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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Revatio® / Sildenafil citrate (generic name)

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See United States Package Insert (USPI)

NATIONAL CLINICAL TRIAL NO.: NCT00454207

PROTOCOL NO: A1481252

PROTOCOL TITLE: A phase 3, multi-center, open-label study to confirm safety, efficacy, and tolerability of sildenafil citrate 20 mg tid in subjects with pulmonary arterial hypertension

Study Centers: Eight centers in Japan

Study Initiation Date and Primary Completion or Completion Dates: 16 April 2007 to 18 February 2009

Phase of Development: Phase 3

Study Objectives: To investigate the following endpoints in Japanese patients with pulmonary arterial hypertension (PAH) who were treated with sildenafil

Primary objectives:

- To confirm the safety of sildenafil 20 mg three times a day (tid) orally administered to PAH patients.
- To confirm the efficacy after 12 weeks of treatment of sildenafil 20 mg tid orally administered to PAH patients (Part I).

Secondary objectives:

- To confirm the efficacy after 12 weeks of treatment of sildenafil 20 mg tid orally administered to PAH patients who have been receiving sildenafil at doses higher than 60 mg/day (Part II).
- To investigate the pharmacokinetics of sildenafil and its metabolite at steady state following oral sildenafil administration at 20 mg tid in PAH patients.

METHODS

Study Design: This was a multi-center, open-label study, consisting of the following 2 dosing periods. Subjects who participated in the study before sildenafil obtained marketing approval, their visiting and treatment schedule remained unchanged during the study.

1) Part I: Screening period and treatment period (12-week dosing period)
Target subjects: PAH patients who had never received sildenafil therapy.

2) Part II: Long-term treatment period
Target subjects: 1. Subjects who completed the treatment period (Part I)
However, if sildenafil received approval for the PAH indication during participation in Part I in Japan and the method for supply of sildenafil to the subjects was established, subjects could not transfer to Part II.

2. Subjects with PAH who were continuously using sildenafil (Viagra) and who agreed that their data could be used for the meta-analysis of the physician-led research.

In Part I, the study consisted of five visits (screening period [Day -28 to -1], start of treatment [Day 1], and Weeks 4, 8, and 12) and one telephone call (Week 1). The subjects enrolled in Part II had a clinic visit at Week 4 and telephone contact (Week 1) and clinic visits every 12 weeks.

For the subjects who participated in the study from Part I, the data on the 6-minute walk distance, WHO functional class, BORG dyspnoea score, and plasma brain natriuretic peptide (BNP) level evaluated at Day 1 were defined as the baseline data. However, if the BNP tests for screening were conducted within 2 weeks before Day 1, the data from the tests could be used as the baseline data. For the evaluation of the haemodynamic parameters, the right heart catheterization was conducted at screening or Day 1, and either data were used as the baseline data. For the subjects who participated in the study from Part II, the data on all efficacy endpoints (the 6-minute walk distance, WHO functional class, BORG dyspnoea score, and plasma BNP level) evaluated at Visit 5 were defined as the baseline data.

Number of Subjects (Planned and Analyzed): Target sample size was defined as 20 subjects for Part I, 50 subjects for Part II and 6 subjects for PK analysis. 21 subjects were enrolled in Part I and 40 subjects (17 subjects transformed from Part I and 23 subjects participated in the study from Part II) were enrolled in Part II, 9 subjects were assessed for PK analysis.

Diagnosis and Main Criteria for Inclusion:
Part I:

- Male and female subjects aged 16 years or older and diagnosed with PAH with a mean pulmonary artery pressure of ≥25 mmHg and a mean pulmonary capillary wedge pressure of ≤15 mmHg by right heart catheterization (at rest) at screening or baseline

Part II:

- Subjects who completed Part I and gave written consent to participation in Part II

- Subjects who consented to provide their data to the physician-led research meta-analysis conducted by the sponsor, and were continuously using sildenafil (Viagra) for the treatment of PAH at the start of the study

Study Treatment: Throughout Part I and Part II, subjects took a sildenafil citrate 20 mg tablet tid orally at intervals of at least 6 hours. The treatment duration of Part I was 12 weeks. The treatment duration of Part II was not stipulated; however, administration was allowed until sildenafil was available to subjects after regulatory approval in Japan for the indication of PAH.

Efficacy Evaluations:
Primary endpoints
Part I:

- Change in the 6-minute walk distance from baseline to Week 12.
- Change in the haemodynamic parameters (mean pulmonary arterial pressure, pulmonary vascular resistance, and cardiac output) from baseline to Week 12.

Secondary endpoints
Part I:

- Change in the 6-minute walk distance from baseline to Week 8.
- Changes in the WHO functional class from baseline to Weeks 4, 8, and 12.
- Changes in the haemodynamic parameters (pulmonary arterial pressure [systolic, diastolic], systemic blood pressure [systolic, diastolic, mean], pulmonary capillary wedge pressure [PCWP], right atrial pressure, cardiac index, heart rate, pulmonary vascular resistance index, systemic vascular resistance, systemic vascular resistance index, arterial oxygen saturation, arterial oxygen partial pressure, mixed venous oxygen saturation, partial pressure of mixed venous oxygen) from baseline to Week 12.
- Changes in the BORG dyspnoea score from baseline to Weeks 8 and 12.
- Changes in the plasma BNP level from baseline to Weeks 4, 8, and 12.

Part II:
The following parameters were evaluated in PAH subjects who entered the study from Part II and had received sildenafil (Viagra) at doses higher than 60 mg/day before the start of this study.

- Change in the 6-minute walk distance from baseline to Week 12.
- Change in the WHO functional class from baseline to Week 12.
- Changes in the BORG dyspnoea score from baseline to Week 12.
- Changes in the plasma BNP level from baseline to Week 12.

Pharmacokinetic Evaluations: Plasma concentrations and PK parameters of sildenafil and its metabolite, UK-103,320, at steady state following sildenafil administration.

Safety Evaluations: Adverse events, physical examinations, laboratory tests, vital signs (blood pressure, pulse rate, and body weight), 12-lead electrocardiogram (ECG), and

ophthalmological findings (medical examination, visual acuity test, color vision test, and fundus examination)

Statistical Methods:

Analysis sets:

Efficacy was analyzed in the Full Analysis Set (FAS). The analysis of primary endpoints was also performed in the Per Protocol Set (PPS). PPS was defined only in the subjects who participated in the study from Part I.

FAS:

For subjects participated in the study from Part I : FAS consisted of all subjects who took at least one dose of study medication and underwent efficacy assessments at both baseline and post-baseline.

For subjects participated in the study from Part II : Only subjects who received sildenafil (Viagra) at doses higher than 60 mg/day before study start were evaluated for efficacy. For these subjects, FAS consisted of the subjects who took at least one dose of study medication and underwent efficacy assessments at both baseline and post-baseline.

PPS:

PPS was defined as a subset of FAS (subjects from Part I only) who met the following criteria.

Efficacy assessments for the primary endpoints were conducted.

There were no violations of the inclusion criteria and the exclusion criteria that might affect the primary efficacy endpoints.

Any prohibited concomitant medications, which might affect the primary efficacy endpoints, were not taken during the study.

Drug compliance was within the range from 80 to 100% during Part I

Efficacy analysis in the subjects participated in the study from Part I

To investigate the time-course changes in the 6-minute walking distance, haemodynamic parameters, BORG dyspnoea score and plasma BNP level, summary statistics (sample size, mean value, and standard deviation) and the two-sided 95% confidence interval of the mean value of the actual measurements and the changes from baseline were calculated at each evaluation time point. For the primary efficacy endpoints, the two-sided 95% confidence interval of the mean value of the actual measurements and the two-sided 95% confidence interval of the mean value of the changes from baseline were plotted on an evaluation time point. For the primary efficacy endpoints, summary statistics of the actual measurements and the changes from baseline were calculated at each evaluation time point for the subgroups of the sildenafil monotherapy group and the sildenafil and beraprost co-administration group.

Efficacy analysis in the subjects participated in the study from Part II

For the 6-minute walking distance, BORG dyspnoea score and plasma BNP level, summary statistics (sample size, mean, and standard deviation) and the two-sided 95% confidence interval of the mean value of the actual measurements and the changes from baseline (Visit 5) to Week 12 were calculated.

If the values measured at Week 12 were missing in both the efficacy analysis of the subjects who participated in the study from Part I and the efficacy analysis of the subjects who participated in the study from Part II, the values measured at the previous evaluation time point nearest to Week 12 (or the time of discontinuation) were imputed using the LOCF (last observation carried forward) method.

PK analysis

PK parameters of sildenafil and its metabolite, UK-103,320, were evaluated in the subjects who received sildenafil monotherapy, without administration of other treatment drugs for PAH, in Part I or II, and satisfied the inclusion criteria for PK evaluation without violating the exclusion criteria.

Maximum plasma concentrations (Cmax) and time to first occurrence of Cmax (Tmax) were calculated from the observed value of plasma concentrations in each subject. The area under the plasma concentration curve from time zero to time 8 hours (AUC_{0-8}) was calculated using the linear/log trapezoidal rule. The average plasma concentration of sildenafil at steady state (Css,av) was obtained from AUC_{0-8}/ dosing interval (8 hours), and the plasma trough concentration (Ctrough) of sildenfail was obtained from the observed value before administration of the drug in each subject.

Safety analysis

Safety analysis set consisted of all subjects who took at least one dose of study medication. The safety analysis was conducted for the group of subjects participated in the study from Part I, the group of subjects participated in the study from Part II, and the combined group respectively.

RESULTS

Subject Disposition and Demography: The subjects enrolled in the study and those analyzed are shown in Table 1.

Table 1. Subject Disposition and Subjects Analyzed

	Subjects participated in the study from Part I	Subjects participated in the study from Part II
Enrolled	21	23
Treated	21	23
Completed	17[a)]	21
Discontinued:		
Part I	2	-
Part II	2	2
Analyzed for Efficacy:		
FAS	20	7
PPS	16	-[b)]
Analyzed for PK:	7	2
Analyzed for Safety:	21	23
Adverse events	21	23
Laboratory data	20	23

a) Subjects who completed Part I, and completed Part II
b) PPS was not defined for the subjects in Part II.

The demographic characteristics and baseline characteristics are summarized in Table 2.

Table 2 Demographic Characteristics and Baseline Characteristics

		Subjects participated in the study from Part I	Subjects participated in the study from Part II
Sex:	Male	4	2
	Female	17	21
Age (years)	< 18	0	1
	18 - 44	9	8
	45 - 64	10	12
	≥65	2	2
	Mean±SD	47.1±14.7	47.6±14.3
Weight (kg)	Mean±SD	58.5±10.6	53.2±14.5
WHO functional class	I	0	1
	II	7	6
	III	14	0
	IV	0	0

For subjects participated in the study from Part I, 6 subjects were diagnosed with idiopathic PAH, 5 subjects with familial PAH, and 10 subjects with PAH accompanying various underlying diseases. For subjects participated in the study from Part II, 9 subjects were diagnosed with idiopathic PAH and 14 subjects with PAH accompanying various underlying diseases.

Concomitant drug treatment for PAH is shown in Table 3.

Table 3 Concomitant Drug Treatment (Treatment Drugs for PAH and Basic Treatment Drugs for PAH)

	Subjects participated in the study from Part I	Subjects participated in the study from Part II
Number of Subjects	21	23
Treatment drugs for PAH:		
Beraprost	9	15
Bosentan	3 [a)]	7
Basic treatment drugs for PAH:		
Warfarin	9	10
Inotropic agents (digoxin etc.)	0	1
Calcium channel antagonist	12	9
Diuretic agent	22	16
Oxygen therapy	14	12

a)The concomitant use of bosentan was prohibited for subjects in Part I, however it was allowed in Part II and 3 subjects took bosentan after entering Part II.

Efficacy Results:

Subjects participated in the study from Part I:

The 6-minute walk distance, results for subjects participated in the study from Part I are shown in Table 4. A similar result was obtained in the PPS.

Table 4 Observed Values and Changes of the 6-Minute Walk Distance from Baseline to Week 8 and Week 12 in FAS who Participated in the Study from Part I

		6-Minute walk distance (m)	
		Observed values	Changes from baseline
Subjects participated in the study from Part I			
Baseline:	Number of subjects	20	-
	Mean±SD	326.0±86.2	-
	(95% CI of Mean)	(285.7, 366.3)	-
At Week 8:	Number of subjects	19	19
	Mean±SD	410.2±72.9	87.5±75.3
	(95% CI of Mean)	(375.0, 445.3)	(51.2, 123.8)
At Week 12 or at the time of withdrawal (LOCF)	Number of subjects	20	20
	Mean±SD	410.2±66.6	84.2±74.9
	(95% CI of Mean)	(379.0, 441.3)	(49.1, 119.2)
Sildenafil monotherapy			
Baseline:	Number of subjects	11	-
	Mean±SD	374.8±62.6	-
	(95% CI of Mean)	(332.8, 416.8)	-
At Week 8:	Number of subjects	10	10
	Mean±SD	444.4±69.5	71.1±52.4
	(95% CI of Mean)	(394.7, 494.1)	(33.6, 108.6)
At Week 12 or at the time of withdrawal (LOCF)	Number of subjects	11	11
	Mean±SD	440.8±50.1	66.0±50.8
	(95% CI of Mean)	(407.1, 474.5)	(31.9, 100.1)
Sildenafil and beraprost combination therapy			
Baseline:	Number of subjects	9	-
	Mean±SD	266.3±74.0	-
	(95% CI of Mean)	(209.4, 323.2)	-
At Week 8:	Number of subjects	9	9
	Mean±SD	372.1±58.5	105.8±94.6
	(95% CI of Mean)	(327.1, 417.1)	(33.0, 178.5)
At Week 12 or at the time of withdrawal (LOCF)	Number of subjects	9	9
	Mean±SD	372.7±67.3	106.3±95.3
	(95% CI of Mean)	(321.0, 424.4)	(33.1, 179.6)

SD: Standard deviation, CI: confidence interval, LOCF: Last observation carried forward

The hemodynamic parameters results for subjects participated in the study from Part I are shown in Table 5.

Table 5 Hemodynamic Parameters (mean pulmonary arterial pressure, pulmonary vascular resistance, and cardiac output) at Baseline and Week 12 in FAS who Participated in the Study from Part I

	Hemodynamic parameters	Mean pulmonary arterial pressure (mmHg)		Pulmonary vascular resistance (dyne·sec/cm^5)		Cardiac output (L/min)	
		Actual Measurements	Changes from baseline	Actual Measurements	Changes from baseline	Actual Measurements	Changes from baseline
Subjects participated in the study from Part I: N=20							
Baseline	Mean±SD	48.9±13.1	-	979.61±467.99	-	3.704±1.105	-
	95%CI	(42.7, 55.0)	-	(760.58, 1198.63)	-	(3.187, 4.221)	-
Week 12 (LOCF)	Mean±SD	44.2±14.6	-4.7±8.2	733.12±378.01	-246.49 ±301.17	4.26±1.496	0.556±1.000
	95%CI	(37.3, 51.1)	(-8.5, -0.8)	(556.20, 910.03)	(-387.44, -105.53)	(3.560, 4.960)	(0.088, 1.024)
Sildenafil monotherapy: N=11							
Baseline	Mean±SD	48.7±16.1	-	879.77±475.65	-	4.018±1.154	-
	95%CI	(37.9, 59.5)	-	(560.23, 1199.32)	-	(3.243, 4.793)	-
Week 12 (LOCF)	Mean±SD	45.4±17.2	-3.4±6.3	734.53±464.42	-145.24± 221.28	4.581±1.900	0.563±1.136
	95%CI	(33.8, 56.9)	(-7.6, 0.9)	(422.53, 1046.53)	(-293.90, 3.41)	(3.304, 5.858)	(-0.201, 1.326)
Sildenafil and beraprost combination therapy: N=9							
Baseline	Mean±SD	49.0±9.1	-	1101.62±454.85	-	3.320±0.968	-
	95%CI	(42.0, 56.0)	-	(751.99, 1451.25)	-	(2.576, 4.064)	-
Week 12 (LOCF)	Mean±SD	42.8±11.7	-6.2±10.2	731.39±264.12	-370.23± 350.57	3.868±0.697	0.548±0.872
	95%CI	(33.8, 51.8)	(-14.1, 1.6)	(528.37, 934.41)	(-639.70, -100.76)	(3.332, 4.403)	(-0.122, 1.218)

SD: Standard deviation, CI: confidence interval, N: Number of subjects, BL: Baseline, LOCF: Last observation carried forward.

For subjects participated in the study from Part I, improvement in WHO functional class at Week 12 compared to baseline was observed in 6 subjects (class III to II in 5 subjects and class III to I in 1 subject) and worsening was observed in 1 subject (from class II to III).The remaining 13 subjects maintained the same class as at baseline.

For subjects participated in the study from Part I, the change in the pulmonary vascular resistance index from baseline (mean±SD) to Week 12 (LOCF) was -382.00±491.80 dyne·sec/cm^5/m^2. The observed value (mean±SD) of the pulmonary vascular resistance index at Week 12 (LOCF) was 1199.31±660.73 dyne·sec /cm^5/m^2.

For subjects participated in the study from Part I, the changes in the BORG dyspnoea score from baseline (mean±SD) to Weeks 8 and Week 12 (LOCF) were -0.84±1.89 and -0.95±1.94, respectively; thus the BORG dyspnoea score decreased compared to those at baseline. The plasma BNP level decreased at Week 4 (decrease by 78.00 pg/mL on average) compared to that at baseline (mean±SD: 216.52±204.70 pg/mL), and the decrease was maintained at both Week 8 and Week 12.

Subjects participated in the study from Part II:
Of the 23 subjects participated in the study from Part II, 7 were eligible for efficacy evaluation (FAS) and had received sildenafil 75 mg/day.

In those 7 subjects, the mean 6-minute walk distance at Week 12 (LOCF) decreased by 23.5 m compared to that at baseline (mean±SD: 395.4±97.1 m), and the mean plasma BNP level increased by 15.91 pg/mL compared to that at baseline (mean±SD: 78.64±96.26 pg/mL). The BORG dyspnoea score slightly increased. For WHO functional class at Week 12, the classes at baseline were maintained, except for 1 subject who showed worsening (class II to III) compared to that at baseline.

Pharmacokinetic Results: The pharmacokinetics of sildenafil and its metabolite, UK-103,320, at steady state were investigated when sildenafil was orally administered at doses of 20 mg tid in 9 evaluable subjects. The mean value of Tmax of sildenafil was approximately 1.1 hours post-dose. The mean values (coefficient of variance) of Cmax, AUC_{0-8}, Css,av, and Ctrough of sildenafil at steady state were 164.88 ng/mL (45.4%), 545.14 ng·h/mL (54.1%), 68.14 ng/mL (54.1%), and 19.61 ng/mL (63.4%), respectively, showing relatively large individual variability. UK-103,320 was rapidly produced after undergoing the first pass effect, and the mean value of Tmax was approximately 1.6 hours post-dosing. The mean values (coefficient of variance) of Cmax and AUC_{0-8} of UK-103,320 were 87.27 ng/mL (35.1%) and 365.85 ng·h/mL (51.0%), respectively.

Safety Results: The adverse events reported in the study are summarized in Table 6. Serious adverse events were observed in 7 subjects, and adverse events leading to discontinuation of the study in 4 subjects; however, none of these events was treatment-related. Treatment was temporarily discontinued in 2 subjects due to treatment-related adverse events.

Table 6 Summary of the Adverse Events

Subjects	Subjects participated in the study from Part I	Subjects participated in the study from Part II	Total
Number of subjects	21	23	44
All-causality			
Number of adverse events	101	96	197
Subjects with adverse events	20 (95.2)	22 (95.7)	42 (95.5)
Subjects with serious adverse events	3 (14.3)	4 (17.4)	7 (15.9)[a)]
Subjects with severe adverse events	2 (9.5)	2 (8.7)	4 (9.1)
Subjects who discontinued the study due to adverse events	3 (14.3)	1 (4.3)	4 (9.1)
Subjects with dose reduced or temporarily discontinued due to adverse events	2 (9.5)	0	2 (4.5)

( ): %

a) One subject who developed a serious adverse event before treatment and withdrew from the study was excluded from this table.

The incidence of all-causality adverse events reported in the study are shown in Table 7. The severity of most of these events was mild or moderate and 6 severe adverse events were observed in 4 subjects. The severe adverse events were oedema peripheral/platelet count decreased/anorexia observed in 1 subject, and pneumonia, syncope, and scleroderma renal crisis in 1 subject each.

Table 7 Incidence of All-Causality Adverse Events

Subjects	Subjects participated in the study from Part I	Subjects participated in the study from Part II	Total
Number of subjects	21	23	44
MedDRA (ver. 11.1) System Organ Class and Preferred Term			
Cardiac disorders	3 (14.3)	6 (26.1)	9 (20.5)
Cardiac failure	0	3 (13.0)	3 (6.8)
Gastrointestinal disorders	5 (23.8)	7 (30.4)	12 (27.3)
Diarrhoea	2 (9.5)	2 (8.7)	4 (9.1)
General disorders and administration site conditions	6 (28.6)	2 (8.7)	8 (18.2)
Oedema peripheral	2 (9.5)	1 (4.3)	3 (6.8)
Pyrexia	3 (14.3)	2 (8.7)	5 (11.4)
Infections and infestations	11 (52.4)	12 (52.2)	23 (52.3)
Nasopharyngitis	9 (42.9)	8 (34.8)	17 (38.6)
Injury, poisoning and procedural complications	3 (14.3)	5 (21.7)	8 (18.2)
Fall	1 (4.8)	3 (13.0)	4 (9.1)
Investigations	6 (28.6)	6 (26.1)	12 (27.3)
Platelet count decreased	1 (4.8)	3 (13.0)	4 (9.1)
Musculoskeletal and connective tissue disorders	8 (38.1)	4 (17.4)	12 (27.3)
Back pain	2 (9.5)	1 (4.3)	3 (6.8)
Nervous system disorders	11 (52.4)	3 (13.0)	14 (31.8)
Dizziness	3 (14.3)	1 (4.3)	4 (9.1)
Headache	8 (38.1)	3 (13.0)	11 (25.0)
Psychiatric disorders	3 (14.3)	0	3 (6.8)
Insomnia	3 (14.3)	0	3 (6.8)
Respiratory, thoracic and mediastinal disorders	6 (28.6)	4 (17.4)	10 (22.7)
Cough	2 (9.5)	1 (4.3)	3 (6.8)
Epistaxis	2 (9.5)	1 (4.3)	3 (6.8)
Vascular disorders	7 (33.3)	5 (21.7)	12 (27.3)
Flushing	7 (33.3)	3 (13.0)	10 (22.7)

( ): %

a) This table listed the adverse events reported in 3 subjects or more in the total number of subjects who participated in the study from Part I and Part II.

There were no deaths. The serious adverse events observed in this study are shown in Table 8. Serious adverse events were observed in 7 subjects during the study period; however, none of these events was treatment-related. In addition, 1 subject discontinued from the study after giving informed consent because pulmonary hypertension developed as a serious adverse event before administration of the study drug.

Table 8 Serious adverse events

Sex	Age (yrs)	Adverse event Verbatim Term	Outcome	Study drug action	Causality with study drug
Subjects participated in the study from Part I					
F	41	Pulmonary hypertension aggravated	Not recovered	Discontinued	Not related
F	61	Scleroderma renal crisis	Recovering	Discontinued	Not related
F	54	Pulmonary hypertension aggravated	Recovered [a)]	Discontinued	Not related
Subjects participated in the study from Part II					
F	46	Pneumonia	Recovered	No action taken	Not related
		Cardiac failure aggravated	Recovered	No action taken	Not related
F	54	Anorexia	Recovered	No action taken	Not related
	54	Common cold	Recovered	No action taken	Not related
	54	Queasy	Recovered	No action taken	Not related
	55	Cardiac failure aggravated	Recovered	No action taken	Not related
F	72	Aggravated Cataract (left)	Recovered	No action taken	Not related
F	60	Anorexia	Recovered	No action taken	Not related
	61	Platelets decreased	Not recovered	No action taken [b)]	Not related
Before the treatment of study drug					
M	42	Pulmonary hypertension aggravated	Recovered	No action taken	Not related

a) The subject was recovered after follow up visit.
b) The subject was discontinued the study, but did not discontinue the treatment of sildenafil.

The adverse events leading to discontinuation of the study are shown in Table 9. None of these events was treatment-related.

Table 9 Adverse events leading to discontinuation of the study

Sex	Age (yrs)	Adverse event MedDRA preffered term	Severity	Outcome	Causality with study drug	Seriousness
Subjects participated in the study from Part I						
F	40	Pulmonary hypertension	Moderate	Not recovered	Not related	Serious
F	61	Scleroderma renal crisis	Severe	Not recovered	Not related	Serious
F	53	Pulmonary hypertension	Moderate	Not recovered	Not related	Serious
Subjects participated in the study from Part II						
F	60	Platelet count decreased	Severe	Not recovered	Not related	Serious

Laboratory test abnormalities, without regard to the laboratory findings at baseline, were observed in 35 of 43 subjects (81%). Median change in laboratory test values from baseline to the last observation time-point was small, and there were no clinically significant changes.

The results of vital signs and ECG indicated no significant findings leading to safety problems.

CONCLUSIONS: In this study, sildenafil 20 mg was administered tid orally to patients with PAH to investigate the efficacy, safety and PK of the drug, and the following conclusions were drawn:

- In subjects who participated in the study from Part I (PAH patients who have never received sildenafil therapy), the mean 6-minute walk distance at Week 12 increased by 84.2 m from baseline, and similar improvement to that at Week 12 was achieved at the time point of Week 8. Hemodynamic parameters (mean pulmonary arterial pressure, pulmonary vascular resistance, and cardiac output) also improved from the values at baseline. In addition, other hemodynamic parameters, the BORG dyspnoea score, and plasma BNP level also improved. As for the WHO functional class, most of the subjects showed improvement or maintained the class at baseline. Thus, sildenafil 20 mg administered tid orally for 12 weeks confirmed the improvements in the efficacy endpoints representing the pathological conditions of PAH.

- Among the subjects who participated in the study from Part II, efficacy was evaluated in the 7 subjects who had been receiving sildenafil at the doses higher than 60 mg/day before the start of the study. The 6-minute walk distance at Week 12 decreased and the plasma BNP level at Week 12 slightly increased from baseline. The BORG dyspnoea score increased slightly. As for WHO functional classes at Week 12, the classes at baseline were maintained in those subjects, excluding 1 subject who showed worsening by ≥1 grade from baseline. Regarding the reasons why improvements from baseline were not confirmed in those efficacy endpoints, the following factors were considered to have influenced the study results: PAH which was examined in this study is a progressive disease. The subjects in whom the efficacy of sildenafil was evaluated in Part II had been receiving the drug at the doses higher than 60 mg/day for a long term prior to participation in this study, and after participating in the study, the dose of sildenafil administered to those subjects was decreased to 60 mg/day in Part II.

- When PK evaluation was examined in 9 subjects, the mean values (coefficient of variance) of Cmax, AUC_{0-8}, Css,av, and Ctrough of sildenafil at steady state were 164.88 ng/mL (45.4%), 545.14 ng·h/mL (54.1%), 68.14 ng/mL (54.1%), and 19.61 ng/mL (63.4%), respectively, showing relatively large variations among individuals; the mean values (coefficient of variance) of Cmax and AUC_{0-8} of its metabolite, UK-103,320, were 87.27 ng/mL (35.1%) and 365.85 ng·h/mL (51.0%), respectively.

- All-causality adverse events were observed in 42 of 44 subjects (95.5%). The most of the events were mild or moderate in severity. Treatment-related severe adverse events or treatment-related adverse events leading to discontinuation of the treatment were not observed. During the study, serious adverse events were observed in 7 subjects (pulmonary hypertension aggravated in 2 subjects, scleroderma renal crisis in 1 subject, pneumonia and cardiac failure aggravated in 1 subject, anorexia, common cold, nausea and cardiac failure aggravated in 1 subject, left eye cataract aggravated in 1 subject, and anorexia and platelet count decreased in 1 subject); however, none of these events was treatment-related. There were no deaths. The results of laboratory tests, vital signs and ECG indicated no significant findings leading to safety problems. In conclusion, no safety problems were observed in PAH patients to whom sildenafil 20 mg was orally administered tid.