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

PROTOCOL NO.: B1321003

PROTOCOL TITLE: 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 Study B1321001

Study Centers: A total of 44 centers took part in the study and randomized subjects; 12 in the United States (US), 8 in India, 4 in China, 3 in Argentina, 2 each in Romania, the Russian Federation, and Ukraine, and 1 each in Bulgaria, Colombia, Chile, the Czech Republic, Malaysia, Mexico, Peru, Serbia, South Africa, Thailand, and Turkey.

Study Initiation Date and Final Completion Date: 27 May 2009 to 23 March 2011. The study was terminated prematurely.

Phase of Development: Phase 3

Study Objectives:

Primary Objective: To evaluate the efficacy of sitaxsentan sodium (100 mg once daily [QD]) plus sildenafil citrate (20 mg 3 times per day [TID]) versus sitaxsentan monotherapy by determining time to clinical worsening (TTCW) in subjects with pulmonary arterial hypertension (PAH) and who had completed a previous sitaxsentan study (Study B1321001: a Phase 3, multicenter, randomized, double-blind, placebo-controlled, safety, and efficacy study of sitaxsentan sodium in subjects with pulmonary arterial hypertension [NCT00795639]).

Secondary Objective: To evaluate the safety and efficacy of sitaxsentan (100 mg QD) plus sildenafil (20 mg TID) as compared to sitaxsentan monotherapy in the treatment of subjects with PAH who had completed previous sitaxsentan study by determining change from Baseline/Day 1 to Weeks 12, 24, and 48 in 6-minute walk distance (6MWD), World Health Organization (WHO) functional class, and Quality of Life (Short-Form 36 Health Survey [SF-36] and European Quality of Life 5 Dimensional [EQ-5D]).

METHODS

Study Design: This was a randomized, double-blind, efficacy, and safety study of monotherapy sitaxsentan versus combination therapy with sitaxsentan and sildenafil in subjects with PAH who had completed a previous sitaxsentan study.

A Baseline/Day 1 evaluation of all Week 12 or early termination study procedures from the lead-in/previous sitaxsentan study was conducted within a 2-week period prior to subject randomization in the study. The end-of-treatment visit for the previous sitaxsentan study could have served as Baseline/Day 1 for study procedures. Under exceptional circumstances, the subject was allowed up to a further 2 weeks before starting the study. In these cases, procedures were repeated before Day 1 and concomitant medications could not be changed or added. Subjects were stratified at randomization with regard to the particular treatment they received in the previous sitaxsentan study and their functional status upon entry into this study.

Subjects were randomized to receive either monotherapy sitaxsentan (100 mg dosed orally QD and concomitantly with placebo), or to receive combination treatment with sitaxsentan (100 mg orally QD) dosed concomitantly with sildenafil (20 mg orally TID). Subjects had on-site clinic assessments performed at specified time during the study (Table 1). There was a follow-up visit at 28±4 days to assess safety for all subjects who discontinued early/completed this study and did not enter into the succeeding sitaxsentan study (Study B1321002: a Phase 3, multicenter, open-label study to evaluate the long-term safety of monotherapy sitaxsentan and combination therapy with sitaxsentan sodium and sildenafil citrate in subjects with pulmonary arterial hypertension [NCT00796510]).

A subject remained on his or her blinded treatment until 1 of the study discontinuation criteria was met, or until all active subjects reached Week 48 of the study. Following subject completion, each subject (including those subjects who discontinued the study early) was contacted every 12 weeks to collect survival status data.

Upon study closure, all subjects completed an end-of-treatment visit. A follow-up visit was conducted at 28±4 days for subjects who did not continue into the succeeding sitaxsentan study. If a subject's participation in the study was discontinued prior to study closure, all safety evaluations were performed during an early termination visit and a follow-up visit was conducted.

The schedule of activities for the study is presented in Table 1.

Table 1. Schedule of Activities

	Treatment Phase							
	Clinic Visit				Phone/ Remote Visit	Clinic Visit	Clinic Visit[a]	Phone/ Remote Visit
	Baseline/ Day 1[b]	Week 4	Week 8	Week 12	Every 4 Weeks	Every 12 Weeks	EOT/Early Termination	Survival Follow-Up
		(±4 Days)	(±4 Days)	(±4 Days)	(±4 Days)	(±4 Days)	(±4 Days)	(±4 Days)
Informed consent documentation[c]	X							
Inclusion/exclusion evaluation[d]	X							
Medical history update[e]	X							
Physical examination[f]	X	X	X	X		X	X	
Vital sign measurements[g]	X	X	X	X		X	X	
SF-36 and EQ-5D health survey[h]	X			X		X	X	
6-Minute walk test	X	X	X	X		X	X	
WHO functional class	X	X	X	X		X	X	
Hemoglobin[i]	X	X	X	X		X	X	
AST, ALT, direct and total bilirubin[j]	X	X	X	X	X	X	X	
Serum/urine pregnancy test[k]	X	X	X	X	X	X	X	
Pharmacokinetic (PK) sample[l]	X	X	X	X		X	X	
Coagulation[m]	X	X	X	X	X	X	X	
Concomitant medication notation[n]	X	X	X	X	X	X	X	
AE collection[n]	X	X	X	X	X	X	X	
Dispense/return study drug[o]	X	X	X	X		X	X	
Survival assessment[p]								X

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; EOT = end-of-treatment; EQ-5D = European Quality of Life 5 dimensional; PK = pharmacokinetics; SF-36 = Short Form 36; WHO = World Health Organization.

a. Follow-up visit 28±4 days after discontinuation/study completion for those subjects not going onto the succeeding sitaxsentan study. The following assessments were made: physical examination, vital signs, urine pregnancy test for women of childbearing potential, concomitant treatment(s)/AE(s), clinical chemistry safety labs (hemoglobin and liver chemistries) and coagulation testing (if indicated).

b. All Week 12 or early termination study procedures from the lead-in/previous sitaxsentan study could have been used as this study's Baseline/Day 1 assessments if they were performed within 2 weeks of the first dose, otherwise they were repeated.

c. Informed consent was obtained prior to any study procedures being performed.

d. Inclusion and exclusion criteria for this study was assessed at a Baseline/Day 1 evaluation visit.

e. Medical history included any medical condition that was still ongoing as of baseline from the lead-in study.

f. Physical examinations included measurements of height and weight at the Baseline/Day 1 Visit. Thereafter, height was not measured.

g. Vital sign measurements included sitting blood pressure, respiratory rate, heart rate, and temperature. Note that, at the Baseline/Day 1 Visit, vital signs were assessed predose and at 1 and 2 hours postdose due to the possible risk of hypotension.

h. SF-36 and EQ-5D were only required at Baseline, Weeks 12, 24, 48, and EOT. SF-36 and EQ-5D were not required between Weeks 48 and EOT.

i. Hemoglobin concentration testing was obtained at Baseline, Week 4, Week 8, Week 12, and every 12 weeks, and at EOT or early termination visits.

j. AST, ALT, and direct and total bilirubin concentration testing was obtained at Baseline, Week 4, every 4 weeks, and at EOT or early termination visits. New AST or

Table 1. Schedule of Activities

ALT values >1.5 were to be reported immediately to the Sponsor, with weekly testing until resolution of the elevation or return to Baseline/Day 1 value.

k. A serum pregnancy test was performed on female subjects of childbearing potential at Baseline/Day 1, Week 4, every 4 weeks, and at EOT or early termination visits. A urine pregnancy test was collected at Baseline/Day 1, and only at Baseline/Day 1. Any subject who became pregnant was immediately discontinued

l. A predose and postdose PK sample was required at Baseline. After Baseline, the sample did not have to be drawn predose, but the time drug was taken and the time the sample was drawn was documented.

m. Coagulation testing was required at Baseline, Week 4, and every 4 weeks thereafter for all subjects who were taking warfarin or other vitamin K antagonists. For subjects who began taking warfarin or other vitamin K antagonists during the study (ie, at any point beyond baseline), coagulation testing was required at the every 4-week blood draw.

n. 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.

o. Study drug was dispensed during every clinic visit. A 1-month supply of study drug was dispensed at each study visit from Baseline/Day 1 through Week 8. Thereafter, a 3-month supply was dispensed at every clinic visit for the duration of the study.

p. All subjects (regardless of early termination) were followed every 12 weeks to assess survival status.

Number of Subjects (Planned and Analyzed): One-hundred eighty subjects were planned for enrollment; 131 were randomized (67 in monotherapy sitaxsentan group and 64 in combination sitaxsentan group), and 130 received study treatment (66 in monotherapy sitaxsentan group and 64 in combination sitaxsentan group).

Of 131 subjects; 43 were randomized in India, 35 in China, 14 in the US, 9 in Ukraine, 5 in Romania, 4 in the Russian Federation, 3 each in Argentina, Peru, and Thailand, 2 each in Mexico, South Africa, and Turkey, and 1 each in Bulgaria, Chile, Colombia, the Czech Republic, Malaysia, and Serbia.

Diagnosis and Main Criteria for Inclusion: Subjects who had enrolled in and completed the preceding sitaxsentan study were included in this study. Subjects were excluded from this study if he or she was treated with an investigational drug other than sitaxsentan within the 30 days before Baseline/Day 1, during the preceding sitaxsentan study, or were treated with a device that had not received regulatory approval.

Study Treatment: Sitaxsentan sodium 100-mg tablets, sildenafil citrate 20-mg tablets and matching placebo were supplied by Sponsor in a formulation for oral dosing.

Subjects were randomized to receive either sitaxsentan 100 mg orally QD, dosed concomitantly with matching placebo or combination treatment with sitaxsentan 100 mg orally QD dosed concomitantly with sildenafil 20 mg orally TID. Each daily dose of sitaxsentan, consisting of a single 100-mg oral tablet, or matching placebo was to be taken with or without food and with water at a similar time each day. Sildenafil (or the matching placebo for sildenafil) was taken TID, with or without food and with water. Each dose of sildenafil (or the matching placebo for sildenafil) was 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 be resumed according to the original schedule.

Efficacy Endpoints:

Primary Endpoint: The primary efficacy endpoint was TTCW. This was assessed and evaluated as the number of days between the first dose of study drug and the occurrence of a predefined clinical worsening event as adjudicated by a blinded Adjudication Committee:

A composite endpoint was used for the primary endpoint of TTCW:

The following components were used:

- All-cause death
- Hospitalization for worsening PAH (defined as hospitalization for at least 24 hours occasioned by a clinical condition clearly related to PAH such as right heart failure, arrhythmia, syncope, atrial septostomy, heart or heart-lung transplantation, requirement for intravenous (IV) diuretic or inotropic medications such as dobutamine, or for initiation of other PAH disease specific therapies such as IV epoprostenol)
- Time to PAH-related deterioration, identified by:

- A reduction of >15% in 6MWD on at least 2 consecutive occasions, performed on different days or

- Increase in WHO functional class on at least 2 consecutive occasions assessed on different days

Secondary Endpoints: The secondary efficacy endpoints included a change in 6MWD, WHO functional class, SF-36 health survey, and EQ-5D changes from Baseline/Day 1 at Weeks 12, 24, and 48.

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

Statistical Methods:

Analysis Sets: The Full Analysis Set (FAS) was defined according to the Intent-to-Treat (ITT) principle. The ITT population was defined as all subjects who were randomized in this study.

The Per-Protocol (PP) population included all subjects who satisfied the ITT criteria and also had:

- Taken 100%±25% of specified dosage of drug for the duration of the study. If the Investigator's assessment of compliance at Weeks 4, 8 and 12 was not 100%±25% the subject was excluded

- 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 Safety Population included all subjects who received at least 1 dose of study drug during the study.

Statistical Methods: Subjects who had no clinical worsening were censored at the last date on study. However, in the case where there was a loss of information for any component of the clinical worsening endpoint prior to discontinuation, subjects were censored at that point. TTCW was calculated as the duration between the first dose date in this study and the date when the first clinical worsening event (CWE) occurred. The hazard ratio (combination therapy versus sitaxsentan monotherapy) and 95% confidence interval (CI) based on the Cox proportional hazards model was presented.

The change from Baseline in 6MWD and WHO functional class was summarized with descriptive statistics by treatment and stratification. The mean treatment difference

(combination therapy – sitaxsentan monotherapy) at Week 12 was estimated from an analysis of covariance (ANCOVA) by stratification for 6MWD and using the Cochran-Mantel-Haenszel (CMH) test for WHO functional class.

Time to all-cause mortality was summarized based on the ITT population, presenting mortality percentages and Kaplan-Meier estimates. A plot of the survival curve was produced. Subjects who did not die were censored at the last date on study.

No formal hypothesis testing of safety data was performed. Results from the safety assessments and any AEs were listed and summarized according to the Sponsor's data standards. Safety data were presented based on the safety population.

RESULTS

Subject Disposition and Demography: A summary of subject disposition and subjects analyzed is presented in Table 2.

Table 2. Subject Disposition and Evaluation Groups

Number (%) of Subjects	Monotherapy Sitaxsentan	Combination Sitaxsentan
Screened=131		
Assigned to study treatment	67	64
Treated[a]	66	64
Completed	0	0
Discontinued	66 (98.5)	64 (100.0)
Subject died[b]	2 (3.0)	4 (6.3)
Relation to study drug not defined	57 (86.4)	55 (85.9)
No longer willing to participate in study	2 (3.0)	0
Other	1 (1.5)	0
Protocol violation	1 (1.5)	0
Study terminated by Sponsor	53 (80.3)	55 (85.9)
Related to study drug	4 (6.1)	4 (6.3)
Adverse events	4 (6.1)	4 (6.3)
Not related to study drug	3 (4.5)	1 (1.6)
Adverse events	3 (4.5)	1 (1.6)
Analyzed for efficacy		
Per protocol population	60 (89.6)	61 (95.3)
Intent-to-treat population	67 (100.0)	64 (100.0)
Analyzed for safety		
Adverse events	66 (98.5)	64 (100.0)
Laboratory data	66 (98.5)	64 (100.0)
Safety population	66 (98.5)	64 (100.0)

Discontinuations occurring outside the lag period have been attributed to the last study treatment received.

a. One subject was randomized and not treated.

b. Only deaths leading to study discontinuation are summarized in this table. Two additional subjects in the monotherapy group died in this study.

Table 3 presents a summary of demographic and baseline characteristics.

Table 3. Demographic and Baseline Characteristics

Number (%) of Subjects	Monotherapy Group N=67	Combination Therapy N=64
Demographic Characteristics - ITT Population		
Gender (n)		
Male	12	15
Female	55	49
Age (years)		
Mean ± SD	41.8±15.6	41.3±15.0
Range (minimum-maximum)	16-77	19-80
Race (n [%])		
White	23 (34.3)	19 (29.7)
Black	2 (3.0)	1 (1.6)
Asian	39 (58.2)	44 (68.8)
Other	3 (4.5)	0
Weight (kg)		
Mean ± SD	61.9±14.5	63.0±16.5
Range (minimum-maximum)	42.0-105.0	40.0-114.0
Height (cm)		
Mean ± SD	161.0±8.7	162.4±8.6
Range (minimum-maximum)	141.0-201.0	139.0-187.0
Baseline Characteristics - Safety Population		
PAH etiology (n [%])[a]		
Connective tissue disease	23 (34.3%)	18 (28.1%)
Systemic sclerosis (scleroderma)	9	3
Limited scleroderma	2	1
Mixed connective tissue disease	3	7
Systemic lupus erythematosus	9	7
Idiopathic PAH	44 (65.7%)	46 (71.9%)
Previous sitaxsentan study (B1321001) treatment		
Sitaxsentan 100 mg	33 (49.3%)	33 (51.6%)
Placebo	34 (50.7%)	31 (48.4%)
WHO functional class		
I	0 (0.0%)	0 (0.0%)
II	12 (17.9%)	11 (17.2%)
III	55 (82.1%)	52 (81.3%)
IV	0 (0.0%)	1 (1.6%)
6-Minute walk distance category		
≥150 meters and ≤450 meters	60 (89.6%)	56 (87.5%)
<150 meters or >450 meters	6 (9.0%)	8 (12.5%)
No baseline assessment	1 (1.5%)[b]	0 (0.0%)
6-Minute walk distance (m)		
n	66	64
Mean	350.9	354.7
Minimum	195	130
Maximum	488	517
Median	358.0	360.0
Standard deviation	74.47	79.88

Study B1321001: a Phase 3, multicenter, randomized, double-blind, placebo-controlled, safety, and efficacy study of sitaxsentan in subjects with pulmonary arterial hypertension (NCT00795639).
ITT = intent to treat; N = number of subjects in each group; n = number of subjects with the specific characteristic; PAH = pulmonary arterial hypertension; SD = standard deviation; WHO = World Health Organization.

a. This information was collected from the primary diagnosis page of the case report form from the previous sitaxsentan study (B1321001). This information may differ from the medical history page as sites were not expected to record primary indication in medical history. However, some recorded primary indication on both pages, and some did not, which resulted in different numbers. Also, note that the primary diagnosis information was the data utilized for the subgroup analyses.

b. One subject.

Efficacy Results: The trial was prematurely terminated on 09 December 2010, due to safety concerns, specifically new emerging evidence of hepatic injury.

Due to early termination of the study, subjects discontinued treatment earlier than planned. The median duration of treatment was 155 days (about 22 weeks) for the combination group and 146 days (about 21 weeks) for the monotherapy group.

Time to Clinical Worsening: Due to the early termination of the study, there were few subjects who experienced a CWE. Five (7.5%) subjects in the monotherapy group had CWEs (3 subjects were hospitalized for worsening PAH and 3 subjects died during the study; 1 subject had 2 CWEs, initially hospitalization due to PAH and subsequently an on-study death), and 4 (6.3%) subjects in the combination group had CWEs (1 subject was hospitalized for worsening PAH and 3 subjects died during the study; Table 4). There was no statistical difference between the treatment groups (p=0.5416, Log-rank test). Failure to demonstrate any difference between treatment groups was impacted by the early termination of the study and the resultant low number of CWEs.

Table 4. Incidence of Clinical Worsening Events - ITT Population

Reason for Clinical Worsening	Monotherapy Sitaxsentan N=67	Combination Sitaxsentan N=64
Worsening[a] (n [%])	5 (7.5)[b]	4 (6.3)
Hospitalization for worsening PAH	3 (4.5)	1 (1.6)
On-study death	3 (4.5)	3 (4.7)
Life table estimates of worsening		
Proportion worsened[c]	0.340	0.246
95% CI for proportion worsened[c]	(0.075, 0.604)	(0.001, 0.491)
No worsening (n [%])	62 (92.5)	60 (93.8)
Completed study[d]	0 (0.0)	0 (0.0)
Discontinued study[d]	62 (92.5)	60 (93.8)

The median time to clinical worsening was not presented as <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 in the group; n = number of subjects with specified criteria; PAH = pulmonary arterial hypertension.

a. Subjects who had >1 CWE were counted separately under each type of event they experienced (but the total number only counted subjects, irrespective of the number of events they had).
b. One subject had 2 CWEs, initially hospitalization due to PAH and subsequently an on-study death.
c. Kaplan-Meier estimates (1-Kaplan-Meier survival [event free] probability).
d. Week 84 was considered as the last week in the study, as data were collected only up to Week 84; however, the study was terminated prior to any subject attending the Week 84 visit.

The hazard ratio was 0.8616 (p=0.4148) with a 95% CI = (0.602, 1.233). The proportional hazard assumptions were considered not particularly robust, and therefore it was recommended that conclusions drawn from these analyses should be interpreted with care.

All-Cause Mortality: After 18 months, there were 4 deaths in each treatment group. There was an insufficient number of events to calculate the median time to death.

Six-Minute Walk Distance: Due to the early termination of the study, not all subjects received study medication for 24 weeks. Thus, only 97 subjects (46 in the monotherapy group and 51 in the combination group) completed a Week-24 6MWT and contributed actual 6MWD for Week 24.

The 6MWD change from Baseline to Week 12 for the ITT population is provided in Table 5. It should be noted that for the monotherapy group at Week 12, there were a few subjects with relatively large changes in 6MWD. Thus, the distributional assumptions of the ANCOVA (based on mean changes) were not met due to a few extreme values and the results of this analysis should therefore be interpreted with caution.

Table 5. Change From Baseline to Weeks 12 and 24 in 6-Minute Walk Distance - ITT Population

	Monotherapy Sitaxsentan N=66	Combination Sitaxsentan N=64
Baseline		
Mean ± standard deviation	350.9±74.47	354.7±79.88
Median (minimum, maximum)	358.0 (195, 488)	360.0 (130, 517)
6MWD change from Baseline to Week 12[a], meters		
Mean ± standard deviation	-6.9±71.00	23.2±56.49
Median (minimum, maximum)	11.0 (-405, 95)	18.5 (-190, 234)
6MWD change from Baseline to Week 24[a], meters		
Mean ± standard deviation	-5.4±62.74	17.5±66.84
Median (minimum, maximum)	3.5 (-390, 100)	15.0 (-190, 276)
Treatment difference at Week 12 (combination - monotherapy)[b]		
Least squared mean	31.04	
95% confidence interval	(9.57, 52.51)	
p-Value	0.0049	

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Study B1321003: 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 study B1321001 (NCT00796666).
Baseline was defined as the last observation prior to initiation of the first dose of study drug on Day 1.
ITT = intent-to-treat; LOCF = last observation carried forward; 6MWD = 6-minute walk distance; N = number of subjects in the group; WHO = World Health Organization.

a. Missing values at Week 12 and Week 24 were imputed with the last nonmissing 6MWD based on the LOCF method.
b. The least squared mean and p-value are based on the analysis of covariance on change from Baseline with B1321003 treatment, B1321001 treatment, and B1321003 baseline WHO functional class as fixed effects and baseline 6MWD as a covariate.

World Health Organization Functional Class: All subjects had WHO functional Class III at Baseline except 23 subjects with WHO functional Class II and I subject with WHO functional Class IV. Overall, most subjects in both treatment groups showed no change in WHO functional class at Weeks 12 and 24 (Table 6).

The observed treatment effect at Week 12, applying CMH analysis and controlling for stratification variables, was not statistically significant (p=0.8223).

Table 6. WHO Functional Class Change From Baseline to Weeks 12 and 24 - ITT Population

Number (%) of Subjects	Monotherapy Sitaxsentan N=67	Combination Sitaxsentan N=64
Change from Baseline to Week 12[a]		
Improvement	14 (20.9%)	14 (21.9%)
No change	52 (77.6%)	49 (76.6%)
Deterioration	1 (1.5%)	1 (1.6%)
Change from Baseline to Week 24[a]		
Improvement	13 (19.4%)	16 (25.0%)
No change	53 (79.1%)	47 (73.4%)
Deterioration	1 (1.5%)	1 (1.6%)

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.
ITT = intent-to-treat; LOCF = last observation carried forward; N = number of subjects in each group; WHO = World Health Organization.

a. Missing values at Week 12 and Week 24 were imputed with the last nonmissing WHO functional class based on the LOCF method.

Change From Baseline to Weeks 12 and 24 in Short-Form 36 Health Survey: The change from Baseline (a positive score indicates improvement in health) to Weeks 12 and 24 in the SF-36 composite physical health and mental health scores for the ITT population is provided in Table 7.

Table 7. Change From Baseline to Weeks 12 and 24 in SF-36 - ITT Population

	Monotherapy Sitaxsentan	Combination Sitaxsentan
Composite Physical Health Score[a]		
Baseline		
N	66	62
Mean ± standard deviation	39.7±8.01	39.1±7.97
Median (minimum, maximum)	40.9 (21, 59)	39.8 (24,60)
Change from Baseline at Week 12[b]		
N	58	59
Mean ± standard deviation	-0.1±6.79	2.4±5.54
Median (minimum, maximum)	0.2 (-16, 15)	2.4 (-12, 12)
Change from Baseline at Week 24[b]		
N	62	61
Mean ± standard deviation	-0.1±6.49	3.1±6.34
Median (minimum, maximum)	-0.3 (-16, 15)	3.0 (-12, 16)
Treatment difference at Week 12 (combination - monotherapy)[c]		
Least squared mean	2.47	
95% confidence interval	(0.43, 4.51)	
p-Value	0.0179	
Composite Mental Health Score[a]		
Baseline		
N	66	62
Mean ± standard deviation	45.1±11.98	43.9±11.29
Median (minimum, maximum)	45.5 (12, 65)	43.9 (15, 65)
Change from Baseline at Week 12[b]		
N	58	59
Mean ± standard deviation	-0.4±8.67	1.6±9.36
Median (minimum, maximum)	-0.5 (-28, 16)	0.0 (-25, 34)
Change from Baseline at Week 24[b]		
N	62	61
Mean ± standard deviation	0.3±8.45	-0.6±10.16
Median (minimum, maximum)	-0.2 (-18, 25)	-1.8 (-30, 22)
Treatment difference at Week 12 (combination - monotherapy)[c]		
Least squared mean	1.53	
95% confidence interval	(-1.32, 4.37)	
p-Value	0.2897	

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Baseline was defined as the last observation prior to initiation of the first dose of study drug on Day 1.
ITT = intent to treat; N = number of subjects in the group; SF-36 = Short-Form 36.

a. The scores are summarized using norm-based calculations. Higher scores indicate better health. A score of 50±10 is the norm.
b. Missing values at Week 12 and Week 24 were imputed using the last observation carried forward method.
c. The least squared mean and p-value were based on the analysis of covariance on change from Baseline with B1321003 treatment, B1321001 treatment, and B1321003 baseline World Health Organization functional class as fixed effects and baseline composite score as a covariate.

Changes From Baseline in European Quality of Life-5 Dimension: Due to late inclusion of the EQ-5D in a global protocol amendment, as well as the early termination of the study, too few subject observations were collected to enable suitable analyses.

Safety Results:

Treatment-Emergent All-Causality and Treatment-Related Adverse Events (TEAEs): The all-causality and treatment-related TEAEs reported in subjects during the study are presented in Table 8.

Table 8. Treatment-Emergent Nonserious Adverse Events by System Organ Class and Preferred Term in >5% of Subjects in Any Treatment Group

Number (%) of Subjects With Adverse Events by:	Monotherapy Sitaxsentan			Combination Sitaxsentan		
System Organ Class MedDRA (v14.0) Preferred Term	n (%)	n1	n2	n (%)	n1	n2
Number (%) of subjects evaluable for adverse events	66			64		
Number (%) of subjects with adverse events	17 (25.8)			18 (28.1)		
General disorders and administration site conditions	6 (9.1)	7	0	5 (7.8)	8	0
Oedema peripheral	6 (9.1)	7	0	5 (7.8)	8	0
Infections and infestations	6 (9.1)	8	0	1 (1.6)	1	0
Upper respiratory tract infection	6 (9.1)	8	0	1 (1.6)	1	0
Investigations	1 (1.5)	1	0	4 (6.3)	4	2
Alanine aminotransferase increased	1 (1.5)	1	0	4 (6.3)	4	2
Musculoskeletal and connective tissue disorders	5 (7.6)	8	1	4 (6.3)	4	1
Myalgia	4 (6.1)	6	1	0	0	0
Pain in extremity	2 (3.0)	2	0	4 (6.3)	4	1
Nervous system disorders	8 (12.1)	8	1	8 (12.5)	9	5
Dizziness	6 (9.1)	6	0	1 (1.6)	1	0
Headache	2 (3.0)	2	1	7 (10.9)	8	5
Psychiatric disorders	0	0	0	4 (6.3)	4	1
Insomnia	0	0	0	4 (6.3)	4	1
Respiratory, thoracic and mediastinal disorders	9 (13.6)	11	1	9 (14.1)	14	0
Cough	4 (6.1)	4	1	3 (4.7)	3	0
Dyspnoea	4 (6.1)	4	0	1 (1.6)	1	0
Dyspnoea exertional	2 (3.0)	3	0	5 (7.8)	10	0

Includes data up to 9999 days after last dose of study drug.
Percentages of gender specific events are calculated using the corresponding gender count as denominator.
MedDRA (v14.0) coding dictionary applied.
MedDRA (v14.0) = Medical Dictionary for Regulatory Activities (version 14.0); 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 (optional) = the number of occurrences of treatment-emergent causally related to treatment adverse events; v = version.

All-Causality and Treatment-Related Serious Adverse Events (SAEs): The all-causality and treatment-related SAEs reported during the study are presented in Table 9.

Table 9. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

Number (%) of Subjects With Adverse Events by: System Organ Class MedDRA (v14.0) Preferred Term	Monotherapy Sitaxsentan n (%)	n1	n2	Combination Sitaxsentan n (%)	n1	n2
Number (%) of subjects evaluable for adverse events	66			64		
Number (%) of subjects with adverse events	14 (21.2)			15 (23.4)		
Blood and lymphatic system disorders	2 (3.0)	2	0	0	0	0
Anaemia	1 (1.5)	1	0	0	0	0
Haemorrhagic anaemia	1 (1.5)	1	0	0	0	0
Cardiac disorders	5 (7.6)	7	0	6 (9.4)	8	1
Atrial tachycardia	1 (1.5)	1	0	0	0	0
Bradycardia	1 (1.5)	1	0	0	0	0
Cardiac arrest	0	0	0	1 (1.6)	1	0
Cardiac asthma	0	0	0	1 (1.6)	1	0
Cardiac failure	0	0	0	1 (1.6)	1	0
Cardiac failure congestive	0	0	0	1 (1.6)	1	0
Cardio-respiratory arrest	0	0	0	1 (1.6)	1	1
Pericardial effusion	0	0	0	1 (1.6)	1	0
Right ventricular failure	3 (4.5)	4	0	1 (1.6)	1	0
Torsade de pointes	0	0	0	1 (1.6)	1	0
Ventricular fibrillation	1 (1.5)	1	0	0	0	0
Endocrine disorders	1 (1.5)	1	0	0	0	0
Adrenocortical insufficiency acute	1 (1.5)	1	0	0	0	0
Gastrointestinal disorders	1 (1.5)	1	0	1 (1.6)	1	0
Gastritis	0	0	0	1 (1.6)	1	0
Gastroduodenal ulcer	1 (1.5)	1	0	0	0	0
General disorders and administration site conditions	2 (3.0)	3	0	0	0	0
Chest pain	1 (1.5)	1	0	0	0	0
Oedema peripheral	1 (1.5)	1	0	0	0	0
Pyrexia	1 (1.5)	1	0	0	0	0
Hepatobiliary disorders	2 (3.0)	3	2	2 (3.1)	2	2
Acute hepatic failure	1 (1.5)	1	1	0	0	0
Hepatic function abnormal	2 (3.0)	2	1	1 (1.6)	1	1
Liver disorder	0	0	0	1 (1.6)	1	1
Immune system disorders	1 (1.5)	1	0	0	0	0
Hypersensitivity	1 (1.5)	1	0	0	0	0
Infections and infestations	4 (6.1)	4	0	4 (6.3)	5	0
Lower respiratory tract infection	1 (1.5)	1	0	1 (1.6)	1	0
Malaria	0	0	0	1 (1.6)	1	0
Pneumonia	0	0	0	1 (1.6)	1	0
Postoperative abscess	1 (1.5)	1	0	0	0	0
Sepsis	0	0	0	1 (1.6)	1	0
Septic shock	0	0	0	1 (1.6)	1	0
Upper respiratory tract infection	1 (1.5)	1	0	0	0	0
Viral infection	1 (1.5)	1	0	0	0	0
Injury, poisoning and procedural complications	1 (1.5)	1	0	1 (1.6)	1	0
Drug exposure during pregnancy	0	0	0	1 (1.6)	1	0
Incision site haematoma	1 (1.5)	1	0	0	0	0
Investigations	4 (6.1)	4	3	3 (4.7)	3	3
Hepatic enzyme increased	1 (1.5)	1	0	0	0	0
Liver function test abnormal	3 (4.5)	3	3	3 (4.7)	3	3
Musculoskeletal and connective tissue disorders	1 (1.5)	1	0	0	0	0
Systemic sclerosis	1 (1.5)	1	0	0	0	0
Nervous system disorders	2 (3.0)	2	1	1 (1.6)	2	0
Dizziness	1 (1.5)	1	0	0	0	0
Hepatic encephalopathy	1 (1.5)	1	1	0	0	0
Syncope	0	0	0	1 (1.6)	2	0
Psychiatric disorders	1 (1.5)	1	0	0	0	0
Insomnia	1 (1.5)	1	0	0	0	0

Table 9. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

Number (%) of Subjects With Adverse Events by: System Organ Class MedDRA (v14.0) Preferred Term	Monotherapy Sitaxsentan			Combination Sitaxsentan		
	n (%)	n1	n2	n (%)	n1	n2
Renal and urinary disorders	0	0	0	1 (1.6)	1	0
Renal colic	0	0	0	1 (1.6)	1	0
Respiratory, thoracic and mediastinal disorders	4 (6.1)	5	0	3 (4.7)	4	0
Acute respiratory failure	0	0	0	1 (1.6)	1	0
Dyspnoea	1 (1.5)	2	0	1 (1.6)	1	0
Haemoptysis	0	0	0	1 (1.6)	1	0
Pleural effusion	0	0	0	1 (1.6)	1	0
Pulmonary arterial hypertension	2 (3.0)	2	0	0	0	0
Pulmonary hypertension	1 (1.5)	1	0	0	0	0

Except for 'n1' and 'n2' subjects are only counted once per treatment for each row.
Includes data up to 9999 days after last dose of study drug.
Percentages of gender specific events are calculated using the corresponding gender count as denominator.
MedDRA (v14.0) coding dictionary applied.
MedDRA (v14.0) = Medical Dictionary for Regulatory Activities (version 14.0); 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; v = version.

Permanent Discontinuations due to Adverse Events: A summary of permanent discontinuations due to AEs is provided in Table 10.

Table 10. Permanent Discontinuations due to Adverse Events, Safety Population

Serial Number	Gender/Age[a] (Years)	MedDRA Preferred Term	Start/Stop Day[b]	Severity	Outcome	Causality
Monotherapy						
1	F/29	Pulmonary arterial hypertension[c]	185/>185[d]	Severe	Still present	Unrelated
2	M/54	Liver function test abnormal	65/121	Moderate	Resolved	Related
3	F/49	Liver function test abnormal	33/>56[d]	Severe	Still present	Related
4	F/29	Liver function test abnormal	223/>251[d]	Moderate	Still present	Related
5	F/52	Hepatic function abnormal	230/235	Severe	Resolved	Unrelated
6	F/16	Hepatic encephalopathy	104/>112[d]	Severe	Still present	Related
7	F/35	Adrenocortical insufficiency acute	84/>97[d]	Severe	Still present	Unrelated
8[e]	M/46	Pulmonary arterial hypertension[c]	356/>357[d]	Severe	Still present	Unrelated
9[e]	F/50	Ventricular fibrillation	328/>328[d]	Severe	Still present	Unrelated
Combination						
10[e]	M/20	Haemoptysis	67/>119[d]	Severe	Still present	Unrelated
11	F/31	Liver disorder	114/174	Severe	Resolved	Related
12	F/28	Drug exposure during pregnancy	3/>7[d]	Severe	Still present	Unrelated
13	F/58	Hepatic function abnormal	61/>85[d]	Severe	Still present	Related
14	M/46	Liver function test abnormal	197/>220[d]	Moderate	Still present	Related
15[e]	F/31	Acute respiratory failure	467/>467[d]	Severe	Still present	Unrelated
16[e]	F/37	Cardiac asthma	406/>409[d]	Severe	Still present	Unrelated
17	F/36	Liver function test abnormal	94/>121[d]	Moderate	Still present	Related
18[e]	M/25	Cardio-respiratory arrest	339/>339[d]	Severe	Still present	Related

MedDRA (version 14.0) coding dictionary applied.
CRF = case report form; F = female; M = male; MedDRA = Medical Dictionary for Regulatory Activities.
a. Age at date of screening.
b. Day relative to start of study treatment. First day of study treatment = Day 1.
c. Worsening of underlying condition.
d. Imputed from incomplete dates and times.
e. For these subjects, discontinuation due to adverse events was marked on the CRF adverse event page, whereas death was marked on the subject summary page.

Dose Reductions or Temporary Discontinuations due to Adverse Events: Two (3.0%) subjects in the monotherapy group and 5 (7.8%) subjects in the combination group had dose reductions or temporary discontinuations of the study medication due to AEs. In the monotherapy group, these AEs were alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased and hypersensitivity. In the combination group, the AEs that led to dose reductions or temporary discontinuations were decreased BP; gastritis; congestive cardiac failure, lower respiratory tract infection, and septic shock; ALT increased; and liver function test abnormal.

Death: A summary of deaths is presented in Table 11.

Table 11. Summary of Deaths, Safety Population

Serial Number	Gender/Age[a] (Years)	Day of Death[b]	Event With Fatal Outcome	Cause of Death	Causality[c]
Monotherapy					
1	F/30	266	Cardio-respiratory arrest	Cardiorespiratory arrest following severe PAH with right sided failure	Related/unrelated
2	M/47	357	Pulmonary arterial hypertension[d]	Disease progression of pulmonary hypertension	Unrelated
3	F/51	328	Ventricular fibrillation	Ventricular fibrillation	Unrelated
4	F/16	123	Acute hepatic failure Hepatic encephalopathy	Acute liver cell failure with hepatic encephalopathy	Related Related
Combination					
5	F/32	467	Acute respiratory failure	Acute respiratory failure	Unrelated
6	M/20	119	Haemoptysis	Hemoptysis	Unrelated
7	F/38	409	Cardiac asthma	Cardiac asthma	Unrelated
8	M/26	339	Cardio-respiratory arrest	Acute cardiorespiratory arrest	Related

MedDRA (version 14.0) coding dictionary applied.
F = female; M = male; MedDRA = Medical Dictionary for Regulatory Activities; PAH = pulmonary arterial hypertension.
a. Age at date of serious adverse event 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).
d. Worsening of underlying condition.

Laboratory Results, Physical Examination, and Vital Signs: A total of 11 subjects experienced elevations in AST and /or ALT, 5 of whom experienced concurrent elevations in bilirubin (4 subjects with elevations in total bilirubin and 1 direct bilirubin). A greater proportion of subjects experienced significant elevations (>8 × upper limit of normal [ULN]) in AST and/or ALT in the monotherapy group (6%), with a higher number of subjects experiencing elevations >3 × and ≤5 × ULN in AST and/or ALT in the combination group (9%).

Elevated International Normalized Ratio (INR) values occurred marginally more often in subjects in the monotherapy group compared with subjects in the combination group. Most often, the elevated INR values were >3.5 and ≤5; an elevated INR value of >9 was observed in subjects in the monotherapy group only.

A higher proportion of subjects in the combination group compared with subjects in the monotherapy group experienced a hemoglobin decrease from Baseline of at least 1 g/dL (45 versus 29 subjects, respectively). A small proportion of subjects in the combination and monotherapy groups (8 and 5 subjects, respectively) experienced a decrease >15% with resultant values below the LLN.

At the final visit, 9 (13.6%) subjects in the monotherapy group and 1 (1.6%) subject in the combination group reported significant changes in physical examination findings. The absolute mean and median values for vital signs (weight, temperature, respiration rate, BP, and heart rate) were comparable in both groups at all visits. The mean changes for vital signs were generally small and were similar between the treatment groups.

CONCLUSIONS:

- The treatment groups were well balanced with regard to all predefined baseline characteristics

- Due to early termination of the study and the resulting low number of CWEs, the study failed to show a difference between treatment groups in the primary endpoint of TTCW

- The reported mean change in 6MWD was approximately 31 meters in favor of combination treatment (p=0.0049) at Week 12. A mean deterioration of approximately 9 meters was observed in the monotherapy group

- Change in 6MWD at Week 12 was found to have significantly improved in the combination treatment arm compared to monotherapy for the following groups: subjects with WHO functional Class III score and 6MWD 150 to 450 meters, subjects recorded as idiopathic PAH, and subjects who received placebo treatment in previous sitaxsentan study

- The median change from Baseline in 6MWD for the monotherapy group showed an improvement of 11.0 meters and 3.5 meters at Weeks 12 and 24, respectively, and in combination therapy improvements of 18.5 meters and 15.0 meters at Weeks 12 and 24, respectively

- The number of subjects with an improvement in their WHO functional class was comparable between the treatment groups

- Combination therapy appeared comparable in tolerability to monotherapy as evidenced through type and incidence in AEs (nonserious and serious), events resulting in discontinuation, and events with fatal outcome

- Overall, the safety profile was generally comparable to that observed in prior sitaxsentan studies conducted in subjects with pulmonary hypertension. However, the overall incidence rate observed for increases in liver transaminases and SAEs attributed to liver function abnormalities in this study was marginally higher than previously reported in studies with an equivalent dose level of sitaxsentan. Moreover, a higher incidence of

subjects meeting the biochemical criteria for potential Hy's Law was observed in this study compared to previous studies with sitaxsentan

- Moreover, it is noteworthy that 1 subject who received monotherapy experienced liver cell failure with hepatic encephalopathy that resulted in death approximately 4 months following treatment in the study. Postmortem liver biopsy demonstrated severe necrotizing hepatitis, possibly drug induced