Original Article

Efficacy and Safety of Sildenafil in Japanese Pediatric Patients with Pulmonary Arterial Hypertension

Shigetoyo Kogaki, MD[1, 2], Tsutomu Saji, MD[3), †], Hiroshi Ono, MD[4)], Masahiro Ishii, MD[5, 6)], Shintaro Hiro, PhD[7)], and Michinori Terada, PhD[7)]

[1)] Department of Pediatrics and Neonatology, Osaka General Medical Center, Osaka, Japan
[2)] Department of Pediatrics, Osaka University Graduate School of Medicine, Osaka, Japan
[3)] Advanced and Integrated Cardiovascular Research Course in the Young and Adolescence, Toho University, Tokyo, Japan
[4)] Division of Cardiology, National Center for Child Health and Development, Tokyo, Japan
[5)] Ishii Pediatrics and Pediatric Cardiology Office, Kanagawa, Japan
[6)] Department of Pediatrics, Kitasato University Hospital, Kanagawa, Japan
[7)] Development Japan, Pfizer R&D Japan, Tokyo, Japan
[†] Deceased on May 22, 2017

Background: An international multicenter, placebo-controlled, double-blind study (STARTS-1) and its subsequent extension study (STARTS-2) demonstrated that sildenafil monotherapy with medium dose was well tolerated and improved exercise tolerance, functional class, and hemodynamics in patients with pediatric pulmonary arterial hypertension (PAH). However, clinical studies of pediatric PAH had not been performed in Japan at the time. We therefore aimed to investigate the efficacy, safety and pharmacokinetics of sildenafil in Japanese pediatric patients with PAH.
Methods: We conducted an open-label study consisting of both a 16-week treatment period (Part 1) and a long-term treatment period (Part 2). The efficacy endpoints were improvement in the parameters of pulmonary vascular resistance index (PVRI), mean pulmonary arterial pressure (mPAP), World Health Organization functional class, brain natriuretic peptide (BNP) and N-terminal pro-BNP. The patients received sildenafil at 10 mg or 20 mg that was administered 3 times a day based on body weight.
Results: Six children aged 1 to 14 years with PAH were screened, and sildenafil was assigned. Four patients completed Part 1, and one patient completed Part 2. In Part 1, among the 5 patients with available cardiac catheterization data, PVRI and mPAP decreased in 3 and 2 patients, respectively. There were 11 treatment-related adverse events that were already known, but no serious adverse events including death occurred.
Conclusions: This study suggests that oral sildenafil is well tolerated and acceptable as a therapeutic option in Japanese pediatric patients with PAH. (Clinical Trial Registration: NCT01642407)

Keywords: efficacy, pediatric, pulmonary arterial hypertension, safety, sildenafil

Background

Pulmonary arterial hypertension (PAH) is a progressive, life-threatening disease of both children and adults. There are some differences in the disease characteristics between pediatric and adult patients with PAH. Mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR) are higher in pediatric patients, who also show a higher incidence of syncope, but the overall presentation of the disease, pathogenesis, pathophysiology, response to long-term treatment and prognosis are similar.[1, 2)] The prevalence of pediatric patients with idiopathic PAH in the EU/US is very low, namely, 1 to 2 patients per million population.[3)] In Japan, the num-

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Corresponding author: Shigetoyo Kogaki, MD, Department of Pediatrics and Neonatology, Osaka General Medical Center, 3–1–56 Bandaihigashi, Sumiyoshi-ku, Osaka 558–8558, Japan
E-mail: skogaki@gh.opho.jp
ORCiD: Shigetoyo Kogaki (https://orcid.org/0000-0001-6557-437X)
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ber of pediatric patients is also very small (219 patients were seen at 103 hospitals during the 1997–1998 period, 149 patients at 59 hospitals during the 1998–1999 period,[4] and 18 patients at 185 hospitals in 2009.[5] The currently approved medical drugs for adult PAH include prostacyclin analogs, a prostacyclin-receptor agonist, PDE5 inhibitors, endothelin receptor antagonists, and a soluble guanylate cyclase (sGC) stimulator. However, very few clinical studies have targeted pediatric patients, and high-level results are lacking due to the difficulty of conducting studies in pediatric patients. The current treatment options for pediatric patients therefore remain limited.

Sildenafil is an oral PDE5 inhibitor that was developed for the treatment of PAH.[6] An international multicenter, placebo-controlled, double-blind study (STARTS-1) of sildenafil [dose range: 10 to 80 mg administered 3 times a day (ter in die: t.i.d.)] for pediatric PAH demonstrated improvement in peak oxygen uptake, World Health Organization functional class (WHO-FC), and hemodynamics.[7] The subsequent extension study (STARTS-2) demonstrated that the optimal dosages are 10 mg t.i.d. for ≥8–20 kg body weight, 20 mg t.i.d. for >20–45 kg, and 40 mg t.i.d. for >45 kg, but the high dose was associated with increased mortality.[8] Based on the results of these studies, sildenafil was approved for the treatment of PAH in pediatric patients aged 1 to 17 years by the European Commission in 2011. The recommended dose is 10 mg t.i.d. in pediatric patients with a body weight of ≤20 kg and 20 mg t.i.d. in patients with a body weight of >20 kg. However, the US FDA has not approved the use of sildenafil in pediatric patients.

This time we conducted an open-label study to investigate the efficacy, safety and pharmacokinetics (PK) of sildenafil in Japanese pediatric patients with PAH.

Methods

This study was conducted from August 2012 at a total of 10 hospitals in Japan. The protocol and informed consent documentation were reviewed and approved by the Institutional Review Board and/or Independent Ethics Committee of each hospital, and the study was registered with Clinicaltrials.gov (NCT01642407). Signed and dated informed consent was obtained from the parent or legal representative of each subject before any screening procedures were performed.

Study Design

The study consisted of a screening period, a 16-week treatment period (Part 1) and a long-term treatment period (Part 2). All inclusion and exclusion criteria are listed in Table 1. Eligible patients received oral sildenafil at either 10 mg t.i.d. (10 mg group) or 20 mg t.i.d. (20 mg group) based on the body weight at baseline with intervals of at least 6 hours between doses. The treatment phase included telephone contact at Weeks 1 and 3, and additional clinic visits at Weeks 4, 8, and 16 to collect efficacy and safety data for the Part 1 period. Beraprost could be used concomitantly on condition that the same dosage had been used for at least 3 months before the start of the study treatment and that the dosage regimen would not be modified during Part 1. Blood samples for the determination of PK were collected during Part 1 of the study. If patients completed Part 1 and then needed to continue using sildenafil until approval, long-term treatment was available after the investigator's evaluation in Part 2. The dosage in Part 2 was based on the actual weight at each visit. In Part 2, clinic visits were set at every 12 weeks to collect safety and efficacy data.

Efficacy Evaluations (Part 1 and Part 2)

In Part 1, the efficacy endpoints were the changes from baseline to Week 16 in the parameters of PVR index (PVRI), mPAP, WHO-FC, BNP, and N-terminal (NT) pro-BNP.

In Part 2, the efficacy endpoints were the changes from baseline to every 12 weeks after Week 16 in WHO-FC and the changes from baseline to Week 52 or End of Treatment (EoT) in BNP and NT pro-BNP.

Principal investigators and pediatric cardiology specialists discussed the efficacy evaluation for each subject at a post-hoc data review meeting.

Pharmacokinetic Evaluation (Part 1)

Plasma sildenafil concentration was determined at the following steady-state points: pre-dose at Weeks 4, 8 and 16, and 1, 2, 4, and 8 hours post-dose at Week 16. The following PK parameters were calculated at Week 16: maximum observed plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the plasma concentration-time curve over the dosing interval (AUC_{tau}), terminal half-life ($t_{½}$), average plasma concentration at the steady state ($C_{ss,av}$), trough plasma concentration (C_{trough}), apparent oral clearance (CL/F), and apparent

Table 1 Patient inclusion and exclusion criteria

Inclusion criteria for Part 1
1. Male and female patients aged 1 to 17 years. Negative urine pregnancy test at study entry (for females of childbearing potential).
2. Body weight ≥8 kg.
3. Patients with symptomatic PAH due to 1 of the following conditions: Idiopathic PAH, Heritable PAH or PAH associated with congenital heart disease.
4. Patients with mean pulmonary artery pressure ≥25 mmHg at rest, PCWP ≤15 mmHg, and pulmonary vascular resistance index ≥3 Wood units×m^2. If PCWP is not available, then mean left atrial pressure ≤15 mmHg or left ventricular end-diastolic pressure ≤15 mmHg in the absence of left atrial obstruction.
Inclusion criteria for Part 2
1. Patients who were willing to continue sildenafil administration after the completion of Part 1.
Exclusion criteria for Part 1
1. Left-sided heart disease
2. Patients with Down's syndrome
3. Patients with obstructive sleep apnea
4. Pericardial constriction
5. Patients with significant other valvular disease than tricuspid or pulmonary regurgitation.
6. Acute decompensated heart failure within the 30 days before screening.
7. Patients who had an atrial septostomy within 6 months before screening.
8. Patients with hemodynamic instability, or hypo- or hypertension at screening.
9. Patients with a history of stroke, myocardial infarction or life-threatening arrhythmia within 6 months before screening.
10. Patients with moderate to severe restrictive pulmonary disease or a history of severe lung disease.
11. Patients with bronchopulmonary dysplasia or other chronic lung diseases.
12. Patients with a history of pulmonary embolism.
13. Patients with known hereditary degenerative retinal disorders or a history of non-arteritic anterior ischemic optic neuropathy.
14. Patients with a known positive result for human immunodeficiency virus.
15. Patients with impairment of renal function.
16. Patients with severe hepatic dysfunction (Child-Pugh classification C).
17. Change in class of medication for heart failure or PAH within 10 days prior to qualifying for right heart catheterization.
18. Patients prescribed and/or taking nitrates or nitric oxide donors in any form.
19. Patients taking chronic arginine supplementation.
20. Patients who had received parenteral inotropic medication or parenteral vasodilators within 30 days before Day 1.
21. Patients receiving alpha-blockers, nicorandil, amiodarone or potent cytochrome P450 3A4 inhibitors.
22. Patients receiving long-term treatment with off-label sildenafil within 30 days before Day 1. Patients receiving an endothelin receptor antagonist, PDE5 inhibitor, riociguat or prostacyclin/prostacyclin analogue within 30 days before screening, excluding beraprost.
23. Pregnant females; breastfeeding females; males and females of childbearing potential not using highly effective contraception or not agreeing to continue highly effective contraception until at least 28 days after administration of the study drug for the last time.
24. Current or past illicit drug use or alcoholism, except in case of documented abstinence for ≥1 year.
25. Participation in another clinical trial of a study drug or device within 30 days before screening for entry into this study.
26. Other severe acute or chronic medical or psychiatric conditions or laboratory abnormalities that could increase the risk associated with study participation or study drug administration or could interfere with the interpretation of the study results, and in the judgment of the investigator, would make the subject inappropriate for entry into this study.
Exclusion criteria for Part 2
1. Patients with impairment of renal or hepatic function. Clinically significant hematological abnormalities at the time of transition to Part 2.
2. Pregnant females; breastfeeding females; males and females of childbearing potential not using highly effective contraception or not agreeing to continue highly effective contraception until at least 28 days after administration of the study drug for the last time.
3. Any condition that would make the patient inappropriate for entry into this study in the judgment of the investigator.

PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure

volume of distribution (V_z/F) of sildenafil.

Safety Evaluation (Part 1 and Part 2)

In Part 1, safety evaluation included monitoring of adverse events (AEs), electrocardiogram (ECG), vital signs (BP and pulse rate), laboratory tests, physical examinations, and ophthalmologic tests (external examination of the eye, funduscopic study, and assessment of visual acuity and color vision). AEs were monitored at Weeks 0, 1, 4, 8, and 16. ECG and ophthalmologic tests were performed at screening and Week 16. Data of other safety parameters were recorded at screening and Weeks

0, 4, 8, and 16.

In Part 2, the AEs were monitored at each visit until sildenafil dry syrup formulation became available on the market. ECG and ophthalmologic tests were performed at Week 52 and EoT, and other safety parameters were recorded at each visit until EoT.

Serious AEs were monitored from the time of obtaining consent to 28 days after the last study drug administration. Assessment of AEs was based on the System Organ Class and the Preferred Terms of the Medical Dictionary for Regulatory Activities, version 20.1.

Statistical Analyses

The targeted number of patients with a body weight of >20 kg and a body weight of ≤ 20 kg were determined as ≥ 2 and ≥ 3, respectively, based on the study feasibility perspective without considering statistical testing or inference.

Efficacy was assessed in the efficacy analysis set, which was defined as all patients who took at least 1 dose of the study drug. Baseline values, actual values, and the changes from baseline in all efficacy endpoints were summarized using summary statistics (n, mean, standard deviation [*SD*], median, minimum, and maximum).

The PK parameter analysis set was defined as all patients who had at least 1 PK parameter of interest. The PK parameters of sildenafil were calculated using a non-compartmental analysis method and were summarized by body weight.

The safety analysis set was defined as all patients who took at least 1 dose of the study drug. The AEs were summarized by the number of patients with AEs and the incidence (%).

Results

Patient Characteristics

Six patients were screened and assigned to the present study. Among them, 5 patients were diagnosed with idiopathic PAH (IPAH) and were PAH drug-naïve. One patient, who had been treated with oral beraprost before study entry, was diagnosed with congenital heart disease-associated PAH (CHD-PAH, co-incidental small defect). Three patients were assigned to the 10-mg group and the others were assigned to the 20-mg group based on their body weight. Patients' demographic data are summarized in Table 2.

There were two patients (one patient in the 10-mg group and the other in the 20-mg group) who discontinued the study before completion of Part 1 due to no clinical improvement and clinical worsening of PAH. Another patient in the 20-mg group also discontinued upon completion of Part 1 because the principal investigator decided to add another PAH drug even though the patient showed no clinical worsening of PAH. There were 2 patients (one patient in the 10-mg group and the other in the 20-mg group) who discontinued before completion of Part 2 due to treatment of the underlying disease and a change in the PAH drugs. Only one patient completed Part 1 and Part 2 (Table 3).

Table 2 Baseline subject demographic characteristics

	Sildenafil		Total (n = 6)
	10 mg t.i.d. (n = 3)	20 mg t.i.d. (n = 3)	
Sex			
Male, n	1	2	3
Female, n	2	1	3
Age, in years, mean ± *SD* (range)	2.0 ± 1.7 (1–4)	11.3 ± 2.3 (10–14)	6.7 ± 5.4 (1–14)
< 7, n	3	0	3
7–17, n	0	3	3
PAH clinical classification			
IPAH	2	3	5
CHD-PAH	1	0	1
PAH drugs			
PAH drug naïve	2	3	5
Beraprost	1	0	1
Weight, kg, mean ± *SD* (range)	11.9 ± 4.3 (9–17)	45.9 ± 16.6 (27–56)	28.9 ± 21.5 (9–56)
Height, cm, mean ± *SD* (range)	86.9 ± 13.3 (78–102)	143.3 ± 8.2 (134–150)	115.1 ± 32.4 (78–150)
Body mass index, kg/m^2, mean ± *SD* (range)	15.3 ± 1.0 (14–16)	21.9 ± 6.1 (15–26)	18.6 ± 5.3 (14–26)

n, number of subjects in the treatment group; IPAH, idiopathic pulmonary arterial hypertension; CHD-PAH, congenital heart disease associated pulmonary arterial hypertension; *SD*, standard deviation; t.i.d., 3 times a day (ter in die)

Table 3 Profiles of subjects and analysis sets

	Sildenafil		Total (n=6)
	10 mg t.i.d. (Body weight ≤20 kg) (n=3)	20 mg t.i.d. (Body weight >20 kg) (n=3)	
Screened, assigned to study treatment, and treated	3 (100)	3 (100)	6 (100)
Discontinued during Part 1	1 (33.3)	1 (33.3)	2 (33.3)
Discontinued upon completion of Part 1	0	1 (33.3)	1 (16.7)
Entered Part 2	2 (66.7)	1 (33.3)	3 (50.0)
Completed	1 (33.3)	0	1 (16.7)
Discontinued during Part 2	1 (33.3)	1 (33.3)	2 (33.3)
Analyzed for efficacy	3 (100)	3 (100)	6 (100)
Analyzed for pharmacokinetics	3 (100)	3 (100)	6 (100)
Analyzed for safety	3 (100)	3 (100)	6 (100)

Values indicate the number of subjects (%). n, number of subjects in the treatment group; t.i.d., 3 times a day (ter in die)

Efficacy (Part 1 + Part 2)

Changes in efficacy endpoints are summarized in Table 4. In Part 1, among the 5 patients for whom cardiac catheterization data was available, PVRI and mPAP levels decreased in 3 and 2 patients, respectively. The WHO-FC improved in one patient and remained unchanged in 5 patients. BNP and NT pro-BNP levels decreased in 3 and 4 patients, respectively. Only one out of six patients presented with significant clinical worsening of PAH during the study. In Part 2, the WHO-FC, BNP and NT pro-BNP levels improved in one patient by the time of completion of the study, but did not improve in 2 patients by the time of study discontinuation.

The efficacy evaluation of each patient was discussed at the post-hoc data review meeting and the details are as follows.

Subject 2 showed decreased levels of PVRI and mPAP as well as BNP and NT pro-BNP levels at Week 16. The WHO-FC also improved. All efficacy endpoints showed improvement at Week 16 and the patient completed Part 1 and Part 2 on sildenafil monotherapy. Sildenafil was clearly effective in this case.

Subject 6 showed decreased levels of PVRI, mPAP, BNP and NT pro-BNP but the WHO-FC remained unchanged at Week 16. It was considered that sildenafil is effective and the patient was enrolled in Part 2. However, the principal investigator decided to change the PAH treatment and the patient discontinued the study before completion of Part 2.

Subject 5 showed stable levels of PVRI, mPAP and WHO-FC at Week 16 and no clinical worsening was observed excluding slight elevation of the BNP and NT pro-BNP levels. Sildenafil seemed to suppress the progression of PAH. However, the principal investigator decided to add another PAH drug and the patient discontinued the study upon completion of Part 1.

Subject 1 had a diagnosis of CHD-PAH with co-incidental small patent ductus arteriosus (PDA; 1–2 mm in diameter, Qp/Qs = 1.00–1.11). No clinical worsening was observed while BNP and NT pro-BNP levels had improved by Week 16. However, PVRI and mPAP were elevated, probably because the patient's respiratory condition was unstable under sedation for cardiac catheterization. After completion of Part 1, the patient underwent coil embolization of PDA and then discontinued the study before completion of Part 2.

Subject 4 was very sick with severe PAH at baseline and clinical worsening was rapid after administration of sildenafil. The principal investigator decided to discontinue the study before completion of Part 1 and added other PAH drugs.

Subject 3 was enrolled in Part 1, but the principal investigator decided to discontinue the study because no apparent clinical improvement was observed.

Pharmacokinetics (Part 1)

The PK parameters of plasma sildenafil are shown in Table 5. Following multiple oral doses of sildenafil at 10 mg t.i.d. (body weight ≤20 kg, 10-mg group) and 20 mg t.i.d. (body weight >20 kg, 20-mg group), C_{max} was observed at 1 hour post-dose in both dose groups. Total exposure (geometric mean AUC_{tau}) in the 10-mg group (365.2 ng·h/mL) and the 20-mg group (314.5 ng·h/mL) of sildenafil was comparable, but the geometric mean value of C_{max} was higher in the 10-mg group (184.9 ng/mL) than the 20-mg group (103.2 ng/mL). The geometric mean $C_{ss.av}$ was higher in the 10-mg group (45.67 ng/mL) than the 20-mg group

Table 4 Changes in efficacy endpoints from baseline

Parameter	PVRI (Wood Units × m^2)	mPAP (mmHg)	WHO functional class	BNP (pg/mL)	NT Pro-BNP (pg/mL)
Sildenafil 10 mg t.i.d. (body weight ≤ 20 kg)					
Subject 1					
Baseline	4.21	26	I	17.3	84.0
Week 16/EoT	7.32	33	I	7.7	43.5
Change from baseline	3.11	7	0	−9.6	−40.5
Week 52	NA	NA	I	18.1	81.2
Change from baseline	NA	NA	0	0.8	−2.8
Subject 2					
Baseline	10.89	45	II	275.0	2370.0
Week 16/EoT	2.56	28	I	17.0	164.0
Change from baseline	−8.33	−17	−1	−258.0	−2206.0
Week 52	NA	NA	I	10.8	73.3
Change from baseline	NA	NA	−1	−264.2	−2296.7
Subject 3					
Baseline	18.21	62	I	211.0	2200.0
Week 16/EoT	NA	NA	I	213.0	1770.0
Change from baseline	NA	NA	0	2.0	−430.0
Sildenafil 20 mg t.i.d. (body weight > 20 kg)					
Subject 4					
Baseline	33.52	82	III	276.0	271.0
Week 16/EoT	40.86	105	III	776.0	2450.0
Change from baseline	7.34	23	0	500.0	2179.0
Subject 5					
Baseline	12.92	50	II	8.2	62.0
Week 16/EoT	12.18	56	II	22	150.0
Change from baseline	−0.74	6	0	13.8	88.0
Subject 6					
Baseline	31.65	86	II	8.2	71.2
Week 16/EoT	21.16	64	II	5.6	42.3
Change from baseline	−10.49	−22	0	−2.6	−28.9
Week 52	NA	NA	II	16.1	106
Change from baseline	NA	NA	0	7.9	34.8
Part 1 Total number of subjects (n = 6)					
Baseline, mean	18.57	58.5	1.8	132.6	843.0
Week 16/EoT, mean	16.82*	57.2*	1.7	173.6	770.0
Change from baseline, mean ± *SD*	−1.82 ± 7.53*	−0.6 ± 18.6*	−0.2 ± 0.41	40.9 ± 247.7	−73.1 ± 1398.4
Median (min, max)	−0.74* (−10.49, 7.34)	6.0* (−22.0, 23.0)	0.0 (−1.0, 0.0)	−0.30 (−258.0, 500.0)	−34.7 (−2206.0, 2179.0)
Part 2 Total number of subjects (n = 3)					
Baseline, mean	NA	NA	1.7	100.17	841.73
Week 52, mean	NA	NA	1.3	15.0	86.83
Change from baseline, mean ± *SD*	NA	NA	−0.3 ± 0.58	−85.17 ± 155.09	−754.90 ± 1335.37
Median (min, max)	NA	NA	0.0 (−1.0, 0.0)	0.80 (−264.2, 7.9)	−2.80 (−2296.7, 34.8)

*n = 5, as only 2 subjects in the sildenafil 10 mg t.i.d. group were evaluated at Week 16/EoT. BNP, brain natriuretic peptide; EoT, end of treatment; mPAP, mean pulmonary artery pressure; n, number of subjects; NA, not available; NT pro-BNP, N-terminal pro-BNP; PVRI, pulmonary vascular resistance index; *SD*, standard deviation; t.i.d., 3 times a day (ter in die); WHO, World Health Organization

(39.31 ng/mL), and the geometric mean value of C_{trough} was higher in the 20-mg group (16.69 ng/mL) than the 10-mg group (7.41 ng/mL). Only a limited number of patients had a reportable terminal $t_{½}$ and the values were comparable in the 10-mg and 20-mg groups.

Inter-patient variability in the 6 patients for plasma sildenafil exposure based on the geometric %CV of the geometric mean was 54% and 73% for AUC_{tau} and C_{max}, respectively.

Safety (Part 1 + Part 2)

A total of 45 AEs in 6 patients were reported. Eleven AEs were considered to be treatment-related, including vision blurred, visual acuity transiently reduced, blood urine present, myalgia, feeling abnormal, headache, erection increased, epistaxis and flushing. All AEs were mild to moderate in severity, except one that was reported as severe PAH, but was not considered to be treatment related. There were no deaths or serious AEs. Although one patient in the 20-mg group temporarily discontinued sildenafil administration due to headache

Table 5 Descriptive summary of plasma sildenafil pharmacokinetic parameters at the steady state by body weight following oral doses of sildenafil for 16 weeks

Parameter	Sildenafil		Total
	10 mg t.i.d. (Body weight ≤20 kg)	20 mg t.i.d. (Body weight >20 kg)	
N, n	3, 1	3, 1	6, 2
AUC_{tau} (ng·h/mL)	365.2 (53)	314.5 (69)	338.9 (54)
C_{max} (ng/mL)	184.9 (84)	103.2 (58)	138.1(73)
C_{trough} (ng/mL)	7.41 (52)	16.69 (61)	11.12 (72)
$C_{ss,av}$ (ng/mL)	45.67 (53)	39.31 (68)	42.37 (54)
T_{max} (h)	1.00 (1.00–1.97)	1.00 (1.00–1.02)	1.00 (1.00–1.97)
$t_{½}$ (h)*	1.63	1.94	1.63, 1.94
CL/F (L/h)	27.35 (53)	63.67 (68)	41.73 (77)
V_z/F (L)*	62.4	93.4	62.4, 93.4

Data are shown with the geometric mean (geometric %CV) for all parameters, except T_{max} for which the median (range) is shown. *Individual values are listed in the table when the number of subjects with reportable values in the group was <3. %CV, percent coefficient of variation; N, number of subjects in the treatment group; n, number of subjects with reportable $t_{½}$ and V_z/F; t.i.d., 3 times a day (ter in die)

and vomiting, no patients discontinued the study due to AEs. Ophthalmologic tests did not show abnormal findings in any patients.

Discussion

This study was conducted to investigate the efficacy, safety and pharmacokinetics of sildenafil in Japanese pediatric patients with PAH.

Although the number of enrolled patients was small, the present study showed that sildenafil was generally well tolerated without any severe treatment-related AEs. Most AEs were mild or moderate, and there were no deaths or life-threatening AEs. In STARTS-1, the most frequently reported AEs in the 16-week study were headache, pyrexia, upper respiratory tract infections, vomiting, and diarrhea. Pyrexia, abnormal erection, and upper respiratory tract infection occurred in 5% and more patients in the sildenafil combined group versus placebo.[7] The safety results in the present study were consistent with those of the previous studies (STARTS-1 and -2[7, 8]), and no new signals were detected in this study.

It was difficult to statistically verify the efficacy of sildenafil in this study because only 6 patients were enrolled and only one patient completed both Part 1 and Part2. However, 2 patients (subjects 2 and 6) actually showed a higher than 20% decrease in PVRI and mPAP from baseline to Week 16 and improvement in BNP and NT pro-BNP levels as well. Sildenafil was considered to be effective in these cases. In addition, one patient (subject 5) showed a slight decrease in PVRI, a slight increase in mPAP and stable WHO-FC, which suggested that sildenafil may suppress the progression of PAH. Only one patient (subject 4) presented with rapid clinical worsening of PAH during the study, which suggested that monotherapy with sildenafil may not be sufficient for the treatment of severely ill children with advanced PAH. In the remaining 2 patients (subjects 1 and 3), the efficacy of sildenafil could not be evaluated due to insufficient hemodynamic data.

We could not reach a conclusion on the efficacy of sildenafil based only on the present data. Therefore, we compared the results of the present study with those of STARTS-1. Since changes in logarithm of PVRI were normally distributed in STARTS-1, we used the geometrical mean value of the ratio of PVRI of Week 16 to baseline to compare the efficacy results. The results of the ratio of PVRI at Week 16 (last observation carried forward: LOCF) to baseline in the present study as well as STARTS-1 are shown in Table 6. The geometrical mean value of the ratio of PVRI was 0.79 in the present study, which was lower than the value in the placebo group (1.08) and ranged between the value of the medium- (0.85) and high-dose (0.75) groups in STARTS-1. Therefore, the effect of sildenafil in Japanese pediatric patients with PAH is likely to be similar to that in the medium-dose group in STARTS-1, although it is difficult to make a final conclusion due to the limited number of Japanese patients.

Based on the PK analysis, the total exposure (AUC_{tau}) in the 10 mg group was comparable to that in the 20 mg group in the present study. The PK results obtained in the present study are also comparable to those of the PK data of non-Japanese pediatric and adult patients with

Table 6 The ratio of PVRI at Week 16 (LOCF) to baseline: Comparison between this study and the STARTS-1 study

	This study	STARTS-1 study			
	All subjects N = 5	Placebo group N = 52	Low-dose group N = 37	Medium-dose group N = 51	High-dose group N = 68
The ratio of PVRI at Week 16 (LOCF) to baseline					
Geometric mean value	0.7932	1.0844	0.9778	0.8531	0.7474
Geometric standard deviation	2.1482	1.5314	1.5265	1.6696	1.7249
Medium	0.9427	1.0696	0.9808	0.9020	0.7348
Range (Minimum value, Maximum value)	0.2351, 1.7387	0.4226, 3.7037	0.4028, 2.2934	0.2904, 2.6083	0.1532, 2.1551

LOCF, last observation carried forward; PVRI, pulmonary vascular resistance index

PAH.[9]

The dosages used in the present study are the same as the approved dosages in the EU, and the recommended dosages in the guidelines of the American Heart Association/the American Thoracic Society[10] and the European Society of Cardiology/European Respiratory Society.[11] Our results suggest that sildenafil at these dosages is well tolerated by Japanese pediatric patients with PAH. On the other hand, the guidelines mention optimal dosages of sildenafil for patients of <1 year and those with a body weight of <8 kg, who were not included in this study. Further studies in infants at these dosages also recommended in the guidelines will provide valuable information if shared with physicians who are expected to treat Japanese infants with PAH.

In summary, these results suggest that the efficacy, safety and PK of oral sildenafil in Japanese pediatric patients with PAH are comparable to those in the previous international study.

Study Limitations

This study was an open-label study, not a double-blind study, due to ethical considerations with the use of placebo. In Japan, it was quite difficult to enroll children with PAH in the clinical study because the incidence of pediatric IPAH itself is very low and Japanese parents did not want their children to participate in a clinical study. We spent four years and could enroll only 6 pediatric patients in this study. The results are also not statistically verified due to the small sample size of 6 patients. In accordance with the pre-determined inclusion and exclusion criteria, only patients with specific characteristics of PAH were included in this study, and the results may therefore not be generalizable or applicable to all pediatric patients with PAH.

Conclusions

This study suggests that treatment with oral sildenafil 10 mg t.i.d. (body weight $\leq$20 kg) or 20 mg t.i.d. (body weight $>$20 kg) is well tolerated and acceptable as a therapeutic option in Japanese pediatric patients with PAH.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

Disclosures

Shigetoyo Kogaki and Tsutomu Saji are coordinating investigators, and Hiroshi Ono and Masahiro Ishii are principal investigators at their respective study sites. Shintaro Hiro and Michinori Terada are employees of Pfizer. Shin-

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