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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Thelin® / Sitaxsentan sodium

PROTOCOL NO.: B1321002 (FPH-STRIDE-05X-FPH05X)

PROTOCOL TITLE: 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

Study Centers: Three (3) centers took part in the study and randomized subjects; 1 in Romania, 1 in Ukraine and 1 in the United States.

Study Initiation and Final Completion Dates:
30 July 2010 to 28 January 2011. The study was terminated prematurely.

Phase of Development: Phase 3

Study Objectives:

Primary Objective: To evaluate the long-term safety of sitaxsentan and sitaxsentan plus sildenafil in subjects with pulmonary arterial hypertension (PAH) who were eligible for this study if they had discontinued early or completed a previous combination therapy 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 who Have Completed Placebo Controlled Study (NCT00796666)" or if early escape was met in a previous placebo controlled study, "A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Safety and Efficacy Study of Sitaxsentan Sodium in Subjects With Pulmonary Arterial Hypertension (NCT00795639)".

Secondary Objective: To evaluate the efficacy of sitaxsentan and sitaxsentan plus sildenafil in subjects with PAH who were eligible for this study if they had discontinued early or completed the combination therapy study or if early escape was met in the placebo controlled study by determining change from Baseline/Day 1 to Weeks 12 and 24 in 6-minute walk distance.

METHODS

Study Design: This was a phase 3, multicenter, open-label, long-term safety study of sitaxsentan and sitaxsentan plus sildenafil given orally to subjects with PAH. Subjects participating in the lead-in studies, the placebo controlled or combination therapy study, were

originally planned to be enrolled into this study. Subjects enrolled in this study had access to open-label sitaxsentan and/or sildenafil provided the study inclusion and exclusion criteria were met. A Baseline/Day 1 evaluation was conducted within a 2-week period prior to the subject being enrolled in the study. The End of Treatment Visit for the placebo controlled or the combination therapy study could serve as the Baseline/Day 1 study procedures. Subjects eligible for this study had on-site clinic assessments performed at Baseline/Day 1 and every 12 weeks thereafter until the End of Treatment or Early Termination Visit. All subjects could receive additional PAH-specific, regulatory approved, chronic treatment at the Investigator's discretion. Subjects were allowed to remain on the study until the Sponsor elected to discontinue the study at that investigational site; the study was intended to run until approval of sitaxsentan was granted. Upon study closure, all subjects were required to complete an End of Treatment Visit. If a subject's participation in the study was discontinued prior to study closure, all safety evaluations were to be performed during an Early Termination Visit. Following subject completion, each enrolled subject (including those subjects who terminated from the study early) was to be contacted every 12 weeks to collect survival status until the Sponsor elected to discontinue the study. Due to study termination, Survival Follow-Up or any other Post-28-day Follow-Up Visit was not required. However, as only 3 subjects entered in this study, a 28-day Follow-Up Visit was to be performed. Rather than entering the data into the case report form, they were only to be recorded in the source notes.

The schedule of activities is provided in Table 1.

Table 1. Schedule of Activities

	Treatment Phase					
	Clinic Visit	Phone/Remote Visit		Clinic Visits		Phone/Remote Visit
	Baseline/ Day 1[a]	Week 4 (Placebo Controlled Study Lead-In Subjects Only) (±2 Days)	Every 4 Weeks (±2 Days)	Every 12 Weeks (±2 Days)	EOT/Early Termination	Survival Follow-Up Every 12 Weeks (±2 Days)
Informed consent documentation[b]	X					
Inclusion/exclusion evaluation	X					
Medical history update[c]	X					
Physical examination[d]	X			X	X	
Vital sign measurements[e]	X			X	X	
6-minute walking test[f]	X			X	X	
WHO functional class	X			X	X	
Hemoglobin	X	X		X	X	
AST, ALT, direct and total bilirubin[g]	X	X	X	X	X	
Serum/urine pregnancy test[h]	X	X	X	X	X	
Coagulation[i]	X	X	X	X	X	
Concomitant medication notation[j]	X	X	X	X	X	
AE collection[j]	X	X	X	X	X	
Dispense/return study drug[k]	X			X	X	
Survival assessment[l]						X

AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase, EOT = End of Treatment, WHO = World Health Organization.

a. All end of treatment or early termination study procedures from the lead-in protocols (placebo controlled study or combination therapy study) could be used as the Baseline/Day 1 assessments if they were performed within 2 weeks of the first dose, otherwise they had to be repeated on Day 1.
b. Informed consent form had to be obtained prior to any study procedures being performed.
c. Medical history was to include any medical condition that was still ongoing as of Baseline from the lead-in studies.
d. Physical examinations included measurements of height and weight at the Baseline/Day 1 Visit. Thereafter, height was not measured.
e. Vital sign measurements were to include sitting blood pressure, respiratory rate, heart rate and temperature.
f. 6-minute walking test was only required at Baseline, Weeks 12 and 24 and End of Treatment. Between Week 24 and End of Treatment, if a subject proceeded with the study, 6-minute walking test was not required.
g. AST, ALT, direct and total bilirubin concentration testing were to be obtained at Baseline, Week 4, every 4 weeks, and at End of Treatment or Early Termination Visits. AST or ALT values >1.5 were to be reported immediately to the Sponsor, with weekly testing to follow until resolution of the elevation or return to Baseline value.
h. A serum pregnancy test was performed on female subjects of childbearing potential. In addition, a urine pregnancy test was only collected at Baseline/Day 1. Any subject who became pregnant was immediately discontinued from the study.
i. Coagulation testing was required at Baseline/Day 1, Week 4, and every 4 weeks thereafter 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/Day 1), coagulation testing was required at every 4-week blood draw.
j. Every 4 weeks a phone call was made to the subject, unless there was a scheduled clinic visit, to record concomitant medication use and the occurrence of any AEs.
k. Study drug (90-day supply) was dispensed at the applicable clinic visits (ie, enough to last for 12 weeks). Drug supplies were collected and accounted for at each clinic visit.
l. All completed or discontinued subjects were to be followed every 12 weeks until the study was closed to assess survival status. Due to study termination, Survival Follow-Up or any other post 28-day Follow-Up Visit data was not required.

Number of Subjects (Planned and Analyzed): Up to 180 subjects from 103 investigational sites participating in the lead-in studies, the placebo controlled study or the combination therapy study, were originally planned to be enrolled into this study.

On 6 December 2010, the independent data monitoring committee recommended discontinuation of dosing in the 3 ongoing clinical studies for the sitaxsentan registration program in the United States, including this study, based on their assessment of newly emerging evidence of serious hepatic toxicity associated with administration of sitaxsentan. The Sponsor decided to prematurely terminate the study upon completion of its own assessment. On 9 December 2010, at which time 3 subjects had been entered into this study, the Investigators were informed of this decision.

Diagnosis and Main Criteria for Inclusion: The study included subjects:

- Previously enrolled in the placebo controlled study for at least 4 weeks and discontinued from the study after the Adjudication Committee granted discontinuation based on early escape or the need to add or increase the dose of a chronic medication for worsening PAH.

- Previously enrolled in the combination therapy study and discontinued from the study after the Adjudication Committee granted early discontinuation due to the need to add or increase the dose of a chronic medication for worsening PAH.

- Completed the placebo controlled study but were unable to enroll in the combination therapy study or completed the combination therapy study as planned.

Study Treatment: Subjects received 1 of 2 treatments:

- 100 mg of sitaxsentan monotherapy taken once daily.

- 100 mg of sitaxsentan taken once daily with 20 mg of sildenafil taken 3 times a day.

Each daily dose of sitaxsentan was to be taken with or without food and with water at a similar time each day. Sildenafil was to be administered 3 times a day, with or without food and with water. Each dose of sildenafil was to be taken approximately 4 to 6 hours apart, and at a similar time each day. Doses of sildenafil were not to be combined. If a dose was missed, dosing was to resume according to the original schedule. Study medication was supplied by the Sponsor as tablets for oral use (sitaxsentan sodium 100 mg and sildenafil citrate 20 mg).

Efficacy Endpoints:

Efficacy was a secondary objective of the study.

- Survival status (data collected every 12 weeks).

- The 6 minute walk test (MWT) (data collected at Baseline, at Weeks 12 and 24, and at the end of study).

- World health organization (WHO) functional class (data collected at Baseline, every 12 weeks and end of study).

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

Statistical Methods: As only 3 subjects were recruited into the study at the time of study termination, the data were listed only and no analyses or data summarization were performed. All subjects were included in the data listings.

RESULTS

Subject Disposition and Demography: Three subjects who participated in the lead-in placebo controlled study and met the early escape criteria were enrolled in the current study with prior approval from an Adjudication Committee member.

All 3 subjects were assigned to the sitaxsentan 100 mg group, and received open-label study drug. All 3 subjects discontinued the study: 1 subject died and 2 subjects were discontinued due to the study termination by the Sponsor. All 3 subjects were analyzed for AEs and laboratory evaluations.

One subject was female, 54 years, white, had a weight of 75.5 kg and a height of 165.0 cm. Second subject was also female, 29 years, Hispanic, had a weight of 72.5 kg and a height of 162.6 cm. Third subject was male, 44 years, white, had a weight of 86.8 kg and a height of 182.0 cm.

Efficacy Endpoints:

One subject had an incomplete 6MWT performed on Day 1 and, due to the subject's death on Day 8, no further 6MWTs were performed. The subject was assessed to have WHO functional class IV PAH on Day 1 and at the End of Treatment Visit (on the same day that the subject died).

The other 2 subjects each completed 3 6MWTs. One subject walked 258 meters on Day 1, 236 m at an unplanned assessment, and 373 meters at the End of Treatment Visit. This subject had WHO functional class IV PAH on Day 1 and WHO functional class III PAH at the End of Treatment Visit. The other subject walked 172 meters on Day 1, 212 meters at Week 12, and 218 meters at the End of Treatment Visit. This subject had WHO functional class IV PAH on Day 1 and WHO functional class III PAH at Week 12 and at the End of Treatment Visit.

Due to premature study termination, only 3 subjects were included in this study and there was insufficient data to analyze the efficacy of sitaxsentan and sitaxsentan plus sildenafil in subjects with PAH.

Safety Results:

A total of 5 treatment-emergent adverse events (TEAEs) were reported for 2 subjects.

One subject experienced the TEAEs noncardiac chest pain, musculoskeletal pain, and pain in jaw. All 3 AEs resolved and were assessed by the Investigator to be of moderate intensity and unrelated to the study drug.

Treatment-emergent non serious adverse events by system organ class and preferred term (all causalities) are summarized in Table 2.

Table 2. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v14.0) Preferred Term	Sitaxentan 100 mg n (%)	n1	n2
Evaluable for adverse events	3		
With adverse events	1 (33.3)		
General disorders and administration site conditions	1 (33.3)	1	0
Non-cardiac chest pain	1 (33.3)	1	0
Musculoskeletal and connective tissue disorders	1 (33.3)	2	0
Musculoskeletal pain	1 (33.3)	1	0
Pain in jaw	1 (33.3)	1	0

Includes data up to 9999 days after last dose of study drug.
Except for 'n1' and 'n2', subjects are 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.
MedDRA = Medical Dictionary for Regulatory Activities, v = version.

One subject experienced the TEAEs cytolytic hepatitis and the fatal event cardiac arrest (see 'Permanent Discontinuations Due to Adverse Events / Deaths, Other Serious Adverse Events, and Other Significant Adverse Events').

Treatment-emergent serious adverse events by system organ class and preferred term are summarized in Table 3.

Table 3. 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	Sitaxentan 100 mg n (%)	n1	n2
Evaluable for adverse events	3		
With adverse events	1 (33.3)		
Cardiac disorders	1 (33.3)	1	0
Cardiac arrest	1 (33.3)	1	0
Hepatobiliary disorders	1 (33.3)	1	1
Cytolytic hepatitis	1 (33.3)	1	1

Includes data up to 9999 days after last dose of study drug.
Except for 'n1' and 'n2', subjects are 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.
MedDRA = Medical Dictionary for Regulatory Activities, v = version.

There were no temporary discontinuations or dose reductions due to AEs.

Permanent Discontinuations Due to Adverse Events / Deaths, Other Serious Adverse Events, and Other Significant Adverse Events: A 54-year-old female subject, received sitaxsentan 100 mg from Days 1 to 7. On Study Day 7, the subject experienced cytolytic hepatitis reflected in several-fold increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) along with clinical worsening which was assessed by the Investigator as serious and related to study drug (see 'Evaluation of Laboratory Parameters' for further details). On Study Day 8, the subject died of cardiac arrest (asystole). The event was assessed by the Investigator as unrelated to the study drug and probably caused by congestive heart failure attributed to disease progression.

Evaluation of Laboratory Parameters: Laboratory test abnormalities of potential clinical concern (ALT and AST >3.0 x upper limit normal [ULN]) were reported for 1 subject. The subject had AST values of 34 IU/L at Baseline, 48 IU/L (above ULN) on Day 4, and 461 IU/L (>3.0 x ULN) on Day 7. The subject had ALT values of 17 IU/L at Baseline, 19 IU/L on Day 4, and 123 IU/L (>3.0 x ULN) on Day 7. On Day 7, the SAE cytolytic hepatitis was reported, and on Day 8, the subject died of cardiac arrest. On Day 1, total bilirubin was 18 μmol/L and direct bilirubin was 9 μmol/L.

Vital Signs, Electrocardiogram, Physical Findings, and Other Observations Related to Safety: No significant vital signs changes from Baseline were observed, except for 1 subject, where vital sign values of 0 were measured on Day 8 during a cardiac arrest.

Physical examination changes from Baseline were recorded for 1 subject on Day 8 (during cardiac arrest) and for another subject on Day 85 (the bilateral lower extremity edema resolved).

CONCLUSION: On 6 December 2010, the independent Data Monitoring Committee informed the Sponsor that they had reviewed available safety information (deaths, serious

adverse events, and liver enzyme elevations and recommended discontinuation of dosing in the 3 ongoing clinical studies, including this study. Due to newly emerging evidence of hepatic injury associated with the administration of sitaxsentan, this study was terminated. At the time, only 3 subjects were included in this study with insufficient data to draw any conclusions on the long-term safety of sitaxsentan and sitaxsentan plus sildenafil in subjects with PAH. A total of 5 TEAEs were reported for 2 subjects. Two of the events were severe SAEs and occurred in the same subject: cytolytic hepatitis (with concurrent increases in AST and ALT) assessed as related to sitaxsentan and cardiac arrest, resulting in fatal outcome, assessed as not related to sitaxsentan.