A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of Oral Sildenafil Citrate in Treatment-Naive Children With Pulmonary Arterial Hypertension

Robyn J. Barst, MD; D. Dunbar Ivy, MD; Guillermo Gaitan, MD; Andras Szatmari, MD; Andrzej Rudzinski, MD; Alberto E. Garcia, MD; B.K.S. Sastry, MD; Tomas Pulido, MD; Gary R. Layton, MSc; Marjana Serdarevic-Pehar, MD; David L. Wessel, MD

***Background*—**Safe, effective therapy is needed for pediatric pulmonary arterial hypertension.

***Methods and Results*—**Children ($n=235$; weight $\geq$8 kg) were randomized to low-, medium-, or high-dose sildenafil or placebo orally 3 times daily for 16 weeks in the Sildenafil in Treatment-Naive Children, Aged 1–17 Years, With Pulmonary Arterial Hypertension (STARTS-1) study. The primary comparison was percent change from baseline in peak oxygen consumption ($P\dot{V}O_2$) for the 3 sildenafil doses combined versus placebo. Exercise testing was performed in 115 children able to exercise reliably; the study was powered for this population. Secondary end points (assessed in all patients) included hemodynamics and functional class. The estimated mean$\pm$SE percent change in $P\dot{V}O_2$ for the 3 doses combined versus placebo was 7.7$\pm$4.0% (95% confidence interval, −0.2% to 15.6%; $P=0.056$). $P\dot{V}O_2$, functional class, and hemodynamics improved with medium and high doses versus placebo; low-dose sildenafil was ineffective. Most adverse events were mild to moderate in severity. STARTS-1 completers could enter the STARTS-2 extension study; patients who received sildenafil in STARTS-1 continued the same dose, whereas placebo-treated patients were randomized to low-, medium-, or high-dose sildenafil. In STARTS-2 (ongoing), increased mortality was observed with higher doses.

***Conclusions*—**Sixteen-week sildenafil monotherapy is well tolerated in pediatric pulmonary arterial hypertension. Percent change in $P\dot{V}O_2$ for the 3 sildenafil doses combined was only marginally significant; however, $P\dot{V}O_2$, functional class, and hemodynamic improvements with medium and high doses suggest efficacy with these doses. Combined with STARTS-2 data, the overall profile favors the medium dose. Further investigation is warranted to determine optimal dosing based on age and weight.

***Clinical Trial Registration*—**http://www.clinicaltrials.gov. Unique identifier: NCT00159913.

(*Circulation*. 2012;125:324-334.)

Key Words: cardiopulmonary exercise ■ clinical trials ■ pediatrics ■ pulmonary arterial hypertension ■ sildenafil

Pulmonary arterial hypertension (PAH) is a chronic disorder of the pulmonary vasculature, characterized by a progressive increase in pulmonary vascular resistance leading to right heart failure and death if untreated.[1,2] PAH may be idiopathic (IPAH), heritable (HPAH), or associated with other conditions (APAH), such as congenital heart disease or connective tissue disease.[3] Treatment aims to improve quality of life and survival.

Clinical Perspective on p 334

Currently, 8 drugs are approved for adult PAH; however, no therapies are approved for children. On the basis of similar clinical characteristics and histopathology, recommendations for treatment for children have been extrapolated from evidence-based adult guidelines. Although the disease[4,5] and its response to treatment[6] can differ between children and adults, limited data suggest benefits for children utilizing the drugs approved for adults.[7–12] However, better information is required to provide optimal pediatric dosing and to ensure safety in children of all ages. This 16-week, placebo-controlled, dose-ranging study evaluated the effects in a trial of oral Sildenafil in Treatment-Naive Children, Aged 1 to 17 Years, With Pulmonary Arterial Hypertension (STARTS-1).

Received December 23, 2010; accepted November 7, 2011.

From Columbia University, New York, NY (R.J.B.); Department of Pediatrics, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora (D.D.I.); Department of Pediatric Cardiology, UNICAR, Guatemala City, Guatemala (G.G.); Department of Pediatric Cardiology, Gottsegen György Hungarian Institute of Cardiology, Budapest, Hungary (A.S.); Pediatric Cardiology, Jagiellonian Univeristy, Cracow, Poland (A.R.); Fundacion Cardioinfantil, Bogotá, Colombia (A.E.G.); Department of Cardiology, CARE Hospital, Nampally, Hyderabad, India (B.K.S.S.); Cardiopulmonary Department, Instituto Nacional de Cardiologia, Ignacio Chávez, Mexico City, Mexico (T.P.); Pfizer Worldwide Pharmaceutical Operations, Pfizer Ltd, Sandwich, United Kingdom (G.R.L., M.S.-P.); and Children's National Medical Center, Washington, DC (D.L.W.).

Correspondence to Robyn J. Barst, MD, 31 Murray Hill Rd, Scarsdale, NY 10583. E-mail robyn.barst@gmail.com

***Circulation* is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.110.016667**

Table 1. Sildenafil Thrice Daily Dose to Achieve Target Sildenafil Steady State Maximum Concentrations of 47, 140, and 373 ng/mL*

	Sildenafil Dose, mg		
Body Weight, kg	Low	Medium	High
≥8 to 20	NA†	10†	20
>20 to 45	10	20	40
>45	10	40	80

NA indicates not applicable.

*These concentrations were selected on the basis of concentrations of non–protein-bound sildenafil that would be expected to be similar to those that achieved ≈53%, 77%, and 90% inhibition of phosphodiesterase type 5 activity in vitro.

†Modeling of the plasma concentrations for each dose level showed that the low and medium doses were predicted to be similar for the 8- to 20-kg patients (ie, patients would receive the same dose because of the available tablet strengths); consequently, there was no low dose for this group.

Methods

Selection of Patients

Children (aged 1–17 years) weighing ≥8 kg with IPAH, HPAH, or PAH associated with connective tissue disease or congenital heart disease (unrepaired or partially repaired shunts with oxygen saturation at rest ≥88%, D-transposition of the great arteries repaired at ≤30 days of life, or congenital lesions surgically repaired ≥6 months) were eligible. Children with unrepaired shunts were enrolled only if their condition was considered inoperable because of their pulmonary vascular obstructive disease. PAH, defined as mean pulmonary artery pressure (mPAP) ≥25 mm Hg at rest, pulmonary capillary wedge pressure ≤15 mm Hg, and pulmonary vascular resistance index (PVRI) ≥3 Wood units·m^2, was confirmed by right heart catheterization at baseline. Nitrates, cytochrome P450 3A4 inhibitors, prostacyclin analogues, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and L-arginine were prohibited.

Local institutional review boards approved the protocol; written informed consent was obtained from each child's guardian, and child assent was obtained when applicable. An independent data and safety monitoring board reviewed all safety and efficacy data throughout the study.

Study Design

This double-blind, placebo-controlled, parallel-group, dose-ranging study (STARTS-1) was conducted in 16 countries (32 centers) in North, South, and Central America; Asia; and Europe between August 2003 and June 2008. Randomization was stratified by weight and developmental ability to perform cardiopulmonary exercise testing (CPET) (assessed with the use of bicycle ergometry). The central computer-generated pseudorandom code used the method of random permuted blocks within stratum (block size=4). An automated interactive voice response system assigned randomization numbers to eligible patients.

The 3 sildenafil dose levels (low, medium, and high) were selected to achieve maximum plasma concentrations of 47, 140, and 373 ng/mL, respectively, at steady state after oral administration 3 times a day (Table 1). These target concentrations were selected so that the concentrations of unbound sildenafil would be expected to be similar to sildenafil concentrations that produced ≈53%, 77%, and 90% inhibition of phosphodiesterase type 5 activity in vitro, respectively.[13,14] Actual doses administered within a dose group were dependent on body weight because the pharmacokinetics of sildenafil in pediatric patients were expected to vary as a function of body weight. Because sildenafil pharmacokinetics were not previously characterized in pediatric patients, parameters were predicted by scaling adult parameters with general scaling factors based on other drugs.[15–17]

To provide a practical dosing scheme based on body weight, 3 body weight categories were specified. Modeling of the plasma concentrations for each dose level showed that the low and medium doses were predicted to be similar for the 8- to 20-kg patients (ie, patients would receive the same dose because of the available tablet strengths); consequently, these patients were not randomized to low-dose sildenafil (Revatio, Pfizer Inc, New York, NY). Patients <20 kg were randomized 1:2:1 to placebo, medium-, and high-dose sildenafil, respectively. Patients >20 kg were randomized 1:1:1:1 to placebo and sildenafil low-, medium-, and high-dose groups.

Only children who were developmentally able to reliably perform CPET were evaluated for the primary end point. Developmental ability was determined by the investigator. In addition, a screening exercise test was evaluated by a core exercise laboratory for suitability. Enrollment criteria required achieving a peak oxygen consumption ($P\dot{V}O_2$) ≥10 mL/kg per minute and ≤28 mL/kg per minute (normal, ≈≥35 mL/kg per minute) during screening CPET. Computer-controlled cycle ergometers were used. Ergometers were calibrated per the manufacturer's instructions. Most sites used Med-Graphics Cardio-Respiratory Diagnosis System (Medical Graphics, St Paul, MN). A core exercise laboratory, blinded to study treatment, monitored and validated CPET during the study, derived CPET parameters for analysis, and verified all parameters at all sites. CPET was performed according to standardized protocol at screening, baseline, and week 16 or end of treatment (before sildenafil dosing or ≥4 hours after dose).

CPET began with up to 3 minutes (≥1 minute recommended) of data collection with the patient seated on the cycle at rest; a warm-up (ie, no tension/resistance with cycling) of up to 3 minutes (≥1 minute recommended) followed. Workload was then increased continuously (5 W/min for patients weighing ≤40 kg and 10 W/min for patients >40 kg; 2 W/min possible if necessitated by patient weight/PAH severity). Patients were encouraged to exercise for as long as possible but could stop at any time; they were instructed to maintain between 50 and 60 rpm for ≈8 to 12 minutes. CPET was stopped for intolerable dyspnea/fatigue or for safety concerns (eg, chest pain, presyncopal symptoms). Recovery was monitored for ≥10 minutes, including a cool down of ≥3 minutes. Exercise data were sent to a core laboratory; treatment was not started until a baseline test was deemed adequate.

For all patients, hemodynamics and N-terminal–pro-brain natriuretic peptide levels were assessed at baseline and week 16 (or end of treatment); World Health Organization functional class (FC) and quality-of-life measurements were assessed at baseline and weeks 4, 8, and 16. Hemodynamic parameters were obtained with right heart catheterization standard techniques. Whether general anesthesia or moderate sedation was used was determined by the judgment of the investigator; the same method was applied at baseline and week 16. For patients without shunts, cardiac output was determined with the use of thermodilution or Fick methods; for patients with shunts, the Fick method was used. If the Fick method was used, oxygen consumption was estimated with the use of standard tables.[18] If supplemental oxygen was administered at baseline, the same concentration (FIO_2) or flow rate (L/min) was used at week 16; if room air was used at baseline, room air was used at week 16 (barring safety concerns).

Drug supply consisted of a list of package numbers and corresponding treatment types. A unique package number identified each package of medication. The interactive voice response system assigned patients with a package number from the list corresponding to the treatment assigned. Medication was administered orally 3 times daily, ≥6 hours apart, for 16 weeks. All patients randomized to sildenafil received sildenafil 10 mg 3 times daily for 1 week followed by titration to assigned dose; placebo was dummy titrated. Patients were permitted one 50% dose reduction (after ≥1 week of treatment) for drug intolerance; if intolerance persisted, treatment was discontinued in those patients.

Patients who completed STARTS-1 were eligible to enroll in an extension study (STARTS-2). Patients who received sildenafil monotherapy in STARTS-1 were maintained on the same sildenafil dose they received while in the 16-week study, whereas placebo-treated patients were randomized to receive low-, medium-, or high-dose sildenafil monotherapy. Randomization was stratified by body weight. Dose titrations were permitted, but patients requiring additional PAH-specific therapy were discontinued from the study. Attempts were made to continue collecting survival information from patients who were discontinued from STARTS-1 or -2.

Outcome Measures

The primary end point, performed only in the developmentally able patients, was percent change in $P\dot{V}O_2$, normalized to body weight, from baseline to week 16.

Secondary end points, performed in all patients, included change from baseline to week 16 in mPAP, PVRI, FC, cardiac index, right atrial pressure, physical and psychosocial scales of the Child Health Questionnaire–Parent Form 28 (for patients aged ≥5 years), and percent change from baseline in exercise duration. Tertiary end points, also performed in all patients, included patient/parent and physician global assessments, changes in medications, and clinical worsening (defined as death, transplantation, hospitalization due to PAH, or initiation of a prostacyclin analogue or bosentan for worsening PAH).

Complete physical examinations and laboratory tests were performed in all patients, and investigators recorded adverse events (AEs) and serious AEs (SAEs) throughout the study.

The primary objective of the ongoing STARTS-2 extension study was to assess the safety and tolerability of long-term treatment with oral sildenafil monotherapy in children with PAH. The secondary objective was to assess long-term outcomes.

Statistical Analyses

The database was retained by the sponsor; statistical analyses were performed by statisticians employed by the sponsor.

The study was powered for evaluating the primary end point (percent change in $P\dot{V}O_2$, normalized to body weight, from baseline to week 16) in children developmentally able to perform CPET. A final sample size of 104 developmentally able patients was deemed necessary for 90% power of achieving statistical significance if there is a 15% improvement with the combined sildenafil groups compared with placebo, with the use of a 2-sided test at the 5% significance level. The primary comparison was based on combining the sildenafil groups after the adult data became available showing a lack of dose response on exercise capacity (assessed by the 6-minute walk [6MW] test) over the 20- to 80-mg dose range. Averaging across dose groups offered potential benefits with respect to sample size and/or reducing the treatment effect size on which to base study powering. Given the uncertainty concerning the likely effect size and the recruitment challenges for the study, this was an important consideration and formed the basis for the decision to average across sildenafil groups.

Because a study in pediatric PAH had not been performed previously and assumptions regarding variability were guided by limited literature, blinded interim analyses reassessed variability.[19] The final sample size, after the second blinded reestimation, was based on a 20.2% SD. Although the final sample size required for the primary end point was 104 developmentally able patients, all patients meeting the entry criteria, whether developmentally able or not, were enrolled until the number of patients required for analyzing the primary end point had been enrolled. All secondary and tertiary end points were assessed in all enrolled patients. Safety and tolerability were monitored in all enrolled patients.

Intention-to-treat analyses were performed for all variables. The intention-to-treat population included all randomized patients who received ≥1 dose of medication with the exception that for the percent change in $P\dot{V}O_2$, the intention-to-treat population included only developmentally able randomized patients who received ≥1 dose of medication. Because CPET and hemodynamic end points had 1 postbaseline assessment (week 16), analyses excluded patients with a missing end-of-treatment measurement; similarly, patients without baseline values were excluded. The influence of missing data was assessed by alternative analyses based on the assumptions of the data being missing at random (multiple imputation) or possibly informative (with the use of worst-case values).

The primary end point (percent change in $P\dot{V}O_2$) was evaluated with the use of ANCOVA. Mean response across the 3 sildenafil doses was compared with placebo. Although comparisons of the individual doses with placebo were performed, the study was not powered for these comparisons. The ANCOVA model included terms for treatment (low-, medium-, or high-dose sildenafil or placebo), baseline $P\dot{V}O_2$, etiology, and weight group. The analysis was repeated for the per-protocol population and with the use of sensitivity analyses assessing the impact of missing data.

An ANCOVA analysis assessed change from baseline to week 16 for mPAP, which included terms for treatment, etiology, weight group, and capability of reliably performing CPET. Because PVRI and cardiac index data were log normally distributed, natural logarithm–transformed week-16 data were analyzed. Log baseline was included as an additional term in these analyses. For PVRI and cardiac index, treatment comparisons with placebo on the log scale give rise to ratio comparisons to placebo when back transformed.

A proportional odds logistic regression model was used for FC and included terms for treatment, baseline FC, etiology, weight group, and ability to perform CPET. Missing FC values were handled with a last observation carried forward approach. Confidence intervals (CIs) and significance were assessed with Wald tests.

An ANCOVA analysis assessed changes from baseline to week 16 for Child Health Questionnaire–Parent Form 28 end points. The model included covariates of baseline scale, etiology, weight group, ability to perform CPET, and treatment. The remaining secondary end points were analyzed with the use of ANCOVA, with etiology, weight, and ability to perform CPET as covariates, with a last observation carried forward approach.

No adjustments were made for multiple end points or multiple comparisons in these analyses.

AEs and SAEs for all patients were summarized.

Kaplan-Meier survival estimates were derived for the sildenafil low-, medium-, and high-dose groups from the start of STARTS-1 (ie, they do not include placebo-treated STARTS-1 patients). These were determined for subjects ≤20 and >20 kg at STARTS-1 baseline separately. The incidence of death for the combined STARTS-1 and -2 studies (ie, including placebo-treated STARTS-1 patients) was assessed in June 2011. Patients lost to follow-up were censored from the date they were last known to be alive in survival analyses.

Results

Patient Population

Of 234 patients randomized and treated, 33% had IPAH/HPAH; the remainder had PAH/congenital heart disease (Table 2). Across the 3 sildenafil dose groups, etiology, baseline FC, $P\dot{V}O_2$, mPAP, and PVRI were comparable. The placebo group appeared to have less severe disease (assessed by $P\dot{V}O_2$, hemodynamics, and FC). Patient distribution across groups was uneven because patients weighing ≤20 kg were not randomized to low-dose sildenafil monotherapy; proportionally more of these patients were randomized to high-dose sildenafil versus the other treatment groups.

CPET was performed in 115 developmentally able patients (Figure 1), of which 106 were evaluable. None of the 63 patients aged <7 years were able to perform the exercise test. Among 171 patients aged ≥7 years, 56 patients were developmentally unable to reliably exercise. Reasons provided were Down syndrome (n=31); inability to reach bicycle

Table 2. Baseline Patient Characteristics in the 16-Week STARTS-1 Study*

		Sildenafil Dose			
	Placebo (n=60)	Low (n=42)	Medium (n=55)	High (n=77)	Combined (n=174)
Female sex, n (%)	38 (63)	25 (60)	31 (56)	51 (66)	107 (62)
Age, y, n					
1–4	7	0	9	19	28
5–12	37	25	28	36	89
13–17	16	17	18	22	57
Race, n					
White	24	19	26	28	73
Black	2	1	1	1	3
Asian	7	6	13	15	34
Other	27	16	15	33	64
BMI, kg/m^2, mean (SD)	17 (4)	18 (5)	18 (4)	16 (3)	17 (4)
WHO functional class, n (%)					
I	25 (42)	9 (21)	20 (36)	21 (27)	50 (29)
II	29 (48)	23 (55)	25 (45)	43 (56)	91 (52)
III	6 (10)	9 (21)	8 (15)	12 (16)	29 (17)
IV	0	0	1 (2)	0	1 (1)
Missing	0	1 (2)	1 (2)	1 (1)	3 (2)
Etiology, n					
IPAH/HPAH	21	12	19	26	57
APAH	39	30	36	51	117
Surgical repair†	15	13	15	24	52
Congenital systemic-to-pulmonary shunt with Sa_{O_2} ≥88% at rest	23	16	20	26	62
Postrepair D-transposition of great arteries	1	1	1	1	3
Concomitant medications, n					
Calcium channel blockers	12	5	11	11	27
Diuretics	9	10	15	20	45
Anticoagulants	10	5	9	3	17
Peak $\dot{V}_{O_2}$, mL/kg/min, mean (SD)‡	20 (4)	18 (4)	18 (5)	17 (4)	18 (4)
Mean pulmonary artery pressure, mm Hg, mean (SD)§	59 (22)	66 (23)	62 (18)	62 (24)	63 (22)
Cardiac index, L/min/m^2, mean (SD)‖	3.9 (2.1)	3.1 (1.1)	3.3 (1.5)	3.4 (1.6)	3.3 (1.5)
Pulmonary vascular resistance index, Wood units · m^2, mean (SD)¶	15 (10)	22 (13)	19 (14)	20 (16)	20 (15)
Mean pulmonary capillary wedge pressure, mm Hg, mean (SD)#	10 (3)	9 (3)	9 (3)	10 (4)	10 (4)
Mean right atrial pressure, mm Hg, mean (SD)§	8 (5)	8 (4)	8 (5)	9 (5)	8 (5)

STARTS-1 indicates Sildenafil in Treatment-Naive Children, Aged 1 to 17 Years, With Pulmonary Arterial Hypertension; BMI, body mass index; WHO, World Health Organization; IPAH, idiopathic pulmonary arterial hypertension; HPAH, heritable pulmonary arterial hypertension; APAH, associated pulmonary arterial hypertension; Sa_{O_2}, systemic arterial oxygen saturation; and $\dot{V}_{O_2}$, oxygen consumption.

*The groups shown represent all treated patients.

†Surgical repairs included atrial septal defect, ventricular septal defect, patent ductus arteriosus, aortopulmonary window, and others.

‡Subset of patients developmentally able to perform cardiopulmonary exercise testing (n=30, 28, 28, 29, 85 for placebo, sildenafil low-, medium-, and high-dose groups, and sildenafil combined-dose group, respectively).

§n=59, 42, 55, 75, and 172 for placebo, sildenafil low-, medium-, and high-dose groups, and sildenafil combined-dose group, respectively.

‖n=59, 41, 52, 74, and 167 for placebo, sildenafil low-, medium-, and high-dose groups, and sildenafil combined-dose group, respectively.

¶n=57, 40, 52, 73, and 165 for placebo, sildenafil low-, medium-, and high-dose groups, and sildenafil combined-dose group, respectively.

#n=59, 41, 55, 75, and 171 for placebo, sildenafil low-, medium-, and high-dose groups, and sildenafil combined-dose group, respectively.

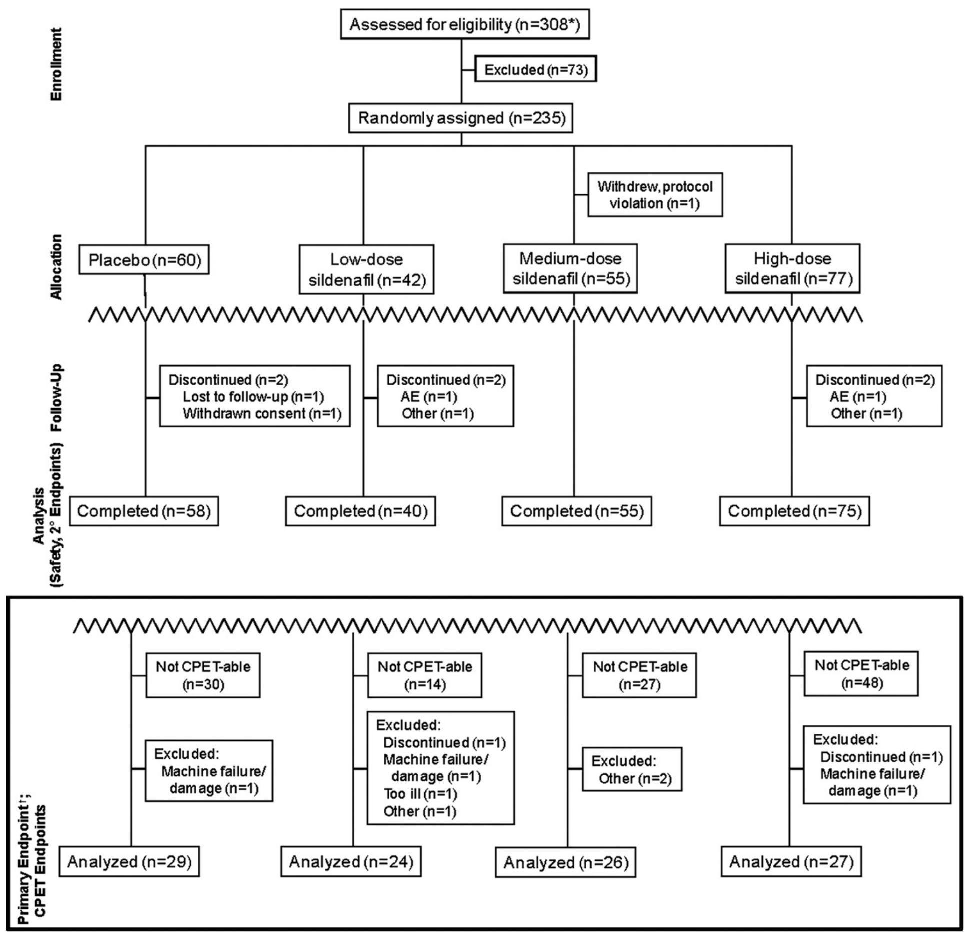

Figure 1. Patient flow and assessment for peak oxygen consumption in the 16-week Sildenafil in Treatment-Naive Children, Aged 1 to 17 Years, With Pulmonary Arterial Hypertension (STARTS-1) study. AE indicates adverse events; CPET, cardiopulmonary exercise testing. *Sixteen patients were screened twice (ie, 308 patients and 324 screenings). †One hundred six of the 115 developmentally able patients were included in the primary analysis.

pedals; and various other reasons, including unwillingness to wear mask, dyspnea, and low physical activity.

Three patients (1 medium dose, 2 placebo) underwent a 50% dose reduction in STARTS-1 due to AEs; all other patients received their assigned dose.

Of the 228 patients who completed STARTS-1, 220 continued into STARTS-2. In total, 229 patients received sildenafil treatment in STARTS-1 and/or -2.

Efficacy Outcomes

Primary Outcome

At week 16, mean $P\dot{V}O_2$ was 18.4, 20.4, and 19.0 mL/kg per minute for the low-, medium-, and high-dose groups, respectively, versus baseline values of 17.4, 18.0, and 17.4 mL/kg per minute. Placebo mean $P\dot{V}O_2$ was 20.0 mL/kg per minute at baseline and at week 16. The placebo-corrected estimated mean±SE percent change in $P\dot{V}O_2$ from baseline to end of treatment for the low-, medium-, and high-dose groups combined was 7.7±4.0% (95% CI, −0.2% to 15.6%); this prespecified end point was not statistically significant (P=0.056) (Figure 2).

Placebo-corrected estimates were made for the low-dose (3.8±5.0% [95% CI, −6.1% to 13.7%]), medium-dose (11.3±4.8% [95% CI, 1.7–20.9%]), and high-dose (8.0±4.9% [95% CI, −1.6% to 17.6%]) groups. Sensitivity analyses were consistent with the primary analysis. Patients with IPAH/HPAH receiving sildenafil had a greater placebo-corrected percent change in $P\dot{V}O_2$ compared with APAH patients (12.5±7.7% [−3.1% to 28.2%] versus 4.7±4.6% [−4.5% to 14.0%], respectively) (Figure 2).

Secondary Outcomes

Changes from baseline in mPAP and PVRI, assessed in all patients, showed improvements with sildenafil treatment; medium- and high-dose groups showed improvements versus placebo, whereas the low-dose group was similar to placebo (Table 3 and Figure 2). Greater mPAP improvements were observed for patients 20 to 45 kg and >45 kg versus 8 to 20 kg and for patients developmentally able versus those not developmentally able to exercise (Figure 2). Cardiac index increased 9.6% (95% CI, 0–21%) in the sildenafil groups combined compared with placebo (Table 3).

A dose response was observed for FC improvement. Compared with placebo, the odds ratios for FC improvement were 0.6 (95% CI, 0.2–2.0), 2.3 (95% CI, 0.8–6.7), and 4.5 (95% CI, 1.6–13.1) for sildenafil low-, medium-, and high-dose groups, respectively. Greater proportions of patients in

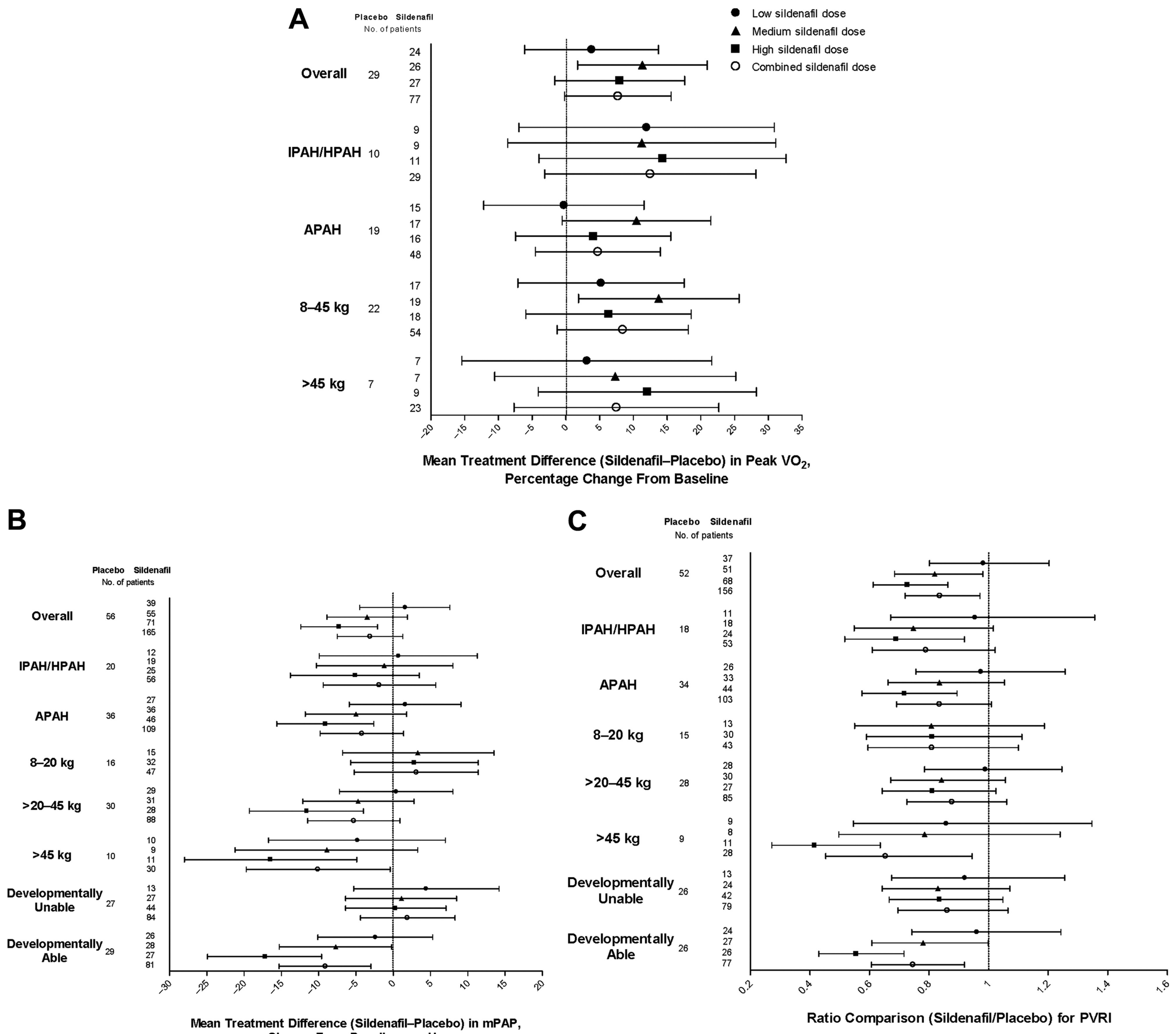

Figure 2. Estimated treatment effects (±95% confidence interval) (sildenafil vs placebo) in the Sildenafil in Treatment-Naive Children, Aged 1 to 17 Years, With Pulmonary Arterial Hypertension (STARTS-1) study from baseline to week 16 in peak oxygen consumption ($\dot{V}O_2$) (**A**), mean pulmonary artery pressure (mPAP) (**B**), and pulmonary vascular resistance index (PVRI) (**C**), overall and by subgroups including pulmonary arterial hypertension pathogenesis, weight, and developmental ability to perform cardiopulmonary exercise testing. For percent change in peak $\dot{V}O_2$ (**A**), because there were few developmentally able children in the 8- to 20-kg group, this group was combined with the 20- to 45-kg group. APAH indicates associated pulmonary arterial hypertension; IPAH/HPAH, idiopathic pulmonary arterial hypertension/heritable pulmonary arterial hypertension.

the sildenafil low-, medium-, and high-dose groups improved by ≥1 FC compared with placebo (14.3%, 18.2%, and 22.1%, respectively, versus 6.7%).

Additional secondary end points are presented in Table 3. No apparent differences were observed between the 3 sildenafil dose groups and placebo for the Child Health Questionnaire–Parent Form 28 questionnaire.

Tertiary Outcomes

Improvements from baseline in patient/parent and physician global assessments occurred in all treatment groups, including placebo. Greater proportions of patients/parents reported moderate or marked improvement with low-, medium-, and high-dose sildenafil compared with placebo (35.7%, 34.6%, and 45.5%, respectively, versus 21.6%); similarly, greater proportions of physicians reported moderate or marked improvement with low-, medium- and high-dose sildenafil versus placebo (26.2%, 27.2%, and 28.6%, respectively, versus 10.0%).

Approximately half of the patients in any group were not receiving conventional PAH therapy at baseline; few patients in any group required additions (≤6.5%) or discontinuations (≤9.1%) of conventional therapy.

Because only 3 patients (1 and 2 patients in the low- and high-dose groups, respectively) had clinical worsening, no conclusions were drawn.

Safety

The most frequently reported AEs in the 16-week study were headache, pyrexia, upper respiratory tract infections, vomit-

Table 3. Placebo-Corrected Change in Secondary Outcomes Between Baseline and End of 16-Week, Double-Blind STARTS-1 Treatment

	Treatment Difference (Sildenafil vs Placebo)			
Statistic	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose	Sildenafil Combined Dose
Mean PAP, mm Hg	n=39	n=55	n=71	n=165
Mean±SE difference	1.6±3.1	−3.5±2.7	−7.3±2.6	−3.1±2.2
95% CI	−4.5 to 7.6	−8.9 to 1.9	−12.4 to − 2.1	−7.5 to 1.3
P	0.610	0.199	0.006	0.172
PVRI	n=37	n=51	n=68	n=156
Ratio*	0.982	0.819	0.727	0.836
95% CI	0.802 to 1.203	0.684 to 0.981	0.612 to 0.863	0.720 to 0.971
P	0.859	0.031	<0.001	0.019
Cardiac index	n=37	n=51	n=69	n=157
Ratio*	1.100	1.043	1.148	1.096
95% CI	0.963 to 1.258	0.925 to 1.176	1.026 to 1.286	0.994 to 1.210
P	0.161	0.486	0.017	0.066
Mean RAP, mm Hg	n=39	n=55	n=71	n=165
Mean±SE difference	−0.2±0.9	−0.2±0.8	−1.1±0.8	−0.5±0.6
95% CI	−1.9 to 1.6	−1.7 to 1.4	−2.6 to 0.3	−1.8 to 0.8
P	0.849	0.811	0.128	0.440
Exercise duration, %†	n=24	n=26	n=27	n=77
Mean±SE difference	10.3±7.8	11.4±7.7	6.0±7.6	9.2±6.2
95% CI	−5.2 to 25.9	−3.8 to 26.6	−9.2 to 21.1	−3.1 to 21.5
P	0.190	0.139	0.436	0.139

STARTS-1 indicates Sildenafil in Treatment-Naive Children, Aged 1 to 17 Years, With Pulmonary Arterial Hypertension; PAP, pulmonary artery pressure; CI, confidence interval; PVRI, pulmonary vascular resistance index; and RAP, right atrial pressure. With the exception of the primary comparison, *P* values should be interpreted descriptively because no adjustments were made for multiple comparisons. n=56, 52, 55, 56, and 29 for the placebo group for mean PAP, PVRI, cardiac index, mean RAP, and exercise duration, respectively.

*Because PVRI and cardiac index data were log-transformed before analysis, comparisons are presented as ratios (active/placebo) when back-transformed.

†Baseline was the average of all assessments on or before the first day of study treatment.

ing, and diarrhea. Pyrexia, increased erection, and upper respiratory tract infection occurred in >5% more patients in the sildenafil combined group versus placebo. Pyrexia, vomiting, and nausea appeared to be dose related. The majority of AEs were of mild or moderate intensity. AEs that occurred in ≥3% of patients in the sildenafil combined group are presented in Table 4.

Six patients discontinued participation in the trial: 4 sildenafil-treated (for AEs [weight loss, n=1; stridor, n=1], or other [n=2]) and 2 placebo-treated (withdrew consent, n=1; lost to follow-up, n=1) patients. Eleven patients reported SAEs; 2 were considered treatment related (both high-dose sildenafil): stridor in 1 patient during the first week of therapy (sildenafil 10 mg 3 times daily) and ventricular arrhythmia in 1 patient (sildenafil 80 mg 3 times daily). Two patients died before randomization, 1 during and 1 before cardiac catheterization; no additional deaths occurred during STARTS-1 treatment. Over the 16-week study, sildenafil treatment did not appear to affect laboratory parameters, vital signs, growth or development, ocular assessments, or ECG across time with dose.

Extension Study

A higher risk of mortality occurred among patients randomized to high-dose compared with lower-dose sildenafil monotherapy in STARTS-2; the increased risk appeared to occur after 2 years of treatment.

As of June 2011, for patients weighing >20 kg at STARTS-1 baseline, Kaplan-Meier estimates of survival were 100%, 100%, and 100% at 1 year; 95%, 95%, and 92% at 2 years; and 92%, 90%, and 84% at 3 years for patients randomized to low-, medium-, and high-dose sildenafil, respectively (placebo-treated STARTS-1 patients are not included in this calculation). For patients weighing ≤20 kg at STARTS-1 baseline, Kaplan-Meier estimates of survival were 100% and 97% at 1 year; 93% and 94% at 2 years; and 93% and 94% at 3 years for patients randomized to medium- and high-dose sildenafil, respectively (there was no low-dose sildenafil group for children weighing <20 kg).

With all patients having the potential to complete ≥3 years of treatment (including some receiving 7 years of treatment), 35 deaths have been reported. Deaths were reported on treatment (n=26) or during follow-up (n=9). The incidence

Table 4. Adverse Events That Occurred in ≥3% of Patients in the Sildenafil Combined Group in the 16-Week, Double-Blind STARTS-1 Study

		Sildenafil Dose			
	Placebo (n=60), n (%)	Low (n=42), n (%)	Medium (n=55), n (%)	High (n=77), n (%)	Combined (n=174), n (%)
Headache	8 (13)	5 (12)	6 (11)	12 (16)	23 (13)
Pyrexia	1 (2)	3 (7)	8 (15)	9 (12)	20 (12)
Upper respiratory tract infection	4 (7)	5 (12)	9 (16)	7 (9)	21 (12)
Vomiting	4 (7)	3 (7)	5 (9)	11 (14)	19 (11)
Erection increased*	0	0	3 (13)	3 (12)	6 (9)
Diarrhea	5 (8)	2 (5)	3 (6)	7 (9)	12 (7)
Bronchitis	1 (2)	2 (5)	5 (9)	3 (4)	10 (6)
Cough	3 (5)	2 (5)	4 (7)	2 (3)	8 (5)
Nasopharyngitis	4 (7)	3 (7)	3 (6)	2 (3)	8 (5)
Nausea	0	0	4 (7)	4 (5)	8 (5)
Pharyngitis	0	3 (7)	3 (6)	1 (1)	7 (4)
Dizziness	2 (3)	2 (5)	2 (4)	2 (3)	6 (3)
Epistaxis	2 (3)	1 (2)	2 (4)	3 (4)	6 (3)
Rhinorrhea	0	0	4 (7)	2 (3)	6 (3)
Upper abdominal pain	1 (2)	0	3 (6)	3 (4)	6 (3)

STARTS-1 indicates Sildenafil in Treatment-Naive Children, Aged 1 to 17 Years, With Pulmonary Arterial Hypertension.

*Also includes the term *spontaneous penile erection*. Percentage shown is for boys only; n=22, 17, 24, and 26 for placebo, sildenafil low-, medium-, and high-dose groups, and sildenafil combined-dose group, respectively.

of deaths is currently 9% (5 of 55), 14% (10 of 74), and 20% (20 of 100) for patients randomized in STARTS-1 or -2 to low-, medium-, and high-dose sildenafil, respectively.

Deaths were related to etiology and baseline disease severity. Of patients who died, 74%, 69%, and 71% had baseline values above median values for PVRI (15.1 Wood units·m^2), mPAP (62 mm Hg), and right atrial pressure (7 mm Hg), respectively; 40% were classified as FC III or IV at baseline (versus 15% of the overall study population). The majority of deaths (74%) occurred in patients with IPAH/HPAH, although these patients represented only 33% of the study population. Baseline N-terminal–pro-brain natriuretic peptide data were available for 30 of 35 patients who died and 157 who were alive at last follow-up; 80% of patients who died had values above the median of 233 pg/mL (versus 44% of patients still alive).

Discussion

PAH is a progressive fatal disease in children and adults.[1] To date, effective therapies, developed only for adults, have used exercise capacity as the primary end point. Because the 6MW test is easy to perform and is a maximal test in the majority of adults, it has been the test of choice. However, the 6MW test is not a maximal test in the majority of children. Additionally, cooperation and motivation for the 6MW test may vary in children, challenging consistency, reproducibility, and interpretability.[20,21] Because CPET is a maximal test in adults and children, and in adult PAH patients $P\dot{V}O_2$ correlates with 6MW distance,[22] $P\dot{V}O_2$ was chosen for this study.

At the outset, it was recognized that young children and those with specific comorbid conditions (eg, PAH associated with Down syndrome) would be unable to reliably perform CPET. The sample size was therefore based on patients who were developmentally able to reliably perform CPET. However, patients unable to reliably perform CPET were enrolled to assess secondary efficacy end points and evaluate safety in a wider age range (1–17 years) because these children are routinely treated with PAH-specific therapy. Secondary efficacy end points included hemodynamic parameters, which physicians use to assess disease severity and which predict PAH prognosis in children and adults,[23–26] and World Health Organization FC, used to assess clinical symptoms and predict prognosis in both pediatric and adult patients with PAH.[4,23–26]

The primary end point ($P\dot{V}O_2$) showed a placebo-corrected percent change from baseline in the sildenafil low-, medium-, and high-dose groups combined versus placebo of 7.7% (P=0.056). Although the P value was >0.05, multiple lines of evidence suggest that the result is not a chance observation. First, the prespecified procedure of averaging response across treatment groups is vulnerable to the possibility that ineffective doses will reduce the treatment effect. In this study, low-dose monotherapy was ineffective; results were similar to placebo for exercise capacity, hemodynamic parameters, and World Health Organization FC. A post hoc analysis excluding the low-dose sildenafil group resulted in a placebo-corrected increase in $P\dot{V}O_2$ for the combined medium- and high-dose groups of 9.7% (95% CI, 1.3% to 18.0%; P=0.023). The ineffectiveness of low-dose sildenafil is consistent with pharmacokinetic data showing lower than predicted concentrations with the sildenafil 10-mg dose in children >20 kg[27,28] and is useful for dosing recommendations.

Additionally, it is important to assess the consistency between end points observed within this pediatric study and between this study and the adult PAH sildenafil study in which similar end points were used. Within this study, $P\dot{V}O_2$, hemodynamic parameters, World Health Organization FC, and parent/physician global assessments all showed dose-related improvements with sildenafil monotherapy, with the low dose being ineffective. Because these secondary end points were assessed in all enrolled patients (children aged 1–17 years) and the results are consistent across all-aged children, they imply that sildenafil effectiveness is applicable to a greater number of pediatric PAH patients (ie, not only patients developmentally able to reliably perform CPET). In addition, the magnitude of effects with sildenafil monotherapy in treatment-naive pediatric patients in this study is similar to that observed with treatment-naive adult patients with PAH.[29] Therefore, we believe that the improvements observed in this study are not a chance finding.

The improvements in the secondary and tertiary end points support clinical relevance of the effects observed with sildenafil monotherapy on the primary end point. Studies of adults with other cardiovascular disorders have shown significant $P\dot{V}O_2$ changes of the magnitude observed in this study, which were accompanied by significant changes in 6MW, FC, and quality of life measures, supporting the utility of $P\dot{V}O_2$ and FC to assess clinically useful changes.[30,31] Additionally, because PVRI correlates with outcomes in children and in adults[4,25] and changes in PVRI correlate with changes in exercise capacity,[32] the significant improvement in PVRI in this study is consistent with the change in $P\dot{V}O_2$ being clinically relevant.

Sildenafil monotherapy appeared to be safe and well tolerated. Most AEs were mild to moderate. There were 2 deaths before randomization, no deaths during the 16-week study, and few discontinuations; SAEs were reported in 11 patients. Additionally, there were no differences from placebo regarding any ocular AEs (all patients received complete ocular assessments at baseline and week 16).

Although the 16-week study included an analysis of clinical worsening events, few events were reported. To investigate morbidity and/or mortality, a study of longer duration would be required. However, in a placebo-controlled study in treatment-naive children, a longer study was not considered ethical. The heterogeneity of PAH etiology of patients in this study can be considered a weakness or a strength. The IPAH/HPAH-to-APAH ratio of etiologies differed from several observational studies[33–36] but is consistent with children not receiving epoprostenol.[36] Likely, because therapies approved for adult PAH were available, fewer treatment-naive IPAH/HPAH patients (in whom rapid deterioration occurs[37]) enrolled in this study. No APAH/connective tissue disease patients enrolled, consistent with pediatric epidemiology.[35,36] A greater treatment effect on $P\dot{V}O_2$ occurred in IPAH/HPAH versus APAH, consistent with adult PAH observations.[29,38–40] However, with only 33% of the children enrolled having IPAH/HPAH, the effects of sildenafil may have been underestimated.

Patients who completed STARTS-1 were eligible to enroll in the long-term STARTS-2 extension study. Because STARTS-2 did not include a placebo arm, the impact of sildenafil monotherapy on long-term survival is difficult to discern. However, 1-, 3-, and 5-year survival rates for pediatric PAH patients before the availability of PAH-specific therapy range from 37% to 66%, 33% to 52%, and 33% to 35%, respectively.[41–43] STARTS-2 survival rates, assessed from STARTS-1 baseline, compare favorably with these historical rates. Most deaths were investigator assessed as being associated with disease progression, and none were considered to be causally related to study treatment. Available data support a recommendation for STARTS-2 patients receiving high-dose sildenafil to down titrate.

In conclusion, sildenafil monotherapy for 16 weeks is well tolerated for pediatric PAH. Although the primary comparison of percent change in $P\dot{V}O_2$ for the 3 sildenafil groups combined was only marginally statistically significant, the improvements in exercise capacity, FC, and hemodynamics with medium- and high-dose sildenafil suggest efficacy with these doses. Combined with interim data from the ongoing extension study, the overall profile favors the medium dose. Further investigation is warranted to determine optimal dosing based on age and body weight.

Acknowledgments

The authors wish to thank Stuart Russell and his colleagues at the CPET core laboratory for their work providing CPET parameters and Helen Richardson and Irina Konourina for substantial work on this study. The following investigators participated in this study: Dr Maria Virginia Tavares Santana (Brazil); Dr James Y. Coe (Canada); Dr Lida Toro (Chile); Drs Luz E. Arbelaez, Alberto E. Garcia, and Luis D. Medina (Colombia); Dr Guillermo Gaitan (Guatemala); Drs Marta Katona and Andras Szatmari (Hungary); Drs B.K.S. Sastry and Krishna R. Kumar (India); Dr Nazzareno Galie (Italy); Professor Tsutomu Saji (Japan); Dr Sim Seng (Malaysia); Dr Tomas Pulido (Mexico); Professor Wanda Kawalec, Professor Jacek Bialkowski, and Dr Andrzej Rudzinski (Poland); Professor Yuri M. Belozerov (Russian Federation); Professor Erkki Pesonen (Sweden); Professors Betau Hwang, Kai-Sheng Hsieh, and Me-Hwan Wu (Taiwan); and Drs Robyn J. Barst, Curtis J. Daniels, Jeffrey A. Feinstein, D.D. Ivy, Nikoleta S. Kolovos, Robert Gajarski, Michael A. Portman, Andrew M. Atz, Mary Mullen, and David L. Wessel (United States).

Sources of Funding

This study was sponsored by Pfizer Inc. Editorial support was provided by Tiffany Brake, PhD, and Janet E. Matsuura, PhD, from Complete Healthcare Communications, Inc, and was funded by Pfizer Inc.

Disclosures

Financial support and potential conflicts of interest are as follows: Dr Barst has served as a consultant and/or advisory board member to Actelion, Eli Lilly, GlaxoSmithKline, GE, Gilead, Ikaria, Merck, Novartis, and Pfizer; Dr Ivy has served as a consultant to Actelion, Gilead, Pfizer, and United Therapeutics and has received investigator-initiated research funding from Gilead and United Therapeutics; Dr Sastry has received research funding from Pfizer and is a consultant to GlaxoSmithKline and Actelion; Dr Pulido has served as a consultant and/or advisory board member for Actelion, Pfizer, Lilly, GlaxoSmithKline, and Bayer, has received travel support from Pfizer and Bayer, and has received research funding from Actelion, Pfizer, Gilead, Bayer, and United Therapeutics; Gary R. Layton and Dr Serdarevic-Pehar are Pfizer employees and hold shares of Pfizer stock; Dr Serdarevic-Pehar's husband is also a Pfizer employee; and Dr Wessel has received consulting fees from Ikaria.

References

1. Humbert M, Morrell NW, Archer SL, Stenmark KR, MacLean MR, Lang IM, Christman BW, Weir EK, Eickelberg O, Voelkel NF, Rabinovitch M. Cellular and molecular pathobiology of pulmonary arterial hypertension. *J Am Coll Cardiol.* 2004;43:13S–24S.
2. Machado RD, Eickelberg O, Elliott CG, Geraci MW, Hanaoka M, Loyd JE, Newman JH, Phillips JA III, Soubrier F, Trembath RC, Chung WK. Genetics and genomics of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2009;54:S32–S42.
3. Humbert M, Trembath RC. Genetics of pulmonary hypertension: from bench to bedside. *Eur Respir J*. 2002;20:741–749.
4. Moledina S, Hislop AA, Foster H, Schulze-Neick I, Haworth SG. Childhood idiopathic pulmonary arterial hypertension: a national cohort study. *Heart*. 2010;96:1401–1406.
5. van Loon RL, Roofthooft MT, van Osch-Gevers M, Delhaas T, Strengers JL, Blom NA, Backx A, Berger RM. Clinical characterization of pediatric pulmonary hypertension: complex presentation and diagnosis. *J Pediatr.* 2009;155:176–182, e171.
6. van Loon RL, Hoendermis ES, Duffels MG, Vonk-Noordegraaf A, Mulder BJ, Hillege HL, Berger RM. Long-term effect of bosentan in adults versus children with pulmonary arterial hypertension associated with systemic-to-pulmonary shunt: does the beneficial effect persist? *Am Heart J*. 2007;154:776–782.
7. Abrams D, Schulze-Neick I, Magee AG. Sildenafil as a selective pulmonary vasodilator in childhood primary pulmonary hypertension. *Heart*. 2000;84:E4.
8. Humpl T, Reyes JT, Holtby H, Stephens D, Adatia I. Beneficial effect of oral sildenafil therapy on childhood pulmonary arterial hypertension: twelve-month clinical trial of a single-drug, open-label, pilot study. *Circulation*. 2005;111:3274–3280.
9. Kothari SS, Duggal B. Chronic oral sildenafil therapy in severe pulmonary artery hypertension. *Indian Heart J*. 2002;54:404–409.
10. Prasad S, Wilkinson J, Gatzoulis MA. Sildenafil in primary pulmonary hypertension. *N Engl J Med*. 2000;343:1342.
11. Sastry BK, Narasimhan C, Reddy NK, Anand B, Prakash GS, Raju PR, Kumar DN. A study of clinical efficacy of sildenafil in patients with primary pulmonary hypertension. *Indian Heart J*. 2002;54:410–414.
12. Sastry BK, Narasimhan C, Reddy NK, Raju BS. Clinical efficacy of sildenafil in primary pulmonary hypertension: a randomized, placebo-controlled, double-blind, crossover study. *J Am Coll Cardiol*. 2004;43:1149–1153.
13. Ghofrani HA, Osterloh IH, Grimminger F. Sildenafil: from angina to erectile dysfunction to pulmonary hypertension and beyond. *Nat Rev Drug Discov*. 2006;5:689–702.
14. Ballard SA, Gingell CJ, Tang K, Turner LA, Price ME, Naylor AM. Effects of sildenafil on the relaxation of human corpus cavernosum tissue in vitro and on the activities of cyclic nucleotide phosphodiesterase isozymes. *J Urol*. 1998;159:2164–2171.
15. Anderson BJ, Meakin GH. Scaling for size: some implications for paediatric anaesthesia dosing. *Paediatr Anaesth*. 2002;12:205–219.
16. Holford NH. A size standard for pharmacokinetics. *Clin Pharmacokinet*. 1996;30:329–332.
17. West GB, Brown JH, Enquist BJ. A general model for the origin of allometric scaling laws in biology. *Science*. 1997;276:122–126.
18. LaFarge CG, Miettinen OS. The estimation of oxygen consumption. *Cardiovasc Res*. 1970;4:23–30.
19. Kieser M, Friede T. Simple procedures for blinded sample size adjustment that do not affect the type I error rate. *Stat Med*. 2003;22:3571–3581.
20. Lammers AE, Hislop AA, Flynn Y, Haworth SG. The 6-minute walk test: normal values for children of 4–11 years of age. *Arch Dis Child*. 2008;93:464–468.
21. Smith G, Reyes JT, Russell JL, Humpl T. Safety of maximal cardiopulmonary exercise testing in pediatric patients with pulmonary hypertension. *Chest*. 2009;135:1209–1214.
22. Miyamoto S, Nagaya N, Satoh T, Kyotani S, Sakamaki F, Fujita M, Nakanishi N, Miyatake K. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension: comparison with cardiopulmonary exercise testing. *Am J Respir Crit Care Med*. 2000;161:487–492.
23. Badesch DB, Champion HC, Sanchez MA, Hoeper MM, Loyd JE, Manes A, McGoon M, Naeije R, Olschewski H, Oudiz RJ, Torbicki A. Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2009;54:S55–S66.
24. McLaughlin VV, Presberg KW, Doyle RL, Abman SH, McCrory DC, Fortin T, Ahearn G. Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest.* 2004;126:78S–92S.
25. Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, Frost A, Barst RJ, Badesch DB, Elliott CG, Liou TG, McGoon MD. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation*. 2010;122:164–172.
26. Ivy DD, Rosenzweig EB, Lemarie JC, Brand M, Rosenberg D, Barst RJ. Long-term outcomes in children with pulmonary arterial hypertension treated with bosentan in real-world clinical settings. *Am J Cardiol*. 2010;106:1332–1338.
27. Hayashi N, Harnisch L. Population PK of sildenafil and PK/PD assessment of exercise tolerability in children with pulmonary arterial hypertension (PAH). Paper presented at: European Respiratory Society Annual Congress; September 12–16, 2009; Vienna, Austria.
28. Watt S, Hayashi N, Harnish L, Gao X. Population pharmacokinetics (PK) of sildenafil in paediatric and adult patients with pulmonary arterial hypertension (PAH). Paper presented at: European Society of Cardiology Annual Meeting; August 28–September 1, 2010; Stockholm, Sweden.
29. Galie N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, Fleming T, Parpia T, Burgess G, Branzi A, Grimminger F, Kurzyna M, Simonneau G. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med*. 2005;353:2148–2157.
30. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, Garrigue S, Kappenberger L, Haywood GA, Santini M, Bailleul C, Daubert JC; Multisite Stimulation in Cardiomyopathies Study I. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med*. 2001;344:873–880.
31. Auricchio A, Stellbrink C, Butter C, Sack S, Vogt J, Misier AR, Bocker D, Block M, Kirkels JH; on behalf of the Pacing Therapies in Congestive Heart Failure II Study Group; Kramer A, Huvelle E; on behalf of the Guidant Heart Failure Research Group. Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. *J Am Coll Cardiol*. 2003;42:2109–2116.
32. Brar S, Jadhav P, Stockbridge N, Gobburu J, Madabushi R. Hemodynamic determinants of clinical endpoints in pulmonary arterial hypertension trials. Paper presented at: American Conference on Pharmacometrics; October4–7, 2009; Mashantucket, CT.
33. Beghetti M, Haworth SG, Bonnet D, Barst RJ, Acar P, Fraisse A, Ivy DD, Jais X, Schulze-Neick I, Galie N, Morganti A, Dingemanse J, Kusic-Pajic A, Berger RM. Pharmacokinetic and clinical profile of a novel formulation of bosentan in children with pulmonary arterial hypertension: the FUTURE-1 study. *Br J Clin Pharmacol*. 2009;68:948–955.
34. Fasnacht MS, Tolsa JF, Beghetti M. The Swiss registry for pulmonary arterial hypertension: the paediatric experience. *Swiss Med Wkly*. 2007;137:510–513.
35. Fraisse A, Jais X, Schleich JM, di Filippo S, Maragnes P, Beghetti M, Gressin V, Voisin M, Dauphin C, Clerson P, Godart F, Bonnet D. Characteristics and prospective 2-year follow-up of children with pulmonary arterial hypertension in France. *Arch Cardiovasc Dis*. 2010;103:66–74.
36. Rosenzweig EB, Ivy DD, Widlitz A, Doran A, Claussen LR, Yung D, Abman SH, Morganti A, Nguyen N, Barst RJ. Effects of long-term bosentan in children with pulmonary arterial hypertension. *J Am Coll Cardiol*. 2005;46:697–704.
37. Haworth SG, Beghetti M. Assessment of endpoints in the pediatric population: congenital heart disease and idiopathic pulmonary arterial hypertension. *Curr Opin Pulm Med*. 2010;16(suppl 1):S35–S41.
38. Barst RJ. Sitaxsentan: a selective endothelin-A receptor antagonist, for the treatment of pulmonary arterial hypertension. *Expert Opin Pharmacother*. 2007;8:95–109.
39. Galie N, Badesch D, Oudiz R, Simonneau G, McGoon MD, Keogh AM, Frost AE, Zwicke D, Naeije R, Shapiro S, Olschewski H, Rubin LJ. Ambrisentan therapy for pulmonary arterial hypertension. *J Am Coll Cardiol*. 2005;46:529–535.
40. Galie N, Humbert M, Vachiery JL, Vizza CD, Kneussl M, Manes A, Sitbon O, Torbicki A, Delcroix M, Naeije R, Hoeper M, Chaouat A,

Morand S, Besse B, Simonneau G. Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol*. 2002;39:1496–1502.

41. Barst RJ, Maislin G, Fishman AP. Vasodilator therapy for primary pulmonary hypertension in children. *Circulation*. 1999;99:1197–1208.
42. Houde C, Bohn DJ, Freedom RM, Rabinovitch M. Profile of paediatric patients with pulmonary hypertension judged by responsiveness to vasodilators. *Br Heart J*. 1993;70:461–468.
43. Simpson CM, Penny DJ, Cochrane AD, Davis AM, Rose ML, Wilson SE, Weintraub RG. Preliminary experience with bosentan as initial therapy in childhood idiopathic pulmonary arterial hypertension. *J Heart Lung Transplant*. 2006;25:469–473.

CLINICAL PERSPECTIVE

Pulmonary arterial hypertension is an important cause of morbidity and mortality in children and adults. Currently, 8 drugs are approved for adult pulmonary arterial hypertension, yet no drugs are approved for children. Because of similar clinical characteristics and histopathology, treatment for children has been extrapolated from evidence-based adult guidelines. However, better information is required to provide optimal pediatric dosing and to ensure safety in children of all ages. The 16-week, randomized, double-blind, placebo-controlled Sildenafil in Treatment-Naive Children, Aged 1 to 17 Years, With Pulmonary Arterial Hypertension (STARTS-1) study evaluated the effects of sildenafil in childhood pulmonary arterial hypertension. Treatment-naive children with pulmonary arterial hypertension ($n=234$; aged 1–17 years; $\geq$8 kg) received low-, medium-, or high-dose sildenafil or placebo orally 3 times daily. Peak oxygen consumption, measured only in children who were able to reliably perform exercise testing (using cycle ergometry), was the primary end point. Hemodynamic parameters and World Health Organization functional class were assessed across all patients, including those unable to reliably perform exercise testing. Although the primary comparison of percent change in peak oxygen consumption for the 3 sildenafil groups combined was only marginally statistically significant, the improvements in exercise capacity, functional class, and hemodynamics with medium- and high-dose sildenafil suggest efficacy with these doses. Combined with interim data from the ongoing extension study, the overall profile favors the medium dose. Further investigation is warranted to determine optimal dosing based on age and body weight.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of Oral Sildenafil Citrate in Treatment-Naive Children With Pulmonary Arterial Hypertension

Robyn J. Barst, D. Dunbar Ivy, Guillermo Gaitan, Andras Szatmari, Andrzej Rudzinski, Alberto E. Garcia, B.K.S. Sastry, Tomas Pulido, Gary R. Layton, Marjana Serdarevic-Pehar and David L. Wessel

Circulation. 2012;125:324-334; originally published online November 29, 2011;
doi: 10.1161/CIRCULATIONAHA.110.016667
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539