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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Revatio® / Sildenafil Citrate

PROTOCOL NO.: A1481156

PROTOCOL TITLE: A Multicenter, Long-Term Extension Study to Assess Safety of Oral Sildenafil in the Treatment of Subjects Who Have Completed Study A1481131

Study Centers: A total of 31 centers took part in the study and randomized subjects; 1 each in Brazil, Chile, Guatemala, Italy, Japan, Malaysia, Mexico, Sweden, and the Russian Federation, 3 centers each in Colombia, Poland, and Taiwan, 2 centers each in Hungary and India, and 9 centers in the United States.

Study Initiation and Final Completion Dates: 13 January 2004 to 24 December 2012

Phase of Development: Phase 3

Study Objectives:

Primary Objective: The primary objective was to assess the safety and tolerability of oral sildenafil in the chronic treatment of pediatric subjects with pulmonary arterial hypertension (PAH).

Secondary Objective: The secondary objective was to describe long-term (≥1 year) efficacy of oral sildenafil in these subjects.

METHODS

Study Design: This was a multicenter, open-label, long-term extension study for subjects who had completed the initial short-term, double-blind study in pediatric PAH: (A Randomized, Double-Blind, Placebo Controlled, Dose Ranging, Parallel Group Study of Oral Sildenafil in the Treatment of Children, aged 1-17 Years, With Pulmonary Arterial Hypertension [NCT00159913]). The extension study was conducted to evaluate long-term safety and tolerability of sildenafil in the chronic treatment of pediatric subjects with PAH.

Subjects remained in the dose group they were randomly assigned to in the initial double-blind study with the exception of subjects randomly assigned to the placebo group. The subjects in the placebo group were randomly assigned (stratified by weight) in a double-blind fashion to 1 of the 3 active study treatment dose groups used in the initial double-blind study. Subjects in the low weight category were randomly assigned to medium or high dose only, in the ratio 1:2. Subjects in the other weight category were randomly assigned to the low, medium or high sildenafil dose, in the ratio 1:1:1. As with initial

double-blind study, any subjects randomly assigned into the medium and high dose groups had a titration from the low dose (10 mg three times a day dosing [TID]) to their randomly assigned dose. Subjects in the initial study remained on double-blind treatment in the extension study until the last subject had completed the initial study and the database was locked. After the lock occurred, all subjects switched to open-label treatment with their existing dose and were further titrated as indicated by the protocol and its amendments.

The schedule of events is presented in Table 1.

Table 1. Schedule of Events

Study Visit	T1[a] Baseline	P1 Phone Contact Day 7	T2	T3	T4[b]	T5	Repeat Visits[c,d]	Unsched. Visits[d]	Follow-Up[d,e]	Survival Status[f]	End of Study
Week	**1**	**1**	**12**	**24**	**36**	**48**					
Day	**1**	**7**	**84±4**	**168±4**	**252±4**	**336±4**					
Obtain informed consent[g]	X								X	X	
Medical history	X										
Physical exam	X				X						
Study medication (included return of unused medication)[h]	X[i]		X	X	X	X	X	X (if dose adjusted)	X		
Vital signs	X		X	X	X	X	X	X	X		
Weight	X		X	X	X	X	X				
Height and head circumference	X[j]				X[j]						
Urine pregnancy test[k]	X		X	X	X	X	X				
Clinical labs[l]–complete set	X[l]		X		X		X				
Ocular measures	X				X		X (annual)[m]	If ocular AE			
Adverse events	X	X	X	X	X	X	X	X	X		
Survival status[n]										X	X
CPX (bicycle ergometer)[o]	X				X			X[o]			
QoL questionnaire[p]	X		X		X						
Pediatric development questionnaire	X				X						
WHO PH functional class	X		X	X	X	X	X				
Parent/physician global assessment	X		X	X	X						
Digoxin level[q]	X				X						
Concomitant medication	X		X	X	X	X	X	X	X		

AE = adverse event; CPX = cardiopulmonary exercise test; CRF = Case Report Form; P1 = phone contact at Day 7, Week 1; PAH = pulmonary arterial hypertension; QoL = quality of life; T1 = treatment at Week 1; T2 = treatment at Week 12; T3 = treatment at Week 24; T4 = treatment at Week 36; T5 = treatment at Week 48; Unsched = unscheduled; WHO PH = World Health Organization pulmonary hypertension.

a. Week 16 visit in initial double-blind study.
b. Week 52 from initial double-blind study baseline visit T1 Day 364±4.
c. Every 12 weeks.
d. Until registration of sildenafil in this indication in children, oral sildenafil was proven ineffective or unsafe in the treatment of PAH, or the sponsor decided to discontinue development for PAH or the study was terminated.
e. Occurred 30-40 days after study completion or treatment discontinuation.
f. Every 3 months ±2 weeks.
g. Informed consent obtained from parents or guardians of subjects to be monitored for survival status every 3 months after discontinuation of the study drug. Parents or legal

Table 1. Schedule of Events

guardians of subjects who had already discontinued from the study were contacted by the investigator and asked to consent for this survival status follow-up also.

h. As soon as possible, following locking of the database for initial double-blind study, the subjects received unblinded study medication. This was dispensed at the next scheduled visit.

i. In initial double-blind study placebo subjects were randomized to 1 of the active treatment doses on enrollment. Titration from low dose occurred for the medium and high dose groups at Week 1, other dose groups underwent a dummy titration to maintain blind. Phone contact was made to assess occurrence of AEs.

j. Head circumference (subjects ≤3 years).

k. Pregnancy test for menarchial female subjects.

l. Complete set of clinical labs included hematology, urinalysis, and a complete chemistry. After Week 36, repeated every 24 weeks.

m. Annual ocular tests from treatment Week 36, performed at the appropriate 12-week visit.

n. Assessed every 3 months after study drug discontinuation and at the end of study. The investigator contacted the subject to enquire if they had undergone heart and/or lung transplantation, whether they were alive or deceased. The date and cause of death were recorded. If unknown then the last known date the subject was known to be alive was recorded. Details were recorded in the CRF and medical records. End of study was defined as the time of registration of sildenafil for pediatric PAH, oral sildenafil was proven ineffective or unsafe in the treatment of PAH, or the sponsor decided to discontinue development for PAH or the study was terminated.

o. Subjects developmentally able to perform exercise paradigm. Subjects who chose to withdraw from study treatment after at least 10 weeks and before the Week 36 visit were also required to perform the CPX. Performed at trough plasma sildenafil levels.

p. QoL CHQ-PF28 for subjects ≥5 years old.

q. Digoxin therapy subjects only.

Number of Subjects (Planned and Analyzed): A formal sample size calculation was not conducted since this study enrolled subjects who completed the initial study. Of the 234 subjects treated in initial study, 220 subjects were enrolled in this extension study (33 in the United States and Colombia, 32 in Poland, 12 in the Russian Federation, 21 in Hungary, 14 in Mexico, 24 in India and Guatemala, 8 in Malaysia, 3 in Sweden, 2 in Italy and Chile, 6 in Brazil, 5 in Taiwan, and 1 in Japan) and 110 subjects completed the study.

Diagnosis and Main Criteria for Inclusion: Male and female subjects, between 1 and 17 years of age, with primary pulmonary hypertension or PAH associated with congenital heart disease or collagen vascular disease, who completed the 16-week initial study were eligible for this extension study.

Excluded were subjects with known hereditary degenerative retinal disorders (such as retinitis pigmentosa) or history of non-arteritic anterior ischemic optic neuropathy.

Study Treatment: Double-blind and then open-label oral sildenafil was administered at the low, medium, and high dose level, 3 times daily (TID; ≥6 hours apart), to pediatric subjects as described in Table 2.

Subjects on sildenafil in the initial study continued to receive the same sildenafil dose (low, medium, or high) as was administered in the initial study. Subjects receiving placebo in the initial study, were randomized to sildenafil at the Baseline Visit of the extension study as follows:

- Subjects in the >20–45 kg and >45 kg weight strata were randomized (1:1:1 ratio; Table 2) to 1 of 3 sildenafil dose-groups: low, medium, or high dose sildenafil TID.
- Subjects in the ≥8–20 kg weight stratum were randomized (1:2 ratio; Table 2) to medium or high dose sildenafil TID.

Table 2. Sildenafil Doses by Body Weight

Body Weight (kg)[a]	Low Dose	Medium Dose	High Dose
≥8-20	Not applicable	10 mg	20 mg
>20-45	10 mg	20 mg	40 mg
>45	10 mg	40 mg	80 mg

a. Weight at the Baseline of initial study for subjects randomized to sildenafil groups; and for placebo subjects in initial study: weight in initial study prior to entry in extension study.

Safety Endpoints:

- Standard safety evaluations;
- Ocular safety measures: Change from extension study Baseline in ocular safety tests;
- Need for down-titration in dose due to intolerability;

- Need for discontinuation due to intolerability; and
- Growth and development.

Safety Evaluations: The following standard safety evaluations were performed:

- Adverse events (AEs) were recorded throughout the study.
- Laboratory tests were performed at initial study Baseline, Weeks 4 and 8 in initial study, extension study baseline (Week 16 in initial study), and extension study Weeks 12, 36, and every 24 weeks after Week 36 of extension study (Week 52).
- Parents or legal guardians of subjects who permanently discontinued study drug in this study were asked for their consent for their children to be followed up every 3 months for the evaluation of survival status.
- For all subjects, development status was assessed at initial study baseline, extension study Baseline (Week 16 in initial study) and Week 36 of extension study (Week 52) using the physician assessment questions.
- A physical examination was performed at initial study Baseline, extension study baseline (Week 16 in initial study) and Week 36 (Week 52 in initial study).

Additional safety evaluations included:

- Blood pressure and heart rate measurements (sitting/resting) were recorded at all visits (or follow-up if withdrawn earlier).
- Ocular tests were performed to determine the general health of the eye at initial study Baseline, extension study baseline (Week 16 in initial study) and after 1 year of treatment since initiation of initial study (corresponding to Week 36 in extension study) or in the event of an ocular AE. Subjects who withdrew from the study prior to the Week 36 of extension study (Week 52) visit were to have 1 annual ocular follow-up test at the time the Week 36 of extension study (Week 52) test would have occurred. In addition, as part of the assessment of treatment on development, ocular tests were performed annually from the Week 36 of extension study (Week 52) visit until completion of the study.

Statistical Methods: Analysis Populations:

Intent-to-Treat Population: The ITT population included all subjects who had taken at least 1 dose of study medication in initial study.

Safety Population: The safety population consisted of all subjects who had taken at least 1 dose of study medication in initial study.

Laboratory Population: Subjects in the laboratory population consisted of all subjects who had taken at least 1 dose of study medication in initial study, and who had at least 1 post-baseline, on-treatment laboratory data assessment.

The safety population was used in the analysis of safety. A separate laboratory population subset was used for all laboratory analyses.

Survival rates at 1, 2, 3, or more years were calculated using Kaplan-Meier estimates for different subject groupings.

A stratified Cox-proportional hazards model was fitted to test for a difference in survival between treatment groups in the extension study. The model was stratified by weight category (≤20 kg and >20 kg).

No statistical significance testing was performed on any of the safety assessments. Additional displays especially suited to the reporting of AEs in the context of a long-term extension study were produced. Safety data were summarized by treatment group in the extension study or by initial/extension study treatment sequence.

RESULTS

Subject Disposition and Demography: A total of 324 subjects were screened for the initial study, of which 235 subjects were assigned to study treatment and 234 subjects were treated (Table 3). One subject was randomized (to sildenafil medium dose) but not treated. Of the 234 subjects treated in the initial study, 220 subjects entered the extension study, as 6 subjects discontinued treatment during the initial study, and 8 subjects did not consent to enter the extension study.

Table 3. Subject Evaluation Groups by Initial study/Extension Study Treatment Sequence

Number (%) of Subjects	Sildenafil Low/ Low Dose	Sildenafil Medium/ Medium Dose	Sildenafil High/ High Dose	Placebo/ Low Dose	Placebo/ Medium Dose	Placebo/ High Dose	Placebo Non-Rand.
Screened 324							
Assigned to Study treatment	42	55	77	13	19	23	5
Treated	42	55[a]	77	13	19	23	5
Completed	22 (52.4)	25 (45.5)	34 (44.2)	7 (53.8)	11 (57.9)	11 (47.8)	0
Discontinued	20 (47.6)	30 (54.5)	43 (55.8)	6 (46.2)	8 (42.1)	12 (52.2)	5 (100)
Adverse event	2 (4.8)	2 (3.6)	5 (6.5)	1 (7.7)	1 (5.3)	2 (8.7)	0
Does not meet entrance criteria	1 (2.4)	0	1 (1.3)	0	0	0	0
Insufficient clinical response	2 (4.8)	0	1 (1.3)	1 (7.7)	0	3 (13.0)	0
Lost to follow-up	1 (2.4)	0	3 (3.9)	0	1 (5.3)	2 (8.7)	1 (20.0)
Other	8 (19.0)	8 (14.5)	8 (10.4)	0	2 (10.5)	1 (4.3)	3 (60.0)
Protocol violation	0	5 (9.1)	2 (2.6)	0	0	0	0
Subject died	3 (7.1)	8 (14.5)	15 (19.5)	0	1 (5.3)	2 (8.7)	0
Subject no longer willing to participate in study	2 (4.8)	6 (10.9)	8 (10.4)	4 (30.8)	3 (15.8)	2 (8.7)	1 (20.0)
Withdrawn due to pregnancy	1 (2.4)	1 (1.8)	0	0	0	0	0
Did not enter current study	2 (4.8)	2 (3.6)	1 (1.3)	0	0	0	3 (60.0)
Analyzed for efficacy							
ITT[b]	42 (100)	55 (100)	77 (100)	13 (100)	19 (100)	23 (100)	5 (100)
Age ≥5 years	42 (100)	46 (83.6)	58 (75.3)	12 (92.3)	16 (84.2)	21 (91.3)	4 (80.0)
Developmentally able	28 (66.7)	28 (50.9)	29 (37.7)	10 (76.9)	8 (42.1)	11 (47.8)	1 (20.0)
CHQ-PF28[c]	37 (88.1)	34 (61.8)	48 (62.3)	12 (92.3)	14 (73.7)	17 (73.9)	3 (60.0)
Year 1	42 (100)	55 (100)	77 (100)	13 (100)	19 (100)	23 (100)	5 (100)
Year 2	42 (100)	55 (100)	77 (100)	13 (100)	19 (100)	23 (100)	5 (100)
Year 3	42 (100)	55 (100)	77 (100)	13 (100)	19 (100)	23 (100)	5 (100)
Year 4	42 (100)	55 (100)	77 (100)	13 (100)	19 (100)	23 (100)	5 (100)
Year 5	42 (100)	55 (100)	77 (100)	13 (100)	19 (100)	23 (100)	5 (100)
Analyzed for safety							
Safety	42 (100)	55 (100)	77 (100)	13 (100)	19 (100)	23 (100)	5 (100)
Adverse events	41 (97.6)	55 (100)	73 (94.8)	13 (100)	19 (100)	22 (95.7)	3 (60.0)
Laboratory data	42 (100)	55 (100)	76 (98.7)	13 (100)	19 (100)	23 (100)	5 (100)

Initial study: NCT00159913.
CHQ = Child Health Questionnaire; CHQ-PF28 = Child Health Questionnaire Parent Report; ITT = Intent-to-Treat; non-rand = non-randomized.
a. One subject was randomly assigned but not treated.
b. Subjects randomly assigned to treatment and received at least 1 dose of study medication.
c. Subjects who fulfilled the criteria for ITT, were ≥5 years old and had all CHQ-PF28 assessments in their first language.

A total 229 subjects received sildenafil in initial and extension study. Demographic characteristics are summarized by treatment group in the extension study in Table 4. Overall, 87/229 subjects (38.0%) were male and 142/229 subjects (62.0%) were female.

Table 4. Demographic Characteristics by Extension Study Treatment Group - ITT Population

	Sildenafil Dose Groups (N=229[a])		
	Low (N=55)	**Medium (N=74)**	**High (N=100)**
Age (years), n			
Mean (SD)	11.2 (3.2)	9.7 (4.5)	8.7 (4.5)
Min, max	4, 17	2, 17	1, 17
Sex, n (%)			
Male	21 (38.2)	32 (43.2)	34 (34)
Female	34 (61.8)	42 (56.8)	66 (66)
Race, n (%)			
Caucasian	23 (41.8)	33 (44.6)	40 (40.0)
Black	1 (1.8)	3 (4.1)	1 (1.0)
Asian	6 (10.9)	14 (18.9)	20 (20.0)
Other	25 (45.5)	24 (32.4)	39 (39.0)
Weight (kg), n (%)			
Mean (SD)	36.9 (16.7)	31.5 (16.4)	26.3 (14.2)
Min, max	19.5, 105.0	8.6, 106.0	8.2, 61.0
Height (cm)			
Mean (SD)	139.6 (15.8)	129.6 (24.1)	122.6 (26.3)
Min, max	110.0, 172.0	77.0, 192.5	72.0, 180.0
Body mass index (kg/m^2)			
Mean (SD)	18.1 (4.6)	17.6 (4.0)	16.2 (3.2)
Min, max	11.7, 36.8	11.8, 29.5	10.6, 30.0
Region, n (%)			
America[b]	16 (29.1)	16 (21.6)	20 (20.0)
Asia	6 (10.9)	14 (18.9)	20 (20.0)
Europe	20 (36.4)	23 (31.1)	29 (29.0)
South America	13 (23.6)	21 (28.4)	31 (31.0)

Initial study: NCT00159913.
BMI = body mass index; CRF = Case Report Form; N = number of subjects; n = number of subjects in specified category; SD = standard deviation.
BMI is calculated as $weight/(height/100)^2$.
Subjects weight, height and BMI were taken from demographic CRF for initial study.
a. 229 subjects received sildenafil in initial and extension study; only 220 subjects were treated in extension study.
b. America = United States America, Canada and Mexico.

Safety Results:

All Causality Adverse Events: All causality AEs experienced by ≥5% of subjects in any treatment group by preferred term are summarized in Table 5. The most commonly reported all causality AEs preferred terms in those subjects who received sildenafil (excluding data from the placebo non-randomized group) were upper respiratory tract infection, headache, and vomiting.

Table 5. Treatment Emergent Non-Serious Adverse Events in ≥5% of Subjects in Any Treatment Group in the Extension Study

Number (%) of Subjects With Adverse Events by: System Organ Class Preferred Term	Sildenafil Low Dose n (%)	Sildenafil Medium Dose n (%)	Sildenafil High Dose n (%)
Number (%) of subjects:			
Evaluable for adverse events	55 (100.0)	74 (100.0)	100 (100.0)
With treatment emergent non serious adverse events	51 (92.7)	70 (94.6)	87 (87.0)
Discontinued due to adverse events[a]	1 (1.8)	0	2 (2.0)
Endocrine disorders	0	4 (5.4)	0
Hypothyroidism	0	4 (5.4)	0
Eye disorders	8 (14.5)	19 (25.7)	27 (27.0)
Conjunctival hyperaemia	3 (5.5)	5 (6.8)	6 (6.0)
Conjunctivitis	1 (1.8)	3 (4.1)	9 (9.0)
Conjunctivitis allergic	0	4 (5.4)	3 (3.0)
Retinal vascular disorder	1 (1.8)	4 (5.4)	6 (6.0)
Visual acuity reduced	2 (3.6)	4 (5.4)	5 (5.0)
Visual impairment	3 (5.5)	1 (1.4)	2 (2.0)
Gastrointestinal disorders	27 (49.1)	38 (51.4)	46 (46.0)
Abdominal pain	4 (7.3)	4 (5.4)	13 (13.0)
Abdominal pain upper	3 (5.5)	5 (6.8)	9 (9.0)
Dental caries	6 (10.9)	3 (4.1)	2 (2.0)
Diarrhoea	10 (18.2)	11 (14.9)	16 (16.0)
Dyspepsia	3 (5.5)	6 (8.1)	5 (5.0)
Gastritis	2 (3.6)	4 (5.4)	5 (5.0)
Nausea	2 (3.6)	5 (6.8)	12 (12.0)
Vomiting	14 (25.5)	13 (17.6)	24 (24.0)
General disorders and administration site conditions	15 (27.3)	26 (35.1)	27 (27.0)
Chest pain	5 (9.1)	4 (5.4)	12 (12.0)
Fatigue	4 (7.3)	8 (10.8)	7 (7.0)
Pyrexia	7 (12.7)	16 (21.6)	16 (16.0)
Infections and infestations	39 (70.9)	55 (74.3)	71 (71.0)
Bronchitis	10 (18.2)	16 (21.6)	16 (16.0)
Bronchopneumonia	0	4 (5.4)	2 (2.0)
Ear infection	3 (5.5)	8 (10.8)	4 (4.0)
Gastroenteritis	4 (7.3)	3 (4.1)	7 (7.0)
Influenza	10 (18.2)	6 (8.1)	12 (12.0)
Laryngitis	5 (9.1)	1 (1.4)	4 (4.0)
Nasopharyngitis	15 (27.3)	11 (14.9)	17 (17.0)
Otitis media	2 (3.6)	4 (5.4)	4 (4.0)
Pharyngitis	16 (29.1)	13 (17.6)	13 (13.0)
Pharyngitis streptococcal	3 (5.5)	3 (4.1)	2 (2.0)
Pneumonia	2 (3.6)	4 (5.4)	0
Respiratory tract infection	2 (3.6)	4 (5.4)	5 (5.0)
Rhinitis	6 (10.9)	10 (13.5)	7 (7.0)
Sinusitis	2 (3.6)	3 (4.1)	8 (8.0)
Tonsillitis	9 (16.4)	6 (8.1)	13 (13.0)
Upper respiratory tract infection	9 (16.4)	22 (29.7)	37 (37.0)
Urinary tract infection	3 (5.5)	2 (2.7)	6 (6.0)
Varicella	3 (5.5)	3 (4.1)	4 (4.0)
Investigations	6 (10.9)	5 (6.8)	7 (7.0)
Blood pressure diastolic decreased	3 (5.5)	3 (4.1)	4 (4.0)
Weight decreased	3 (5.5)	2 (2.7)	3 (3.0)
Metabolism and nutrition disorders	2 (3.6)	2 (2.7)	5 (5.0)
Decreased appetite	2 (3.6)	2 (2.7)	5 (5.0)
Musculoskeletal and connective tissue disorders	5 (9.1)	3 (4.1)	3 (3.0)
Back pain	3 (5.5)	0	1 (1.0)
Pain in extremity	5 (9.1)	3 (4.1)	2 (2.0)

Table 5. Treatment Emergent Non-Serious Adverse Events in ≥5% of Subjects in Any Treatment Group in the Extension Study

Number (%) of Subjects With Adverse Events by: System Organ Class Preferred Term	Sildenafil Low Dose n (%)	Sildenafil Medium Dose n (%)	Sildenafil High Dose n (%)
Nervous system disorders	25 (45.5)	20 (27.0)	30 (30.0)
Dizziness	7 (12.7)	4 (5.4)	10 (10.0)
Headache	18 (32.7)	18 (24.3)	26 (26.0)
Syncope	5 (9.1)	7 (9.5)	5 (5.0)
Psychiatric disorders	3 (5.5)	0	1 (1.0)
Insomnia	3 (5.5)	0	1 (1.0)
Respiratory, thoracic and mediastinal disorders	25 (45.5)	35 (47.3)	39 (39.0)
Cough	11 (20.0)	14 (18.9)	17 (17.0)
Dyspnoea	4 (7.3)	6 (8.1)	6 (6.0)
Epistaxis	6 (10.9)	12 (16.2)	9 (9.0)
Haemoptysis	3 (5.5)	4 (5.4)	2 (2.0)
Oropharyngeal pain	3 (5.5)	5 (6.8)	5 (5.0)
Pulmonary arterial hypertension	4 (7.3)	4 (5.4)	9 (9.0)
Pulmonary hypertension	2 (3.6)	4 (5.4)	3 (3.0)
Rhinitis allergic	4 (7.3)	1 (1.4)	2 (2.0)
Rhinorrhoea	0	5 (6.8)	2 (2.0)
Skin and subcutaneous tissue disorders	3 (5.5)	1 (1.4)	3 (3.0)
Rash	3 (5.5)	1 (1.4)	3 (3.0)

Subjects are only counted once per treatment for each row.
MedDRA (v15.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of evaluable subjects; v = version.
a. Subjects that permanently discontinued study medication.

Treatment Related Adverse Events: Treatment related AEs by initial study/extension study treatment sequence and preferred term reported in more than 5% of subjects are presented in Table 6.

The most commonly reported treatment-related AE preferred terms in those subjects who received sildenafil (excluding data from the placebo non-randomized group) were headache and vomiting. There did not appear to be any relationship between sildenafil dose and the incidence of these treatment-related AEs.

Table 6. Treatment-Related Adverse Events (in ≥5% of Subjects in any Initial Study/Extension Study Treatment Sequence) by Preferred Term: Safety Population

System Organ Class Preferred Term	Number (%) of Subjects						
	Sildenafil Low/Low Dose (N=42)	Sildenafil Medium/ Medium Dose (N=55)	Sildenafil High/High Dose (N=77)	Placebo/ Low Dose (N=13)	Placebo/ Medium Dose (N=19)	Placebo/High Dose (N=23)	Placebo Non-Rand (N=5)
Cardiac disorders	0	1 (2)	3 (4)	0	1 (5)	0	0
Tachycardia	0	0	0	0	1 (5)	0	0
Ear and labyrinth disorders	1 (2)	1 (2)	4 (5)	0	1 (5)	0	0
Hypocausis	0	0	0	0	1 (5)	0	0
Eye disorders	8 (19)	6 (11)	10 (13)	1 (8)	4 (21)	5 (22)	1 (20)
Conjuctival hyperaemia	1 (2)	2 (4)	2 (3)	1 (8)	1 (5)	3 (13)	0
Ocular hyperaemia	2 (5)	0	0	0	0	0	1 (20)
Retinal vascular disorder	0	2 (4)	4 (5)	0	2 (11)	1 (4)	0
Vision blurred	0	1 (2)	0	0	1 (5)	0	0
Gastrointestinal disorder	6 (14)	7 (13)	19 (25)	4 (31)	2 (11)	3 (13)	1 (20)
Abdominal pain	0	1 (2)	6 (8)	2 (15)	0	1 (4)	0
Abdominal pain upper	0	0	4 (5)	1 (8)	0	0	0
Diarrhoea	0	0	2 (3)	1 (8)	0	0	0
Dyspepsia	1 (2)	3 (5)	1 (1)	0	1 (5)	0	0
Gastritis	0	0	2 (3)	1 (8)	0	0	0
Glossodynia	0	0	0	0	1 (5)	0	0
Nausea	1 (2)	2 (4)	6 (8)	0	0	1 (4)	0
Vomiting	4 (10)	3 (5)	8 (10)	0	0	0	1 (20)
General disorders and administration site conditions	4 (10)	4 (7)	5 (6)	2 (15)	1 (5)	2 (9)	1 (20)
Fatigue	1 (2)	0	0	0	1 (5)	0	0
Gait disturbance	0	0	0	1 (8)	0	0	0
Irritability	0	1 (2)	0	0	0	0	1 (20)
Infections and infestations	0	0	0	0	1 (5)	1 (4)	0
Conjuctivitis infective	0	0	0	0	1 (5)	0	0
Investigations	5 (12)	4 (7)	6 (8)	1 (8)	2 (11)	2 (9)	1 (20)
Blood pressure decreased	1 (2)	0	0	1 (8)	0	0	0
Blood pressure diastolic decreased	2 (5)	2 (4)	2 (3)	1 (8)	1 (5)	2 (9)	0
Transaminase increased	0	0	0	0	1 (5)	0	0
Weight decreased	1 (2)	0	1 (1)	0	0	0	1 (20)
Metabolism and nutrition disorders	1 (2)	0	2 (3)	1 (8)	0	1 (4)	1 (20)
Decreased appetite	1 (2)	0	2 (3)	0	0	0	1 (20)
Increased appetite	0	0	0	1 (8)	0	0	0
Musculoskeletal and connective tissue disorders	4 (10)	1 (2)	2 (3)	0	0	0	1 (20)
Pain in extremity	2 (5)	1 (2)	1 (1)	0	0	0	1 (20)
Nervous system disorders	8 (19)	10 (18)	14 (18)	5 (38)	2 (11)	3 (13)	1 (20)
Headache	7 (17)	8 (15)	11 (14)	5 (38)	2 (11)	3 (13)	1 (20)
Psychiatric disorders	1 (2)	2 (4)	0	2 (15)	1 (5)	0	1 (20)
Disturbance in social behaviour	0	0	0	0	0	0	1 (20)
Insomnia	1 (2)	0	0	0	0	0	1 (20)
Mental disorder	0	0	0	1 (8)	0	0	0
Nervousness	0	0	0	0	1 (5)	0	0
Personality disorder	0	0	0	1 (8)	0	0	0

Table 6. Treatment-Related Adverse Events (in ≥5% of Subjects in any Initial Study/Extension Study Treatment Sequence) by Preferred Term: Safety Population

System Organ Class Preferred Term	Number (%) of Subjects						
	Sildenafil Low/Low Dose (N=42)	Sildenafil Medium/ Medium Dose (N=55)	Sildenafil High/High Dose (N=77)	Placebo/ Low Dose (N=13)	Placebo/ Medium Dose (N=19)	Placebo/High Dose (N=23)	Placebo Non-Rand (N=5)
Reproductive system and breast disorders	1 (2)	4 (7)	5 (6)	1 (8)	0	1 (4)	0
Painful erection	0	0	0	1 (8)	0	0	0
Spontaneous penile erection	0	3 (5)	1 (1)	0	0	1 (4)	0
Respiratory thoracic and mediastinal disorders	4 (10)	3 (5)	10 (13)	3 (23)	1 (5)	0	1 (20)
Cough	1 (2)	1 (2)	4 (5)	0	0	0	0
Dyspnoea	0	1 (2)	2 (3)	1 (8)	0	0	0
Epistaxis	3 (7)	0	5 (6)	0	1 (5)	0	0
Nasal congestion	0	0	0	2 (15)	0	0	0
Pulmonary hypertension	0	1 (2)	0	0	0	0	1 (20)
Skin and subcutaneous tissue disorders	1 (2)	4 (7)	6 (8)	1 (8)	0	0	1 (20)
Pruritis	0	1 (2)	0	0	0	0	1 (20)
Rash macular	0	0	0	1 (8)	0	0	0
Vascular disorders	2 (5)	2 (4)	1 (1)	0	2 (11)	3 (13)	0
Flushing	1 (2)	1 (2)	1 (1)	0	2 (11)	1 (4)	0

Initial study: NCT00159913.
Subjects are only counted once per treatment for each row.
Includes data up to 7 days after last dose of study drug.
N = number of subjects; NR=Not randomized; Rand = randomized.

Serious Adverse Events: All causality serious adverse events (SAEs) experienced by subjects in any treatment group are summarized by system organ class (SOC) and preferred term in Table 7. The most commonly reported SAEs in those subjects who received sildenafil (excluding placebo/non-randomized) were in the SOCs of cardiac disorders; gastrointestinal disorders; infections and infestations; and respiratory, thoracic and mediastinal disorders. Non-fatal treatment-related SAEs were reported in 6 subjects. In the sildenafil low/low dose group, enterocolitis (1 subject); in the sildenafil medium/medium dose group, convulsion (1 subject); and in the sildenafil high/high dose group, hypersensitivity and stridor (1 subject), hypoxia (1 subject), neurosensory deafness (1 subject), and ventricular arrhythmia (1 subject).

Table 7. Treatment-Emergent Serious Adverse Events

Number (%) of Subjects With Adverse Events by: System Organ Class Preferred Term	Sildenafil Low Dose n (%)	Sildenafil Medium Dose n (%)	Sildenafil High Dose n (%)
Number (%) of subjects:			
Evaluable for adverse events	55 (100.0)	74 (100.0)	100 (100.0)
With treatment-emergent non-serious adverse events	14 (25.5)	37 (50.0)	48 (48.0)
Discontinued due to adverse events[a]	1 (1.8)	4 (5.4)	7 (7.0)
Blood and lymphatic system disorders	0	0	2 (2.0)
Anaemia	0	0	1 (1.0)
Polycythaemia	0	0	1 (1.0)
Cardiac disorders	5 (9.1)	8 (10.8)	15 (15.0)
Bradycardia	0	0	1 (1.0)
Cardiac failure	2 (3.6)	2 (2.7)	6 (6.0)
Cardiac failure congestive	1 (1.8)	0	1 (1.0)
Cardiogenic shock	0	1 (1.4)	2 (2.0)
Cyanosis	1 (1.8)	1 (1.4)	0
Pericardial effusion	0	1 (1.4)	0
Right ventricular failure	2 (3.6)	3 (4.1)	3 (3.0)
Supraventricular tachycardia	1 (1.8)	0	0
Tachycardia paroxysmal	0	1 (1.4)	0
Ventricular arrhythmia	0	0	1 (1.0)
Ventricular fibrillation	0	0	2 (2.0)
Congenital, familial and genetic disorders	1 (1.8)	3 (4.1)	0
Cystic fibrosis	0	1 (1.4)	0
Eisenmenger's syndrome	0	1 (1.4)	0
Hip dysplasia	1 (1.8)	1 (1.4)	0
Ventricular septal defect	0	1 (1.4)	0
Ear and labyrinth disorders	0	0	1 (1.0)
Deafness neurosensory	0	0	1 (1.0)
Eye Disorders	1 (1.8)	0	1 (1.0)
Corneal oedema	0	0	1 (1.0)
Keratoconus	0	0	1 (1.0)
Vision blurred	1 (1.8)	0	0
Gastrointestinal disorders	2 (3.6)	7 (9.5)	5 (5.0)
Abdominal pain	0	0	1 (1.0)
Ascites	0	1 (1.4)	0
Dental caries	0	1 (1.4)	3 (3.0)
Diarrhoea	0	2 (2.7)	0
Duodenal ulcer	0	1 (1.4)	0
Enteritis	0	1 (1.4)	0
Enterocolitis	1 (1.8)	0	0
Food poisoning	0	0	1 (1.0)
Haematemesis	0	1 (1.4)	0
Haematochezia	1 (1.8)	0	0
Vomiting	0	1 (1.4)	0
General disorders and administration site conditions	4 (7.3)	1 (1.4)	5 (5.0)
Chest pain	3 (5.5)	0	2 (2.0)
Disease progression	0	1 (1.4)	0
Gait disturbance	1 (1.8)	0	0
Pyrexia	0	0	3 (3.0)

Table 7. Treatment-Emergent Serious Adverse Events

Number (%) of Subjects With Adverse Events by: System Organ Class Preferred Term	Sildenafil Low Dose n (%)	Sildenafil Medium Dose n (%)	Sildenafil High Dose n (%)
Infections and infestations	4 (7.3)	17 (23.0)	24 (24.0)
Acute tonsillitis	0	1 (1.4)	0
Bacteraemia	0	1 (1.4)	0
Brain abscess	0	1 (1.4)	0
Bronchitis	1 (1.8)	1 (1.4)	3 (3.0)
Bronchopneumonia	1 (1.8)	1 (1.4)	3 (3.0)
Cellulitis	0	1 (1.4)	0
Dengue fever	0	1 (1.4)	0
Gastroenteritis	0	3 (4.1)	3 (3.0)
Gastroenteritis salmonella	1 (1.8)	0	0
Gastroenteritis viral	0	1 (1.4)	1 (1.0)
Gastrointestinal infection	0	0	1 (1.0)
Gastrointestinal viral infection	0	0	1 (1.0)
Gingivitis	1 (1.8)	0	0
Laryngitis	0	1 (1.4)	1 (1.0)
Lower respiratory tract infection	0	0	1 (1.0)
Lung infection	0	1 (1.4)	0
Peritonitis	0	1 (1.4)	0
Peritonsillar abscess	0	1 (1.4)	0
Pharyngitis	1 (1.8)	1 (1.4)	0
Pneumonia	1 (1.8)	7 (9.5)	10 (10.0)
Pneumonia bacterial	0	1 (1.4)	0
Pneumonia respiratory syncytial viral	0	0	1 (1.0)
Respiratory tract infection	0	0	1 (1.0)
Tonsillitis	0	1 (1.4)	0
Tooth abscess	1 (1.8)	0	0
Upper respiratory tract infection	0	1 (1.4)	6 (6.0)
Urinary tract infection	0	0	3 (3.0)
Viral infection	0	1 (1.4)	0
Injury, poisoning and procedural complications	2 (3.6)	4 (5.4)	0
Contusion	0	1 (1.4)	0
Exposure via father	1 (1.8)	0	0
Hip fracture	0	1 (1.4)	0
Skull fracture	0	1 (1.4)	0
Subdural haematoma	0	1 (1.4)	0
Tibia fracture	0	1 (1.4)	0
Toxicity to various agents	0	1 (1.4)	0
Upper limb fracture	1 (1.8)	0	0
Investigations	0	2 (2.7)	1 (1.0)
Catheterisation cardiac	0	1 (1.4)	0
Oxygen saturation decreased	0	0	1 (1.0)
Pulmonary arterial pressure increased	0	1 (1.4)	0
Metabolism And Nutrition Disorders	1 (1.8)	2 (2.7)	2 (2.0)
Dehydration	1 (1.8)	0	1 (1.0)
Electrolyte imbalance	0	1 (1.4)	1 (1.0)
Hypoalbuminaemia	0	1 (1.4)	0
Nervous system disorders	4 (7.3)	4 (5.4)	3 (3.0)
Convulsion	1 (1.8)	1 (1.4)	0
Dizziness	1 (1.8)	0	1 (1.0)
Headache	0	0	1 (1.0)
Loss of consciousness	1 (1.8)	0	0
Syncope	2 (3.6)	2 (2.7)	1 (1.0)
Transient ischaemic attack	0	1 (1.4)	0
Psychiatric disorders	1 (1.8)	0	0
Anorexia nervosa	1 (1.8)	0	0

Table 7. Treatment-Emergent Serious Adverse Events

Number (%) of Subjects With Adverse Events by: System Organ Class Preferred Term	Sildenafil Low Dose n (%)	Sildenafil Medium Dose n (%)	Sildenafil High Dose n (%)
Renal and urinary disorders	0	1 (1.4)	0
Enuresis	0	1 (1.4)	0
Reproductive system and breast disorders	1 (1.8)	0	0
Menorrhagia	1 (1.8)	0	0
Respiratory, Thoracic And Mediastinal disorders	4 (7.3)	11 (14.9)	18 (18.0)
Adenoidal hypertrophy	0	0	1 (1.0)
Bronchospasm	0	0	1 (1.0)
Cough	0	0	1 (1.0)
Dyspnoea	1 (1.8)	0	0
Dyspnoea exertional	0	0	1 (1.0)
Epistaxis	0	1 (1.4)	0
Haemoptysis	0	2 (2.7)	0
Hypoxia	0	0	2 (2.0)
Nasal turbinate hypertrophy	0	0	1 (1.0)
Pneumonia aspiration	0	1 (1.4)	0
Pulmonary arterial hypertension	0	2 (2.7)	7 (7.0)
Pulmonary embolism	0	0	1 (1.0)
Pulmonary haemorrhage	0	1 (1.4)	0
Pulmonary hypertension	2 (3.6)	4 (5.4)	5 (5.0)
Respiratory arrest	0	0	1 (1.0)
Respiratory failure	1 (1.8)	0	0
Sleep apnoea syndrome	0	0	1 (1.0)
Stridor	0	0	1 (1.0)
Tonsillar hypertrophy	0	0	1 (1.0)
Skin and subcutaneous tissue disorders	0	0	1 (1.0)
Excessive granulation tissue	0	0	1 (1.0)
Surgical and medical procedures	0	2 (2.7)	0
Cardiac operation	0	1 (1.4)	0
Central venous catheterisation	0	1 (1.4)	0
Vascular disorders	1 (1.8)	0	0
Circulatory collapse	1 (1.8)	0	0
Hypotension	1 (1.8)	0	0

Subjects are only counted once per treatment for each row.
MedDRA (v15.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of evaluable subjects; v = version.
a. Subjects that permanently discontinued study medication.

Serious Adverse Events Leading to Study Treatment Discontinuation: Overall, 12 subjects had SAEs leading to permanent discontinuation from study treatment (ie, subjects were discontinued from study treatment but were followed-up for survival and safety). These SAEs were mainly considered to be related to the disease under study.

Adverse Events Leading to Dose Reduction or Temporary Discontinuation: Overall, 49 subjects who received sildenafil at some point in the study (excluding placebo/non-randomized) had 1 or more dose reductions or temporary discontinuation due to AE(s)/SAE(s), 10 subjects in the low dose group, 18 subjects in the medium dose group and 21 subjects in the high dose group. Events were most commonly gastrointestinal (eg, nausea, vomiting, diarrhea, gastroenteritis).

Non-Serious Adverse Events Leading to Discontinuation of Study Treatment: Eight subjects had non-serious AEs leading to permanent discontinuation of the study treatment (ie, subjects were discontinued from study treatment but were followed-up for survival and safety).

Laboratory Evaluations: The most common clinical laboratory abnormality from a normal Baseline was an increase in basophils (absolute) >1.2 x upper limit of normal, which was reported for 90/188 (47.9%) subjects with post-baseline measurement of basophils.

Physical Examinations: There were no marked changes in mean or median sitting blood pressure and heart rate for any of the treatment sequences. Mean weight and height increased over time, consistent with the aging of the pediatric subjects.

Electrocardiograms: Most subjects had no clinically significant changes in their electrocardiogram in initial study compared to Baseline.

Dose Down/Up Titrations: Based on review of the survival data (data cut in June, 2011), the DMC unanimously concluded, that in the context of this clinical trial, the high dose of sildenafil was associated with a harmful effect on survival when compared to the low dose. The DMC also expressed concern as to the potential dose-response relationship between increasing dose and mortality. Therefore, on 04 August 2011, the DMC recommended discontinuation of the 40 mg and 80 mg TID doses, as well as the 20 mg TID dose in children with body weight ≤20 kg. The study was amended per DMC recommendations. At the time of DMC recommendation of dose down titration, 120 (52.4%) of the 229 subjects ever treated with sildenafil were still on treatment, with 29/55 (52.7%), 39/74 (52.7%) and 52/100 (52%) subjects in sildenafil low, medium and high dose group respectively.

Prior to 04 August 2011, few subjects had dose down titration; for subjects randomly assigned in the sildenafil low dose group, 28/55 (50.9%) subjects had dose up titration; for subjects randomly assigned in the sildenafil medium dose group, 12/74 (16.2%) subjects had dose up titration.

Survival: There were a total of 42 deaths reported. Of these 42 deaths, 28 had been reported as being 'on treatment' (ie, within 7 days of the last dose). No deaths occurred during the initial study. None of the 42 deaths were considered to be treatment-related by the Investigators. The causes of deaths were generally consistent with the known clinical consequences of the progression of PAH. The number (%) of deaths was 5/55 (9.1%), 13/74 (17.6%) and 24/100 (24%) in sildenafil low, medium, and high dose groups, respectively, in the extension study (Table 8).

Table 8. Summary of Deaths n (%) by Weight Group[a] and Sildenafil Dose Group[b]

Body Weight (kg)	Sildenafil Low Dose (N=55)	Sildenafil Medium Dose (N=74)	Sildenafil High Dose (N=100)
≥8-20	NA	N=20 n=1 (5.0%)	N=44 n=6 (13.6%)
>20-45	N=40 n=3 (7.5%)	N=40 n=10 (25.0%)	N=41 n=15 (36.6%)
>45	N=15 n=2 (13.3%)	N=14 n=2 (14.3%)	N=15 n=3 (20.0%)
Total	N=55 n=5 (9.1%)	N=74 n=13 (17.6%)	N=100 n=24 (24.0%)

CRF = case report form; N = number of subjects; n = number of evaluable subjects; NA = not applicable.

a. For placebo subjects in initial study (NCT00159913), their weights collected on the vital signs CRF at Week 16 of initial study were used. One subject randomly assigned to sildenafil medium dose in initial study had a baseline weight of 44.6 kg, but was incorrectly assigned to the >45 kg weight group for randomization stratification. On this table, the subject is correctly assigned to the weight group of >20-45 kg based on weight collected on the vital signs CRF.

b. Produced by summation of sildenafil dose group with placebo + sildenafil dose group.

As of 04 August 2011 (DMC recommendation of dose down titration), the number (%) of deaths was 5/55 (9.1%), 10/74(13.5%), and 22/100 (22%) in sildenafil low, medium, and high dose groups, respectively, in extension study (Table 9).

Table 9. Summary of Deaths n (%) by Weight Group[a] and Sildenafil Dose Group[b], as of 04 August 2011

Body Weight (kg)	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose
≥8-20	NA	N=20 n=1 (5.0%)	N=44 n=5 (11.4%)
>20-45	N=40 n=3 (7.5%)	N=40 n=7 (17.5%)	N=41 n=15 (36.6%)
>45	N=15 n=2 (13.3%)	N=14 n=2 (14.3%)	N=15 n=2 (13.3%)
Total	N=55 n=5 (9.1%)	N=74 n=10 (13.5%)	N=100 n=22 (22.0%)

CRF = case report form; N = number of subjects; n = number of evaluable subjects; NA = not applicable.

a. For placebo subjects in initial study (NCT00159913), their weights collected on the Vital Signs CRF at Week 16 of initial study were used. One subject randomly assigned to sildenafil medium dose in initial study had a baseline weight of 44.6 kg, but was incorrectly assigned to the >45 kg weight group for randomization stratification. On this table, the subject is correctly assigned to the weight group of >20-45 kg based on weight collected on the Vital Signs CRF.

b. Produced by summation of sildenafil dose group with placebo + sildenafil dose group.

From the start of sildenafil treatment, the Kaplan-Meier estimates for the low, medium, and high dose groups at 3 years were 94%, 93%, and 88%, respectively. The 3-year survival rates were the same using the data cutoff of 04 August 2011 (Table 10).

Table 10. Survival Estimates Relative to the Start of Sildenafil Dose by Weight Group[a] and Overall, as of 04 August 2011

Weight	Dose Group	1 Year	2 Years	3 Years	4 years	5 Years
≤20 kg	Medium	100%	94%	94%	94%	94%
	High	98%	95%	93%	88%	88%
>20 kg	Low	100%	96%	94%	94%	94%
	Medium	100%	96%	93%	88%	78%
	High	100%	90%	85%	80%	71%
Total	Low	100%	96%	94%	94%	94%
	Medium	100%	96%	93%	90%	82%
	High	99%	93%	88%	84%	79%

a. For placebo subjects in initial study (NCT00159913), their weights at the start of sildenafil treatment (Week 16 of initial study) were used.

Table 11 provides the hazard ratio comparisons for survival from the start of sildenafil by sildenafil dose groups, as of 04 August 2011. The hazard ratio showed subjects randomly assigned to sildenafil high dose had 3.95 times the hazard of death compared with subjects randomly assigned to sildenafil low dose. The hazard ratio of 3.95 was statistically significantly >1 with 95% CI of 1.46 to 10.65. The hazard ratios of medium dose over low dose (1.91) and high dose over medium dose (2.07) were not statistically significantly different from 1 (Table 11).

Table 11. Cox Proportional Hazards Analysis (Relative to Start of Sildenafil) by Extension Study Treatment Group, as of 04 August 2011

	Sildenafil Low Dose (N=55)	Sildenafil Medium Dose (N=74)	Sildenafil High Dose (N=100)
Stratified hazard ratio (95% CI)			
Comparison with low dose		1.91 (0.65, 5.61)	3.95 (1.46, 10.65)
Comparison with medium dose			2.07 (0.97, 4.41)

CI = confidence interval; N = number of subjects.

Ocular Safety Measurements:

- For visual acuity monitoring, 46 subjects were reported as deteriorated post extension study baseline. Of these 46, ten (10) were in the sildenafil low/low dose group, 11 in the sildenafil medium/medium dose group, 17 in the sildenafil high/high dose group, 4 in the sildenafil placebo/medium dose group, and 4 in the sildenafil placebo/high dose group.

- For the color vision monitoring, 7 subjects were reported as deteriorated post extension study baseline. Of these 7, five (5) subjects had a reliable worsening post-baseline. The other 2 subjects were reported as having a worsening, but the assessment was reported to be unreliable. Of the 5 subjects who had a reliable worsening post-baseline, 3 occurred while on sildenafil treatment and 2 occurred while on placebo treatment. One subject (sildenafil high dose) was reported with normal color vision at the end of the study; 1 subject (sildenafil medium dose) was reported with no change post-baseline at the end of the study; 1 subject had color

vision worsening at Week 16 while on placebo treatment, randomly assigned to sildenafil high dose and was reported with no change post-baseline at Week 52; both subjects had no further color vision assessments reported post Week 16 (the visit worsening in color vision was noted).

Growth and Development: The pediatric cognitive and motor development are summarized in Table 12 and Table 13, respectively. The majority of subjects for all treatment sequences were not limited in their cognitive and motor development at Baseline and Week 52. Few subjects had changes in cognitive and motor development from Baseline to Week 52.

Table 12. Summary of Paediatric Cognitive Development Assessment by Initial/Extension Treatment Sequence

Visit	Treatment	Paediatric Cognitive Development Post-Baseline	Paediatric Cognitive Development at Baseline			
			Severely Limited n (%)	Moderately Limited n (%)	Mildly Limited n (%)	Not Limited n (%)
Week 52	Sildenafil low/low dose	Severely limited	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
		Moderately limited	0 (0.0)	2 (4.8)	2 (4.8)	1 (2.4)
		Mildly limited	0 (0.0)	1 (2.4)	2 (4.8)	0 (0.0)
		Not limited	0 (0.0)	1 (2.4)	2 (4.8)	24 (57.1)
	Sildenafil medium/medium dose	Severely limited	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
		Moderately limited	2 (3.6)	4 (7.3)	3 (5.5)	1 (1.8)
		Mildly limited	0 (0.0)	1 (1.8)	3 (5.5)	1 (1.8)
		Not limited	0 (0.0)	1 (1.8)	1 (1.8)	34 (61.8)
	Sildenafil high/high dose	Severely limited	1 (1.3)	1 (1.3)	0 (0.0)	0 (0.0)
		Moderately limited	0 (0.0)	4 (5.2)	2 (2.6)	0 (0.0)
		Mildly limited	1 (1.3)	5 (6.5)	2 (2.6)	0 (0.0)
		Not limited	0 (0.0)	0 (0.0)	5 (6.5)	45 (58.4)
	Placebo/low dose	Severely limited	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Moderately limited	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)
		Mildly limited	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Not limited	0 (0.0)	0 (0.0)	0 (0.0)	11 (84.6)
	Placebo/medium dose	Severely limited	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Moderately limited	1 (5.3)	3 (15.8)	1 (5.3)	0 (0.0)
		Mildly limited	0 (0.0)	2 (10.5)	0 (0.0)	1 (5.3)
		Not limited	0 (0.0)	0 (0.0)	0 (0.0)	10 (52.6)
	Placebo/high dose	Severely limited	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Moderately limited	1 (4.3)	1 (4.3)	0 (0.0)	0 (0.0)
		Mildly limited	1 (4.3)	0 (0.0)	2 (8.7)	0 (0.0)
		Not limited	0 (0.0)	0 (0.0)	1 (4.3)	14 (60.9

Initial study: NCT00159913.
n = number of subjects.

Table 13. Summary of Paediatric Motor Development Assessment by Initial / Extension Study Treatment Sequence

Visit	Treatment	Paediatric Cognitive Development Post-Baseline	Paediatric Cognitive Development at Baseline			
			Severely Limited n (%)	Moderately Limited n (%)	Mildly Limited n (%)	Not Limited n (%)
Week 52	Sildenafil low/low dose	Severely limited	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Moderately limited	1 (2.4)	2 (4.8)	1 (2.4)	0 (0.0)
		Mildly limited	0 (0.0)	2 (4.8)	5 (11.9)	1 (2.4)
		Not limited	0 (0.0)	0 (0.0)	3 (7.1)	21 (50.0)
	Sildenafil medium/medium dose	Severely limited	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Moderately limited	1 (1.8)	3 (5.5)	4 (7.3)	1 (1.8)
		Mildly limited	0 (0.0)	1 (1.8)	4 (7.3)	3 (5.5)
		Not limited	1 (1.8)	1 (1.8)	2 (3.6)	31 (56.4)
	Sildenafil high/high dose	Severely limited	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Moderately limited	0 (0.0)	2 (2.6)	2 (2.6)	1 (1.3)
		Mildly limited	0 (0.0)	3 (3.9)	7 (9.1)	5 (6.5)
		Not limited	0 (0.0)	2 (2.6)	3 (3.9)	41 (53.2)
	Placebo/low dose	Severely limited	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Moderately limited	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Mildly limited	0 (0.0)	0 (0.0)	1 (7.7)	2 (15.4)
		Not limited	0 (0.0)	0 (0.0)	0 (0.0)	9 (69.2)
	Placebo/medium dose	Severely limited	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Moderately limited	0 (0.0)	2 (10.5)	0 (0.0)	0 (0.0)
		Mildly limited	0 (0.0)	0 (0.0)	5 (26.3)	1 (5.3)
		Not limited	0 (0.0)	0 (0.0)	3 (15.8)	7 (36.8)
	Placebo/high dose	Severely limited	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Moderately limited	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Mildly limited	0 (0.0)	0 (0.0)	3 (13.0)	0 (0.0)
		Not limited	0 (0.0)	1 (4.3)	3 (13.0)	13 (56.5)

Initial study: NCT00159913.
n = number of subjects.

CONCLUSIONS:

- Sildenafil was generally well-tolerated at all doses studied, with most AEs being of mild or moderate intensity. Few discontinuations from the study were due to treatment-related AEs. Treatment-related SAEs were experienced by 6 subjects. There was no evidence that frequently observed AEs increased with time and the AE profile was consistent with the AE profile of sildenafil in adult PAH clinical trials and for marketed sildenafil in adults with PAH.

- At Year 3, the probability of survival was 94%, 93% and 88% in the low, medium and high dose groups respectively. Even with dose up-titration for subjects randomly assigned to sildenafil low dose (50.9%), subjects randomly assigned to high sildenafil doses had a statistically significant increased mortality compared with low dose. None of the 42 deaths reported were regarded by the Investigator to be treatment-related. The causes of deaths and associated conditions were consistent with the known clinical consequences of the progression of PAH in children.