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

PROTOCOL NO.: A1481298

PROTOCOL TITLE:

A Phase 3, Multi-Center, Open-Label Study to Investigate Safety, Efficacy, and Tolerability of Sildenafil Citrate in Pediatric Patients With Pulmonary Arterial Hypertension

Study Centers:

Three (3) centers in Japan took part in the study and enrolled subjects.

Study Initiation, Primary Completion and Final Completion Dates:

Study Initiation Date: 24 August 2012
Primary Completion Date: 20 May 2016
Final Completion Date: 12 March 2018

Phase of Development:

Phase 3

Study Objectives:

Primary Objective:

- The primary objective was to investigate changes of subject status with sildenafil treatment (>20 kg: 20 mg ter in die [TID] [60 mg/day], ≤20 kg: 10 mg TID [30 mg/day]) for individual Japanese pediatric subjects with pulmonary arterial hypertension (PAH) based on right heart catheter test, World Health Organization (WHO) functional class, brain natriuretic peptide (BNP) and pro-BNP at Week 16.

Secondary Objectives:

- To investigate safety of sildenafil in Japanese pediatric subjects with PAH during 16 weeks.
- To investigate pharmacokinetics (PK) of sildenafil and desmethyl sildenafil (UK-103,320) at steady state in Japanese pediatric subjects with PAH.
- To investigate long-term safety and efficacy of sildenafil in Japanese pediatric subjects with PAH who completed Part 1 and were willing to continue sildenafil treatment (Part 2).

METHODS

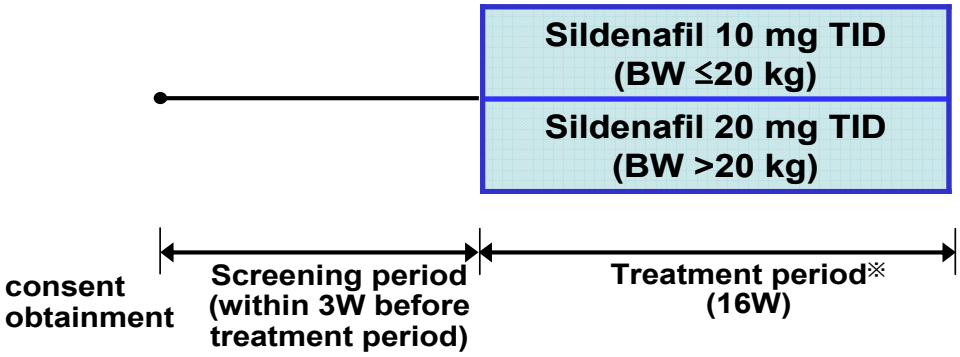
Study Design:

This study was a 16-week, multicenter, open-label study to investigate efficacy and safety of sildenafil in pediatric subjects with PAH aged 1 to 17 years. If subjects required continuing treatment with the study drug until approval, study drug was made available past the 16-week treatment period and subjects were investigated for long-term safety and efficacy of sildenafil. The study consisted of 2 parts: a screening period and a treatment period.

Subjects who met the eligibility criteria were enrolled in the treatment period, where either sildenafil 20 mg TID (60 mg/day) or 10 mg TID (30 mg/day) was selected based on their body weight at baseline. The treatment phase consisted of a telephone contact at Weeks 1 and 3 additional clinic visits, during which efficacy and safety data were collected. Subjects were treated for 16 weeks (Part 1). Blood samples for the determination of PK were collected during the study. If subjects completed Part 1 and required continuing treatment with the study drug until approval, it was made available in Part 2 after the investigator's evaluation. The dosage in Part 2 was based on the actual weight at each visit. If, in the investigator's opinion, the subject was experiencing drug-related intolerance at any point during Part 2, the subject's dose could be reduced from 20 mg TID to 10 mg TID. The subject then remained on the reduced dose for the remainder of the protocol-specified treatment period. In Part 2, clinic visits were set at every 12 weeks to collect safety and efficacy data.

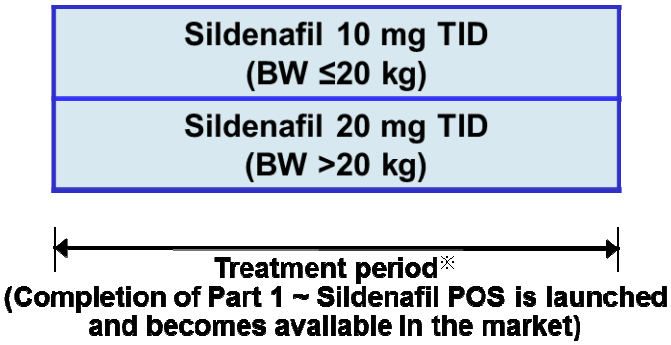
The study design for Part 1 is presented in Figure 1 and for Part 2 is presented in Figure 2.

Figure 1. Study Design - Part 1



∗ Dosage of permitted concomitant drug (beraprost) could be constant before/during Part 1.
Abbreviations: BW=body weight; TID=ter in die; W=week.

Figure 2. Study Design - Part 2



∗ When beraprost had been administered as a concomitant drug in Part 1, increasing or decreasing of beraprost was allowed during Part 2, if needed.
Abbreviations: BW=body weight; POS=powder for oral suspension; TID=ter in die.

The schedule of activities for Part 1 (screening period ~ Week 16) is presented in Table 1 and Part 2 (after Week 16) is presented in Table 2.

Table 1. Schedule of Activities - Part 1 (Screening Period ~ Week 16)

	Screening Period	Treatment Period (Part 1)						Follow-Up[a]
Week (Allowable Range)	**-21 Days Prior to V1 to Prior to the First Administration**	**0**	**1 ±3 Days**	**4 ±7 Days**	**8 ±7 Days**	**(12)[b] ±7 Days**	**16 ±7 Days**	**28 Days After the Last Administration or Later**
Visit Point	**S1**	**V1**	**P1**	**V2**	**V3**	**Vt**	**V4 (T)**	**PF**
Informed consent	X							
Confirmation of inclusion/exclusion criteria	X	X						
Medical history	X							
Height	X						X	
Body weight	X	X					X	
Pregnancy test (urine)[c]		X					X	
Physical examinations	X	X		X	X		X	
Chest X-ray[d]	X							
Twelve (12)-lead ECG	X						X	
Vital signs (BP and pulse rate)	X	X		X	X		X	
Hematology	X	X		X	X		X	
Biochemical examination	X	X		X	X		X	
Urinalysis	X	X		X	X		X	
Ocular measures	X						X	
Evaluation of AEs		X	X	X	X		X	
SAEs	← From obtaining consent to 28 days after the last administration →							
Hemodynamic evaluation[e]	X						X	
WHO functional class		X		X	X		X	
BNP, NT pro-BNP		X[f]					X	
PK sampling[g]				X	X		X	
Prescription of the study drug		X		X	X	(X)		
Concomitant drugs and therapy	X	X		X	X		X	
Compliance checking			X	X	X	(X)	X	

Abbreviations: AE=adverse event; BNP=brain natriuretic peptide; BP=blood pressure; ECG=Electrocardiogram; mPAP=mean pulmonary artery pressure; NT pro-BNP=N-terminal pro-brain natriuretic peptide; P=phone contact; PF=follow-up phone contact; PK=pharmacokinetics; S=screening; SAE=serious adverse event; T=termination; V=visit; Vt=visit at Week 12; WHO=World Health Organization.

a. For subjects not elected to transfer to Part 2.
b. This visit was to be set if the prescription of the study drug was needed.
c. Pregnancy test for female subjects of childbearing potential.
d. If not performed within the last 6 months.
e. Could be performed within 21 days prior to the first administration. Hemodynamic inclusion criteria were based on the screening catheterization and might be met before the subject could be enrolled to treatment period. Included mPAP.
f. Blood samples collected 72 hours prior to Week 0 could be used as Week 0 samples.
g. The PK sampling points were predose at Weeks 4 and 8, and predose and 1, 2, 4, 8 hours postdose at Week 16.

Table 2. Schedule of Activities - Part 2 (After Week 16)

	Treatment Period						Follow-Up
	Part 1	Part 2					
Week (Allowable Range)	**16**	**28**	**40**	**52**	**52 Plus Every 12 Weeks**	**EoT/ Termination**	**28 Days After the Last Administration or Later**
	±7 Days	**±7 Days**	**±7 Days**	**±7 Days**	**±7 Days**	**±7 Days**	
Visit Point	**V4**	**V5**	**V6**	**V7**	**V8~**	**VL/Termination**	**PF**
Confirmation willingness to transfer Part 2	X						
Height	X			X		X	
Body weight	X	X	X	X	X	X	
Pregnancy test (urine)[a]	X	X	X	X	X	X	
Physical examinations	X	X	X	X	X	X	
Twelve (12)-lead ECG	X			X		X	
Vital signs (BP and pulse rate)	X	X	X	X	X	X	
Hematology[b]	X	X		X	X	X	
Biochemical examination[b]	X	X		X	X	X	
Urinalysis[b]	X	X		X	X	X	
Ocular measures	X			X		X	
Evaluation of AEs	X	X	X	X	X	X	
SAEs	← From obtaining consent to 28 days after the last administration →						
WHO functional class	X	X	X	X	X	X	
BNP, NT pro-BNP	X			X		X	
Prescription of the study drug	X	X	X	X	X		
Concomitant drugs and therapy	X	X	X	X	X	X	
Compliance checking	X	X	X	X	X	X	

Abbreviations: AE=adverse event; BNP=brain natriuretic peptide; BP=blood pressure; ECG=electrocardiogram; EoT=end of treatment; eg=for example; etc=and the rest; NT pro-BNP=N-terminal pro-brain natriuretic peptide; PF=follow-up phone contact; SAE=serious adverse event; V=visit; VL=end of treatment visit; WHO=World Health Organization.

a. Pregnancy test for female subjects of childbearing potential.
b. After Week 28 or later, repeated every 24 weeks; eg, Weeks 52, 76, 100, etc.

Number of Subjects (Planned and Analyzed):

The following target sample sizes were established for this study.

- Pediatric PAH subjects with body weight >20 kg in Part 1: 2 or more subjects;
- Pediatric PAH subjects with body weight ≤20 kg in Part 1: 3 or more subjects.

Subjects who took at least 1 dose of study drug and had both a baseline and at least 1 post-baseline observation of efficacy were required for the above target sample size.

A total of 6 subjects were screened and assigned to study treatment in Part 1 and further 3 subjects entered Part 2 of the study. All 6 subjects were analyzed for PK, efficacy and safety in Part 1. All 3 subjects were analyzed for safety and efficacy in Part 2.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Main Inclusion Criteria:

Male or female subjects aged 1 to 17 years old who weighed ≥8 kg and had symptomatic PAH. Subjects with a mean pulmonary artery pressure (mPAP) ≥25 mm Hg at rest, pulmonary capillary wedge pressure (PCWP) ≤15 mm Hg, and pulmonary vascular resistance index (PVRI) ≥3 Wood units × m^2. If PCWP was not available, then mean left arterial pressure ≤15 mm Hg or left ventricular end-diastolic pressure ≤15 mm Hg in the absence of left atrial obstruction were included in Part 1. Subjects who were willing to continue sildenafil administration after the completion of Part 1 were included in Part 2.

Main Exclusion Criteria:

Subjects with left-sided heart disease; Down's syndrome; obstructive sleep apnea, regardless of treatment status; pericardial constriction; significant (2+ for regurgitation) valvular disease other than tricuspid or pulmonary regurgitation; hemodynamic instability or hypo- or hypertension at screening; a history of stroke, myocardial infarction or life threatening arrhythmia within 6 months of screening; moderate to severe restrictive pulmonary disease (total lung capacity or forced vital capacity ≤60% of normal) or history of severe lung disease; bronchopulmonary dysplasia and other chronic lung diseases; history of pulmonary embolism; known hereditary degenerative retinal disorders (such as retinitis pigmentosa) or history of non-arteritic anterior ischemic optic neuropathy; impairment of renal function (serum creatinine >2.5 × the upper limit of normal [ULN]) or hepatic function (alanine aminotransferase and/or aspartate aminotransferase >3 × ULN; and/or bilirubin ≥2 mg/dL); clinically significant hematological abnormalities; severe hepatic dysfunction (Child-Pugh classification C) were excluded from this study.

Study Treatment:

The following study treatments were provided to the sites by the Sponsor:

- Sildenafil citrate powder for oral suspension (POS) (10 mg/mL).
- Sildenafil citrate tablet 20 mg.

The doses of study drug were taken TID, at least 6 hours apart. At Weeks 4, 8 and 16 for PK sampling, food intake was avoided for 2 hours prior to dosing. In addition, food intake was avoided for 2 hours after the dosing at Week 16. The dosage in Part 1 was based on weight, as assessed at Week 0 (≤20 kg or >20 kg). For ≤20 kg subjects, 10 mg TID (30 mg/day) was taken by POS. For >20 kg subjects, 20 mg TID (60 mg/day) was taken by film-coated tablet or POS. The dosage in Part 2 was based on the actual weight at each visit.

Efficacy and Pharmacokinetic Endpoints:

Efficacy Endpoints:

Endpoints in Part 1:

Change from baseline to Week 16:

- PVRI;
- mPAP;
- WHO functional class at Weeks 0, 4, 8 and Weeks 16 (or Termination). This functional classification was to be performed by the same evaluator at each assessment when possible;
- BNP and N-terminal pro-brain natriuretic peptide (NT pro-BNP). Blood samples for BNP and NT pro-BNP were to be collected at Week 0 (blood samples collected 72 hours prior to Week 0 could be used as Week 0 samples) and Week 16 (or at Termination) in Part 1.

Endpoints in Part 2:

Change from baseline:

- WHO functional class at Weeks 28, 40, 52, Week 52 + every 12 weeks, end of treatment (EoT) (or Termination) in Part 2;
- BNP and NT pro-BNP. Blood samples for BNP and NT pro-BNP were to be collected at Week 52 and EoT (or at Termination) in Part 2.

Pharmacokinetic Endpoints:

Part 1 Only:

- Plasma concentration of sildenafil and UK-103,320 at steady state: Predose at Week 4 and 8, predose, 1, 2, 4 and 8 hours post-dosing at Week 16/ Termination;
- PK parameters at steady state, as data permitted: maximum observed plasma concentration (C_{max}), time for C_{max} (T_{max}), area under the plasma concentration-time curve over dosing interval tau (τ), where tau=8 hours (AUC_{tau}), terminal half-life ($t_{½}$), average plasma concentration at steady state ($C_{ss,av}$), trough plasma concentration (C_{trough}), apparent total clearance of drug from plasma after oral administration (CL/F) and apparent volume of distribution estimated from terminal phase after oral administration (V_z/F) for sildenafil, C_{max}, T_{max}, AUC_{tau} and $t_{½}$ for UK-103,320 at Week 16/Termination.

Safety Evaluations:

Safety evaluations included assessment of adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests, vital signs (blood pressure and pulse rate), 12-lead electrocardiogram (ECGs), physical examinations, ocular measures, and pregnancy testing.

Statistical Methods:

Efficacy Analysis:

The efficacy analysis set was defined as all subjects who took at least 1 dose of study drug. The change of subject status was investigated as primary efficacy assessment based on the efficacy endpoints. Although summary statistics from aggregated data added little value due to its small sample size, both summary statistics and individual measurements were provided for investigating efficacy. Efficacy evaluation was based mainly on the careful data review of individual case. All efficacy analyses were conducted on the efficacy analysis set. Subgroup analysis by body weight (≤20 kg or >20 kg) were also conducted for the following efficacy analyses in Part 1. Efficacy analysis was conducted for each part.

Part 1: Baseline values, actual value and change from baseline at Week 16 and at Week 16/EoT in the all efficacy endpoints except for WHO functional class, were summarized with summary statistics (n, mean, standard deviation [SD], median, minimum and maximum). For baseline value and actual value at Week 16 and at Week 16/EoT in PVRI, geometric mean and geometric SD was calculated. In addition, for log-transformed PVRI, the mean difference and its 95% confidence interval (CI) of actual value at Week 16 and at Week 16/EoT from baseline was calculated. The mean differences and its 95% CI was exponentiated to provide estimates of the ratio of geometric means and its 95% CI. For WHO functional class, baseline values, actual value and change from baseline at Weeks 4, 8, 16 and 16/EoT were summarized with summary statistics.

Part 2: Baseline values in Part 1 were used for Part 2 analysis. For BNP, NT pro-BNP and WHO functional class, actual value and change from baseline at each evaluated visit including Week 52/EoT were summarized with summary statistics and listed for each subject. Week 52/EoT used observations at Week 52 or the last observations before Week 52 if a subject discontinued before Week 52.

Pharmacokinetic Analysis:

The PK concentration set was defined as all subjects who had at least 1 concentration. The PK parameter analysis set was defined as all subjects who had at least 1 PK parameter of interest. PK analysis was conducted only in Part 1 of the study.

Plasma concentrations of sildenafil and UK-103,320 were summarized by visit and PK sampling point at Week 16 for subjects in the PK concentration set. Subgroup analysis by body weight and by use of concomitant PAH treatments (none or beraprost) was also conducted separately. Individual, mean and median plasma concentration-time plots were prepared.

PK parameters for sildenafil and UK-103,320 were evaluated by means of non-compartmental analysis and nonlinear mixed effect approach. The following PK parameters at Week 16/Termination was determined by non-compartmental analysis approach, as data permitted, C_{max}, T_{max}, AUC_{tau}, $t_{½}$, $C_{ss,av}$, C_{trough}, CL/F and V_z/F for sildenafil, C_{max}, T_{max}, AUC_{tau} and $t_{½}$ for UK-103,320. C_{max}, C_{trough} and T_{max} were obtained from the actual time-concentration data.

AUC_{tau} was calculated using the linear/log trapezoidal rule from time 0 to time τ, dosing interval. $t_{½}$ was calculated as $ln2/k_{el}$, where k_{el} was terminal phase rate constant and was estimated as the absolute value of the slope of a linear regression during the terminal phase of the natural-logarithm transformed concentration-time profile. $C_{ss,av}$ was calculated as AUC_{tau}/dosing interval (τ). CL/F was calculated as Dose/AUC_{tau}. The V_z/F was calculated as CL/F/k_{el}. To assess the PK of sildenafil and UK-103,320 at steady state, the PK parameters were summarized for subjects in the PK parameter analysis set. Subgroup analysis for each parameter was also conducted by the body weight and by use of concomitant PAH treatments (none or beraprost) separately.

Safety Analysis:

The safety analysis set was defined as all subjects who took at least 1 dose of study drug. Safety assessments were investigated during 16 weeks treatment period (Part 1) and during long-term treatment period (Part 2), including AEs, vital signs, laboratory tests, 12-lead ECG and ocular safety. All safety analyses were reported on the safety analysis set. Safety endpoints were summarized following sponsor data standards. Summary tables for safety data during Part 1 were provided. Also, the summary tables during whole period of Parts 1 and 2 were provided. Subgroup analysis by body weight (≤20 kg or >20 kg) was conducted for Part 1 data in safety analysis. As this was a single arm study, a 3-tier approach was not used to summarize AEs.

RESULTS

Subject Disposition and Demography:

Table 3 presents a summary of subject disposition in the study. A total of 6 subjects were screened and assigned to study treatment in Part 1 and further 3 subjects entered Part 2 of the study. All 6 subjects were analyzed for safety and efficacy in Part 1. All 3 subjects were analyzed for safety and efficacy in Part 2.

Table 3. Subject Evaluation Groups

Number (%) of Subjects	Sildenafil	
	Part 1	Part 2
Screened 6		
Assigned to study treatment	6	3
Treated	6	3
Withdrawn during active/double-blind treatment period (Part 1)	2 (33.3)	-
Withdrawn upon completion of initial treatment phase (Part 1)	1 (16.7)	-
Enter to the Part 2 period	3 (50.0)	-
Completed	-	1 (33.3)
Discontinued	-	2 (66.7)
Analyzed for efficacy		
Efficacy analysis set	6 (100.0)	3 (100.0)
Analyzed for PK		
PK concentration analysis set	6 (100.0)	-
PK parameter analysis set	6 (100.0)	-
Analyzed for safety		
Adverse events	6 (100.0)	3 (100.0)
Laboratory data	6 (100.0)	3 (100.0)

Discontinuations were attributed to the last study treatment received.
Abbreviation: PK=pharmacokinetic.

Subject discontinuations are presented in Table 4. During Part 1 of the study, 3 subjects discontinued (2 subjects were withdrawn during active/double blind treatment period and 1 subject was withdrawn upon completion of initial treatment phase); while in Part 2 of the study, 2 subjects discontinued.

Table 4. Discontinuations From Study

	Sildenafil 10 mg TID (Body Weight ≤20 kg)	Sildenafil 20 mg TID (Body Weight >20 kg)	Total
Part 1			
Number (%) of Subjects	**N=3**	**N=3**	**N=6**
Discontinuations			
Relation to study drug not defined	1 (33.3)	2 (66.7)	3 (50.0)
Insufficient clinical response	1 (33.3)	2 (66.7)[a]	3 (50.0)
Total	1 (33.3)	2 (66.7)	3 (50.0)
Part 2			
Number (%) of Subjects	**N=2**	**N=1**	**N=3**
Relation to study drug not defined	1 (50.0)	1 (100.0)	2 (66.7)
Other	1 (50.0)	1 (100.0)	2 (66.7)
Total	1 (50.0)	1 (100.0)	2 (66.7)

Abbreviations: N=number of subjects; TID=ter in die.
a. One (1) subject was withdrawn upon completion of Part 1.

During Part 1 of the study, all 6 subjects (3 males and 3 females) were of Asian race. The mean age of subjects was 6.7 years with an age range of 1-14 years. The mean weight of the subjects was 28.9 kg with the range of 9-56 kg. The mean body mass index (BMI) was 18.6 kg/m^2 with the range of 14.2-26.1 kg/m^2. The mean height was 115.1 cm with the range of 78-150 cm.

A total of 3 subjects (1 male and 2 females) entered Part 2 of the study; the mean age of subjects was 5.0 years with the age range of 1-10 years. The mean weight of the subjects was 27.1 kg with the range of 9-56 kg. The mean BMI was 18.8 kg/m^2 with the range of 14.2-26.1 kg/m^2. The mean height was 108.9 cm with the range of 78-146 cm.

Efficacy and Pharmacokinetic Results:

Efficacy Results:

Part 1: The summary of efficacy endpoints during Part 1 of the study is presented in Table 5. The efficacy endpoints were the change from baseline to Week 16/EoT for PVRI, mPAP, WHO functional class, BNP and NT pro-BNP. For all 6 subjects the change from baseline to Week 16/EoT on PVRI during Part 1, the mean (SD) change was -1.822 (7.5320) Wood Units × m^2. The mean (SD) change in mPAP was -0.6 (18.61) mm Hg. The mean (SD) change from baseline in WHO functional class was -0.2 (0.41). The mean (SD) change from baseline in BNP was 40.93 (247.711) pg/mL and for NT pro-BNP was -73.07 (1398.397) pg/mL.

Table 5. Summary of Efficacy Endpoints (Part 1)

Parameter (Units)	PVRI (Wood Units × m^2)	mPAP (mm Hg)	WHO Functional Class	BNP (pg/mL)	NT Pro-BNP (pg/mL)
Sildenafil 10 mg TID (body weight ≤20 kg)					
Subject 1					
Baseline	4.21	26	CLASS I	17.3	84
Week 16/EoT	7.32	33	CLASS I	7.7	43.5
Change from baseline	3.11	7	0	-9.6	-40.5
Subject 2					
Baseline	10.89	45	CLASS II	275	2370
Week 16/EoT	2.56	28	CLASS I	17	164
Change from baseline	-8.33	-17	-1	-258	-2206
Subject 3					
Baseline	18.21	62	CLASS I	211	2200
Week 16/EoT	Not done	Not done	CLASS I	213	1770
Change from baseline	-	-	0	2	-430
Total (N=3)	3	3	3	3	3
Baseline: Mean	11.103	44.3	1.3	167.77	1551.33
Week 16/EoT: Mean	4.940	30.5	1.0	79.23	659.17
Change from baseline: Mean (SD)	-2.610 (8.0893)[a]	-5.0 (16.97)[a]	-0.3 (0.58)	-88.53 (146.877)	-892.17 (1154.360)
Median	-2.610[a]	-5.0[a]	0.0	-9.60	-430.00
Minimum, maximum	-8.33, 3.11	-17, 7	-1, 0	-258.0, 2.0	-2206.0, -40.5
Sildenafil 20 mg TID (body weight >20 kg)					
Subject 4					
Baseline	33.52	82	CLASS III	276	271
Week 16/EoT	40.86	105	CLASS III	776	2450
Change from baseline	7.34	23	0	500	2179
Subject 5					
Baseline	12.92	50	CLASS II	8.2	62
Week 16/EoT	12.18	56	CLASS II	22	150
Change from baseline	-0.74	6	0	13.8	88
Subject 6					
Baseline	31.65	86	CLASS II	8.2	71.2
Week 16/EoT	21.16	64	CLASS II	5.6	42.3
Change from baseline	-10.49	-22	0	-2.6	-28.9
Total (N=3)	3	3	3	3	3
Baseline: Mean	26.030	72.7	2.3	97.47	134.73
Week 16/EoT: Mean	24.733	75.0	2.3	267.87	880.77
Change from baseline: Mean (SD)	-1.297 (8.9280)	2.3 (22.72)	0.0 (0.00)	170.40 (285.560)	746.03 (1242.361)
Median	-0.740	6.0	0.0	13.80	88.00
Minimum, maximum	-10.49, 7.34	-22, 23	0, 0	-2.6, 500.0	-28.9, 2179.0
Total (N=6)					
Baseline: Mean	18.567	58.5	1.8	132.62	843.03

Table 5. Summary of Efficacy Endpoints (Part 1)

Parameter (Units)	PVRI (Wood Units × m^2)	mPAP (mm Hg)	WHO Functional Class	BNP (pg/mL)	NT Pro-BNP (pg/mL)
Week 16/EoT: Mean	16.816[b]	57.2[b]	1.7	173.55	769.97
Change from baseline: Mean (SD)	-1.822 (7.5320)[b]	-0.6 (18.61)[b]	-0.2 (0.41)	40.93 (247.711)	-73.07 (1398.397)
Median	-0.740[b]	6.0[b]	0.0	-0.30	-34.70
Minimum, maximum	-10.49, 7.34	-22, 23	-1, 0	-258.0, 500.0	-2206.0, 2179.0

Abbreviations: BNP=brain natriuretic peptide; EoT=end of treatment; mPAP=mean pulmonary artery pressure; N=number of subjects; NT pro-BNP=N-terminal pro-brain natriuretic peptide; PVRI=pulmonary vascular resistance index; SD=standard deviation; TID=ter in die; WHO=World Health Organization.

a. Evaluation was performed on 2 subjects.

b. Total number of subjects here were 5, as only 2 subjects in the sildenafil 10 mg TID group were evaluated at Week 16/EoT.

Part 2: The summary of efficacy endpoints during Part 2 of the study is presented in Table 6. Three (3) subjects were excluded from efficacy evaluations (due to not entering Part 2). The efficacy endpoints were change from baseline to every 12 weeks after Week 16 for WHO functional class and change from baseline to Week 52/EoT for BNP and NT pro-BNP. The mean (SD) change from baseline to Week 52/EoT in average WHO functional class was -0.3 (0.58). The mean (SD) change from baseline to Week 52/EoT in BNP was -85.17 (155.088) pg/mL and for NT pro-BNP was -754.90 (1335.370) pg/mL.

Table 6. Summary of Efficacy Endpoints (Part 2)

Parameter (Units)	WHO Functional Class	BNP (pg/mL)	NT Pro-BNP (pg/mL)
Sildenafil			
Subject 1			
Baseline	CLASS I	17.3	84
Week 52/EoT	CLASS I	18.1	81.2
Change from baseline	0	0.8	-2.8
Subject 2			
Baseline	CLASS II	275	2370
Week 52/EoT	CLASS I	10.8	73.3
Change from baseline	-1	-264.2	-2296.7
Subject 3			
Baseline	CLASS II	8.2	71.2
Week 52/EoT	CLASS II	16.1	106
Change from baseline	0	7.9	34.8
Total (N=3)	3	3	3
Baseline: Mean	1.7	100.17	841.73
Week 52/EoT: Mean	1.3	15.00	86.83
Change from baseline Mean (SD)	-0.3 (0.58)	-85.17 (155.088)	-754.90 (1335.370)
Median	0.0	0.80	-2.80
Minimum, maximum	-1, 0	-264.2, 7.9	-2296.7, 34.8

Abbreviations: BNP=brain natriuretic peptide; N=number of subjects; NT pro-BNP=N-terminal pro-brain natriuretic peptide; SD=standard deviation; Week 52/End of Treatment (EoT)=observations at Week 52 or the last observations before Week 52 if a subject discontinued before Week 52; WHO=World Health Organization.

Pharmacokinetic Results:

Sildenafil: Plasma sildenafil PK parameter values at steady state are summarized descriptively by body weight and by concomitant PAH treatment (beraprost) in Table 7 and Table 8, respectively.

Following administration of sildenafil TID dosing for 16 weeks, C_{max} was observed at 1 hour postdose. Total exposure (AUC_{tau}) following 10 mg TID (body weight ≤20 kg) and 20 mg TID (body weight >20 kg) dosing of sildenafil were comparable, but peak exposure (C_{max}) was higher for 10 mg TID dosing than that in 20 mg TID group. The geometric means for AUC_{tau} were 365.2 and 314.5 ng•h/mL for 10 mg and 20 mg TID dosing groups, respectively, and the geometric means for C_{max} were 184.9 and 103.2 ng/mL, respectively. The geometric mean $C_{ss,av}$ was higher in 10 mg TID dosing group than that in 20 mg TID group, and the geometric mean C_{trough} was higher in 20 mg TID dosing group than that in 10 mg dosing group. Only very limited number of subjects had reportable terminal $t_{½}$ and the values were comparable between 10 mg and 20 mg TID dosing groups.

When grouped by concomitant PAH treatment (beraprost), only 1 subject (out of total 6 subjects) was with PAH treatment. The geometric means for AUC_{tau} and C_{max} for sildenafil without PAH treatment were 331.8 ng•h/mL and 130.1 ng/mL, respectively, and the values for the 1 subject in the group with PAH treatment were 377 ng•h/mL and 186 ng/mL for AUC_{tau} and C_{max}, respectively. Total exposure (AUC_{tau}) was comparable for

the subjects with or without PAH treatment, but peak exposure (C_{max}) seemed to be higher in the subject with concomitant PAH treatment as compared to the subjects without PAH treatment. $C_{ss,av}$ and C_{trough} were comparable for the subjects with or without PAH treatment. Only a very limited number of subjects had reportable terminal $t_{½}$ and the values were comparable between the subjects with or without PAH treatment.

Inter-subject variability for plasma sildenafil exposure (based on geometric percent coefficient of variation [%CV] of geometric means) was 54% and 73% for AUC_{tau} and C_{max}, respectively.

Table 7. Descriptive Summary of Plasma Sildenafil Pharmacokinetic Parameter Values at Steady State by Body Weight Following Oral Doses of Sildenafil for 16 Weeks

Parameter (Units)	Parameter Summary Statistics[a] by Treatment		
	10 mg TID (Body Weight ≤20 kg)	20 mg TID (Body Weight >20 kg)	All Subjects
N, n	3, 1	3, 1	6, 2
AUC_{tau} (ng•h/mL)	365.2 (53)	314.5 (69)	338.9 (54)
CL/F (L/h)	27.35 (53)	63.67 (68)	41.73 (77)
$C_{ss,av}$ (ng/mL)	45.67 (53)	39.31 (68)	42.37 (54)
C_{max} (ng/mL)	184.9 (84)	103.2 (58)	138.1 (73)
C_{trough} (ng/mL)	7.408 (52)	16.69 (61)	11.12 (72)
T_{max} (h)	1.00 (1.00-1.97)	1.00 (1.00-1.02)	1.00 (1.00-1.97)
V_z/F (L)[b]	62.4	93.4	62.4, 93.4
$t_{½}$ (h)[b]	1.63	1.94	1.63, 1.94

Abbreviations: %CV=percent coefficient of variation; AUC_{tau}=area under the plasma concentration-time curve over dosing interval tau (τ), where tau=8 hours; CL/F=apparent total clearance of drug from plasma after oral administration; C_{max}=maximum observed plasma concentration; $C_{ss,av}$=average plasma concentration at steady state; C_{trough}=trough plasma concentration; N=number of subjects in the treatment group; n=number of subjects with reportable $t_{½}$ and V_z/F; $t_{½}$=terminal half-life; TID=ter in die; T_{max}=time for C_{max}; V_z/F=apparent volume of distribution estimated from terminal phase after oral administration.

a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}.
b. Individual values were listed in the table when the number of subjects with reportable values in the group was <3.

Table 8. Descriptive Summary of Plasma Sildenafil Pharmacokinetic Parameter Values at Steady State by Concomitant PAH Treatment Following Oral Doses of Sildenafil for 16 Weeks

Parameter (Units)	Parameter Summary Statistics[a] by Treatment		
	Sildenafil (PAH Treatment: None)	Sildenafil (PAH Treatment: Beraprost)[b]	All Subjects
N, n	5, 1	1, 1	6, 2
AUC_{tau} (ng•h/mL)	331.8 (61)	377	338.9 (54)
CL/F (L/h)	45.70 (83)	26.5	41.73 (77)
$C_{ss,av}$ (ng/mL)	41.48 (61)	47.1	42.37 (54)
C_{max} (ng/mL)	130.1 (82)	186	138.1 (73)
C_{trough} (ng/mL)	11.57 (82)	9.11	11.12 (72)
T_{max} (h)	1.00 (1.00-1.97)	1.00	1.00 (1.00-1.97)
V_z/F (L)[b]	93.4	62.4	62.4, 93.4
$t_{½}$ (h)[b]	1.94	1.63	1.63, 1.94

Abbreviations: %CV=percent coefficient of variation; AUC_{tau}=area under the plasma concentration-time curve over dosing interval tau (τ), where tau=8 hours; CL/F=apparent total clearance of drug from plasma after oral administration; C_{max}=maximum observed plasma concentration; $C_{ss,av}$=average plasma concentration at steady state; C_{trough}=trough plasma concentration; N=number of subjects in the treatment group; n=number of subjects with reportable $t_{½}$ and V_z/F; PAH=pulmonary arterial hypertension; $t_{½}$=terminal half-life; TID=ter in die; T_{max}=time for C_{max}; V_z/F=apparent volume of distribution estimated from terminal phase after oral administration.

a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}.
b. Individual values were listed in the table when the number of subjects with reportable values in the group was <3.

UK-103,320: Plasma UK-103,320 PK parameter values at steady state are summarized descriptively by body weight and by concomitant PAH treatment (beraprost) in Table 9 and Table 10, respectively.

Following administration of sildenafil TID dosing for 16 weeks, C_{max} was observed at 1 hour postdose. The geometric means for AUC_{tau} were 167.9 and 263.3 ng•h/mL for 10 mg and 20 mg TID dosing groups, respectively, and the geometric means for C_{max} were 62.33 and 87.05 ng/mL, respectively. Total (AUC_{tau}) and peak (C_{max}) UK-103,320 exposure following sildenafil 10 mg TID (body weight ≤20 kg) was lower than that in sildenafil 20 mg TID (body weight >20 kg) group. Only a very limited number of subjects had reportable terminal $t_{½}$ for UK-103,320 and the values were comparable between sildenafil 10 mg and 20 mg TID dosing groups.

When grouped by concomitant PAH treatment (beraprost), only 1 subject (out of total 6 subjects) was with PAH treatment. The geometric means for AUC_{tau} and C_{max} of UK-103,320 following sildenafil without PAH treatment were 227.4 ng•h/mL and 76.85 ng/mL, respectively, and the values for the 1 subject in the group with PAH treatment were 142 ng•h/mL and 59.6 ng/mL for AUC_{tau} and C_{max}, respectively. Total (AUC_{tau}) and peak (C_{max}) exposure was lower in the subject with PAH treatment as compared to the subjects without PAH treatment. Only a very limited number of subjects had reportable terminal $t_{½}$ and the value were comparable between the subjects with or without PAH treatment.

Inter-subject variability for plasma UK-103,320 exposure (based on geometric %CV of geometric means) was 74% and 48% for AUC_{tau} and C_{max}, respectively.

Table 9. Descriptive Summary of Plasma UK-103,320 Pharmacokinetic Parameter Values at Steady State by Body Weight Following Oral Doses of Sildenafil for 16 Weeks

Parameter (Units)	Parameter Summary Statistics[a] by Treatment		
	10 mg TID (Body Weight ≤20 kg)	20 mg TID (Body Weight >20 kg)	All Subjects
N, n	3, 2	3, 1	6, 3
AUC_{tau} (ng•h/mL)	167.9 (19)	263.3 (122)	210.2 (74)
C_{max} (ng/mL)	62.33 (13)	87.05 (72)	73.66 (48)
T_{max} (h)	1.00 (1.00-1.97)	1.00 (1.00-1.02)	1.00 (1.00-1.97)
$t_{½}$ (h)[b]	2.04, 3.26	2.11	2.47±0.685

Abbreviations: %CV=percent coefficient of variation; AUC_{tau}=area under the plasma concentration-time curve over dosing interval tau (τ), where tau=8 hours; C_{max}=maximum observed plasma concentration; N=number of subjects in the treatment group; n=number of subjects with reportable $t_{½}$; $t_{½}$=terminal half-life; TID=ter in die; T_{max}=time for C_{max}.

a. Geometric mean (geometric %CV) for all except: median (range) for T_{max} and arithmetic mean (standard deviation) for $t_{½}$.
b. Individual values were listed in the table when the number of subjects with reportable values in the group was <3.

Table 10. Descriptive Summary of Plasma UK-103,320 Pharmacokinetic Parameter Values at Steady State by Concomitant PAH Treatment Following Oral Doses of Sildenafil for 16 Weeks

Parameter (Units)	Parameter Summary Statistics[a] by Treatment		
	Sildenafil (PAH Treatment: None)	Sildenafil (PAH Treatment: Beraprost)[b]	All Subjects
N, n	5, 2	1, 1	6, 3
AUC_{tau} (ng•h/mL)	227.4 (81)	142	210.2 (74)
C_{max} (ng/mL)	76.85 (53)	59.6	73.66 (48)
T_{max} (h)	1.00 (1.00-1.97)	1.00	1.00 (1.00-1.97)
$t_{½}$ (h)[b]	2.04, 2.11	3.26	2.47±0.685

Abbreviations: %CV=percent coefficient of variation; AUC_{tau}=area under the plasma concentration-time curve over dosing interval tau (τ), where tau=8 hours; C_{max}=maximum observed plasma concentration; N=number of subjects in the treatment group; n=number of subjects with reportable $t_{½}$; PAH=pulmonary arterial hypertension; $t_{½}$=terminal half-life; T_{max}=time for C_{max}.

a. Geometric mean (geometric %CV) for all except: median (range) for T_{max} and arithmetic mean (standard deviation) for $t_{½}$.
b. Individual values were listed in the table when the number of subjects with reportable values in the group was <3.

Safety Results:

Non-Serious Adverse Events: The incidences of all-causality and treatment-related treatment-emergent adverse events (TEAEs) by system organ class (SOC) and preferred term are presented in Table 11. Overall, the Medical Dictionary for Regulatory Activities SOC with the highest number of TEAEs included Infections and infestations, Gastrointestinal disorders, Respiratory, thoracic and mediastinal disorders, Skin and subcutaneous tissue disorders and Investigations.

Table 11. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA Preferred Term	Sildenafil		
Number (%) of Subjects:	**N (%)**	**n[1]**	**n[2]**
Subjects evaluable for AEs	6	-	-
Subjects with AEs	6 (100.00)	-	-
Cardiac disorders	1 (16.67)	1	0
Cardiac failure	1 (16.67)	1	0
Eye disorders	1 (16.67)	3	2
Conjunctivitis allergic	1 (16.67)	1	0
Vision blurred	1 (16.67)	1	1
Visual acuity reduced transiently	1 (16.67)	1	1
Gastrointestinal disorders	4 (66.67)	6	0
Colitis	1 (16.67)	2	0
Dental caries	1 (16.67)	1	0
Diarrhoea	2 (33.33)	2	0
Vomiting	1 (16.67)	1	0
General disorders and administration site conditions	1 (16.67)	2	1
Chest pain	1 (16.67)	1	0
Feeling abnormal	1 (16.67)	1	1
Infections and infestations	5 (83.33)	21	0
Bronchitis	3 (50.00)	4	0
Gastroenteritis	2 (33.33)	2	0
Influenza	1 (16.67)	1	0
Molluscum contagiosum	1 (16.67)	1	0
Nasopharyngitis	3 (50.00)	6	0
Streptococcal infection	1 (16.67)	1	0
Upper respiratory tract infection	3 (50.00)	6	0
Investigations	3 (50.00)	7	1
Alanine aminotransferase increased	1 (16.67)	2	0
Ammonia increased	1 (16.67)	1	0
Aspartate aminotransferase increased	1 (16.67)	2	0
Blood urine present	1 (16.67)	1	1
Weight increased	1 (16.67)	1	0
Musculoskeletal and connective tissue disorders	1 (16.67)	1	1
Myalgia	1 (16.67)	1	1
Nervous system disorders	2 (33.33)	7	7
Headache	2 (33.33)	7	7
Reproductive system and breast disorders	2 (33.33)	3	2
Dysmenorrhoea	1 (16.67)	1	0
Erection increased	1 (16.67)	2	2
Respiratory, thoracic and mediastinal disorders	3 (50.00)	4	2
Epistaxis	2 (33.33)	2	2
Pulmonary arterial hypertension	1 (16.67)	1	0
Rhinitis allergic	1 (16.67)	1	0
Skin and subcutaneous tissue disorders	3 (50.00)	5	0
Acne	1 (16.67)	1	0
Dermatitis diaper	1 (16.67)	1	0
Dry skin	1 (16.67)	1	0

Table 11. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA Preferred Term	Sildenafil		
Number (%) of Subjects:	**N (%)**	**n^1**	**n^2**
Eczema	1 (16.67)	1	0
Rash	1 (16.67)	1	0
Vascular disorders	1 (16.67)	1	1
Flushing	1 (16.67)	1	1

Except for 'n^1' and 'n^2' subjects were only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (Version 20.1) coding dictionary applied.
Abbreviations: AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; N=The number of subjects in this reporting group affected by any occurrence of this adverse event, all-causalities; n^1=the number of occurrences of treatment-emergent all-causalities AEs; n^2=the number of occurrences of treatment-emergent causally related to treatment AEs.

Serious Adverse Events/Deaths: One (1) subject died during the pre-randomization phase of the study due to sudden cardiac death. The subject's medical history included mycoplasma pneumonia and ongoing pulmonary hypertension. The Investigator reported pulmonary hypertension, shock, sudden cardiac death and disease progression as the causes of death. The Investigator classified the event as serious. No other SAEs were reported during the study.

Discontinuations due to Adverse Events: There were no permanent discontinuations due to AE reported in this study. During Part 1 of the study, 1 subject was temporarily discontinued from treatment due to AEs. No subject had dose reductions during Part 1 of the study. There were no temporary discontinuations or dose reductions reported during Part 2 of the study.

Clinical Laboratory Results: Overall, there were no clinically significant observable trends of differences between the treatment groups for any laboratory parameter.

Vital Signs: Overall, there were no clinically observable trends of differences between the treatment groups for any vital signs data.

Electrocardiogram: Five (5) subjects were reported with abnormal, clinically significant changes in ECG at Week 16 during Part 1 of the study. None of them was reported as an AE. During Part 2 of the study at Week 52, 1 subject reported with abnormal clinically significant change in ECG (right axis deviation and right ventricular hypertrophy). No subject showed any abnormal clinically significant change in ECG at Part 2, EoT compared to screening.

Physical Findings: No subjects enrolled in the study had physical findings related to eyes and ocular fundi during study.

CONCLUSIONS:

- For the efficacy endpoints of change from baseline to Week 16 on PVRI, mPAP, WHO functional class for PAH and NT pro-BNP, the mean change with sildenafil treatment (>20 kg: 20 mg TID [60 mg/day], ≤20 kg: 10 mg TID [30 mg/day]) suggested an improvement in efficacy in the Japanese pediatric subjects. The mean (SD) change from baseline to Week 16/EoT in BNP did not show an improvement among 6 subjects in this study.

- For the analysis of long-term efficacy of sildenafil in Japanese pediatric subjects with PAH, the analysis of efficacy endpoints for Part 2 (WHO functional class for PAH, BNP and NT pro-BNP) showed an improvement in efficacy in the Japanese pediatric subjects after 52 weeks of treatment with sildenafil.

- Sildenafil was generally well tolerated with most AEs being of mild or moderate severity. There were no treatment-emergent deaths or SAEs.

- The geometric means of AUC_{tau} and C_{max} of sildenafil at steady state in Japanese pediatric subjects with PAH following 10 mg (body weight ≤20 kg) and 20 mg (body weight >20 kg) TID dosing for 16 weeks were 338.9 ng•h/mL and 138.1 ng/mL, respectively.

- Total sildenafil exposure (AUC_{tau}) following 10 mg TID (body weight ≤20 kg) and 20 mg TID (body weight >20 kg) dosing of sildenafil were comparable in Japanese pediatric subjects with PAH.

- The geometric means of AUC_{tau} and C_{max} of UK-103,320 at steady state in Japanese pediatric subjects with PAH following sildenafil 10 mg (body weight ≤20 kg) and 20 mg (body weight >20 kg) TID dosing for 16 weeks were 210.2 ng•h/mL and 73.66 ng/mL, respectively.