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GENERIC DRUG NAME and/or COMPOUND NUMBER: Sitaxsentan Sodium/PF-01228305

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Not Applicable

NATIONAL CLINICAL TRIAL NO.: NCT00810732

PROTOCOL NO.: B1321005

PROTOCOL TITLE: The Effects of Sitaxsentan Once Daily Dosing on Proteinuria, 24-Hour Blood Pressure, and Arterial Stiffness in Subjects with Chronic Kidney Disease

Study Center: 1 center in the United Kingdom

Study Initiation Date and Completion Dates: 09 May 2007 to 06 March 2009

Phase of Development: Phase 2

Study Objectives: To study the effects of once daily (QID) oral dosing of sitaxsentan 100 mg over a period of 6 weeks on proteinuria, systemic blood pressure (BP) as measured by 24-hour ambulatory BP monitoring and arterial stiffness as measured by pulse wave velocity (PWV).

A sub-study was planned to evaluate the effects of QID oral dosing of sitaxsentan 100 mg over a period of 6 weeks on renal and systemic hemodynamics. Results of the sub-study are out of scope of this report and are not reported here.

METHODS

Study Design: This was a Phase 2, crossover, single center, randomized, 3-period blinded study (sitaxsentan versus placebo) planned in approximately 30 subjects with chronic kidney disease (CKD) with an open-label treatment period (extended release [ER] nifedipine) to act as a positive control for reduction in systemic BP. Of these 30 subjects, at least 6 were planned to be in each of the following baseline proteinuria groups (based on 24-hour urine collection):

- low (0.3 to ≤1.5 g/24 hours);
- intermediate (>1.5 to ≤3.0 g/24 hours); or
- high (>3.0 g/24 hours).

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Number of Subjects (Planned and Analyzed): A total of approximately 30 subjects were planned to be enrolled in the main study, with at least 6 subjects in each of the 3 baseline proteinuria strata: low, intermediate and high. Thirty-three subjects were screened to enter the study and 27 subjects were randomized to study treatment.

Diagnosis and Main Criteria for Inclusion: Subjects with Stage 1-5 CKD between 18 and 70 years of age (inclusive) with body mass index between 18 and 35 kg/m^2 (inclusive).

Study Treatment: There were 3 treatment periods, during each of which subjects were randomized to 1 of the following treatments for 6 weeks:

- dosing with sitaxsentan 100 mg QID;
- active control ER nifedipine 30 mg QID (titrated against systemic BP as needed on an individualized basis) as open-label;
- placebo for sitaxsentan QID.

Each treatment period was separated by a washout period of at least 2 weeks. At the end of the study, or subsequent to early termination, there was a 2-week safety follow-up period.

Efficacy Evaluations:

24-hour Urine Protein and Protein:Creatinine Ratio (PCR)

The primary efficacy endpoint was the mean 24-hour urine total protein level change from baseline (Day 1) at Week 6. Only one 24-hour urine collection was required at screening. All subsequent tests required at least 2 and a maximum of three 24-hour urine collections each. The 3 baseline/Day 1 collections were to be completed within the 7-day period prior to the first dose of study drug in each treatment period.

24-Hour Ambulatory Blood Pressure Monitoring

The 24-hour ambulatory BP monitoring was performed during each period at baseline (Day 1) and the Week 3 and 6 visits and at early termination visit, if applicable. The baseline (Day 1) assessment began at least 24 hours prior to the first dose of study drug in each treatment period.

Pulse Wave Velocity and Arterial Stiffness

The carotid-femoral PWV, using the same body locations throughout the study was performed using an ultrasound probe at the baseline (Day 1), Week 3 and 6 (or early termination) visit of each period immediately predose and 2 hours postdose.

Pharmacokinetic Evaluations: Blood samples for the determination of plasma concentrations of sitaxsentan were collected predose at baseline (Day 1), then at the Weeks 1, 2, 3, 4 and 6. Only those samples collected during the active sitaxsentan treatment period were analyzed for sitaxsentan concentrations.

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Safety Evaluations: Adverse events (AEs) were monitored throughout the study. Vital signs (heart rate, BP at each visit) and safety laboratory tests were performed at screening and for each period at baseline and Weeks 1, 2, 3, 4 and 6 (or early termination) and at the 2-week safety follow-up visit. A 12-lead electrocardiogram (ECG) was performed at screening in order to help determine eligibility for the study.

Statistical Methods: In general, change from baseline to Week 6 was analyzed with an analysis of covariance (ANCOVA) model using PROC MIXED in SAS. For all efficacy endpoints, differences between the least squares (LS) means, standard errors associated with two-sided 95% confidence intervals (CIs) and p-values are presented. If the errors were not normal, a suitable transformation of the data (eg, natural logarithmic) was explored or non-parametric methods were planned to be used to estimate the treatment differences with associated two-sided 95% CIs.

The co-primary efficacy endpoints were the mean 24-hour urine total protein (g/day) level and protein:creatinine ratio (mg/mmol) calculated from the same 24-hour urine collections. Both endpoints were evaluated as change from baseline to Week 6. Baseline was derived from an average of Week 0 (predose) 24-hour urine collections prior to each respective treatment period.

The mean 24-hour urine total protein level change from baseline to Week 6 were analyzed on absolute and percentage scales. Statistical analysis of percentage change from baseline for the secondary endpoints was performed similarly.

A summary of plasma concentrations by treatment, visit and nominal sampling time postdose, where the set of statistics included n, mean, median, minimum, maximum, standard deviation (SD), coefficient of variation (CV) and the number of concentrations above the lower limit of quantification was presented. This was presented for all subjects overall and by baseline proteinuria group.

Population pharmacokinetic analysis is not included in this report.

All safety parameters were tabulated with summary statistics by treatment group. Data collected during the washout period were counted for the previous treatment received.

Results from the safety assessments and any AEs were presented in tabular and/or graphical format adhering to current Data Standards (PDSv1) of the sponsor, wherever possible. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 11.1.

Laboratory data were listed and summarized by treatment in accordance with the sponsor reporting standards (PDSv1) wherever possible. Tables were paged by parameter.

Sitting, standing and supine systolic BP, diastolic BP, heart rate and body temperature were listed and summarized. The set of statistics include n, mean, median, minimum, maximum and SD. Maximum changes from baseline were also listed and summarized.

No interim analysis was planned.

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RESULTS

Subject Disposition and Demography: Thirty-three subjects were screened to enter the study and 27 subjects were randomized to study treatment. Six subjects were not randomized because they did not meet entry criteria (4 subjects) and because they withdrew consent (2 subjects). All 27 randomized subjects completed the study and no subjects discontinued treatment. Table 1 shows subject demographics for all randomized subjects.

Table 1. Study Demographics

	Male N=23	Female N=4	Total N=27
Age (years)			
Mean	47.6	48.3	47.7
Median	48	47.5	48
SD	12.7	4.99	11.8
Range	27-70	43-55	27-70
Race			
White	23	4	27
Height (cm)			
Mean	175	162	173
Median	176	163	174
SD	5.65	6.98	7.4
Range	163-183	153-170	153-183
Weight (kg)			
Mean	89.7	74.6	87.5
Median	84.9	79.1	84
SD	12.6	19.7	14.4
Range	68-110	47.1-93.3	47.1-110
BMI (kg/m^2)			
Mean	29.4	28.1	29.2
Median	29.6	29.9	29.6
SD	4.26	5.5	4.36
Range	21.7-35.7	20.1-32.3	20.1-35.7

BMI=body mass index, SD=standard deviation, N=number of subjects

Efficacy Results: Table 2 and Table 3 summarize the observed changes for the efficacy variables for the FAS in absolute terms (Table 2) and percentage terms (Table 3). Sitaxsentan treatment resulted in a mean change of -0.62 g/day (-32.5%) protein compared with 0.01 g/day (3.2%) and -0.06 g/day (1.6%) with nifedipine and placebo, respectively. Similar reductions were observed with the protein: creatinine ratio; -42.6 mg/mmoL (-30.2%) in the sitaxsentan group, -5.3 mg/mmoL (-5.1%) in the nifedipine group and -4.2 mg/mmoL (0.9%) in the placebo group. Reductions in mean arterial BP were similar for both sitaxsentan (-3.7 mmHg) and nifedipine (-3.5 mmHg) versus placebo (-0.4 mmHg). Sitaxsentan (and nifedipine) produced a significant fall in PWV from baseline to Week 6 compared to placebo.

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Table 2. Mean (SD) Absolute Changes From Baseline (Week 0) to Week 6 for Efficacy Variables (FAS)

Efficacy Variable (SD)	Sitaxsentan 100 mg	Nifedipine 30 mg ER	Placebo
Urine Total Protein Level (g/24 hours)	-0.62 (0.56)	0.01 (0.77)	-0.06 (0.89)
Protein:Creatinine Ratio (mg/mmoL)	-42.6 (40.8)	-5.3 (61.9)	-4.2 (68.2)
Systemic Mean Arterial Blood Pressure (mmHg)	-3.7 (5.6)	-3.5 (5.5)	-0.4 (5.4)
Carotid-Femoral Pulse Wave Velocity (m/s)[a]	-0.41 (0.82)	-0.38 (0.86)	0.29 (1.08)

ER=extended release, FAS=full analysis set, SD=standard deviation
[a] Change from predose at Week 0 to predose at Week 6.

Table 3. Median (Range) Percentage Changes From Baseline (Week 0) to Week 6 for Efficacy Variables (FAS)

Efficacy Variable (Range)	Sitaxsentan 100 mg	Nifedipine 30 mg ER	Placebo
Urine Total Protein Level (%)	-32.5 (-75.4, 43.0)	3.2 (-63.7, 163.8)	1.6 (-52.3, 191.7)
Protein:Creatinine Ratio (%)	-30.2 (-73.7, 40.7)	-5.1 (-53.4, 71.5)	0.9 (-51.5, 237.2)
Systemic Mean Arterial Blood Pressure (%)	-5.2 (-14.8, 8.1)	-4.2 (-14.0, 9.8)	-0.8 (-10.2, 16.5)
Carotid-Femoral Pulse Wave Velocity (%)[a]	-4.76 (-23.67, 19.64)	-3.33 (-30.60, 9.94)	1.67 (-14.47, 48.15)

ER=extended release, FAS=full analysis set
[a] Change from 0-6 hours

Pharmacokinetic Results: Results of the population pharmacokinetic analysis are not included in this report.

Safety Results: There were no deaths or serious adverse events (SAEs) reported during this study. No subjects discontinued treatment due to AEs. More AEs were experienced during nifedipine (32 AEs experienced by 18 subjects [66.6%]) or placebo (27 AEs experienced by 21 subjects [77.7%]) treatment compared to sitaxsentan treatment (15 AEs experienced by 13 subjects [48.1%]) (Table 4). System organ classes (SOCs) of AEs experienced by >10% subjects include Nervous System Disorders, Gastrointestinal Disorders, Infections and Infestations, Respiratory, Thoracic and Mediastinal Disorders and Musculoskeletal and Connective Tissue Disorders.

AEs experienced by more than 1 subject during any 1 of the 3 treatment periods are summarized in Table 5. Headache was experienced by 2 subjects (4.7%) during sitaxsentan treatment, 10 subjects (37.0%) during nifedipine treatment and 10 subjects (37.0%) during placebo treatment. Four subjects were reported to have 5 severe AEs: eye disorder (1 subject), arthralgia (1 subject), pain in extremity (1 subject), asthma (1 subject) and headache (1 subject). None of these severe AEs were thought by the investigator to be treatment-related.

There were no clinically significant clinical laboratory test results, or ECG or vital sign results that were thought to compromise safety.

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Table 4. Summary of All Causality Treatment-Emergent Adverse Events

	Sitaxsentan 100 mg N=27	Nifedipine 30 mg ER N=27	Placebo N=27
Number of Adverse Events	15	32	27
Subjects with Adverse Events	13 (48.1%)	18 (66.6%)	21 (77.7%)
Subjects with Serious Adverse Events	0	0	0
Subjects with Severe Adverse Events	0	3 (11.1%)	1 (3.70%)
Subjects Discontinued due to Adverse Events	0	0	0
Subjects with Dose Reduced or Temporary Discontinuation due to Adverse Events	0	0	0

N=number of subjects, ER=extended release
Individual subjects are only counted once in each treatment group; however, a subject with an adverse event that continued from 1 treatment group to the next is counted in each treatment group in which the adverse event was present.

Table 5. Treatment-Emergent Adverse Events Experienced by >1 Subject in Any Treatment Group

	Sitaxsentan 100 mg N=27	Nifedipine 30 mg ER N=27	Placebo N=27
Headache	2 (1)	10 (5)	10 (4)
Upper Respiratory Tract Infection	2 (0)	3 (1)	1 (0)
Diarrhea	1 (1)	0	2 (0)
Dizziness	1 (1)	1 (1)	2 (1)
Migraine	1 (1)	0	2 (2)
Nasal Congestion	1 (1)	2 (2)	2 (1)
Flushing	1 (0)	2 (2)	0
Nausea	0	0	2 (2)
Vomiting	0	1 (0)	2 (0)
Back Pain	0	2 (0)	2 (0)
Pain in Extremity	0	2 (0)	1 (0)

N=number of subjects, ER=extended release
Treatment-related events in brackets
Individual subjects are only counted once in each treatment group; however, a subject with an adverse event that continued from 1 treatment group to the next is counted in each treatment group in which the adverse event was present.

CONCLUSIONS:

- Sitaxsentan appeared to be an effective renoprotective agent, as evidenced through significant reductions in urinary protein excretion, which were independent on its effect on mean arterial systemic BP.

- Sitaxsentan was well tolerated in this non-diabetic CKD population, as evidenced through the lower incidence, type, and severity of AEs reported.

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