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

Running title: Barst et al.; Sildenafil in pediatric pulmonary hypertension

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Abstract:

**Background** - Safe, effective therapy is needed for pediatric pulmonary arterial hypertension (PAH).

**Methods and Results** - Treatment-naïve children (n=235; 1–17 yrs; ≥8 kg) enrolled in STARTS-1 were randomized to low-, medium-, or high-dose sildenafil or placebo orally thrice daily for 16 weeks. The primary comparison was percentage change from baseline in peak oxygen consumption (pVO₂) for the three sildenafil doses combined versus placebo. Exercise testing was performed in 115 children able to exercise reliably; the study was powered for this population. Secondary endpoints (assessed in all patients) included hemodynamics and functional class (FC). The estimated mean ± SE percentage change in pVO₂ for the three doses combined versus placebo was 7.7% ± 4.0% (95% CI, –0.2% to 15.6%; P=0.056). Peak VO₂, FC, 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 while placebo-treated patients were randomized to low-, medium-, or high-dose sildenafil. In STARTS-2 (ongoing), increased mortality was observed with high- versus lower-dose groups.

**Conclusions** - Sixteen-week sildenafil monotherapy is well tolerated in pediatric PAH. Percentage change in pVO₂ for the three sildenafil doses combined was only marginally significant; however, pVO₂, FC, 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://clinicaltrials.gov](http://clinicaltrials.gov); NCT00159874.

**Key words:** cardiopulmonary exercise, clinical trials, pediatrics, pulmonary arterial hypertension, sildenafil
Introduction

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 (CHD) or connective tissue disease (CTD).\(^3\) Treatment aims to improve quality of life and survival.

Currently, 8 drugs are approved for adult PAH; however, no therapies are approved for children. Based upon similar clinical characteristics and histopathology, treatment for children has 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 assure safety in children of all ages. This 16-week, placebo-controlled, dose-ranging study evaluated the effects of oral Sildenafil in Treatment-naive children, Aged 1–17 years, with pulmonary arterial hypertension (STARTS-1).

Methods

Selection of Patients

Children (aged 1–17 years) weighing ≥8 kg with IPAH, HPAH, or PAH associated with CTD or CHD (unrepaired or partially repaired shunts with oxygen saturation at rest ≥88%, D-transposition of the great arteries repaired ≤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) $\geq 25$ mmHg at rest, pulmonary capillary wedge pressure $\leq 15$ mmHg, and pulmonary vascular resistance index (PVRI) $\geq 3$ Wood units $\cdot m^2$, was confirmed by right heart catheterization at baseline. Nitrates, cytochrome P450 3A4 inhibitors, prostacyclin analogues, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors (PDE5i), 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 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 using 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 (IVRS) assigned randomization numbers to eligible patients.

The 3 sildenafil dose levels, low, medium, and high, were selected to achieve maximum plasma concentrations ($C_{max}$) of 47, 140, and 373 ng/mL, respectively, at steady state after TID oral administration (Table 1). These target concentrations were selected such that the concentrations of unbound sildenafil would be expected to be similar to sildenafil concentrations that produced approximately 53%, 77%, and 90% inhibition of PDE5 activity in vitro,
respectively. 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 using general scaling factors based on other drugs.

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, USA) but randomized 1:2:1 to medium and high doses and placebo, 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 endpoint. 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 (pVO2) ≥10 mL/kg/min and ≤28 mL/kg/min (normal, ~35 mL/kg/min) during screening CPET. Computer-controlled cycle ergometers were used. Ergometers were calibrated per manufacturer instructions. Most sites used Med-Graphics Cardio-Respiratory Diagnosis System (Medical Graphics, St. Paul, MN, USA). 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 postdose).
CPET began with up to 3 minutes (≥1 min 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 min 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 50–60 rpm for approximately 8–12 minutes. CPET was stopped for intolerable dyspnea/fatigue or for safety concerns (ie, 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 (NT-pro-BNP) levels were assessed at baseline and week 16 (or end of treatment); and 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 using 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 using thermodilution or Fick methods; for patients with shunts, the Fick method was used. If the Fick method was used, oxygen consumption was estimated using standard tables. If supplemental oxygen was administered at baseline, the same concentration (FiO2) 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 IVRS assigned patients with
a package number from the list corresponding to the treatment assigned. Medication was administered orally 3 times daily (TID), ≥6 hours apart, for 16 weeks. All patients randomized to sildenafil received sildenafil 10 mg TID for 1 week followed by titration to assigned dose; placebo was dummy titrated. Patients were permitted one 50% dose reduction (following ≥1 week of treatment) for drug intolerance; if intolerance persisted, patients were discontinued.

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, while 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 discontinued from STARTS-1 or -2.

**Outcome Measures**

The primary endpoint, performed only in the developmentally able patients, was percentage change in pVO₂, normalized to body weight, from baseline to week 16.

Secondary endpoints, performed in all patients, included change from baseline to week 16 in mPAP, PVRI, FC, cardiac index (CI), right atrial pressure, physical and psychosocial scales of the Child Health Questionnaire-Parent Form (CHQ-PF28; for patients aged ≥5 years), and percentage change from baseline in exercise duration. Tertiary endpoints, 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 endpoint (percentage change in pVO2, 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, using 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 previously performed and assumptions regarding variability were guided by limited literature, blinded interim analyses reassessed
variability.\textsuperscript{19} The final sample size, after the second blinded re-estimation, was based on a 20.2\% standard deviation. Although the final sample size required for the primary endpoint 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 endpoint had been enrolled. All secondary and tertiary endpoints were assessed in all enrolled patients. Safety and tolerability were monitored in all enrolled patients.

Intention-to-treat (ITT) analyses were performed for all variables. The ITT population included all randomized patients who received \( \geq 1 \) dose of medication with the exception that for the percentage change in pVO\(_2\), the ITT population included only developmentally able randomized patients who received \( \geq 1 \) dose of medication. Because CPET and hemodynamic endpoints had one postbaseline assessment (week 16), analyses excluded patients having a missing end-of-treatment measurement; similarly, patients without baseline values were excluded. The influence of missing data was assessed using alternative analyses based on the assumptions of the data being missing at random (multiple imputation) or possibly informative (using worst-case values).

The primary endpoint (percentage change in pVO\(_2\)) was evaluated using analysis of covariance (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 pVO\(_2\), etiology, and weight group. The analysis was repeated for the per-protocol population and using 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 CI 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 CI, treatment comparisons to 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 using a LOCF approach. Confidence intervals and significance were assessed with Wald tests.

An ANCOVA analysis assessed changes from baseline to week 16 for CHQ-PF28 endpoints. The model included covariates of baseline scale, etiology, weight group, ability to perform CPET, and treatment. The remaining secondary endpoints were analyzed using ANCOVA, with etiology, weight, and ability to perform CPET as covariates, with LOCF.

No adjustments were made for multiple endpoints 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-CHD (Table 2). Across the 3 sildenafil dose groups, etiology, baseline FC, pVO₂, mPAP, and PVRI were comparable. The placebo group appeared to have less severe disease (assessed by pVO₂, 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.

Cardiopulmonary exercise testing 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 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; 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 pVO₂ was 18.4, 20.4, and 19.0 mL/kg/min for the low-, medium-, and high-dose groups, respectively, versus baseline values of 17.4, 18.0, and 17.4 mL/kg/min. Placebo
mean pVO₂ was 20.0 mL/kg/min at baseline and at week 16. The placebo-corrected estimated mean ± SE percentage change in pVO₂ from baseline to end of treatment for the low-, medium-, and high-dose groups combined was 7.7%±4.0% (95% confidence interval [CI], –0.2% to 15.6%); this pre-specified endpoint was not statistically significant (P=0.056) (Figure 2).

Placebo-corrected estimates were made for the low (3.8%±5.0% [95% CI, –6.1% to 13.7%]), medium (11.3%±4.8% [95% CI, 1.7% to 20.9%]), and high (8.0%±4.9% [95% CI, –1.6% to 17.6%]) dose groups. Sensitivity analyses were consistent with the primary analysis.

Patients with IPAH/HPAH receiving sildenafil had a greater placebo-corrected percentage change in pVO₂ compared with APAH patients (12.5%±7.7% [–3.1% to 28.2%] vs 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, 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 to 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 to 2.0), 2.3 (95% CI, 0.8 to 6.7), and 4.5 (95% CI, 1.6 to 13.1) for sildenafil low-, medium-, and high-dose groups, respectively. Greater
proportions of patients in 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 endpoints are presented in Table 3. No apparent differences were observed between the 3 sildenafil dose groups and placebo for the CHQ-PF28 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, vs 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, vs 10.0%).

Approximately half of 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 (URTIs), vomiting, and diarrhea. Pyrexia, erection increased, 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: 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 serious AEs; 2 were considered treatment related (both high-dose sildenafil): stridor in 1 patient during the first week of therapy (sildenafil 10 mg TID) and ventricular arrhythmia in 1 patient (sildenafil 80 mg TID). Two patients died before randomization, one during and one prior to 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 electrocardiography across time with dose.

Extension Study

A higher risk of mortality occurred among patients in 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 receiving 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 receiving
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 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 (14.3 Wood units • m²), mPAP (62 mmHg), and RAP (7 mmHg), respectively; 40% were classified as FC III or IV at baseline (vs 15% of the overall study population). The majority of deaths (74%) occurred in patients with IPAH/FPAH, although these patients represented only 33% of the study population. Baseline NT-pro-BNP 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 (vs 44% of patients still alive).

**Discussion**

Pulmonary arterial hypertension 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 endpoint. 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. Because CPET is a maximal
test in adults and children, and in adult PAH patients pVO2 correlates with 6MW distance, pVO2 was chosen for this study.

At the outset, it was recognized that young children and those with specific comorbid conditions (e.g., 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 endpoints and evaluate safety in a wider age range (1–17 years) because these children are routinely treated with PAH-specific therapy. Secondary efficacy endpoints included hemodynamic parameters, which physicians use to assess disease severity and which predict PAH prognosis in children and adults, and WHO FC, used to assess clinical symptoms and predict prognosis in both pediatric and adult patients with PAH.

The primary endpoint (pVO2) showed a placebo-corrected percentage 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 pre-specified 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 WHO FC. A posthoc analysis excluding the low-dose sildenafil group resulted in a placebo-corrected increase in pVO2 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\textsuperscript{27, 28} and is useful for dosing recommendations.

Additionally, it is important to assess the consistency between endpoints observed within this pediatric study and between this study and the adult PAH sildenafil study using similar endpoints. Within this study, pVO\textsubscript{2}, hemodynamic parameters, WHO FC, and parent/physician global assessments all showed dose-related improvements with sildenafil monotherapy, with the low dose being ineffective. As these secondary endpoints 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-naïve pediatric patients in this study are similar to those observed with treatment-naïve adult patients with PAH.\textsuperscript{29} Therefore, we believe that the improvements observed in this study are not a chance finding.

The improvements in the secondary and tertiary endpoints support clinical relevance of the effects observed with sildenafil monotherapy on the primary endpoint. Studies of adults with other cardiovascular disorders have shown significant pVO\textsubscript{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 pVO\textsubscript{2} and FC to assess clinically useful changes.\textsuperscript{30, 31} Additionally, because PVRI correlates with outcomes in children and in adults,\textsuperscript{4, 25} and changes in PVRI correlate with changes in exercise capacity,\textsuperscript{32} the significant improvement in PVRI in this study is consistent with the change in pVO\textsubscript{2} being clinically relevant.

Sildenafil monotherapy appeared 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-naïve 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:APAH ratio of etiologies differed from several observational studies but is consistent with children not receiving epoprostenol. Likely, because therapies approved for adult PAH were available, fewer treatment-naïve IPAH/HPAH patients (in whom rapid deterioration occurs) enrolled in this study. No APAH-CTD patients enrolled, consistent with pediatric epidemiology. A greater treatment effect on pVO₂ occurred in IPAH/HPAH versus APAH, consistent with adult PAH observations. 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%–66%, 33%–52%, and 33%–35%, respectively. STARTS-2 survival rates, assessed from STARTS-1 baseline, favorably compare 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 higher sildenafil doses to down-titrate.

In conclusion, sildenafil monotherapy for 16 weeks is well tolerated for pediatric PAH. Although the primary comparison of percentage change in pVO₂ for the three 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.

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References:


arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation.* 2010;122:164-172.


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

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Sildenafil Dose (mg)</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥8 to 20</td>
<td>NA†</td>
<td>10 †</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>&gt;20 to 45</td>
<td>10</td>
<td>20</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>&gt;45</td>
<td>10</td>
<td>40</td>
<td>80</td>
<td></td>
</tr>
</tbody>
</table>

*These concentrations were selected based on concentrations of non–protein-bound sildenafil that would be expected to be similar to those that achieved approximately 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.
Table 2. Baseline Patient Characteristics in the 16-Week STARTS-1 Study*

<table>
<thead>
<tr>
<th>Sildenafil Dose</th>
<th>Placebo (N=60)</th>
<th>Low (N=42)</th>
<th>Medium (N=55)</th>
<th>High (N=77)</th>
<th>Combined (N=174)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex, n (%)</td>
<td>38 (63)</td>
<td>25 (60)</td>
<td>31 (56)</td>
<td>51 (66)</td>
<td>107 (62)</td>
</tr>
<tr>
<td>Age, y — no.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–4</td>
<td>7</td>
<td>0</td>
<td>9</td>
<td>19</td>
<td>28</td>
</tr>
<tr>
<td>5–12</td>
<td>37</td>
<td>25</td>
<td>28</td>
<td>36</td>
<td>89</td>
</tr>
<tr>
<td>13–17</td>
<td>16</td>
<td>17</td>
<td>18</td>
<td>22</td>
<td>57</td>
</tr>
<tr>
<td>Race — no.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>24</td>
<td>19</td>
<td>26</td>
<td>28</td>
<td>73</td>
</tr>
<tr>
<td>Black</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Asian</td>
<td>7</td>
<td>6</td>
<td>13</td>
<td>15</td>
<td>34</td>
</tr>
<tr>
<td>Other</td>
<td>27</td>
<td>16</td>
<td>15</td>
<td>33</td>
<td>64</td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>17 (4)</td>
<td>18 (5)</td>
<td>18 (4)</td>
<td>16 (3)</td>
<td>17 (4)</td>
</tr>
<tr>
<td>WHO functional class, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>25 (42)</td>
<td>9 (21)</td>
<td>20 (36)</td>
<td>21 (27)</td>
<td>50 (29)</td>
</tr>
<tr>
<td>II</td>
<td>29 (48)</td>
<td>23 (55)</td>
<td>25 (45)</td>
<td>43 (56)</td>
<td>91 (52)</td>
</tr>
<tr>
<td>III</td>
<td>6 (10)</td>
<td>9 (21)</td>
<td>8 (15)</td>
<td>12 (16)</td>
<td>29 (17)</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (1)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Etiology, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPAH/HPAH</td>
<td>21</td>
<td>12</td>
<td>19</td>
<td>26</td>
<td>57</td>
</tr>
<tr>
<td>APAH</td>
<td>39</td>
<td>30</td>
<td>36</td>
<td>51</td>
<td>117</td>
</tr>
<tr>
<td>Surgical repair†</td>
<td>15</td>
<td>13</td>
<td>15</td>
<td>24</td>
<td>52</td>
</tr>
<tr>
<td>Congenital systemic-to-pulmonary shunt with SaO2 ≥88% at rest</td>
<td>23</td>
<td>16</td>
<td>20</td>
<td>26</td>
<td>62</td>
</tr>
<tr>
<td>Post-repair D-transposition of great arteries</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Concomitant medications, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>12</td>
<td>5</td>
<td>11</td>
<td>11</td>
<td>27</td>
</tr>
<tr>
<td>Diuretics</td>
<td>9</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>45</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>10</td>
<td>5</td>
<td>9</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Peak VO2, mL/kg/min, mean (SD)‡</td>
<td>20 (4)</td>
<td>18 (4)</td>
<td>18 (5)</td>
<td>17 (4)</td>
<td>18 (4)</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure, mmHg, mean (SD)§</td>
<td>59 (22)</td>
<td>66 (23)</td>
<td>62 (18)</td>
<td>62 (24)</td>
<td>63 (22)</td>
</tr>
<tr>
<td>Cardiac index, L/min/m², mean (SD)†</td>
<td>3.9 (2.1)</td>
<td>3.1 (1.1)</td>
<td>3.3 (1.5)</td>
<td>3.4 (1.6)</td>
<td>3.3 (1.5)</td>
</tr>
<tr>
<td>Pulmonary vascular resistance index, Wood units•m², mean (SD)¶</td>
<td>15 (10)</td>
<td>22 (13)</td>
<td>19 (14)</td>
<td>20 (16)</td>
<td>20 (15)</td>
</tr>
<tr>
<td>Mean pulmonary capillary wedge pressure, mmHg, mean (SD)**</td>
<td>10 (3)</td>
<td>9 (3)</td>
<td>9 (3)</td>
<td>10 (4)</td>
<td>10 (4)</td>
</tr>
</tbody>
</table>

APAH=associated PAH; ASD=atrial septal defect; BMI=body mass index; CPET=cardiopulmonary exercise; HPAH=heritable PAH; IPAH=idiopathic PAH; PAH=pulmonary arterial hypertension; SaO2=systemic arterial oxygen saturation; VO2=oxygen consumption; WHO=World Health Organization.

*The groups shown represent all treated patients.
†Surgical repairs included ASD, ventricular septal defect, patent ductus arteriosus, aortopulmonary window, and others.
‡Subset of patients developmentally able to perform CPET testing (n=30, 28, 28, and 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, 42, 55, 75, and 172 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.
Table 3. Placebo-Corrected Change in Secondary Outcomes Between Baseline and End of 16-Week, Double-Blind STARTS-1 Treatment

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Sildenafil Low Dose</th>
<th>Sildenafil Medium Dose</th>
<th>Sildenafil High Dose</th>
<th>Sildenafil Combined Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PAP (mmHg)</td>
<td>n=39</td>
<td>n=55</td>
<td>n=71</td>
<td>n=165</td>
</tr>
<tr>
<td>Mean difference ±SE</td>
<td>1.6±3.1</td>
<td>–3.5±2.7</td>
<td>–7.3±2.6</td>
<td>–3.1±2.2</td>
</tr>
<tr>
<td>95% CI</td>
<td>–4.5, 7.6</td>
<td>–8.9, 1.9</td>
<td>–12.4, –2.1</td>
<td>–7.5, 1.3</td>
</tr>
<tr>
<td>P value</td>
<td>0.610</td>
<td>0.199</td>
<td>0.006</td>
<td>0.172</td>
</tr>
<tr>
<td>PVRI (Wood units•m²)</td>
<td>n=37</td>
<td>n=51</td>
<td>n=68</td>
<td>n=156</td>
</tr>
<tr>
<td>Ratio*</td>
<td>0.982</td>
<td>0.819</td>
<td>0.727</td>
<td>0.836</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.802, 1.203</td>
<td>0.684, 0.981</td>
<td>0.612, 0.863</td>
<td>0.720, 0.971</td>
</tr>
<tr>
<td>P value</td>
<td>0.859</td>
<td>0.031</td>
<td>&lt;0.001</td>
<td>0.019</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>n=37</td>
<td>n=51</td>
<td>n=69</td>
<td>n=157</td>
</tr>
<tr>
<td>Ratio*</td>
<td>1.100</td>
<td>1.043</td>
<td>1.148</td>
<td>1.096</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.963, 1.258</td>
<td>0.925, 1.176</td>
<td>1.026, 1.286</td>
<td>0.994, 1.210</td>
</tr>
<tr>
<td>P value</td>
<td>0.161</td>
<td>0.486</td>
<td>0.017</td>
<td>0.066</td>
</tr>
<tr>
<td>Mean RAP (mmHg)</td>
<td>n=39</td>
<td>n=55</td>
<td>n=71</td>
<td>n=165</td>
</tr>
<tr>
<td>Mean difference ±SE</td>
<td>–0.2±0.9</td>
<td>–0.2±0.8</td>
<td>–1.1±0.8</td>
<td>–0.5±0.6</td>
</tr>
<tr>
<td>95% CI</td>
<td>–1.9, 1.6</td>
<td>–1.7, 1.4</td>
<td>–2.6, 0.3</td>
<td>–1.8, 0.8</td>
</tr>
<tr>
<td>P value</td>
<td>0.849</td>
<td>0.811</td>
<td>0.128</td>
<td>0.440</td>
</tr>
<tr>
<td>Exercise duration† (%)</td>
<td>n=24</td>
<td>n=26</td>
<td>n=27</td>
<td>n=77</td>
</tr>
<tr>
<td>Mean difference ±SE</td>
<td>10.3±7.8</td>
<td>11.4±7.7</td>
<td>6.0±7.6</td>
<td>9.2±6.2</td>
</tr>
<tr>
<td>P value</td>
<td>0.190</td>
<td>0.139</td>
<td>0.436</td>
<td>0.139</td>
</tr>
</tbody>
</table>

*Because PVRI and CI 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.
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, CI, mean RAP, and exercise duration respectively.
CI=cardiac index; PAP=pulmonary artery pressure; PVRI=pulmonary vascular resistance index; RAP=right atrial pressure.
Table 4. Adverse Events That Occurred in ≥3% of Patients in the Sildenafil Combined Group in the 16-Week, Double-Blind STARTS-1 Study

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

*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.

Figure Legends:

**Figure 1.** Patient flow and assessment for peak VO₂ in the 16-week STARTS-1 study. CPET=cardiopulmonary exercise testing; VO₂=oxygen consumption.

*16 patients were screened twice (ie, 308 patients and 324 screenings).
†106 of the 115 developmentally able patients were included in the primary analysis.

**Figure 2.** Estimated treatment effects [±95% CI] (sildenafil vs placebo) in the STARTS-1 study from baseline to week 16 in A) peak VO₂, B) mPAP, and C) PVRI, overall and by subgroups including PAH etiology, weight, and developmental ability to perform cardiopulmonary exercise testing (CPET). For percentage change in peak VO₂ (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=associated pulmonary arterial hypertension (PAH); IPAH/HPAH=idiopathic PAH/heritable PAH; mPAP=mean pulmonary artery pressure; PVRI=pulmonary vascular resistance index; VO₂=oxygen consumption.
Mean Treatment Difference (Sildenafil–Placebo) in Peak VO_{2}, Percentage Change From Baseline
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

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