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

PROTOCOL NO.: B1321001 (FPH-STRIDE-05-FPH 05)

PROTOCOL TITLE: A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Safety and Efficacy Study of Sitaxsentan Sodium in Subjects With Pulmonary Arterial Hypertension

Study Centers: A total of 53 centers took part in the study and randomized subjects; 3 in Argentina, 2 in Bulgaria, 1 in Chile, 5 in China, 1 in Colombia, 1 in Czech Republic, 1 in Dominican Republic, 8 in India, 1 in Malaysia, 2 in Mexico, 2 in Peru, 1 in Philippines, 2 in Romania, 2 in Russian Federation, 1 in Saudi Arabia, 1 in Serbia, 1 in South Africa, 1 in Thailand, 1 in Turkey, 2 in Ukraine and 14 in United States.

Study Initiation and Final Completion Dates: 18 December 2008 to 16 March 2011

The study was terminated prematurely.

Phase of Development: Phase 3

Study Objectives:

Primary Objective:

- To evaluate the efficacy of sitaxsentan (100 mg dose) as compared to placebo in the treatment of subjects with pulmonary arterial hypertension (PAH) for 12 weeks, as determined by change from the Baseline 6-Minute Walk Distance (6MWD) to Week 12.

Secondary Objective:

- To evaluate the safety and efficacy of sitaxsentan (100 mg dose) as compared to placebo in the treatment of subjects with PAH by determining change from Baseline in World Health Organization (WHO) functional class and time to clinical worsening.

METHODS

Study Design: This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, safety and efficacy study of sitaxsentan, given orally to subjects with PAH.

A screening evaluation was conducted over a period of up to 21 days prior to randomization to determine subject eligibility for the study. Treatment for all randomized subjects began on Baseline/Day 1, when subjects received once daily doses of either sitaxsentan 100 mg or matching placebo according to the randomization schedule.

Subjects had onsite clinic assessments performed at Screening, Baseline/Day 1, Weeks 4, 8, and 12 (termination visit). The duration of the treatment phase for all randomized subjects was 12 weeks, unless the subject withdrew from the study. If a subject's participation in the study was discontinued prior to Week 12, all safety and efficacy evaluations were to be performed during an early termination visit. There was a follow-up visit 28±4 days following discontinuation/termination to assess safety for subjects who discontinued early and did not enter to open label, nonrandomized study (A Phase 3, Multi-Center, Open-Label Study to Evaluate the Long-Term Safety of Monotherapy Sitaxsentan Sodium and Combination Therapy With Sitaxsentan Sodium and Sildenafil Citrate in Subjects With Pulmonary Arterial Hypertension [NCT00796510]) or subjects who completed this study but did not enter to double blind, randomized study (A Phase 3, Multi-Center, Randomized, Double-Blind, Efficacy and Safety Study of Monotherapy Sitaxsentan Sodium Versus Combination Therapy With Sitaxsentan Sodium and Sildenafil Citrate in Subjects With Pulmonary Arterial Hypertension [NCT00796666].

After the study was terminated, 28-day post-treatment follow-up visits were implemented as an urgent safety measure to help ensure the subjects' safe transition from study drug. This was done irrespective of regulatory and ethics approvals as long as it was not prohibited by local law.

This study was designed and conducted under a specialized protocol assessment with the United States Food and Drug Administration. This study was undertaken to confirm the findings of the previous placebo-controlled studies with sitaxsentan in PAH subjects. The use of a placebo in this study was warranted as previous studies with sitaxsentan in PAH had indicated that less than 10% of placebo treated subjects declined clinically within 12 weeks.

The schedule of study activities is presented in Table 1.

Table 1. Schedule of Activities

		Treatment Phase			
	Screening[a]	**Baseline[b]**	**Week 4**	**Week 8**	**Week 12 Term/Early Term[c]**
Week	**Up to 21 days**	**Day 1**	**Day 28 (±4 Days)**	**Day 56 (±4 Days)**	**Day 84 (±4 Days)**
Informed consent	X				
Inclusion/exclusion screen	X				
Medical history[d]	X	X			
Concomitant medication collection	X	X	X	X	X
AE collection		X	X	X	X
Dispense/return study drug[e]		X	X	X	X
WHO functional class	X	X	X	X	X
Physical examination	X	X	X	X	X
Height	X				
Weight	X	X	X	X	X
Vital signs measurements[f]	X	X	X	X	X
12-lead electrocardiogram	X	X			
6MWT[g]	X	X	X	X	X
Clinical chemistry	X				X
AST, ALT, direct and total bilirubin	X	X[h]	X	X	X
CBC with platelets and differential	X				X
Hematocrit/hemoglobin	X	X	X	X	X
Serum/urine pregnancy test[i]	X	X	X	X	X
PK blood sample[j]		X	X	X	X
Whole blood for genotyping		X			
NT-proBNP blood sample[k]		X			X
Coagulation[l]	X	X	X	X	X
Pulmonary function testing[m]	X				
Transthoracic or transesophogeal echo[n]	X				
V/Q lung scan or spiral/helical/electron beam CT, or pulmonary angiogram[o]	X				
Cardiac catheterization[p]	X				
SF-36 and EQ-5D questionnaires[q]		X			X

6MWD = 6-Minute Walk Distance, 6MWT = 6-minute walk test, AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase,

Table 1. Schedule of Activities

BP = blood pressure, CBC = complete blood count, CT = computed tomography, echo = echocardiogram, EQ-5D = EuroQol 5D, mPAP = mean pulmonary artery pressure, NT-proBNP = N-terminal pro-brain natriuretic peptide, PAH = pulmonary arterial hypertension, PCWP = pulmonary capillary wedge pressure, PK = pharmacokinetics, PVR = pulmonary vascular resistance, SF-36 = Medical Outcomes Study Short Form 36 instrument, TLC = total lung capacity, V/Q = ventilation-perfusion, WHO = World Health Organization.

a. All screening procedures were completed within 21 days prior to baseline/Day 1.

b. All baseline procedures were performed prior to the first dose of study medication, with the exception of the postdose BP and PK sample. All baseline procedures were performed on the same day.

c. Follow-up visit 4 weeks after discontinuation. The following assessments were made:

- Physical examination.
- Urine pregnancy test for women of childbearing potential.
- Clinical chemistry safety labs and coagulation testing (if indicated).
- Vital signs.
- Concomitant treatment(s)/AEs.

d. The medical history included any medical condition that was ongoing as of screening or baseline, and any significant medical conditions that had resolved.

e. Only 1 blister-pack of study drug (32-day supply) was dispensed at the applicable clinic visits; drug supplies were collected and accounted for at each subsequent visit.

f. Vital sign measurements included sitting BP, respiratory rate, heart rate, and temperature. Day 1 BP was to be measured predose and 30 minutes postdose.

g. The 6MWT distances were ≥150 and ≤450 meters and distance walked within 15% of 1 another on 2 consecutive tests on different days at Screening. Both tests were ≥150 and ≤450 meters. If the test results were not congruent, both of the screening 6MWTs repeated 24 hours to 2 weeks after the first attempt and the results had to be within 15% of 1 another. If after this attempt, the subject was still not eligible, the subject was considered a screen failure and denied entry into the study.

h. Blood tests for liver transaminases and bilirubin were rechecked locally at the Baseline visit and meet inclusion criteria prior to randomization.

i. Serum pregnancy tests were collected at Screening, Baseline, and Weeks 4, 8, and 12. A urine pregnancy test was also collected at Baseline. Any subject who became pregnant was immediately discontinued from the study.

j. At the Baseline visit, PK samples were collected at 2 time points, predose and postdose (between 30 minutes to 2 hours). The timing of the single PK sample at all subsequent visits could be obtained in conjunction with other scheduled labs however all times were documented.

k. NT-proBNP blood sample was collected after a minimum of a 1-hour rest period and before the 6MWT.

l. Coagulation testing was required at Screening, Baseline, Weeks 4, 8, and 12 for all subjects who were taking warfarin or another vitamin K antagonist. For subjects who began taking warfarin (or another vitamin K antagonist) during this study (ie, at any point beyond baseline), coagulation testing was required at each of the subsequent clinic visits. Coagulation testing was also required at early termination if discontinuation occurred before Week 12. Additional monitoring could be performed at the discretion of the Investigator.

m. Pulmonary function testing included measurement of TLC, unless performed within 3 months prior to screening.

n. Transthoracic or transesophageal echo unless performed within 3 months prior to screening.

o. A V/Q lung scan or spiral/helical/electron beam CT, or pulmonary angiogram were performed within 3 years prior to study screening that showed

Table 1. Schedule of Activities

no evidence of thromboembolic disease (normal or low probability for pulmonary embolism). If a V/Q scan was abnormal (ie, not normal or low probability), then a confirmatory CT, angiography or selective pulmonary angiography were exclude chronic thromboembolic disease.

p. The diagnosis of PAH was confirmed by a cardiac catheterization within 6 months prior to study screening as evidenced by the following values: mPAP >25 mmHg (at rest); PCWP or left ventricular-end diastolic pressure ≤15 mmHg; and PVR >3 mm Hg/L/min or 240 dynes*sec/cm^5.

q. Outcome research questionnaires were completed at the Baseline and final visit.

Number of Subjects (Planned and Analyzed): Approximately 180 subjects from approximately 100 investigational sites were to be randomized into this study. A total of 286 subjects screened for entry into the study, 91 subjects were randomized to receive sitaxsentan 100 mg and 92 subjects were randomized to receive placebo. A total of 182 subjects were analyzed. All but 1 randomized subject in the placebo group were treated with study drug.

Diagnosis and Main Criteria for Inclusion: Subjects between 16 and 80 years of age who had a current diagnosis of symptomatic PAH classified by 1 of the following: idiopathic arterial hypertension (IPAH), primary pulmonary hypertension (PPH), familial pulmonary arterial hypertension (FPAH) or PAH associated with connective tissue diseases (CTD). The subject as WHO functional Class III symptoms. The subject having previous exposure to an endothelin receptor antagonist (ETRA) such as sitaxsentan, bosentan, or ambrisentan was excluded.

Study Treatment: Subjects received 1 of 2 treatments, once daily doses of either 100 mg sitaxsentan or matching placebo (active medication form matched for placebo). The duration of the treatment phase for all randomized subjects was 12 weeks, unless the subject was discontinued from the study. Each daily dose of sitaxsentan, consisting of a single 100 mg oral tablet, or matching placebo was taken with or without food and with water at a similar time each day.

Efficacy and Safety Endpoints:

Primary Endpoint:

- 6-Minute Walk Distance (6MWD) change from Baseline to Week 12. Baseline was defined as the last observation prior to initiation of the first dose of study drug on Day 1.

Secondary Endpoints:

- World Health Organization (WHO) functional class change from Baseline to Week 12.

- Time to clinical worsening (TTCW). The clinical worsening event (CWE) was defined as any of the following, which was adjudicated by a blinded Adjudication Committee: hospitalization for worsening PAH; on-study death; heart-lung or lung transplant; atrial septostomy; withdrawal due to the addition of the following chronic medications for the treatment of worsening PAH: prostacyclin, prostacyclin analogues, phosphodiesterase-5 inhibitors, ETRAs, intravenous inotropes; initiation of chronic oxygen therapy for worsening PAH.

Safety Evaluations: Safety evaluations included clinical monitoring, vital signs (systolic and diastolic systemic blood pressure, respiratory rate, heart rate, body weight, and body temperature), clinical chemistry, adverse events (AEs), and safety laboratory tests.

Statistical Methods:

Intent-to-Treat (ITT) Population: The ITT population is defined as all subjects who are randomized and receive at least one dose of study drug. All efficacy analyses will be conducted on the ITT population.

Per Protocol (PP) Population: The Per Protocol (PP) population will include all subjects who satisfy the ITT criteria and who in addition have:

- Not violated any of the inclusion or exclusion criteria that could, if the subject was erroneously included, affect the primary efficacy assessment.
- Not deviated from the protocol in any way that could affect the primary efficacy assessment.
- Received the randomized treatment.

The null hypothesis of no difference between sitaxsentan 100 mg and placebo was tested using the nonparametric analysis of covariance (ANCOVA) controlling for baseline 6MWD and PAH etiology (PAH secondary to a CTD and PAH not secondary to a CTD [others]).

The median of the treatment difference in the primary efficacy endpoint was calculated using the Hodges-Lehmann estimator, which was the median of all possible differences in 6MWD change from Baseline at Week 12 between subjects randomized to sitaxsentan 100 mg and those randomized to placebo.

WHO functional class change from Baseline to Week 12 (improved, no change, or deterioration) was summarized with frequency counts and percentages by treatment group. The treatment difference was analyzed using the Cochran-Mantel-Haenszel (CMH) test, stratified by baseline 6MWD (<310 meters and ≥310 meters) and PAH etiology (CTD and others). The CMH test used modified ridit scores, and the p-value corresponding to ANCOVA (raw mean scores) statistic was used.

Kaplan-Meier estimates were used to analyze TTCW for each treatment group. Treatment difference was analyzed using the stratified log rank test, stratified by baseline 6MWD (<310 meters and ≥310 meters) and PAH etiology (CTD and others).

The incidence rate for treatment-emergent AEs was tabulated by preferred term and system organ class, and stratified by maximum intensity and the highest relationship to study drug. AEs leading to premature discontinuation and serious adverse events (SAEs) were tabulated by preferred term and system organ class. All deaths, SAEs, AEs leading to premature discontinuation, and bleeding AEs were listed by subject.

Laboratory data were collected from central laboratories and from local laboratories for some tests. The raw laboratory data and original normal ranges were used for laboratory abnormalities tables. All data were converted to standard units using the appropriate conversions. In addition to the standard laboratory summaries, the following were summarized for the liver function tests (LFT)-specific laboratory data tests:

- Clinical laboratory results by visit in LFTs.

- Incidence of subjects with abnormal liver enzymes at any postbaseline time point were summarized by treatment group for aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) values based on the upper limit of normal (ULN): >3 × and ≤5 × ULN, >5 × and ≤8 × ULN, and >8 × ULN.

- Incidence of subjects with AST and/or ALT values >3 × ULN, and concurrent direct and/or total bilirubin >2 × ULN.

Vital signs and body weight at Baseline, as well as changes from Baseline to each postbaseline visit were summarized with descriptive statistics by visit and treatment group based on the safety population. Electrocardiogram (ECG) data from Screening and Baseline were listed.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized in Table 2. Seventy subjects (76.9%) in the sitaxsentan 100 mg group and 66 subjects (71.7%) in the placebo group completed the study. The most frequent reason for discontinuation was the study termination by the Sponsor (13 subjects [14.3%] in the sitaxsentan 100 mg group and 12 subjects [13.2%] in the placebo group).

Table 2. Subject Disposition

Number (%) of Subjects	Sitaxsentan 100 mg	Placebo
Screened 286		
Assigned to study treatment	91	92
Treated	91	91[a]
Completed	70 (76.9)	66 (71.7)
Discontinued	21 (23.1)	25 (27.2)
Subject died[b]	1 (1.1)	6 (6.6)
Relation to study drug not defined	15 (16.5)	17 (18.7)
No longer willing to participate in study	1 (1.1)	3 (3.3)
Other	0	2 (2.2)
Study terminated by Sponsor	13 (14.3)	12 (13.2)
Withdrawn due to pregnancy	1 (1.1)	0
Related to study drug	1 (1.1)	1 (1.1)
AE[c]	1 (1.1)	1 (1.1)
Not related to study drug	4 (4.4)	1 (1.1)
AE[c]	4 (4.4)	1 (1.1)
Analyzed for efficacy		
ITT population	91 (100.0)	92 (100.0)
PP population	75 (82.4)	73 (79.3)
Analyzed for safety		
AEs	91 (100.0)	91 (98.9)
Laboratory data	90 (98.9)	87 (94.6)
Safety population	91 (100.0)	91 (98.9)

Discontinuations occurring outside the lag period have been attributed to the last study treatment received.
AE = adverse event, CRF = case report form, ITT = intent-to-treat, PP = per protocol.

a. Subject was randomized and not treated.
b. Only deaths leading to study discontinuation are summarized in this table. Four additional subjects in the sitaxsentan 100 mg died in this study.
c. Five subjects in the sitaxsentan 100 mg group and 8 subjects in the placebo group as discontinued due to AEs.

Demographic characteristics are summarized in Table 3. Most subjects in this study were female and Asian. The subjects' age ranged from 16 to 80 years, the weight ranged from 40 to 121 kg, and the height ranged from 139 cm to 201 cm. The demographic characteristics were well balanced across the treatment groups.

Table 3. Demographic Characteristics, Safety Population

Number (%) of Subjects	Sitaxsentan 100 mg N=91	Placebo N=91
Gender (n)		
Male	20	23
Female	71	68
Age (n [%])		
<18	0	3 (3.3)
18-44	53 (58.2)	53 (58.2)
45-64	30 (33.0)	26 (28.6)
≥65	8 (8.8)	9 (9.9)
Age (years)		
Mean ± SD	42.0±14.9	41.1±15.9
Range	18-80	16-78
Race (n [%])		
White	31 (34.1)	34 (37.4)
Black	2 (2.2)	1 (1.1)
Asian	55 (60.4)	52 (57.1)
Other	3 (3.3)	4 (4.4)
Weight (kg)		
Mean ± SD	62.6±16.2	63.1±14.9
Range	40.0–114.0	40.0±121.0
Height (cm)		
Mean ± SD	162.0±9.1	161.7±8.2
Range	139.0–187.0	141.0–201.0

n = number of subjects, N = number of subjects in the group, SD = standard deviation.

Efficacy Results:

Primary Efficacy Endpoint:

The primary efficacy endpoint was 6MWD change from Baseline to Week 12. The 6MWD change from Baseline to Week 12 for the intent-to-treat (ITT) population is provided in Table 4 and presented graphically in Figure 1.

The baseline median 6MWD was very slightly higher in the sitaxsentan 100 mg group compared to the placebo group (343.0 meters compared to 330.5 meters). The median treatment difference between sitaxsentan 100 mg versus placebo at Week 12 was 14 meters (95% confidence interval [CI] =3, 26) and statistically significant (p-value =0.0104).

Table 4. Change From Baseline to Week 12 in 6-Minute Walk Distance, ITT Population

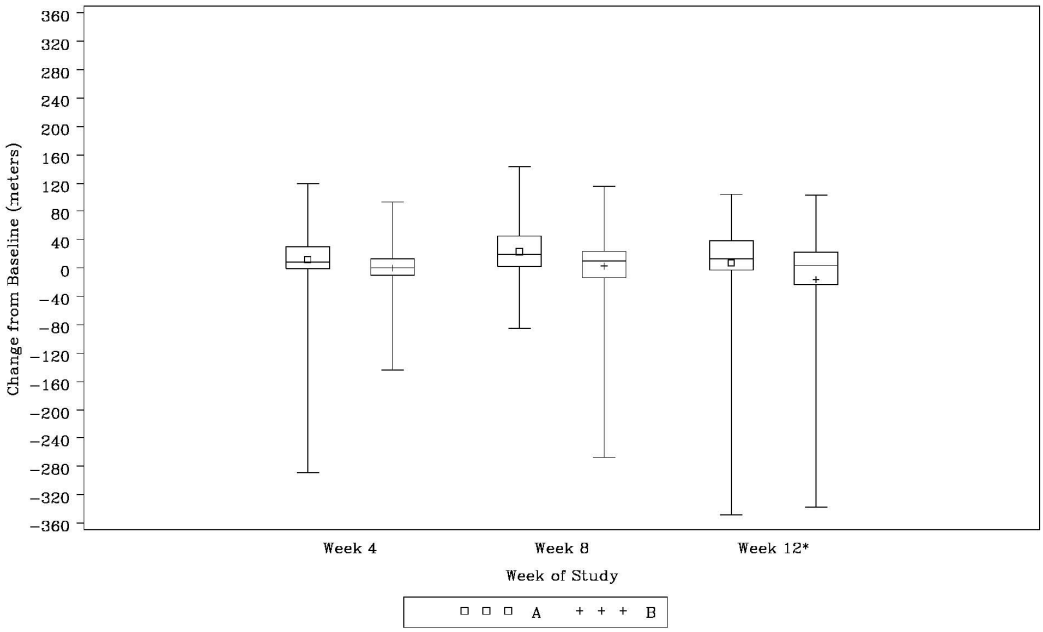
	Sitaxsentan 100 mg N=91	Placebo N=92
6MWD Change From Baseline to Week 12[a], meters		
Baseline mean ± SD	332.4±73.00	329.9±69.39
Baseline median (minimum, maximum)	343.0 (160, 442)	330.5 (169, 456)
Change from Baseline mean ± SD	7.2±69.84	-16.5±87.38
Change from Baseline median (minimum, maximum)	13.0 (-349, 105)	3.0 (-338, 104)
Treatment Difference (Sitaxsentan 100 mg – Placebo)		
Median difference	14	
95% CI	3, 26	
p-Value	0.0104	

Baseline was defined as the last observation prior to initiation of the first dose of study drug on Day 1.
6MWD = 6-Minute Walk Distance, CI = confidence interval, CWE = clinical worsening event, ITT = intent-to-treat, LOCF = last observation carried forward, N = number of subjects in the group, SD = standard deviation.

a. A missing value at Week 12 was assigned as 0 if the subject had a predefined CWE, otherwise, missing a value at Week 12 was imputed with the last nonmissing 6MWD based on the LOCF method.

At Week 12 for the ITT population, the mean change from Baseline was 7.2 meters (95% CI: -7.4, 21.7) for the sitaxsentan 100 mg group and -16.5 meters (95% CI: -34.6, 1.6) for the placebo group. However, it should be noted that no formal statistical analyses have been performed on the unadjusted data. Thus, these heavily skewed data should be interpreted with caution.

Figure 1. Change From Baseline in 6-Minute Walk Distance (meters), ITT Population



A = sitaxsentan 100 mg, B = placebo.
* A missing value at Week 12 was assigned as 0 if the subject had a predefined clinical worsening event, otherwise, missing a value at Week 12 was imputed with the last nonmissing 6-Minute Walk Distance based on the LOCF method.
Baseline was defined as the last observation prior to initiation of the first dose of study drug on Day 1.
The center horizontal line in each box corresponds to the median value and the central plus and square corresponds to the mean values. Error bars show minimum and maximum.
ITT = intent-to-treat, LOCF = last observation carried forward.

For the per protocol (PP) population, the results of the analysis of the primary endpoint were similar to the results for the ITT population. The median treatment difference between sitaxsentan 100 mg versus placebo at Week 12 was 15 meters (95% CI =2, 29) and statistically significant (p =0.0215).

At Week 12 for the PP population, the mean change from Baseline was 6.4 meters (95% CI: -10.8, 23.7) for the sitaxsentan 100 mg group and -22.1 meters (95% CI: -44.4, 0.3) for the placebo group. However, it should be noted that no formal statistical analyses have been performed on the unadjusted data. Thus, these heavily skewed data should be interpreted with caution.

Secondary Efficacy Endpoints:

World Health Organization Functional Class Change From Baseline to Week 12:

The WHO functional class change from Baseline to Week 12 is summarized in Table 5. All subjects had WHO functional Class III at Baseline except 2 subjects in the sitaxsentan 100 mg group with WHO functional Class II. These 2 subjects were class III at Screening and therefore eligible for entry criteria, but had improved to Class II at their subsequent Baseline visit.

Overall, most subjects in both treatment groups showed no change in WHO functional class. More subjects in the sitaxsentan 100 mg group improved in WHO functional class compared to subjects in the placebo group (17 and 7 subjects, respectively) and fewer subjects in the sitaxsentan 100 mg group deteriorated in WHO functional class compared to subjects in the placebo group (5 and 8 subjects, respectively). However, this treatment difference was not statistically significant (p =0.2908).

Table 5. WHO Functional Class Change From Baseline to Week 12, ITT Population

Number (%) of Subjects	Sitaxsentan 100 mg N=91	Placebo N=92
Change From Baseline to Week 12[a]		
Improvement	17 (18.7)	7 (7.6)
No change	69 (75.8)	77 (83.7)
Deterioration	5 (5.5)	8 (8.7)
Treatment Difference (Sitaxsentan 100 mg – Placebo)		
p-Value	0.2908	

Baseline was defined as the last observation prior to initiation of the first dose of study drug on Day 1.
Improvement = reduction in functional class, deterioration = increase in functional class.
Significance tests of WHO functional class were performed using the CMH test, stratified by baseline 6MWD (<310 meters and ≥310 meters) and PAH etiology (CTD and others).
6MWD = 6-Minute Walk Distance, CMH = Cochran-Mantel-Haenszel, CTD = connective tissue disease, CWE = clinical worsening event, ITT = intent-to-treat, LOCF = last observation carried forward, N = number of subjects in the group, PAH = pulmonary arterial hypertension, WHO = World Health Organization.

a. A missing value at Week 12 was assigned as WHO functional Class IV if the subject had a predefined CWE, otherwise, a missing value at Week 12 was imputed with the last nonmissing value based on the LOCF method.

Time to Clinical Worsening (TTCW):

Time to Clinical Worsening is summarized in Table 6. Four (4.4%) subjects in the sitaxsentan 100 mg group had CWEs (2 subjects were hospitalized for worsening PAH and 2 subjects died during the study), and 7 subjects (7.6%) in the placebo group had CWEs (4 subjects were hospitalized for worsening PAH and 6 subjects died during the study).

As specified in the step-down procedure, a formal statistical treatment comparison of TTCW was not performed because there was no significant treatment effect (at the 0.05 level) for the WHO functional class parameter.

Table 6. Incidence of Clinical Worsening Events, ITT Population

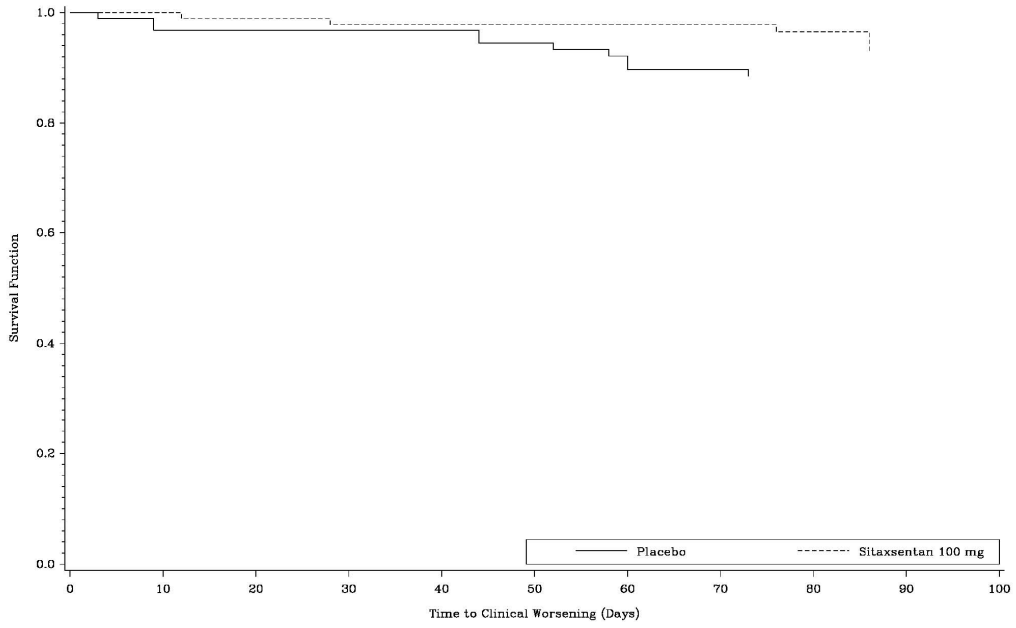
Reason for Clinical Worsening	Sitaxsentan 100 mg N=91	Placebo N=92
Worsening[a] (n [%])	4 (4.4)	7 (7.6)
Hospitalization for worsening PAH	2 (2.2)	4 (4.3)
On-study death	2 (2.2)	6 (6.5)
Life table estimates of worsening		
Proportion worsened[b]	0.073	0.115
95% CI for proportion worsened[b]	(0.000, 0.156)	(0.048, 0.182)
No worsening (n [%])	87 (95.6)	85 (92.4)
Completed 12 weeks of study	74 (81.3)	67 (72.8)
Discontinued before 12 weeks of study	13 (14.3)	18 (19.6)

The median time to clinical worsening was not presented as fewer than 50% of subjects in each treatment group had a CWE.
CI = confidence interval, CWE = clinical worsening event, ITT = intent-to-treat, n = number of subjects, N = number of subjects in the group, PAH = pulmonary arterial hypertension.

a. Subjects who had more than 1 CWE were counted separately under each type of event they experienced (but the total number only counted subjects, irrespective of the number of their events).
b. Kaplan-Meier estimates.

A Kaplan-Meier plot for TTCW is provided in Figure 2. Please note that the data for each treatment group were unstratified and, therefore, not directly representative of the analysis shown in the tables.

Figure 2. Kaplan-Meier Plot for Time to Clinical Worsening, ITT Population



This was unstratified and therefore not directly representative of the analysis shown in the tables.
ITT = intent-to-treat.
The ITT population includes all subjects were randomized.

Safety Results:

Treatment-emergent nonserious AEs (all causalities and treatment-related) by system organ class (SOC) and preferred term that occurred in >5% of subjects in either treatment groups are summarized in Table 7.

The most commonly experienced AEs were edema peripheral, dyspnea, AST increased, dizziness, and vomiting.

Table 7 Treatment-Emergent NonSerious Adverse Events by System Organ Class and Preferred Term (All Causalities) in >5% of Subjects

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v14.0) Preferred Term	Sitaxsentan 100 mg n (%)	n1*	n2**	Placebo n (%)	n1*	n2**
Evaluable for adverse events	91			91		
With adverse events	34 (37.4)			40 (44.0)		
Gastrointestinal disorders	2 (2.2)	2	1	5 (5.5)	5	2
Vomiting	2 (2.2)	2	1	5 (5.5)	5	2
General disorders and administration site conditions	5 (5.5)	6	1	8 (8.8)	9	4
Oedema peripheral	5 (5.5)	6	1	8 (8.8)	9	4
Investigations	5 (5.5)	5	2	2 (2.2)	2	2
Aspartate aminotransferase increased	5 (5.5)	5	2	2 (2.2)	2	2
Nervous system disorders	5 (5.5)	6	1	2 (2.2)	2	1
Dizziness	5 (5.5)	6	1	2 (2.2)	2	1
Respiratory, thoracic and mediastinal disorders	3 (3.3)	4	0	7 (7.7)	8	1
Dyspnoea	3 (3.3)	4	0	7 (7.7)	8	1

Except for 'n1' and 'n2' subjects were only counted once per treatment for each row.
n = the number of subjects in this reporting group affected by any occurrence of this adverse event, all causalities.
n1* = the number of occurrences of treatment emergent all causalities adverse events.
n2** = the number of occurrences of treatment emergent causally related to treatment adverse events.
Includes data up to 999 days after last dose of study drug.
MedDRA (v.14.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities, v = version.

Treatment-emergent SAEs (all causalities and treatment-related) by SOC and preferred term in either treatment group are summarized in Table 8. One subject, who experienced a fatal pretreatment SAE, died during the study. For 4 subjects in the sitaxsentan 100 mg group, the Investigator and Sponsor assessed the serious events as treatment-related and for 2 subjects in the placebo group the causality was assessed by the Investigator as treatment-related and not related by the Sponsor.

Table 8 Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v14.0) Preferred Term	Sitaxsentan 100 mg n (%)	n1*	n2**	Placebo n (%)	n1*	n2**
Evaluable for adverse events	91			91		
With adverse events	9 (9.9)			12 (13.2)		
Blood and lymphatic system disorders	1 (1.1)	1	0	0	0	0
Anaemia	1 (1.1)	1	0	0	0	0
Cardiac disorders	3 (3.3)	3	0	6 (6.6)	6	0
Acute myocardial infarction	0	0	0	1 (1.1)	1	0
Acute right ventricular failure	0	0	0	1 (1.1)	1	0
Arrhythmia	0	0	0	1 (1.1)	1	0
Cardiac failure	1 (1.1)	1	0	2 (2.2)	2	0
Cardiac failure congestive	1 (1.1)	1	0	0	0	0
Right ventricular failure	1 (1.1)	1	0	1 (1.1)	1	0
General disorders and administration site conditions	2 (2.2)	2	0	1 (1.1)	2	0
Chest discomfort	0	0	0	1 (1.1)	1	0
Fatigue	0	0	0	1 (1.1)	1	0
Sudden cardiac death	2 (2.2)	2	0	0	0	0
Hepatobiliary disorders	0	0	0	2 (2.2)	2	2
Hepatic failure	0	0	0	1 (1.1)	1	1
Hepatitis	0	0	0	1 (1.1)	1	1
Infections and infestations	0	0	0	2 (2.2)	2	1
Respiratory tract infection	0	0	0	1 (1.1)	1	0
Sepsis	0	0	0	1 (1.1)	1	1
Injury, poisoning and procedural complications	0	0	0	1 (1.1)	1	0
Ankle fracture	0	0	0	1 (1.1)	1	0
Investigations	4 (4.4)	7	7	0	0	0
Alanine aminotransferase increased	2 (2.2)	2	2	0	0	0
Aspartate aminotransferase increased	2 (2.2)	2	2	0	0	0
Blood bilirubin increased	1 (1.1)	1	1	0	0	0
International normalised ratio increased	1 (1.1)	1	1	0	0	0
Liver function test abnormal	1 (1.1)	1	1	0	0	0
Psychiatric disorders	1 (1.1)	1	0	0	0	0
Decreased activity	1 (1.1)	1	0	0	0	0
Renal and urinary disorders	0	0	0	2 (2.2)	2	1
Nephritis	0	0	0	1 (1.1)	1	1
Renal failure	0	0	0	1 (1.1)	1	0
Reproductive system and breast disorders	0	0	0	1 (1.1)	1	0
Cervix haemorrhage uterine	0	0	0	1 (1.1)	1	0
Respiratory, thoracic and mediastinal disorders	1 (1.1)	1	0	2 (2.2)	2	0
Dyspnoea	1 (1.1)	1	0	1 (1.1)	1	0
Pulmonary embolism	0	0	0	1 (1.1)	1	0
Vascular disorders	0	0	0	1 (1.1)	1	0
Deep vein thrombosis	0	0	0	1 (1.1)	1	0

Except for 'n1' and 'n2' Subjects were only counted once per treatment for each row.
n = the number of subjects in this reporting group affected by any occurrence of this adverse event, all causalities.
n1* = the number of occurrences of treatment-emergent all causalities adverse events.
n2** = the number of occurrences of treatment-emergent causally related to treatment adverse events.
Includes data up to 999 days after last dose of study drug.
MedDRA v.14.0 coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities, v = version.

Five subjects (5.5%) in the sitaxsentan 100 mg group and 8 (8.8%) subjects in the placebo group discontinued the study due to treatment-emergent AEs, some of which had a fatal outcome (Table 9). All but 1 of these AEs in each group were assessed as unrelated to study treatment.

Table 9. Permanent Discontinuations due to AEs, Safety Population

	Gender/Age[a] (years)	MedDRA Preferred Term	Start / Stop Day[b]	Severity	Outcome	Causality
Pretreatment						
Sitaxsentan 100 mg						
1	M, 23	Transaminases increased	-20/>15[c]	Severe	Still present	Unrelated
Treatment Emergent						
Sitaxsentan 100 mg						
2	F, 20	Right ventricular failure	12/>12[c]	Severe	Still present	Unrelated
3	F, 54	Cardiac failure congestive	17/>37[c]	Severe	Still present	Unrelated
4	F, 29	Decreased activity	40/>49[c]	Severe	Still present	Unrelated
5	M, 41	Sudden cardiac death	76/76[c]	Severe	Still present	Unrelated
6	F, 47	Blood bilirubin increased	65/>70[c]	Severe	Still present	Related
Placebo						
7	F, 27	Dyspnoea	9/10[c]	Severe	Still present	Unrelated
8	F, 53	Acute right ventricular failure	52/52[c]	Severe	Still present	Unrelated
9	F, 48	Acute myocardial infarction	73/73[c]	Severe	Still present	Unrelated
10	M, 30	Arrhythmia	3/3[c]	Severe	Still present	Unrelated
11	F, 45	Sepsis	72/82	Severe	Resolved	Related
12	M, 56	Cardiac failure	44/47[c]	Severe	Still present	Unrelated
13	F, 17	Chest discomfort	62/70[c]	Moderate	Still present	Unrelated
14	F, 44	Respiratory tract infection	20/>37[c]	Moderate	Still present	Unrelated

MedDRA (version 14.0) coding dictionary applied.
All of the listed events were SAEs.
AE = adverse event, CRF = case report form, F = female, M = male, MedDRA = Medical Dictionary for Regulatory Activities, SAE = serious adverse event.
a. Age at date of screening.
b. Day relative to start of study treatment. First day of study treatment = Day 1.
c. Imputed from incomplete dates and times.

Deaths: Treatment-emergent death was reported for 5 (5.5%) subjects in the sitaxsentan 100 mg group and for 6 (6.6%) subjects in the placebo group as summarized in Table 10. One death (placebo group) was assessed as treatment-related by the Investigator but unrelated by the Sponsor. In addition, 1 subject died prior to receiving study drug treatment.

Table 10. Individual Listing of Deaths, Safety Population

Serial Number	Gender/Age[a] (years)	Day of Death[b]	Event with Fatal Outcome	Cause of Death	Causality[c]
			Pretreatment Deaths		
1	Unknown	NA	Death	Death	NA
			Treatment-Emergent Deaths		
Sitaxsentan 100 mg					
2	F, 20	12	Anaemia	Sudden cardiac death, disease progression, anaemia, right ventricular failure	Unrelated
		12	Right ventricular failure	Sudden cardiac death, disease progression, anaemia, right ventricular failure	Unrelated
		12	Sudden cardiac death	Sudden cardiac death, disease progression, anaemia, right ventricular failure	Unrelated
3	M, 23	70	Hepatic enzyme increased	Hepatic enzyme increased	Unrelated
4	M, 41	76	Sudden cardiac death	Sudden cardiac death	Unrelated
5	M, 56	126	Cardiac failure	Cardiac failure acute	Unrelated
6	F, 48	83	Cardiac failure acute	Cardiac failure acute, disease progression	Unrelated
		83	Disease progression	Cardiac failure acute, disease progression	Unrelated
Placebo					
7	F, 27	10	Dyspnoea	Disease progression	Unrelated
8	F, 53	52	Right ventricular failure	Disease progression, right ventricular failure	Unrelated
9	F, 48	73	Acute myocardial infarction	Acute myocardial infarction	Unrelated
10	M, 30	3	Arrhythmia	Arrhythmia	Unrelated
11	M, 56	47	Cardiac failure	Hepatic failure, renal failure, cardiac failure	Unrelated
		47	Hepatic failure	Hepatic failure, renal failure, cardiac failure	Related/ unrelated
		47	Renal failure	Hepatic failure, renal failure, cardiac failure	Unrelated
12	F, 18	70	Disease progression	Disease progression	Unrelated

MedDRA (version 14.0) coding dictionary applied.
F = female, M = male, MedDRA = Medical Dictionary for Regulatory Activities, NA = not available or not applicable, SAE = serious adverse event.
a. Age at date of SAE onset.
b. Day of Death was calculated as death date minus first active therapy date plus 1.
c. In all cases with causality assessment, the Investigator and Sponsor agreed on the causality, unless indicated otherwise (Investigator assessment/Sponsor assessment).

There were no marked changes in the median values of any of the laboratory parameters analyzed. Median values of the LFT parameters remained relatively constant across the scheduled visits. The absolute mean and median values for vital signs (weight, temperature, respiration rate, blood pressure, and heart rate) were comparable in both groups at all visits.

CONCLUSIONS:

- In this study of subjects with PAH, the observed median treatment difference for change from Baseline 6MWD to Week 12 between sitaxsentan 100 mg versus placebo of 14 meters (95% CI =3, 26) was statistically significant (p-value =0.0104). Although statistical significance was achieved. The treatment effect was lower than anticipated.

- The largest sitaxsentan treatment effect was reported in China. In the 2 geographical regions (China and Other) where a reasonably large treatment effect was observed. There was a reported reduction in 6MWD on the placebo arm, which was not observed in the US, Eastern Europe, or India. It is therefore possible that an erosion of the treatment effect due to a relatively high placebo response rate may have occurred in these countries.

- More subjects in the sitaxsentan 100 mg group improved in WHO functional class and fewer subjects deteriorated in WHO functional class compared to subjects in the placebo group; however, the difference was not statistically significant. Fewer subjects in the sitaxsentan 100 mg group had a CWE compared to subjects in the placebo group; no statistical analysis was performed.

- Incidence rates for AEs (serious and nonserious events and events leading to discontinuation) was comparable between the treatment arms.

- In general, the safety profile of sitaxsentan was consistent with that observed in prior studies conducted in PAH subjects, with the exception of elevations in liver aminotransferases, for which a marginally higher incidence rate was observed in subjects receiving sitaxsentan in this study compared to that reported in prior sitaxsentan studies with equivalent dose.

- Of note, 1 subject died following a complicated clinical course including persistent elevations in liver aminotransferases with resultant postmortem examination revealing focal areas of liver injury.

- These data contributed to the recommendation of the data monitoring committee to cease further dosing with sitaxsentan and in the Sponsor's overall assessment and observation of a newly identified idiosyncratic pattern of liver injury that resulted in a no longer favorable benefit: risk for sitaxsentan in the treatment of PAH. This resulted in premature termination of this and other ongoing clinical studies and the voluntarily withdrawal of the marketing license in regions where sitaxsentan was approved.