Sponsor

Novartis

Generic Drug Name

SBR759

Therapeutic Area of Trial

Chronic Kidney Disease (CKD)

Approved Indication

Investigational

Study Number

CSBR759A2304

Title

A double-blind, randomized, placebo-controlled multi-center trial to compare the phosphate lowering efficacy of different doses of SBR759 to placebo

Phase of Development

Phase III

Study Start/End Dates

15 Feb 2010 to 05 Oct 2010

Study Design/Methodology

The study was a randomized, placebo-controlled, 5-treatment arm, parallel group design with stratification according to baseline serum phosphate levels. It was designed to compare the phosphate lowering efficacy of different doses of SBR759 (3, 6, 9 and 12 g/day) to placebo after 4

weeks of treatment.

At completion of the 4-week treatment period, if serum phosphate was below or equal to 2.1 mmol/L (≤ 6.5 mg/dL), patients were randomly allocated, in a 1:4 ratio, to either a 2-week additional treatment period (at the same dose level as for week 4) or a 2-week treatment withdrawal period (same treatment as for group I).

Centres

34 centers in 7 countries: Belgium (1), Czech Republic (3), Hungary (5), India (5), Italy (4), Japan (14), USA (2)

Publication

None

Objectives

Primary objective(s)

- evaluate the change from baseline in 72-hour serum phosphate levels of different doses of SBR759 versus placebo over 4 weeks of treatment.

Secondary objective(s)

- evaluate changes in serum phosphate during a 2-week random treatment withdrawal period of SBR759 after 4 weeks treatment.
- evaluate dose-dependent efficacy of SBR759.
- compare the short-term safety profile and dose-dependent tolerability of SBR759, dosed t.i.d. with meals, to that of placebo.

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

Single dose 1 gram sachets of powder for oral suspension of SBR759 (3, 6, 9 and 12 g/day taken during meals)

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

Single dose 1 gram sachets of powder for oral suspension of SBR759 matching placebo (3, 6, 9 and 12 g/day taken during meals)

Criteria for Evaluation

Primary variables

The primary efficacy variable was the change from baseline in 72-hour serum phosphate at 4 weeks. The baseline value was defined as the last 72-hour serum phosphate value obtained by the central laboratory before randomization at baseline and intake of study drug.

However, the original primary analysis was no longer considered relevant due to the reduced total sample size and the focus on the small Japanese sub-group sample. Hence, descriptive statistics of baseline and post-baseline values, as well as change from baseline were summarized by treatment group and visit as for the primary analysis.

Secondary variables

The secondary efficacy variables in the 4-week treatment period were:

- Change from baseline in 72-hour serum phosphate levels by visit.
- Change from baseline in 72-hour serum calcium-phosphate product (CaXP) levels by visit.
- Response to treatment by visit defined as achievement of serum phosphate ≤ 1.78 mmol/L (≤ 5.5 mg/dL).
- Response to treatment by visit defined as achievement of serum phosphate ≤ 1.94 mmol/L (≤ 6.0 mg/dL) (Japanese guideline criteria).
- Change from baseline in iPTH levels by visit.

At a secondary level, an ANCOVA with treatment and baseline serum phosphate as explanatory variables was conducted. A linear trend test of dose response using contrast (-2, -1, 0, 1, 2) was performed at a one-sided 2.5% level. In addition, the estimate and 95% CI of the difference between individual SBR759 doses and placebo was calculated.

Safety and tolerability

The assessment of safety was based mainly on the frequency of AEs and on the number of laboratory values that fell outside of pre-determined notable ranges. Other safety data, including vital signs, electrocardiogram data, and hemodialysis and dialysis adequacy parameters were also evaluated.

Pharmacology

Not applicable

Other

Not applicable

Statistical Methods

Based on the 12-week results of study CSBR759A2201 in which the primary objective was not met, Novartis decided to discontinue this study in all countries, except Japan. This decision was also based on study CSBR759A2202 12-week results which showed significant efficacy in this Asian population. Therefore, this study was conducted to evaluate the efficacy and safety profile of fixed doses of SBR759, primarily in the Japanese population.

Each dose of SBR759 was compared with placebo using descriptive statistics of change from baseline in 72-hour serum phosphate levels. At a secondary level, an analysis of covariance model with treatment, baseline serum phosphate as explanatory variables was conducted. The estimate and 95% CI of the difference between individual SBR dose group and placebo was presented. In addition, the linear trend test using contrast c= (-2, 01, 0, 1, 2) was performed at a one-sided 2.5% level.

No interim or data-driven analyses were performed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Following discontinuation of the study outside of Japan, it was expected that approximately 115 adult CKD patients (stage V) aged 18 years and older on maintenance RRT three times a week, who required phosphate lowering medication would be enrolled (of which about 65 patients would be from Japan).

Men or women of at least 18 years of age, on maintenance renal replacement therapy (i.e. hemodialysis, hemodiafiltration or hemofiltration) 3 times per week for ≥ 3 months and treated with a stable dialysis prescription. Patient were on a stable phosphate binder dose (i.e. no change in prescribed dose for at least 4 weeks prior to screening), and was willing to stop their phosphate binder therapy at start of screening to enter the 2-week wash-out period, or had not received any phosphate binder therapy for at least 4 weeks prior to screening. At the baseline visit, the patient had a serum phosphate level > 1.78 mmol/L (> 5.5 mg/dL) and ≤ 2.9 mmol/L (≤ 9.0 mg/dL). Patient had a Kt/V ≥ 1.2, or Urea Reduction Ratio ≥ 60%. Patients receiving active Vitamin D were on stable regimen at screening and planned to be maintained stable throughout the study duration. Patients receiving calcimimetics were on a stable regimen for at least 4 weeks prior to screening and planned to be maintained stable throughout the study duration and were on phosphate restricted diet at screening and throughout the study.

Key exclusion criteria were: patients on peritoneal dialysis, patients with a transplant scheduled, an uncontrolled hyperparathyroidism (i.e. intact parathyroid hormone (iPTH) > 84.8 pmol/L (> 800 pg/mL), a parathyroidectomy within 3 months prior to screening or for more than 3 months and iPTH < 2.65 pmol/L (< 25 pg/mL), a parathyroidectomy scheduled during the study, a clinically significant (e.g. chronic unstable) GI disorder and/or had a history of major gastrointestinal tract surgery (e.g. gastrectomy, extensive bowel resection), a history of hemochromatosis or serum ferritin > 1000 ng/mL, obtained from central lab at screening, or a transferrin saturation > 60%.

Number of Subjects

Patient disposition (All randomized patients – Japanese population)

Disposition Reason	Placebo N=12 n (%)	SBR759 3 g/day N=13 n (%)	SBR759 6 g/day N=13 n (%)	SBR759 9 g/day N=13 n (%)	SBR759 12 g/day N=12 n (%)
Completed	8 (66.7)	8 (61.5)	10 (76.9)	12 (92.3)	10 (83.3)
Discontinued total/due to:	4 (33.3)	5 (38.5)	3 (23.1)	1 (7.7)	2 (16.7)
Adverse events	0	2 (15.4)	1 (7.7)	0	0
Unsatisfactory therapeutic effect	4 (33.3)	2 (15.4)	0	0	0
Subject's condition no longer requires therapy	0	0	0	1 (7.7)	0
Subject withdrew consent	0	1 (7.7)	2 (15.4)	0	2 (16.7)

Demographic and Background Characteristics

Demographic summary (FAS population – Japanese population)

Variable	Placebo N=12 n (%)	SBR759 3 g/day N=13 n (%)	SBR759 6 g/day N=12 n (%)	SBR759 9 g/day N=13 n (%)	SBR759 12 g/day N=12 n (%)
Age (years)					
n	12	13	12	13	12
Mean	61.8	59.0	67.0	61.3	65.1
SD	8.94	11.30	7.17	12.41	7.93
Median	61.5	61.0	67.5	63.0	66.0
Min-Max	44 - 76	37 - 72	56 - 81	39 - 79	50 - 79
Sex – n (%)					
Male	7 (58.3)	8 (61.5)	6 (50.0)	9 (69.2)	8 (66.7)
Female	5 (41.7)	5 (38.5)	6 (50.0)	4 (30.8)	4 (33.3)
Race – n (%)					
Asian	12 (100.0)	13 (100.0)	12 (100.0)	13 (100.0)	12 (100.0)
Height (cm)					
n	12	13	12	13	12
Mean	158.1	159.1	157.5	163.6	160.0
SD	7.50	13.45	10.30	7.78	8.16
Median	159.0	155.0	154.5	165.0	162.0
Min-Max	146 - 172	141 - 177	146 - 173	150 - 174	147 - 173
Weight (kg)					
n	12	13	12	13	12
Mean	54.14	53.63	55.68	55.84	55.39
SD	6.478	11.945	10.642	8.893	11.249
Median	54.55	56.70	55.65	54.40	54.60
Min-Max	44.3 - 63.8	36.2 - 72.8	39.9 - 75.4	42.9 - 71.4	41.7 - 81.7

Disease characteristics (FAS population – Japanese population)

Variable	Placebo N=12	SBR759 3 g/day N=13	SBR759 6 g/day N=12	SBR759 9 g/day N=13	SBR759 12 g/day N=12
Primary cause of ESRD - n(%)					
Glomerulonephritis / glomerular disease	3 (25.0)	5 (38.5)	5 (41.7)	1 (7.7)	5 (41.7)
Pyelonephritis	0	0	0	0	1 (8.3)
Polycystic disease	0	0	2 (16.7)	1 (7.7)	0
Hypertension / nephrosclerosis	0	0	2 (16.7)	1 (7.7)	3 (25.0)
Diabetes mellitus	5 (41.7)	6 (46.2)	2 (16.7)	5 (38.5)	2 (16.7)
IgA nephropathy	2 (16.7)	2 (15.4)	0	3 (23.1)	1 (8.3)
Unknown	2 (16.7)	0	1 (8.3)	0	0
Other	0	0	0	2 (15.4)	0
Duration of chronic dialysis (years)					
n	12	13	12	13	12
Mean	8.56	10.45	7.98	8.37	10.73
SD	9.806	7.040	6.900	5.793	7.254
Median	5.92	11.14	5.94	8.21	10.18
Min - Max	0.4 - 33.1	1.0 - 21.0	0.3 - 22.6	0.6 - 23.8	2.1 - 24.3
Intact Parathyroid hormone (iPTH) (pmol/L)					
n	12	13	12	13	12
Mean	29.21	45.81	32.21	44.12	32.96
SD	9.905	31.264	19.674	20.806	22.227
Median	29.79	40.36	25.10	37.86	27.65
Min - Max	14.8 - 47.3	11.1 - 110.2	9.8 - 69.4	19.4 - 99.0	7.6 - 87.8

Primary Objective Result(s)

ANCOVA of change from baseline in 72-hour serum phosphate (mmol/L) levels at Week 4 (LOCF) by treatment group (FAS population - Japanese population)

Statistics	Placebo N=12	SBR759 3 g/day N=13	SBR759 6 g/day N=12	SBR759 9 g/day N=13	SBR759 12 g/day N=12
n	12	13	12	13	12
LS Mean (SE)	0.190 (0.0969)	-0.409 (0.0931)	-0.809 (0.0970)	-1.205 (0.0933)	-1.209 (0.0977)
Difference		-0.599	-0.998	-1.395	-1.398
95% CI		(-0.869, -0.330)	(-1.273, -0.723)	(-1.665, -1.125)	(-1.673, -1.124)
Linear trend test p-value = <0.001					

n = Number of patients with baseline and Week 4 (LOCF) serum phosphate values
Estimated pairwise differences (SBR759-placebo) and 95% CIs were based on an ANCOVA model with treatment and baseline serum phosphate value as factors.
P-value was based on a linear trend test using contrast (-2, -1, 0, 1, 2). One-sided 2.5% level was used.

Secondary Objective Result(s)

Summary statistics of change from baseline in 72-hour serum phosphate (mmol/L) levels by treatment and visit (FAS population — Japanese population)

Visit	Statistics	Placebo N=12	SBR759 3 g/day N=13	SBR759 6 g/day N=12	SBR759 9 g/day N=13	SBR759 12 g/day N=12
Week 1	n	12	13	12	13	12
	Mean	0.253	-0.477	-0.563	-0.985	-0.948
	SD	0.2956	0.2788	0.3483	0.3206	0.4426
	Minimum	-0.21	-1.18	-1.28	-1.45	-1.39
	Median	0.215	-0.460	-0.605	-0.850	-1.120
	Maximum	0.76	-0.10	0.07	-0.53	-0.28
Week 2	n	10	12	12	13	11
	Mean	-0.001	-0.438	-0.687	-1.179	-1.198
	SD	0.2294	0.3688	0.4167	0.4221	0.3898
	Minimum	-0.34	-1.00	-1.38	-1.98	-1.70
	Median	-0.005	-0.370	-0.680	-1.140	-1.340
	Maximum	0.39	0.25	0.03	-0.52	-0.23
Week 3	n	11	11	12	13	11
	Mean	-0.021	-0.437	-0.655	-1.197	-1.318
	SD	0.2946	0.4640	0.4124	0.4139	0.2890
	Minimum	-0.40	-0.98	-1.20	-2.02	-1.80
	Median	-0.070	-0.560	-0.810	-1.250	-1.360
	Maximum	0.61	0.56	-0.07	-0.69	-0.83
Week 4	n	10	11	10	12	10
	Mean	0.188	-0.423	-0.754	-1.258	-1.256
	SD	0.2888	0.2921	0.4002	0.3270	0.3473
	Minimum	-0.23	-1.03	-1.51	-1.78	-1.79
	Median	0.200	-0.390	-0.770	-1.175	-1.285
	Maximum	0.73	-0.01	-0.29	-0.79	-0.78

Summary statistics of change from baseline in 72-hour serum calcium-phosphate product ($mmol^2/L^2$) levels by treatment and visit (FAS population — Japanese population)

Visit	Statistics	Placebo N=12	SBR759 3 g/day N=13	SBR759 6 g/day N=12	SBR759 9 g/day N=13	SBR759 12 g/day N=12
Week 1	n	7	6	7	7	7
	Mean	0.259	-0.820	-1.330	-2.049	-2.023
	SD	0.4695	0.6490	0.7446	0.8662	1.0976
	Minimum	-0.53	-1.96	-2.82	-3.40	-3.32

	Median	0.410	-0.755	-1.080	-1.750	-2.360
	Maximum	0.77	-0.05	-0.62	-1.10	-0.79
Week 2	n	5	6	6	6	7
	Mean	-0.054	-1.293	-1.835	-2.463	-2.441
	SD	0.4500	1.0818	1.0198	1.3093	1.0676
	Minimum	-0.58	-2.52	-3.13	-4.55	-3.59
	Median	0.150	-1.150	-1.675	-2.330	-2.580
	Maximum	0.41	0.37	-0.60	-1.13	-0.30
Week 3	n	5	3	4	4	4
	Mean	0.008	-1.597	-1.233	-2.780	-2.955
	SD	0.5047	0.3868	1.2805	1.5258	0.7618
	Minimum	-0.59	-1.96	-2.65	-4.81	-3.62
	Median	0.170	-1.640	-1.095	-2.450	-3.055
	Maximum	0.62	-1.19	-0.09	-1.41	-2.09
Week 4	n	3	2	2	4	3
	Mean	0.163	-1.060	-1.785	-2.490	-3.200
	SD	0.2601	0.1980	0.4313	0.6380	1.1558
	Minimum	-0.10	-1.20	-2.09	-3.35	-4.33
	Median	0.170	-1.060	-1.785	-2.395	-3.250
	Maximum	0.42	-0.92	-1.48	-1.82	-2.02

Proportion of 72-hour serum phosphate responders by treatment and visit (FAS population — Japanese population)

	Placebo N=12 n (%)	**SBR759 3 g/day N=13 n (%)**	**SBR759 6 g/day N=12 n (%)**	**SBR759 9 g/day N=13 n (%)**	**SBR759 12 g/day N=12 n (%)**
Week 1					
Responder	0	2 (15.4)	6 (50.0)	10 (76.9)	9 (75.0)
Non-responder	12 (100.0)	11 (84.6)	6 (50.0)	3 (23.1)	3 (25.0)
Week 2					
Responder	0	2 (15.4)	6 (50.0)	11 (84.6)	11 (91.7)
Non-responder	10 (83.3)	10 (76.9)	6 (50.0)	2 (15.4)	0
Missing	2 (16.7)	1 (7.7)	0	0	1 (8.3)
Week 3					
Responder	0	3 (23.1)	3 (25.0)	11 (84.6)	11 (91.7)
Non-responder	11 (91.7)	8 (61.5)	9 (75.0)	2 (15.4)	0
Missing	1 (8.3)	2 (15.4)	0	0	1 (8.3)
Week 4					
Responder	0	3 (23.1)	4 (33.3)	11 (84.6)	9 (75.0)

Non-responder	10 (83.3)	8 (61.5)	6 (50.0)	1 (7.7)	1 (8.3)
Missing	2 (16.7)	2 (15.4)	2 (16.7)	1 (7.7)	2 (16.7)

Summary statistics of change from baseline in iPTH (pmol/L) levels by treatment and visit (FAS population — Japanese population)

	Statis-tics	Placebo N=12	SBR759 3 g/day N=13	SBR759 6 g/day N=12	SBR759 9 g/day N=13	SBR759 12 g/day N=12
Week 2	n	11	12	12	13	11
	Mean	4.21	-8.61	-5.87	-14.79	-11.21
	SD	6.703	11.073	8.697	11.485	12.608
	Minimum	-3.1	-31.3	-27.4	-40.0	-41.8
	Median	3.14	-8.92	-4.20	-14.82	-7.13
	Maxi-mum	22.2	7.0	6.4	1.0	2.0
Week 4	n	10	11	10	13	10
	Mean	4.14	-9.53	-7.58	-13.15	-12.15
	SD	13.357	11.807	10.765	11.450	14.255
	Minimum	-13.6	-29.7	-31.2	-41.1	-48.8
	Median	0.16	-11.95	-6.13	-12.61	-7.27
	Maxi-mum	35.5	7.9	7.5	3.9	0.3

Change in 72-hour serum phosphate during the treatment withdrawal period by withdrawal period treatment group (WD population)

	Treatment period treatment	Withdrawal period treatment	n	Mean (SD)	Min	Median	Max
Change from beginning of withdrawal period	Placebo	Placebo	5	0.13 (0.290)	-0.3	0.17	0.5
	SBR759 3 g/day	SBR759	2	0.01 (0.262)	-0.2	0.01	0.2
		Placebo	5	0.41 (0.304)	0.2	0.25	0.9
	SBR759 6 g/day	SBR759	2	-0.43 (0.057)	-0.5	-0.43	-0.4
		Placebo	9	0.87 (0.447)	0.2	0.95	1.5
	SBR759 9 g/day	SBR759	2	0.45 (0.672)	0.0	0.45	0.9
		Placebo	15	0.80 (0.405)	-0.1	0.76	1.5
	SBR759 12 g/day	SBR759	2	0.12 (0.262)	-0.1	0.12	0.3
		Placebo	13	1.09 (0.415)	0.2	1.17	1.7
	SBR759 all groups	SBR759	8	0.03 (0.443)	-0.5	-0.05	0.9
		Placebo	42	0.86 (0.445)	-0.1	0.84	1.7

Safety Results

Adverse Events by System Organ Class

Number (%) of patients with AEs overall and by primary system organ class (Safety population – Japanese population)

Primary system organ class	Placebo N=12 n (%)	SBR759 3 g/day N=13 n (%)	SBR759 6 g/day N=13 n (%)	SBR759 9 g/day N=13 n (%)	SBR759 12 g/day N=12 n (%)
Any primary system organ class	6 (50.0)	7 (53.8)	8 (61.5)	8 (61.5)	5 (41.7)
Gastrointestinal disorders	4 (33.3)	4 (30.8)	7 (53.8)	5 (38.5)	3 (25.0)
Injury, poisoning and procedural complications	1 (8.3)	0	3 (23.1)	2 (15.4)	0
Musculoskeletal and connective tissue disorders	1 (8.3)	0	1 (7.7)	1 (7.7)	2 (16.7)
Infections and infestations	1 (8.3)	0	0	2 (15.4)	1 (8.3)
Skin and subcutaneous tissue disorders	1 (8.3)	1 (7.7)	0	0	1 (8.3)
General disorders and administration site conditions	1 (8.3)	0	1 (7.7)	0	0
Investigations	0	0	0	1 (7.7)	1 (8.3)
Metabolism and nutrition disorders	1 (8.3)	1 (7.7)	0	0	0
Nervous system disorders	1 (8.3)	0	0	1 (7.7)	0
Blood and lymphatic system disorders	0	1 (7.7)	0	0	0
Reproductive system and breast disorders	0	0	0	1 (7.7)	0

Primary system organ classes were sorted by descending overall frequency.
A patient with multiple occurrences of an AE on the same treatment was counted only once in the AE category for that treatment.

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

Number (%) of patients with AEs overall and by preferred term (Safety population – Japanese population)

Preferred term	Placebo N=12 n (%)	SBR759 3 g/day N=13 n (%)	SBR759 6 g/day N=13 n (%)	SBR759 9 g/day N=13 n (%)	SBR759 12 g/day N=12 n (%)
Total no. of patients with an AE	6 (50.0)	7 (53.8)	8 (61.5)	8 (61.5)	5 (41.7)
Faeces discoloured	2 (16.7)	2 (15.4)	3 (23.1)	3 (23.1)	2 (16.7)
Diarrhoea	1 (8.3)	1 (7.7)	2 (15.4)	1 (7.7)	1 (8.3)
Abdominal distension	0	0	0	1 (7.7)	1 (8.3)
Nasopharyngitis	1 (8.3)	0	0	0	1 (8.3)
Vomiting	0	1 (7.7)	1 (7.7)	0	0
Abdominal discomfort	0	0	1 (7.7)	0	0
Abdominal pain upper	1 (8.3)	0	0	0	0
Anal fissure	0	0	1 (7.7)	0	0
Animal bite	0	0	1 (7.7)	0	0
Arthralgia	0	0	0	0	1 (8.3)
Arthropod sting	0	0	1 (7.7)	0	0
Blood pressure decreased	0	0	0	1 (7.7)	0
Contusion	0	0	1 (7.7)	0	0
Decreased appetite	0	1 (7.7)	0	0	0
Dermatitis contact	0	0	0	0	1 (8.3)
Fall	0	0	0	1 (7.7)	0
Fatigue	1 (8.3)	0	0	0	0
Flank pain	0	0	1 (7.7)	0	0
Gingival bleeding	0	0	0	0	1 (8.3)
Haematocrit increased	0	0	0	0	1 (8.3)
Haemoglobin increased	0	0	0	0	1 (8.3)
Hordeolum	0	0	0	1 (7.7)	0
Hypoglycaemia	1 (8.3)	0	0	0	0
Joint sprain	0	0	1 (7.7)	0	0
Joint swelling	0	0	0	1 (7.7)	0
Menorrhagia	0	0	0	1 (7.7)	0
Musculoskeletal pain	0	0	0	0	1 (8.3)
Nausea	0	0	0	1 (7.7)	0
Neck pain	1 (8.3)	0	0	0	0
Nephrogenic anaemia	0	1 (7.7)	0	0	0
Oral herpes	0	0	0	1 (7.7)	0
Procedural pain	1 (8.3)	0	0	0	0
Pruritus	1 (8.3)	0	0	0	0
Restless legs syndrome	1 (8.3)	0	0	0	0
Sensory disturbance	0	0	0	1 (7.7)	0
Shunt stenosis	0	0	0	1 (7.7)	0
Skin ulcer	0	1 (7.7)	0	0	0

Vessel puncture site haemorrhage	0	0	1 (7.7)	0	0

Preferred terms were sorted by descending overall frequency.
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

Number (%) of patients who died, had other serious or clinically significant AEs or related discontinuations by treatment group (Safety population – Japanese population)

	Placebo N=12 n (%)	SBR759 3 g/day N=13 n (%)	SBR759 6 g/day N=13 n (%)	SBR759 9 g/day N=13 n (%)	SBR759 12 g/day N=12 n (%)
Deaths	0	0	0	0	0
At least 1 SAE	0	1 (7.7)	0	0	1 (8.3)
Drug discontinuations due to AE	0	2 (15.4)	1 (7.7)	0	0
Dose adjustment or temporary interruption due to AE	0	0	0	0	1 (8.3)

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

SAEs were 1 skin ulcer, 1 arthralgia.

Other Relevant Findings

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

Laboratory test	Criterion	Placebo N=12 n (%)	SBR759 3 g/day N=13 n (%)	SBR759 6 g/day N=13 n (%)	SBR759 9 g/day N=13 n (%)	SBR759 12 g/day N=12 n (%)
Glycosylated hemoglobin (HbA1c) (%)	> 8%	1 (8.3)	1 (8.3)	1 (7.7)	1 (7.7)	0
Serum phosphate (mmol/L)	< 0.65 mmol/L	0	0	0	0	0
	> 2.9 mmol/L	4 (33.3)	1 (7.7)	1 (7.7)	0	0
Calcium (mmol/L)	< 2 mmol/L	3 (25.0)	0	2 (15.4)	0	0
	> 2.54 mmol/L	0	5 (38.5)	2 (15.4)	0	1 (8.3)
Transferrin saturation (%)	> 60%	0	1 (7.7)	0	1 (7.7)	0
Parathyroid Hormone (intact) (pmol/L)	< 2.65 pmol/L	0	0	0	0	0
	> 84.8 pmol/L	0	2 (15.4)	0	0	0

Ferritin (µg/L)	> 500 µg/L	0	0	0	0	1 (8.3)

% is calculated based on the number of patients with evaluable criterion
n = Number of patients meeting the criterion at least once post-baseline.

Summary statistics including change from baseline for iron indices at Week 4/PPW by treatment group (Safety population - Japanese population)

Parameter	---------- Baseline----------				-------- Week 4/PPW -------				----------Change----------			
Treatment	**n**	**Mean**	**SD**	**Median**	**n**	**Mean**	**SD**	**Median**	**n**	**Mean**	**SD**	**Median**
Ferritin (µg/L)												
Placebo	12	77.8	60.87	64.3	10	104.8	98.33	79.0	10	17.1	60.14	2.4
SBR759 3 g/day	13	118.1	100.04	79.4	11	93.7	78.98	63.3	11	-2.6	20.33	-1.3
SBR759 6 g/day	13	140.4	121.34	103.3	10	137.5	113.50	94.5	10	-1.2	46.99	12.2
SBR759 9 g/day	13	82.3	105.11	34.6	13	86.8	68.53	67.6	13	4.5	50.03	20.6
SBR759 12g/day	12	110.3	142.35	65.8	10	126.9	153.15	79.5	10	26.7	18.87	23.3
Transferrin (g/L)												
Placebo	12	1.9	0.33	1.9	10	2.0	0.33	2.1	10	0.1	0.28	0.1
SBR759 3 g/day	13	1.9	0.28	1.9	11	1.8	0.21	1.8	11	-0.2	0.28	0.0
SBR759 6 g/day	13	2.0	0.36	2.1	10	1.8	0.22	1.9	10	-0.1	0.18	-0.2
SBR759 9 g/day	13	1.9	0.44	1.9	13	1.8	0.38	1.7	13	-0.2	0.26	-0.2
SBR759 12g/day	12	2.1	0.48	2.0	10	1.9	0.39	1.9	10	-0.2	0.21	-0.3
Iron (µmol/L)												
Placebo	12	10.9	3.39	11.0	10	12.0	5.09	10.9	10	1.8	3.51	1.1
SBR759 3 g/day	13	10.2	2.82	10.0	11	12.2	3.75	11.2	11	1.6	2.86	2.0
SBR759 6 g/day	13	10.0	2.55	9.3	10	11.1	2.23	11.1	10	1.5	3.07	2.2
SBR759 9 g/day	13	12.4	2.93	11.6	13	14.2	5.19	12.2	13	1.8	6.78	1.1
SBR759 12g/day	12	11.1	3.10	10.6	10	12.0	3.81	12.2	10	1.6	4.23	0.6
Total Iron Binding Capacity (µmol/L)												
Placebo	12	38.3	4.57	38.9	10	39.1	6.33	40.2	10	0.5	3.10	-0.8
SBR759 3 g/day	13	37.6	4.72	36.0	11	36.5	3.38	36.5	11	-1.6	3.84	-2.1
SBR759 6 g/day	13	38.3	6.11	39.4	10	35.9	3.99	36.2	10	-2.2	3.28	-2.4
SBR759 9 g/day	13	38.8	7.43	37.8	13	36.6	7.31	34.7	13	-2.1	5.07	-1.4
SBR759 12g/day	12	39.7	9.29	38.0	10	36.6	7.75	36.2	10	-3.5	3.61	-4.3
Transferrin Saturation (%)												
Placebo	12	28.9	9.66	28.0	10	31.7	14.33	28.0	10	4.5	9.90	4.5
SBR759 3 g/day	13	27.2	8.22	27.0	11	33.2	9.67	33.0	11	5.2	7.48	3.0
SBR759 6 g/day	13	26.0	5.12	27.0	10	30.8	5.88	30.5	10	5.6	8.78	5.5
SBR759 9 g/day	13	33.8	13.21	31.0	13	38.8	11.18	38.0	13	5.1	15.47	2.0
SBR759 12g/day	12	28.8	7.75	27.5	10	32.6	8.10	35.5	10	5.8	9.78	5.0

Baseline was defined as the last 72-hour value before first dose.
PPW = Premature patient withdrawal.

Summary statistics of nPCR and URR by treatment group (Safety population — Japanese population)

Parameter	---------- Baseline ----------			--------- Week 4/PPW ---------		
Treatment	n	Mean	SD	n	Mean	SD

nPCR						
Placebo	12	0.562	0.0814	10	0.540	0.0467
SBR759 3 g/day	13	0.554	0.0675	11	0.553	0.0622
SBR759 6 g/day	12	0.563	0.0756	9	0.536	0.0409
SBR759 9 g/day	13	0.551	0.0588	13	0.511	0.0588
SBR759 12 g/day	12	0.554	0.0574	10	0.542	0.0527
URR (%)						
Placebo	12	73.83	9.998	10	73.70	6.111
SBR759 3 g/day	13	72.08	5.604	11	71.91	5.356
SBR759 6 g/day	12	72.83	6.548	9	70.33	8.930
SBR759 9 g/day	13	70.62	6.777	13	72.15	7.723
SBR759 12 g/day	12	70.25	5.362	10	70.80	7.068

Baseline was defined as the value collected at baseline visit (visit 2).
PPW = Premature patient withdrawal.

Date of Clinical Trial Report

04 April 2011

Date Inclusion on Novartis Clinical Trial Results Database

14 Oct 2011

Date of Latest Update

14 October 2011