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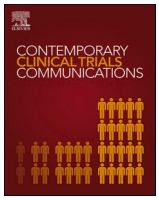

Safety of sildenafil in premature infants at risk of bronchopulmonary dysplasia: Rationale and methods of a phase II randomized trial

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ABSTRACT

Bronchopulmonary dysplasia (BPD) is a disease of chronic respiratory insufficiency stemming from premature birth and iatrogenic lung injury leading to alveolar simplification, impaired alveolar-capillary development, interstitial fibrosis, and often pulmonary hypertension. BPD is the most common pulmonary sequela of prematurity and is often fatal; however, there remains no FDA-approved therapies to treat or prevent BPD. Sildenafil is increasingly used off-label in premature infants despite scant safety and efficacy data. Sildenafil reduces lung injury and preserves normal vasculature in preclinical models, and improves outcomes in children with pulmonary hypertension, and thus is a promising candidate for BPD. Following phase I studies, we developed the phase II SIL02 trial to describe the safety, pharmacokinetics and preliminary effectiveness of intravenous and enteral sildenafil in premature infants at risk for BPD. SIL02 is a randomized, double-blind, placebo-controlled, 3-cohort, sequential dose-escalating trial of enteral or intravenous (IV) sildenafil dosed every 8 h for up to 34 days. The target IV doses were 0.125, 0.5 and 1 mg/kg/dose in cohorts 1, 2 and 3, respectively; while the enteral doses will be double the IV doses. Eligible infants must be < 29 weeks' gestation at birth and requiring respiratory support at 7–28 days' postnatal age. Adverse events and preliminary effectiveness will be compared by treatment group. Using the final population PK model, empirical Bayesian estimates will be generated for each patient. Preliminary effectiveness will be measured by the incidence of moderate to severe BPD or death at 36 weeks and change in the BPD risk estimation.

1. Introduction

For many pediatric conditions, there are either no or very few FDA-indicated treatments. The majority of drugs given to neonates are used off-label (i.e. have not been sufficiently tested) or dosing is extrapolated from adult PK/PD data. Responding to this crisis, Section 409I of the Public Health Service Act, also known as the Best Pharmaceuticals for Children Act (BPCA), mandates the National Institutes of Health (NIH) to prioritize therapeutic areas in critical need for pediatric labeling and to submit data to the Food and Drug Administration (FDA) for consideration for labeling changes. Under the BPCA, the National Institute for Child Health and Human Development (NICHD) awarded a contract to Duke University, which established the Pediatric Trials Network (PTN), and a separate contract to The Emmes Company, LLC to serve as the BPCA Data Coordinating Center (DCC).

One prioritized condition in critical need for safe and effective therapeutics with pediatric labeling is bronchopulmonary dysplasia (BPD) [1]. BPD is the most common pulmonary morbidity associated with premature birth [2]. Approximately 50,000 infants are born each year in the US < 29 weeks' gestational age, and roughly 35% of these infants develop BPD [3,4]. Clinically, BPD is a disease of chronic respiratory insufficiency related to premature birth and lung inflammation

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and injury from hyperoxia [5,6] and mechanical ventilation [7–9]. These factors lead to impaired alveolar-capillary development, alveolar simplification, interstitial fibrosis, and the development of pulmonary hypertension [10–15]. Infants with BPD are particularly challenging for clinicians due to their chronic respiratory distress, recurrent respiratory infections and wheezing episodes, comorbid pulmonary hypertension, and frequent and prolonged hospitalizations [16–18]. The costs of BPD are measured in impaired childhood health and quality of life, family stress and economic hardship, and increased healthcare costs [19–21].

BPD is defined by the NIH as mild, moderate, or severe based on required respiratory support at 36 weeks postmenstrual age [22,23]. (Table 1a).

NICHD-funded Neonatal Research Network investigators identified risk factors for BPD and the outcome of death in 3636 infants 23–30 weeks' gestation [24]. They also developed an accurate prediction model based on postnatal day, gestational age, birth weight, sex, race/ethnicity, and type of ventilator support and F_iO_2 (%) on the postnatal day of interest. This model provides parents and clinicians during the first weeks of life an estimate of BPD risk at 36 weeks postmenstrual age.

Sildenafil is a potent inhibitor of type 5 phosphodiesterase, the predominant isoform in the lung, and is a promising candidate to prevent or treat BPD. In adults, sildenafil is approved by the FDA for the treatment of pulmonary arterial hypertension (PAH) [25]. While sildenafil is not approved in children, the drug improves short term outcomes in children with PAH. Children with PAH (either idiopathic or due to preexisting cardiac disease) treated with sildenafil had improved aerobic capacity, and the effect appeared to be dose dependent [26,27]. Due to an increase in mortality seen occurring after about 1 year with increasing sildenafil dosing in children with PAH [28], the FDA revised the sildenafil drug label to recommend against use in children with PAH [29].

Sildenafil is increasingly being used off-label in premature infants. Within a large consortium of neonatal intensive care units (NICUs) encompassing 20% of all US NICUs, sildenafil use increased >1000% from 2005 to 2010 [30,31]. Our group conducted a Phase I study of sildenafil in 25 premature infants (≤29 weeks' gestational age with BPD; IND 112,374; NCT01670136) who received enteral sildenafil at doses between 0.5 and 2.25 mg/kg in a first cohort. The trial enrolled 9 additional infants ≤28 weeks' gestational age and postnatal age range 7–40 days who received a single intravenous dose of sildenafil 0.25 mg/kg or 0.125 mg/kg in a second cohort. These data indicated a one compartment model and that the enteral to IV conversion of 2:1 would be appropriate, and provided dosing levels for the current sequential cohort study [32,33].

2. Study design

The SIL02 study is a multi-center randomized, placebo-controlled, sequential 3-cohort, dose-escalating, double masked, safety study of up to 34 days of enteral or intravenous sildenafil involving 120 premature infants randomized in a 3-to-1 ratio to either sildenafil or placebo. Forty infants will be enrolled into each cohort sequentially following a safety review. The study was reviewed by the Food and Drug Administration (IND 112374), the BPCA Data/Safety Monitoring Committee (DMC), and by the Institutional Review Board at all participating sites. The data and final study report (CSR) will be submitted to the FDA after completion of the study.

Table 1a
NICHD severity-based definition of BPD for premature infants at 36 weeks postmenstrual age (or discharge).

No BPD	Receiving >21% supplemental oxygen (O2) for ≤28 days and not at 36 weeks PMA
Mild BPD	Receiving >21% O2 for ≥28 days but not at 36 weeks PMA
Moderate BPD	Receiving >21% O2 for ≥28 days plus treatment with <30% O2 at 36 weeks PMA
Severe BPD	Receiving >21% O2 for ≥28 days plus ≥30% O2 and/or positive pressure at 36 weeks PMA

Table 1b
New NICHD Definition (2019) based on support at 36 weeks postmenstrual age.

No BPD	No respiratory support
Grade 1 BPD	Nasal cannula ≤2 L/min
Grade 2 BPD	Nasal cannula >2 L/min or non-invasive positive airway pressure
Grade 3 BPD	Any type of invasive mechanical ventilation

2.1. Study population

SIL02 selection criteria were established to study premature infants at high-risk for BPD.

2.1.1. Criteria for enrollment – inclusion

- Documented informed consent from parent or guardian, prior to study procedures
- Receiving positive airway pressure (nasal continuous airway pressure, nasal intermittent positive pressure ventilation, or nasal cannula flow >1 liter/min) or mechanical ventilation (high frequency or conventional) at the time of randomization
- < 29 weeks' gestational age at birth
- 7–28 days' postnatal age at time of randomization

2.1.2. Criteria for enrollment – exclusion

- Previous enrollment and dosing in the current study
- Exposure to sildenafil within 7 days prior to randomization
- Currently receiving vasopressor medications
- Currently receiving inhaled nitric oxide
- Baseline mean arterial pressure (MAP) less than the infant's gestational age (in weeks) plus postnatal age (in weeks) within 24 h of randomization
- Known sickle cell disease or allergy to sildenafil
- Aspartate aminotransferase (AST) > 225 U/L within 72 h prior to randomization
- Alanine aminotransferase (ALT) > 150 U/L within 72 h prior to randomization
- Any condition which would make the participant, in the opinion of the investigator, unsuitable for the study

2.2. Study drug and dosing

In the U.S., sildenafil, in both intravenous (IV) and for oral suspension, has been approved for use in other populations and for other indications by the FDA [29]. Pfizer has provided the oral suspension (enteral) to all U.S. and Canadian study sites. Route of administration should be via IV route if the infant has IV and this is feasible, but the choice is left to the discretion of the site investigator. Infants may transition from enteral to IV sildenafil (and vice versa) throughout the duration of the study per the investigator's determination. Placebo will be administered either enterally or IV in the same manner.

Participants in Cohort 1 will start at a dose of 0.0625 mg/kg IV (or 0.125 mg/kg enteral) every 8 h and the dose will increase to the target dose of 0.125 mg/kg IV (or 0.25 mg/kg enteral) after 6 doses (48 h). Target doses are show in Table 2. Participants enrolled in Cohort 2 and Cohort 3 will initially start at 0.125 mg/kg IV (or 0.25 mg/kg enteral) every 8 h and the dose will increase by 0.125 mg/kg IV (or 0.25 mg/kg enteral) every 6 doses to the target dose. This means that the dose will increase every 48 h assuming the infant meets the following escalation criteria. An infant will meet respiratory criteria for dose escalation only if the infant is receiving exogenous oxygen or respiratory support (nasal

Table 2
Cohort sizes and dosing schemes.

		N	Sildenafil (IV)	Sildenafil (enteral)	N	Cohort Total N
Cohort 1	Placebo	10	0.125 mg/kg every 8 h	0.25 mg/kg every 8 h	30	40
Cohort 2	Placebo	10	0.5 mg/kg every 8 h	1 mg/kg every 8 h	30	40
Cohort 3	Placebo	10	1 mg/kg q every hours	2 mg/kg every 8 h	30	40

cannula or positive pressure from any device) for at least 12 h, and has had an AST <225 U/L and ALT <150 U/L within the past 7 days. Infants who do not initially qualify for escalation should be reevaluated daily for whether they meet these criteria, and escalation must occur within 24 h of an infant meeting all criteria.

2.3. Drug preparation and administration

The pharmacy at each research site will prepare and distribute the study drug in a masked manner and drug will be administered by the bedside nurse. Intravenous doses of study drug will be administered as infusion over 60 min followed by 30 min of flush. Enteral doses will be administered with feedings. The enteral formulation, if used, will be administered enterally either by mouth, orogastric, nasogastric, gastrostomy tube, or other enteral tubes. For enteral administration in infants receiving bolus feedings, mixing and timing of administration may follow the institutional policy. If there is no specific institutional policy, it is recommended that the study drug be mixed in 10 mL of feedings to be given at the end of the feed. If feeds are administered on pump, timing of administration may follow the institutional policy. If there is no specific institutional policy, it is recommended that study drug be mixed in the last 30 min of feeding volume. An investigational pharmacist at each site will be unmasked and will prepare masked study drug. If the participant experiences signs or symptoms deemed by the investigator to be clinically significant hypotension or other type of serious adverse reaction, the infusion will be stopped. Continued study drug administration will be decided by the clinical team. (see appendix A for additional details on formulation and labeling)

2.4. Masking procedures

Infants randomized to the placebo treatment group will receive the equivalent volume of dextrose 5% appropriate for IV use or enteral use. The pharmacy at each site will prepare and dispense the study drug into appropriate sized syringes in a masked manner (e.g. amber syringe). Staff accessing participant outcomes will be masked to treatment.

2.5. Drug weaning

In clinical practice, it is recommended to wean from higher doses to prevent rebound effects. For cohorts 2 and 3, weaning of study sildenafil or placebo will begin following the last study dose on Day 28 or if the dose escalates to a dose of ≥0.5 mg/kg IV or ≥1 mg/kg enteral and the participant is withdrawn from the study. A wean by 25% of final treatment period study dose will occur every 2 days until off. Thus, participants will complete the wean after 6 days (see Appendix B for additional details on study drug weaning).

2.6. Randomization procedure

Participants who satisfy all eligibility criteria will be randomized 3:1 (sildenafil: placebo). All three cohorts will use the same randomization scheme. The participant's randomized treatment assignment will be obtained through the Advantage eClinical℠ enrollment module.

2.7. Study procedures and data collection

Study procedures and visits are outlined in Table 3.

SIL02 will have distinct study periods described below. A more detailed discussion of each study period is available in Appendix C.

Screening and baseline procedures. Research staff will document informed consent from the parent/guardian for all participants who satisfy eligibility criteria. Demographics and a detailed medical history will be recorded from the clinical medical record.

Treatment Period. The treatment period will include treatment days 1–28 or the last day of study drug if early withdrawal of study drug. Daily and weekly assessments will be collected including weight, concomitant medications, study drug dosing information, MAP evaluations, respiratory assessments, laboratory evaluations, PK collections and adverse events.

Weaning Period (Cohorts 2 and 3). Similar data collected during the treatment period will be collected during the weaning period, which will begin following day 28 of study drug or following the last day of study drug if the participant was withdrawn from study drug prior to day 28 (assuming the dose escalated to ≥0.5 mg/kg IV or ≥1 mg/kg enteral).

Follow-up Period. The follow-up period will include days 1–28 after last study dose. The following information will be collected at Day 7 and 14 of the follow-up period except for SAEs (which will be reported all days 1–28): Weight, physical examination, MAP, respiratory assessments, laboratory evaluations and adverse events.

36-week PMA Assessment/Final Assessment. If the participant is discharged before 36 weeks PMA, sites will record assessments taken closest to discharge date. Similar to the follow-up period, the following will be collected: weight, physical examination, MAP, respiratory assessments, laboratory evaluations and adverse events.

2.8. Safety monitoring

Safety will be assessed starting at the initial study-specific procedures (e.g., screening blood draws) and will continue during dosing through to 14 days' post last study dose (last study dose includes weaning doses). Safety will be assessed by frequency and incidence of AEs and SAEs. A data/safety monitoring committee (DMC) will be convened by NIH to review data and safety information from study participants throughout the study and prior to opening of cohorts 2 and 3. Monitoring for SAEs will continue for a total of 28 days' post last study drug dose (including the weaning doses).

2.8.1. Low blood pressure and hypotension

Blood pressure will be determined using mean arterial pressure (MAP) measurements performed as standard of care at each site. For each participant, MAPs will be taken at timed intervals throughout the study. MAP will be measured using an appropriate size cuff or with an intra-arterial placed catheter that measures continuous blood pressure.

2.8.2. Primary definition of hypotension

Hypotension will be defined as any clinically significant low blood pressure event deemed by the treating physician to require intervention with a fluid bolus or the initiation or escalation of inotropic, vasopressor, or systemic steroid therapy with the specific intent to raise blood pressure.

2.8.3. Halting criteria

Unscheduled DMC reviews will be automatically triggered for multiple similar SAE or SARs. Enrollment will be suspended during DMC review, though study activities will be allowed to proceed on previously enrolled subjects if applicable (see Appendix D for further details on safety assessments).

Table 3
Schedule of study procedures.

	Screen/ Baseline	Treatment	Weaning Cohort 2 and 3	Follow-up	SAE Follow-up	36 weeks PMA assessment	Final study assessment
Time (Day)	Pre-dose	1-28 (±1 Day)	Weaning Day 1–6	Day 1–14 post last study dose	Day 15–28 post last study dose	36 weeks PMA (+6 days)	Discharge or Transfer
Informed consent	X						
Demographics	X						
Physical examination	X			X (weekly)		X	X
Medical history	X						
Actual Weight	X	X (weekly)		X (weekly)		X	X
Mean Arterial Pressure	X	X	Last day of wean	X (weekly)			
Respiratory assessment	X	X (weekly)	Last day of wean	X (weekly)		X	X
Laboratory evaluations	X	X (weekly)		X (weekly)		X	
Study drug		X	X				
Concomitant medications	X	X					
Adverse Events (including SAEs)	X	X	X	X			
SAE/SARs only					X		
Echo and Cardiac catheter reports [1]	X	X	X	X		X	X
PK sampling		X (after day 7)					
Discharge information, including ROP							X

1 – collected only if performed per standard-of-care.
SAE – serious adverse event; SAR – serious adverse reaction; PMA – post menstrual age; ROP – retinopathy of prematurity.

2.9. Outcome measures

Safety. Measuring adverse events (AE) will be the main method for assessing safety. AEs will only be collected following initial study-specific procedure (e.g., screening blood draws, drug administration), through 14 days post last study dose (which includes weaning doses). SAEs will be collected following initial study-specific procedure (e.g., screening blood draws, drug administration), through 28 days post last study dose (which includes weaning doses). Unexpected adverse events are events not listed in the package insert or investigational brochure or investigational plan, or is not listed at the specificity or severity in the package insert or investigational brochure or investigational plan.

Pharmacokinetics. A population PK analysis will be performed. Using the final population PK model, empirical Bayesian estimates of clearance (CL), volume of distribution (V), half-life, and exposure metrics (e.g. AUC, maximum concentration) will be generated for each participant.

Table 4 below provides the optimal PK sampling collection windows. Blood samples will be collected after any dose following completion of 7 days (168 h) of study drug administration. Blood samples should not be drawn during infusions or during the flush. Elimination samples will only be obtained around the last dose of study drug.

Preliminary effectiveness will be measured as a reduction in moderate-severe BPD or death risk from first day of study drug to end of study drug administration. Moderate-severe BPD or death risk will be defined according to the latest consensus definition [23] (Table 1b) and by the NICHD NRN BPD outcome estimator (https://neonatal.rti.org/index.cfm).

Other outcomes assessed will include moderate or severe BPD or death at 36 weeks, death, retinopathy of prematurity (ROP), and evidence of pulmonary hypertension. ROP will be defined as any case involving ROP-treatment including laser photocoagulation, cryotherapy, or intraocular injections such as bevacizumab. Pulmonary hypertension will be defined as present or not present per echocardiogram and/or cardiac catheterization reports, as provided per standard of care. Echocardiogram and cardiac catheterization reports will be reviewed centrally by a single Duke pediatric cardiologist.

Table 4
Target PK Sampling Times (time in relation to end of infusion and flush).

	Intravenous or enteral per clinical care	
	Time[a]	
PK #	*Enteral*[b]	*Intravenous*[c]
1	0–15 min	0–15 min
2	30–60 min	30–60 min
3	1–2 h	1–2 h
4	2–3 h	2–3 h
5	3–4 h	3–4 h
6	4–5 h	4–5 h
7	15 min prior to next dose	15 min prior to next dose
8[d] (elimination)	16–24 h	16–24 h

[a] May be drawn around more than one dose.
[b] Sample is taken after dose of study drug (and flush if given by IV).
[c] Time starts at end of flush which must be less than or equal to 30 min.
[d] Sample taken 16–24 h after last dose.

2.10. Oversight of the study

A DMC was created to monitor the study and an investigational new drug application was submitted under section 505 (i) of the Federal Food, Drug, and Cosmetic Act and granted in 2015 (IND 112,374).

2.11. Study analysis

Study Endpoints. Primary safety endpoints are the incidence of AEs and SAEs. Secondary endpoints include change in BPD risk, BPD incidence, death rate, incidence of death or BPD, incidence of ROP, and incidence of pulmonary hypertension.

Sample size calculation. The sample size of 30 in each dose group is sufficient to estimate AE or SAE incidence with sufficient precision. Table 5 provides widths for 95% Wilson confidence intervals in the dose groups of size 30 and the total sildenafil treatment cohort of 90 with different incidence rates. An event with an incidence rate of 0.05 has a

Table 5
Widths for 95% Wilson confidence intervals.

n = 30			n = 90		
Rate	Width	95% CI	Rate	Width	95% CI
0.1	0.22	0.04–0.26	0.1	0.13	0.05–0.18
0.2	0.28	0.10–0.37	0.2	0.16	0.13–0.29
0.3	0.31	0.17–0.48	0.3	0.19	0.22–0.40

78% chance of being observed at least once in a dose group and a 99% chance of being observed at least once in the total sildenafil cohort.

2.12. Data analysis

Population for Analysis. All participants enrolled, randomized, and dosed will be included in the safety population and the safety analyses. All participants who had at least one interpretable PK sample will be included in the PK analysis.

Interim Safety Analyses. The DMC must complete a review of the safety data after completion of each cohort prior to opening enrollment into the next cohort. The DMC will review individual SAEs in real time, and will review safety report summaries at regular DMC meetings that occur three times per year. The number and percent of AEs and SAEs within each dose group will be summarized overall as well as by each Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Laboratory data will be tabulated by dose groups. Summary statistics for changes from baseline will be presented.

Statistical Plan. Analyses will be presented by treatment groups. There are 4 planned treatment groups: 1) participants randomized to sildenafil in Cohort 1; 2) participants randomized to sildenafil in Cohort 2; 3) participants randomized to sildenafil in Cohort 3 and 4) participants randomized to placebo.

2.12.1. Descriptive statistics

Descriptive statistics such as number of observations, mean, median, standard deviation, standard error, minimum and maximum will be presented by treatment groups for continuous variables (such as age, weight, etc.). Other descriptive statistics such as counts, proportions, and/or percentages will be presented by group to summarize discrete variables (such as race, sex, etc.)

2.12.2. Demographic and baseline characteristics

The number of participants completed and discontinued early from study and the reasons for the discontinuation will be summarized by treatment group. Demographic and baseline characteristics will also be summarized by treatment group. Variables include race, age, sex, and selected clinical variables recorded prior to initiation of study drug. Study drug administration will be summarized in terms of route, number of days of dosing and reasons for final discontinuation of study drug.

2.12.3. Safety

The primary safety endpoint is number and percent of AEs and SAEs and will be summarized by treatment groups. AEs and SAEs will be presented overall and by each Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Prior and concomitant medications will be summarized by World Health Organization (WHO) drug class. Laboratory data will be tabulated by treatment groups. Summary statistics for changes from baseline will be presented. Hypotension (defined as any clinically significant low blood pressure event deemed by the treating physician to require therapeutic intervention to raise blood pressure) will be summarized by treatment group.

2.12.4. Effectiveness analysis

Multivariable mixed-effects model will be used to explore the relationship between the maximum and total dose of sildenafil and change in the risk of moderate BPD, severe BPD or death at 7, 14, 21 and 28 days of study drug. A dose by time interaction term will allow us to estimated change in the risk of BPD within each treatment group and make comparisons between treatment groups.

Death, BPD status, death or moderate/severe BPD, retinopathy of prematurity, and pulmonary hypertension will be evaluated at 36 weeks PMA using logistic regression analyses to evaluate the effect of dose. Adjustments will be made for important covariates such as GA, birth weight, sex and maternal race/ethnicity.

2.12.5. PK analysis plan

PK parameters will be estimated by population PK approach using non-linear mixed effects modeling in NONMEM. The influence of covariates on PK parameters will be explored.

2.12.6. Biomarkers

We will relate the concentration of biomarkers (BNP, IL-1, IL-6, IL-8, TNF-α) to the development of and severity of BPD.

3. Results and discussion

For many pediatric conditions, there are either no or very few FDA-indicated treatments. For pediatric conditions that also affect adults, safe and effective drugs may be able to be approved for children in a somewhat streamlined manner [34]. However, for conditions that only exist in children, the treatment options can be dire. The roughly 15 million infants born prematurely each year are a profoundly vulnerable population with very few approved medications. BPD, the most common respiratory complication of premature birth, leads to lifelong respiratory problems and currently has no approved drug treatments. All neonatologists tasked with managing BPD resort to untested therapies.

The primary research objective of the SIL02 study is to describe the safety of sildenafil in premature infants at risk for BPD over a range of doses most often used in clinical practice. Our secondary objectives are to describe the specific pharmacokinetic characteristics of sildenafil in this vulnerable population and the preliminary effectiveness of the three dosing levels to prevent BPD. Altogether, the main program objective of the SIL01/02 program is to evaluate the collected safety and effectiveness in total to determine if there exists an optimal dose to move ahead for definitive phase 3 testing.

Innovative features of SIL02 include the large number of premature infants given sildenafil in a highly controlled environment with comprehensive evaluations. Completion of the three cohorts would be the largest randomized, placebo-controlled trial of sildenafil in premature infants to date. The study will be completed with FDA regulatory oversight and collected infants from 15 sites across the US and Canada. SIL02 will provide a combined safety, PK and effectiveness dataset involving three levels of dosing. This dose-escalating approach reduces the risk to subjects because it only allows infants to be exposed to the lowest doses thought to be clinically relevant, and then allows increases in dosing in a gradual manner only after an interim independent safety review. The initial dose of 0.125 mg/kg IV (or 0.25 mg enteral) every 8 h was chosen based on our phase I study (NCT01670136). In the phase I study, we enrolled 25 premature infants born at or before 28 weeks gestation who received standard of care doses of 0.5–2.25 mg/kg enteral sildenafil at 7–40 days of life [32,33]. A second cohort of 9 similar infants received a single 0.25 mg/kg IV dose. There were 13 adverse events in cohort 1 (none related to study drug), and 10 adverse events in cohort 2. One AE in cohort 2 was determined as related to study drug. The 1 related event was an episode of hypotension which was determined to be related to a faster than expected infusion rate. The event led to a DMC review of available data, and a review of all clinical sites' infusion methods and equipment. The protocol was changed prior to enrolling the remaining cohort 2 subjects to include a longer infusion time (30 min), and the dose was lowered by 50% to 0.125 mg/kg. When the study re-opened 2 additional subjects were enrolled without any related adverse events. Analysis from these data indicated that a one compartment body model best described the sildenafil PK in premature infants. We concluded that following a single intravenous dose of 0.25 mg/kg, sildenafil exposures were within the range of estimates previously reported for infants following multiple oral dosing, and that enteral to IV conversion of 2:1 would be appropriate.

Unfortunately, few phase I/II trials of this kind are completed in pediatrics. Neonatologists have randomized over 12,000 infants into phase III trials of over 20 drugs in an attempt to reduce the incidence or severity of BPD [35]. Few of these studies were done under regulatory

guidance (i.e., with an IND from the FDA) and most did not leverage preceding phase I and II studies to guide dosing. Unfortunately, it is common for key phase II trials to be either never started or to be ended early due to regulatory or funding challenges. Unfortunately, when phase III trials are not preceded by a rigorous phase II trial providing pharmacokinetic and optimal dosing information, the phase III trial often fails to demonstrate clinical efficacy and fails to advance the care for children [35].

After contributions from more than a dozen research institutions and regulatory authorities in the US and Canada, low (cohort 1) and medium (cohort 2) doses were tested in the SIL02 trial and data were submitted to the SIL02 Data Monitoring Committee (DMC). Recently the DMC reviewed the cumulative data and judged there to be no concerning safety signal, and they approved the start of Cohort 3. SIL02 cohort 3 aims to recruit an additional 40 participants to complete testing at the higher end of dosing commonly used in neonatal practice. The SIL02 study currently has the benefit of a very engaged group of experienced and dedicated North American neonatologists. Completion of SIL02 will allow the largest and most complete safety, efficacy and PK analysis to date for the full range of sildenafil doses used in practice, would likely change current dosing practices in NICUs around the world, and would properly lay the foundation for a definitive phase III sildenafil trial in this high-risk population.

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Declaration of competing interest

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Data availability

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Appendix A. Supplementary data

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