Sponsor

Novartis

Generic Drug Name

SBR759

Therapeutic Area of Trial

Chronic renal failure

Approved Indication

Investigational

Study Number

CSBR759A2101

Title

An open label, multiple dose, time-lagged, switch study to evaluate the safety, tolerability and activity of escalating SBR759 doses in patients with chronic kidney disease on hemodialysis

Phase of Development

I/II

Study Start/End Dates

21-Feb-2007 to 30-Jan-2008

Study Design/Methodology

This was a single center, open label, multiple doses, time-lagged, switch study to evaluate the safety, tolerability and activity of escalating SBR759 doses in patients with chronic kidney disease on hemodialysis. Patients were profiled during a 2-week run-in period while they remained on their prescribed phosphate binder(s). After 2 weeks patients entered a 1 or 2-week wash-out period prior to being assigned to one of the 5 doses of SBR759 for 4 weeks. An End of Study follow up evaluation was conducted 4 weeks after patients stopped SBR759 treatment. Patients were stratified by their screening phosphate binder dose.

Centers

1 center, USA

Publication

NA

Objectives

Primary objectives

- Assess the safety and tolerability of escalating doses of SBR759 in patients with chronic kidney disease on hemodialysis.
- Assess the change in serum phosphorus in patients with chronic kidney disease on hemodialsis treated with escalating doses of SBR759.

Secondary objective(s)

NA

Several biomarkers and patient-reported outcomes were explored at specified time points, before and after treating patients with the study drug.

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

SBR759 1.25 mg oral dose units

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

Oral calcium-based phosphate binders and/or sevelamer HCl at doses consistent with each patient's pre study prescribed phosphate binder dose.

Criteria for Evaluation

Primary variable

Serum phosphorus concentration was frequently measured during the study.

Secondary variables

NA

Safety and tolerability

Vital signs, ECG, clinical laboratory assessment (blood chemistry and hematology), and adverse events

Pharmacology

No pharmacokinetic assessments were planned

Other

NA

Statistical Methods

The activity of SBR759 was assessed from the review of the 2-sided 100*(1-α)% confidence intervals (CI) for the observed mean decrease from end of washout to the end of the SBR759 treatment phase in serum phosphorous. Specifically, SBR759 was considered active if either of the lower limits of the 2 CIs is greater than 1.5 mg/dL. The statistical analyses of serum phosphorus were performed on the PD population which includes all patients who received study drug for at least one week and had at least one serum phosphorous assessment during the SBR759 treatment phase.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

- Male or female patients 18-85 years old, inclusive, who have been treated with maintenance hemodialysis and prescribed a phosphate binder, with a controlled serum phosphorus level.
- Constant dose of concomitant medications.
- Women of child bearing potential must be practicing an acceptable form of birth control (i.e. double barrier method – intrauterine device plus condom, spermicidal gel plus condom). All female patients must have a negative pregnancy test at screening in order to be eligible to participate in the study.

Exclusion criteria:

- Patient has been hospitalized within 30 days prior to screening or has a surgery scheduled during the study.

- Patient has an unstable medical condition, an active infection, active malignancy (except for basal cell carcinoma of the skin), a history of major GI tract surgery, or a history of hemochromatosis.
- Patient is receiving or has received an investigational drug (or is currently using an investigational device) within 30 days prior to screening.

Other protocol-defined inclusion/exclusion criteria may apply.

Number of Subjects

	Number of patients
Enrolled	60
Discontinued before SBR759	16
Exposed to SBR759	44
Completed 4 wks of SBR759 treatment	39
Withdrawn due to adverse events	3
Withdrawn due to other reasons	18

Demographic and Background Characteristics

	Patients treated with SBR759
N (ITT)	44
Females : males	22:22
Mean age, years (SD)	58.5 (12)
Mean weight, kg (SD)	90 (32)
Race Caucasian n (%) Black n (%) Asian n (%) Other n (%)	 13 (30%) 27 (61%) 4 (9%)

Primary Objective Results:

Descriptive statistics for serum phosphorus by cohort in patients with chronic kidney disease (PD population)

Treatment (g/day)	Mean (Range) serum phosphorus (mg/dL)		
	End of washout	End of SBR759 treatment (week 4)	Change from washout
3.75 (n=6)	6.21 (5.7, 6.7)	4.80 (4.1, 5.6)	-1.41 (-2.2, -0.2)
7.5 (n=8)	6.43 (5.6, 7.7)	5.24 (4.2, 6.8)	-1.19 (-2.2, -0.6)
11.25 (n=8)	7.28 (6.3, 9.2)	5.01 (4.2, 6.1)	-2.27 (-3.2, -1.7)
15 (n=6)	7.49 (6.2, 8.2)	5.55 (4.7, 6.7)	-1.94 (-3.4,-0.4)

Safety Results

10 Most Frequently Reported AEs Overall by Preferred Term in Patients Treated With SBR759

	No. of Patients (%)
Discolored feces	20 (45%)
Diarrhea	13 (30%)
Hypocalcemia	6 (14%)
Decreased appetite	3 (7%)
Abdominal discomfort	3 (7%)
Constipation	3 (7%)
Nausea	2 (5%)
Vomiting	2 (5%)
Pyrexia	2 (5%)
Dyspepsia	2 (5%)

Serious Adverse Events and Deaths

	No SBR759*	Cohort 1 3.75 g/d	Cohort 2 7.5 g/d	Cohort 3 11.25 g/d	Cohort 4 15 g/d	Cohort 5 22.5 g/d
No. of patients studied	16	10	10	10	10	4
Number (%) of patients with:						
Death	1 (6%)					
SAE(s)	4 (25%)			4 (40%)	2 (20%)	
Discontinued due to SAE(s)	1 (6%)					
Discontinued due to AE(s)	1 (6%)	1 (10%)				2 (50%)

*Patients were discontinued from the study during the run-in or washout periods

Other Relevant Findings

Date of Clinical Trial Report

Not final

Date Inclusion on Novartis Clinical Trial Results Database

23-Mar-2009

Date of Latest Update

16-Mar-2009