Comparison of the efficacy endpoints between the two treatment groups (SBR759 vs. sevelamer-HCl) at the end of the two week random treatment withdrawal period.
2. Analysis for the following endpoints:

   Number of days with a serum phosphate level ≤ 5.5 mg/dL.

   Number of days with a CaXP level ≤ 55 mg^2/dL^2.
3. Descriptive statistics (mean, standard deviation, minimum, median, and maximum) of quantitative laboratory variables by visit for all biomarkers and change from baseline.
4. Summary table of change from baseline for pulse wave velocity and imaging assessment for vascular calcification and bone mineral density measurements.
5. Correlation between dual-energy x-ray absorptiometry (DEXA) and quantitative computed tomography (QCT) once all scans at 6 and 12 months were collected to investigate the relationship between the two assessments.
6. Summaries statistics for TSQM.

Study Population: Inclusion/Exclusion Criteria and Demographics

Patients eligible for this extension study were those who completed the 12-week core treatment phase. The study population consisted of patients with CKD on maintenance renal replacement therapy (i.e. hemodialysis, hemofiltration or hemodiafiltration). Patients with serum phosphate levels above the target of 5.5 mg/dL (i.e.1.78 mmol/L) at the end of the 12-week core phase were eligible to participate.

Number of Subjects

Patient disposition by treatment group (Extension population)

Disposition Reason	BL phosphate < 2.4 mmol/L SBR759 N=126 n (%)	BL phosphate < 2.4 mmol/L Sevelamer-HCl N=71 n (%)	BL phosphate ≥ 2.4 mmol/L SBR759 N=79 n (%)	BL phosphate ≥ 2.4 mmol/L Sevelamer-HCl N=45 n (%)	Pooled strata SBR759 N=205 n (%)	Pooled strata Sevelamer-HCl N=116 n (%)
Completed	35 (27.8)	26 (36.6)	23 (29.1)	11 (24.4)	58 (28.3)	37 (31.9)
Discontinued	91 (72.2)	45 (63.4)	56 (70.9)	34 (75.6)	147 (71.7)	79 (68.1)
Adverse Event(s)	18 (14.3)	4 (5.6)	6 (7.6)	3 (6.7)	24 (11.7)	7 (6.0)
Abnormal laboratory value(s)	1 (0.8)	0	0	0	1 (0.5)	0
Abnormal test procedure result(s)	0	0	0	1 (2.2)	0	1 (0.9)
Unsatisfactory therapeutic effect	1 (0.8)	0	2 (2.5)	0	3 (1.5)	0
Subject's condition no longer requires study drug	5 (4.0)	1 (1.4)	4 (5.1)	2 (4.4)	9 (4.4)	3 (2.6)
Subject withdrew consent	5 (4.0)	1 (1.4)	3 (3.8)	2 (4.4)	8 (3.9)	3 (2.6)
Lost to follow-up	0	1 (1.4)	1 (1.3)	0	1 (0.5)	1 (0.9)
Administrative problems	57 (45.2)	34 (47.9)	38 (48.1)	24 (53.3)	95 (46.3)	58 (50.0)
Death	1 (0.8)	2 (2.8)	1 (1.3)	0	2 (1.0)	2 (1.7)
Protocol deviation	3 (2.4)	2 (2.8)	1 (1.3)	2 (4.4)	4 (2.0)	4 (3.4)
Other	0	0	0	0	0	0

Patient disposition by treatment group (Withdrawal population)

Disposition Reason	Pooled strata			
	SBR759		Sevelamer-HCl	
	SBR759 N=19 n (%)	No treatment N=27 n (%)	Sevelamer-HCl N=14 n (%)	No treatment N=14 n (%)
Completed	19 (100.0)	24 (88.9)	14 (100.0)	13 (92.9)
Discontinued	0	3 (11.1)	0	1 (7.1)
Adverse Event(s)	0	0	0	0
Abnormal laboratory value(s)	0	0	0	1 (7.1)
Abnormal test procedure result(s)	0	0	0	0
Unsatisfactory therapeutic effect	0	2 (7.4)	0	0
Subject's condition no longer requires study drug	0	0	0	0
Subject withdrew consent	0	0	0	0
Lost to follow-up	0	0	0	0
Administrative problems	0	1 (3.7)	0	0
Death	0	0	0	0
Protocol deviation	0	0	0	0
Other	0	0	0	0

Demographic and Background Characteristics

Demographic summary by stratum and treatment (Full Analysis Set)

	BL phosphate < 2.4 mmol/L		BL phosphate ≥2.4 mmol/L		Pooled strata	
	SBR759 N=179	sevelamer-HCl N=88	SBR759 N=110	sevelamer-HCl N=56	SBR759 N=289	sevelamer-HCl N=144
Age (years)						
n	179	88	110	56	289	144
Mean	58.5	60.1	55.8	59.4	57.5	59.8
SD	15.00	14.58	13.03	12.58	14.32	13.80
Median	60.0	60.5	56.5	60.0	58.0	60.0
Min-Max	20 - 86	28 - 82	19 - 85	24 - 83	19 - 86	24 - 83
Age group–n (%)						
<65years	107 (59.8)	50 (56.8)	80 (72.7)	41 (73.2)	187 (64.7)	91 (63.2)
≥65years	72 (40.2)	38 (43.2)	30 (27.3)	15 (26.8)	102 (35.3)	53 (36.8)
Sex-n (%)						
Male	108 (60.3)	49 (55.7)	66 (60.0)	36 (64.3)	174 (60.2)	85 (59.0)
Female	71 (39.7)	39 (44.3)	44 (40.0)	20 (35.7)	115 (39.8)	59 (41.0)
Race-n (%)						
Caucasian	147 (82.1)	76 (86.4)	94 (85.5)	48 (85.7)	241 (83.4)	124 (86.1)
Black	19 (10.6)	6 (6.8)	9 (8.2)	6 (10.7)	28 (9.7)	12 (8.3)
Asian	4 (2.2)	0	2 (1.8)	1 (1.8)	6 (2.1)	1 (0.7)
Other	9 (5.0)	6 (6.8)	5 (4.5)	1 (1.8)	14 (4.8)	7 (4.9)
Height (cm)						
n	178	88	110	56	288	144
Mean	169.4	168.0	168.5	168.1	169.1	168.0
SD	9.85	8.75	9.82	10.51	9.83	9.44
Median	170.0	168.0	169.5	168.0	170.0	168.0
Min-Max	143 - 198	147 - 188	144 - 188	140 - 190	143 - 198	140 - 190
Weight (kg)						
n	177	87	110	56	287	143
Mean	79.56	75.57	79.41	75.53	79.50	75.56
SD	23.767	18.851	21.188	17.134	22.775	18.136
Median	76.30	73.90	74.30	75.55	75.70	75.30
Min-Max	43.9 - 264.1	36.8 - 141.7	47.5 - 169.6	36.8 - 118.2	43.9 - 264.1	36.8 - 141.7
BMI (kg/m^2)						
n	176	87	110	56	286	143
Mean	27.55	26.59	27.99	26.52	27.72	26.56
SD	6.754	5.546	7.270	4.480	6.947	5.138
Median	26.46	25.96	26.20	26.04	26.29	25.96
Min-Max	17.5 - 67.4	16.8 - 41.9	17.7 - 60.8	16.4 - 39.5	17.5 - 67.4	16.4 - 41.9
Region						
Europe + Australia	125 (69.8)	63 (71.6)	77 (70.0)	40 (71.4)	202 (69.9)	103 (71.5)
North America	54 (30.2)	25 (28.4)	33 (30.0)	16 (28.6)	87 (30.1)	41 (28.5)

BMI = body mass index

Disease characteristics by stratum and treatment (Full Analysis Set)

	BL phosphate < 2.4 mmol/L		BL phosphate ≥ 2.4 mmol/L		Pooled strata	
	SBR759 N=179	sevelamer-HCl N=88	SBR759 N=110	sevelamer-HCl N=56	SBR759 N=289	sevelamer-HCl N=144
Primary cause of ESRD – n (%)						
Glomerulonephritis /glomerular disease	29 (16.2)	15 (17.0)	24 (21.8)	11 (19.6)	53 (18.3)	26 (18.1)
Pyelonephritis	1 (0.6)	3 (3.4)	2 (1.8)	3 (5.4)	3 (1.0)	6 (4.2)
Polycystic disease	22 (12.3)	7 (8.0)	15 (13.6)	4 (7.1)	37 (12.8)	11 (7.6)
Hypertension / nephrosclerosis	27 (15.1)	22 (25.0)	16 (14.5)	11 (19.6)	43 (14.9)	33 (22.9)
Drug induced toxicity	1 (0.6)	1 (1.1)	2 (1.8)	0	3 (1.0)	1 (0.7)
Diabetes mellitus	50 (27.9)	23 (26.1)	19 (17.3)	16 (28.6)	69 (23.9)	39 (27.1)
Interstitial nephritis	3 (1.7)	3 (3.4)	0	2 (3.6)	3 (1.0)	5 (3.5)
Vasculitis	1 (0.6)	1 (1.1)	4 (3.6)	2 (3.6)	5 (1.7)	3 (2.1)
Obstructive disorder/ reflux	8 (4.5)	1 (1.1)	4 (3.6)	0	12 (4.2)	1 (0.7)
Renal hyperplasia /dysplasia	1 (0.6)	0	1 (0.9)	1 (1.8)	2 (0.7)	1 (0.7)
IgA nephropathy	6 (3.4)	1 (1.1)	5 (4.5)	0	11 (3.8)	1 (0.7)
Unknown	9 (5.0)	5 (5.7)	6 (5.5)	2 (3.6)	15 (5.2)	7 (4.9)
Other	21 (11.7)	6 (6.8)	11 (10.0)	4 (7.1)	32 (11.1)	10 (6.9)
Missing	0	0	1 (0.9)	0	1 (0.3)	0
Duration of chronic dialysis (years)						
n	162	80	98	52	260	132
Mean	4.84	4.54	3.97	4.85	4.51	4.66
SD	5.598	5.878	3.655	6.075	4.966	5.936
Median	3.03	2.55	2.56	3.14	2.87	2.77
Min - Max	0.1 - 36.6	0.3 - 35.0	0.3 - 17.3	0.3 - 31.3	0.1 - 36.6	0.3 - 35.0
Baseline serum phosphate at 72-hr post-dialysis interval (mmol/L)						
n	179	88	110	56	289	144
Mean	2.118	2.124	2.745	2.787	2.356	2.381
SD	0.1568	0.1953	0.4079	0.3335	0.4137	0.4137
Median	2.120	2.104	2.649	2.705	2.230	2.320
Min - Max	1.71 - 2.69*	1.61 - 2.65*	1.60* - 4.04	2.39* - 3.52	1.60 - 4.04	1.61 - 3.52
Baseline serum iPTH at 48-hr post-dialysis interval (pmol/L)						
n	178	88	110	56	288	144
Mean	37.84	32.56	42.22	36.90	39.51	34.25
SD	27.789	22.971	29.239	24.181	28.381	23.461
Median	31.35	25.93	35.00	34.65	32.30	29.70
Min - Max	2.0 - 195.3	1.9 - 110.3	3.0 - 180.3	1.8 - 104.2	2.0 - 195.3	1.8 - 110.3

ESRD = End stage renal disease.
* Seven patients were randomized to the wrong stratum, hence values outside expected range.
Duration of chronic dialysis was calculated as (date of visit 1 - date chronic dialysis first started + 1) / 365.25.

Primary Objective Results

See **Safety Results**, below (the primary objective was to evaluate safety and tolerability of SBR759 compared to sevelamer-HCl over a 12-month period).

Secondary Objective Results

Proportion of 72-hr phosphate responders by treatment group (modified FAS population)

	Pooled strata	
	SBR759 N=128 n (%)	**Sevelamer-HCl N=62 n (%)**
End of core (Week 12)	67 (52.3)	41 (66.1)
Extension		
Week 24	55 (43.0)	35 (56.5)
Week 40	48 (37.5)	26 (41.9)
Week 52	42 (32.8)	25 (40.3)

Phosphate responder was defined as patient with a serum phosphate level below or equal to 1.78 mmol/L at the 72-hr post-dialysis interval measurements

Patients with a missing 72-hr post-dialysis phosphate assessment (e.g. due to earlier premature discontinuation) were counted as non-responders at that visit.

Proportion of calcium-phosphate product responders by treatment group (modified FAS population)

	Pooled strata	
	SBR759 N=128 n (%)	**Sevelamer-HCl N=62 n (%)**
End of core phase (Week 12)	78 (60.9)	48 (77.4)
Extension		
Week 24	65 (50.8)	39 (62.9)
Week 40	55 (43.0)	33 (53.2)
Week 52	50 (39.1)	30 (48.4)

Calcium-phosphate product responder was defined as a patient with a calcium-phosphate product level below or equal to 4.44 $mmol^2/L^2$ using the 72-hr post-dialysis interval measurement.

Patients discontinuing the study prior to Week 52 were counted as non-responders. Patients with a missing 72-hr calcium-phosphate product assessment at Week 52 were counted as non-responders.

Safety Results

Adverse Events by System Organ Class

Number (%) of patients with the most frequent AEs (greater than or equal to 10% in any group) by system organ class (Safety population)

	BL phosphate < 2.4 mmol/L		BL phosphate ≥ 2.4 mmol/L		Pooled strata	
Primary system organ class	SBR759 N=179 n (%)	Sevelamer-HCl N=88 n (%)	SBR759 N=110 n (%)	Sevelamer-HCl N=56 n (%)	SBR759 N=289 n (%)	Sevelamer-HCl N=144 n (%)
Any primary system organ class	**151 (84.4)**	**67 (76.1)**	**91 (82.7)**	**46 (82.1)**	**242 (83.7)**	**113 (78.5)**
Gastrointestinal disorders	123 (68.7)	43 (48.9)	60 (54.5)	25 (44.6)	183 (63.3)	68 (47.2)
Infections and infestations	50 (27.9)	36 (40.9)	29 (26.4)	12 (21.4)	79 (27.3)	48 (33.3)
Musculoskeletal and connective tissue disorders	31 (17.3)	24 (27.3)	27 (24.5)	7 (12.5)	58 (20.1)	31 (21.5)
Injury, poisoning and procedural complications	28 (15.6)	21 (23.9)	21 (19.1)	8 (14.3)	49 (17.0)	29 (20.1)
General disorders and administration site conditions	33 (18.4)	16 (18.2)	15 (13.6)	9 (16.1)	48 (16.6)	25 (17.4)
Investigations	38 (21.2)	13 (14.8)	10 (9.1)	10 (17.9)	48 (16.6)	23 (16.0)
Metabolism and nutrition disorders	31 (17.3)	20 (22.7)	16 (14.5)	9 (16.1)	47 (16.3)	29 (20.1)
Nervous system disorders	26 (14.5)	12 (13.6)	17 (15.5)	10 (17.9)	43 (14.9)	22 (15.3)
Respiratory, thoracic and mediastinal disorders	31 (17.3)	18 (20.5)	12 (10.9)	8 (14.3)	43 (14.9)	26 (18.1)
Cardiac disorders	23 (12.8)	15 (17.0)	12 (10.9)	7 (12.5)	35 (12.1)	22 (15.3)
Vascular disorders	20 (11.2)	21 (23.9)	12 (10.9)	7 (12.5)	32 (11.1)	28 (19.4)
Skin and subcutaneous tissue disorders	19 (10.6)	14 (15.9)	12 (10.9)	12 (21.4)	31 (10.7)	26 (18.1)

Primary SOCs are sorted in descending order of frequency in the pooled SBR759 group.
A patient with multiple occurrences of an AE on the same treatment was counted only once in the AE category for that treatment.

Number (%) of patients with most frequent AEs (greater than or equal to 10% in any group) overall and by preferred term (Safety population)

Preferred term	BL phosphate < 2.4 mmol/L		BL phosphate ≥ 2.4 mmol/L		Pooled strata	
	SBR759 N=179 n (%)	Sevelamer-HCl N=88 n (%)	SBR759 N=110 n (%)	Sevelamer-HCl N=56 n (%)	SBR759 N=289 n (%)	Sevelamer-HCl N=144 n (%)
Total no. of patients with an adverse event	151 (84.4)	67 (76.1)	91 (82.7)	46 (82.1)	242 (83.7)	113 (78.5)
Diarrhea	69 (38.5)	15 (17.0)	29 (26.4)	8 (14.3)	98 (33.9)	23 (16.0)
Nausea	30 (16.8)	8 (9.1)	8 (7.3)	7 (12.5)	38 (13.1)	15 (10.4)
Vomiting	21 (11.7)	11 (12.5)	12 (10.9)	8 (14.3)	33 (11.4)	19 (13.2)
Constipation	16 (8.9)	11 (12.5)	9 (8.2)	7 (12.5)	25 (8.7)	18 (12.5)
Feces discolored	12 (6.7)	0	12 (10.9)	0	24 (8.3)	0
Muscle spasms	15 (8.4)	10 (11.4)	9 (8.2)	1 (1.8)	24 (8.3)	11 (7.6)
Cough	12 (6.7)	9 (10.2)	6 (5.5)	4 (7.1)	18 (6.2)	13 (9.0)
Dyspepsia	11 (6.1)	7 (8.0)	7 (6.4)	8 (14.3)	18 (6.2)	15 (10.4)

Preferred terms are sorted in descending order of frequency in the pooled SBR759 column
A patient with multiple occurrences of an AE on the same treatment was counted only once in the AE category for that treatment.

Serious Adverse Events and Deaths

Deaths, other serious or clinically significant adverse events or related discontinuations by treatment group - n (%) of patients (Safety population)

	BL phosphate < 2.4 mmol/L		BL phosphate ≥ 2.4 mmol/L		Pooled strata	
	SBR759 N=179 n (%)	Sevelamer-HCl N=88 n (%)	SBR759 N=110 n (%)	Sevelamer-HCl N=56 n (%)	SBR759 N=289 n (%)	Sevelamer-HCl N=144 n (%)
Deaths	3 (1.7)	4 (4.5)	4 (3.6)	2 (3.6)	7 (2.4)	6 (4.2)
At least 1 SAE (including deaths)	47 (26.3)	31 (35.2)	30 (27.3)	12 (21.4)	77 (26.6)	43 (29.9)
Drug discontinuations due to AE	55 (30.7)	9 (10.2)	23 (20.9)	9 (16.1)	78 (27.0)	18 (12.5)
Dose adjustment or temporary interruption due to AE	64 (35.8)	20 (22.7)	28 (25.5)	15 (26.8)	92 (31.8)	35 (24.3)

A patient with multiple occurrences of an AE on the same treatment was counted only once in the AE category for that treatment.

Other Relevant Findings

Most frequent gastrointestinal-related adverse events (greater than or equal to 10% in any group) by preferred term and maximum severity (Safety population)

	Pooled strata	
Preferred term Maximum severity	**SBR759 N=289 n (%)**	**Sevelamer-HCl N=144 n (%)**
Any gastrointestinal disorder	**183 (63.3)**	**68 (47.2)**
Mild	86 (29.8)	35 (24.3)
Moderate	82 (28.4)	30 (20.8)
Severe	15 (5.2)	3 (2.1)
Diarrhea	98 (33.9)	23 (16.0)
Mild	59 (20.4)	14 (9.7)
Moderate	32 (11.1)	8 (5.6)
Severe	7 (2.4)	1 (0.7)
Nausea	38 (13.1)	15 (10.4)
Mild	24 (8.3)	11 (7.6)
Moderate	12 (4.2)	4 (2.8)
Severe	2 (0.7)	0
Vomiting	33 (11.4)	19 (13.2)
Mild	18 (6.2)	16 (11.1)
Moderate	14 (4.8)	3 (2.1)
Severe	1 (0.3)	0
Constipation	25 (8.7)	18 (12.5)
Mild	14 (4.8)	12 (8.3)
Moderate	11 (3.8)	5 (3.5)
Severe	0	1 (0.7)
Dyspepsia	18 (6.2)	15 (10.4)
Mild	12 (4.2)	9 (6.3)
Moderate	5 (1.7)	6 (4.2)
Severe	1 (0.3)	0

Gastrointestinal-related adverse events are those events in the gastrointestinal disorders system organ class.
Preferred terms are sorted in descending order of frequency in the pooled SBR759 group.
A patient with multiple occurrences of an AE on the same treatment is counted only once in the AE category for that treatment.
A patient with multiple severity ratings for an AE while on a treatment is only counted under the maximum rating.
DAIDS grades were mapped into severity as follows: 1=mild; 2=moderate; 3=severe and 4=severe

Diarrhea adverse events by DAIDS grade (Safety population)

	Pooled strata	
DAIDS grade	**SBR759 N=289 n (%)**	**Sevelamer-HCl N=144 n (%)**
Any diarrhea-related AE	102 (35.3)	25 (17.4)
Grade 1	59 (20.4)	15 (10.4)
Grade 2	34 (11.8)	9 (6.3)
Grade 3	9 (3.1)	1 (0.7)
Grade 4	0	0

Diarrhea adverse events were those selected by the investigator as diarrhea-related on the adverse event eCRF.
DAIDS (Division of Acquired Immune Deficiency Syndrome) definition used to assign severity to diarrhea adverse events.
A patient with multiple grades for an AE while on a treatment was only counted under the maximum grade.

Summary of at least one post-baseline notable laboratory value during treatment (Safety population)

		Pooled strata			
			SBR759 N=289		**Sevelamer-HCl N=144**
Laboratory test	**Criterion**	**Total**	**n (%)**	**Total**	**n (%)**
HbA1c	> 8%	260	26 (10.0)	131	10 (7.6)
48-hr phosphate	< 1.13 mmol/L	264	84 (31.8)	136	47 (34.6)
	> 2.9 mmol/L	264	18 (6.8)	136	7 (5.1)
72-hr phosphate	< 1.13 mmol/L	284	95 (33.5)	144	66 (45.8)
	> 2.9 mmol/L	284	45 (15.8)	144	16 (11.1)
48-hr total calcium	< 2 mmol/L	264	48 (18.2)	136	37 (27.2)
	> 2.54 mmol/L	264	30 (11.4)	136	12 (8.8)
72-hr total calcium	< 2 mmol/L	284	116 (40.8)	144	54 (37.5)
	> 2.54 mmol/L	284	34 (12.0)	144	17 (11.8)
Transferrin saturation	> 60%	276	28 (10.1)	137	10 (7.3)
	> 50%	276	62 (22.5)	137	17 (12.4)
iPTH	> 84.8 pmol/L	269	35 (13.0)	135	18 (13.3)
Serum ferritin	> 1000 µg/L	276	68 (24.6)	137	26 (19.0)
	> 500 µg/L	276	205 (74.3)	137	95 (69.3)
Serum ferritin and Transferrin saturation	> 500 µg/L and > 50%	276	53 (19.2)	137	14 (10.2)
	> 500 µg/L and > 60%	276	27 (9.8)	137	9 (6.6)

Total = Number of patients with evaluable criterion.
n = Number of patients meeting the criterion at least once post-baseline.
Safety laboratory assessments for HbA1c, transferrin saturation, serum ferritin and iPTH were planned to be collected at 48-hr post-dialysis intervals, however some assessments were collected at 72-hr post-dialysis intervals. and therefore all assessments were summarized.

Summary statistics including change from baseline for iron indices at Week 52/PPW by treatment (Safety population)

Parameter	---------- Baseline----------				-------- Week 52/PPW -------				----------Change----------			
Treatment	**n**	**Mean**	**SD**	**Median**	**n**	**Mean**	**SD**	**Median**	**n**	**Mean**	**SD**	**Median**
Serum Ferritin (µg/L)												
SBR759: Pooled strata	287	523.9	330.33	467.0	183	695.9	452.43	647.0	182	173.1	413.30	106.0
Sevelamer-HCl: Pooled strata	144	511.8	280.74	495.5	102	582.3	353.38	524.0	102	65.3	334.61	41.0
Transferrin saturation in %												
SBR759: Pooled strata	289	30.5	12.95	28.0	184	32.0	12.97	29.0	184	2.0	17.05	2.5
Sevelamer-HCl: Pooled strata	144	30.3	13.84	28.0	104	29.8	14.72	26.0	104	-1.0	18.85	-2.0
Iron (µmol/L)												
SBR759: Pooled strata	289	12.1	4.89	11.0	184	12.5	5.03	11.0	184	0.4	6.56	1.0
Sevelamer-HCl: Pooled strata	144	12.2	6.03	11.8	104	12.5	6.25	11.0	104	0.1	8.10	-1.0
Total Iron Binding Capacity (µmol/L)												
SBR759: Pooled strata	289	40.8	8.32	40.7	184	39.7	7.00	38.1	184	-1.6	5.35	-2.0
Sevelamer-HCl: Pooled strata	144	40.9	7.75	39.9	104	43.1	8.44	41.0	104	1.8	6.94	2.2

Baseline was defined as the value collected at baseline visit (visit 4). If this was missing then the last value on or before the date of first dose of study medication was used. PPW = Premature patient withdrawal.
Safety laboratory assessments were planned to be collected at 48-hr post-dialysis intervals, however some assessments were collected at 72-hr post-dialysis intervals; therefore all assessments from scheduled visits were summarized.

Other Relevant Findings

Not applicable.

Date of Clinical Trial Report

3 May 2011.

Date Inclusion on Novartis Clinical Trial Results Database

25 Oct 2011

Date of Latest Update

25 Oct 2011