SIL02 Appendices (Online Supplement Materials)

Appendix A. Drug Formulation, Packaging and Labeling

IV formulation: Only marketed IV formulations may be used for IV administration. This protocol will not specify the brand of product. Each product will be “off the shelf” as provided by the site’s pharmacy. Enteral Formulation: U.S. commercially available REVATIO sildenafil citrate powder for suspension (Pfizer Laboratories Division of Pfizer Inc., U.S.) will be distributed for use to all sites and labeled in accordance with 21 CFR 312.6. Any requisite clinical trial materials will be provided with labeling in accordance with all applicable regulatory requirements. For Canada, drug product will be labeled for investigational use in accordance with Health Canada regulations (C.05.011), prior to shipment to Canadian sites under a CTA.

Appendix B. Drug Weaning

Sildenafil is commonly used at higher doses to treat pulmonary hypertension in infants. In clinical practice, it is recommended to wean from these higher doses to prevent rebound effects that may be seen with abrupt discontinuation. Although sildenafil used in this study is for prevention of BPD, target doses in cohorts 2 and 3 are similar to those used for the treatment of pulmonary hypertension. 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last study dose on Day 28 or if the dose escalates to a dose of ≥0.5 mg/kg IV or ≥1 mg/kg enteral and participant is withdrawn from the study.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.

Weaning is not required for participants in Cohort 1 as the risk of rebound effects is likely minimal for infants receiving sildenafil at these low doses. If a participant in cohort 2 or 3, escalates to a dose of ≥0.5 mg/kg IV (or ≥1mg/kg enteral) and then is withdrawn from study drug, they will be withdrawn using the weaning schedule outlined above. Deviation from the weaning schedule for documented safety concerns will not result in a protocol deviation.

Appendix C. Detailed Visit Procedures

Screening and baseline procedures. Research staff will document informed consent from the parent/guardian for all participants who satisfy eligibility criteria. The following information will be recorded from the clinical medical record:

1. Participant demographics, including birth weight and gestational age at birth
2. Maternal Race/Ethnicity (White/Hispanic/Black)
3. Medical history
4. Physical examination, including actual weight
5. Mean Arterial Pressure. Obtained at screening/baseline. All mean arterial pressure (MAP) values obtained 24 hours before the first dose
6. Concomitant medications (within 24 hours prior to start of study drug)
7. Respiratory assessment
8. Laboratory evaluations
9. Echocardiogram and Cardiac catheterization reports, if performed per local standard of care
10. Adverse events following initial study-specific procedure

Treatment Period. The treatment period will include days 1-28, or the last day of study drug if early withdrawal of study drug. The following information will be collected and recorded while the participant is on study drug:

1. Actual weight on study days 7, 14, 21, and 28 of study drug administration (+/- 1 day for each)
2. Date, time, amount and route of study drug dose
3. All concomitant medications
4. MAP

A. All mean arterial pressure (MAP) values obtained 24 hours after the first dose of study drug regardless of administration route.

B. MAP values will be obtained at a minimum at the following time points

   i. Prior to the first dose of study drug or dose escalation: 2 hours (+/- 5 minutes), 1 hour (+/- 5 minutes), and 15 minutes (+/- 5 minutes)

   ii. If administration route is IV:

      a. During and following the first dose of study drug or dose escalation: MAP at start of infusion, every 15 minutes (+/- 5 minutes) during infusion, at end of infusion (inclusive of flush) (+/- 5 minutes), at 15 and 30 minutes (+/- 5 minutes) after end of infusion, hourly (+/- 15 minutes) for 4 hours, and once in the remaining 2 hours prior to the next dose.

      b. For subsequent IV doses, the lowest valid MAP value should be recorded daily while on study drug.

   iii. If the administration route is enteral:

      a. During and following the first dose of study drug or dose escalation: MAP at start of enteral administration, then every 15 minutes (+/- 5 minutes) for 90 minutes (1.5 hours), then every 30 minutes (+/- 5 minutes) for 60 minutes (one hour), then hourly (+/- 15 minutes) for 4 hours, then and once in the remaining 2 hours prior to the next dose.

      b. For subsequent enteral doses, the lowest valid MAP value should be recorded daily while on study drug.

5. Respiratory assessment, weekly
6. Laboratory evaluations, at least once a week
7. Echocardiogram and Cardiac catheterization reports, if performed per local standard of care
8. PK sampling (after Day 7)

9. Adverse events

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

The following information will be collected and recorded while the participant is weaning from study drug:

1. Date, time, amount and route of study drug dose
2. Adverse events
3. MAP (the lowest valid MAP value on last day of wean should be recorded).
4. Respiratory assessment on last day of wean
5. Echocardiogram and Cardiac catheterization reports, if performed per local standard of care

Follow-up Period. The follow-up period will include days 1-28 after last study dose. The following information will be reported in the electronic data capture (EDC) system at Day 7 and 14 of the follow-up period (or the day closest to and after Day 7 and 14, if >1 assessment is available), except for SAEs (which will be reported from days 1-28):

1. Physical examination, including actual weight
2. MAP (the lowest valid MAP value on Day 7 and Day 14 should be recorded).
3. Respiratory assessment
4. Laboratory evaluations
5. Echocardiogram and Cardiac catheterization reports, if performed per local standard of care
6. Adverse events (only during follow-up period days 1-14)
7. Serious adverse events (during follow-up period days 1-28)

36-week PMA Assessment. The following information will be reported at 36 weeks (+ 6 days) PMA if available. If the participant is discharged before 36 weeks, record assessments will be taken closest to discharge date. If more than one 36-week assessment is available record results obtained closest to Week 36, 0 days:

1. Physical examination, including actual weight
2. Respiratory assessment
3. Laboratory evaluations
4. Echocardiogram and Cardiac catheterization reports, if performed per local standard of care

Final Study Assessment. Final study assessment will occur at the time of discharge or transfer. The following information will be collected:

1. Physical examination, including actual weight
2. Respiratory assessment
3. Echocardiogram and Cardiac catheterization reports, if performed per local standard of care
4. Discharge information (Discharge or transfer, Death, Duration of hospitalization)
5. Record results of ROP, if treatment required

Appendix D. Details of Safety Assessments

Methods and Timing for Assessing, Recording and Analyzing Safety Parameters

Safety will be assessed following initial study-specific procedure e.g., screening blood draws, dosing through 14 days post last study dose (last study dose includes weaning doses) and it will be assessed by frequency and incidence of AEs and SAEs. A 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 (see Sections 8.4 and 10.3).

Monitoring for SAEs will continue for a total of 28 days post last study drug dose (including the weaning doses).

Adverse Event

An adverse event (AE) is any untoward medical occurrence in humans, whether or not considered drug-related, which occurs during the conduct of a clinical trial. (Any change in clinical status, routine labs, x-rays, physical examinations, etc.), that is considered clinically significant by the study investigator is considered an AE.

Suspected adverse reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. A reasonable possibility implies that there is evidence that the drug caused the event.

Adverse reaction is any adverse event caused by the drug.

Serious adverse event or serious suspected adverse reaction or serious adverse reaction as determined by the investigator or the sponsor is any event that results in any of the following outcomes:

1. Death

2. Life-threatening AE (“life-threatening” means that the study participant was, in the opinion of the investigator or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention)
3. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
4. Inpatient hospitalization or prolongation of existing hospitalization
5. Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event
6. Confirmed cases of Hy’s Law

Unexpected Adverse Event or Reaction

This is defined as any adverse event 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.

Presumed low blood pressure and presumed hypotension

Presumed low blood pressure will be considered as one valid MAP (in mmHg):

- < gestational age at birth (in weeks) plus postnatal age (in weeks) in mmHg
- < gestational age at birth (in weeks) in mmHg
- < 30 mmHg
- During times of intensive MAP recording (e.g. during dose escalation), one valid MAP of >30% lower than baseline. Baseline MAP is the mean of the 3 valid MAPs prior to the

first dose or dose escalation (i.e. the mean of the following 3 MAPs: 2 hours [+/- 5 minutes], 1 hour [+/- 5 minutes], and 15 minutes [+/- 5 minutes]).

Presumed hypotension will be defined as 2 valid MAPs (in mmHg), taken 15-60 minutes apart:

- < gestational age at birth (in weeks) plus postnatal age (in weeks) in mmHg
- < gestational age at birth (in weeks) in mmHg
- < 30 mmHg
- During times of intensive MAP recording (e.g. during dose escalation), two valid MAPs of >30% lower than baseline. Baseline MAP is the mean of the 3 MAPs prior to the first dose or dose escalation (i.e. the mean of the following 3 valid MAPs: 2 hours [+/- 5 minutes], 1 hour [+/- 5 minutes], and 15 minutes [+/- 5 minutes]).

Identification of Events and Timeframe for Reporting

As all participants in this study will have pre-existing medical conditions and may be currently hospitalized, those pre-existing conditions will not be considered as adverse events. New events that occur or pre-existing conditions that worsen in terms of frequency or intensity will be reported as adverse events.

All reportable events as defined above, determined to be an AE based on physical examination, laboratory findings, or other means, will be reported in the electronic case report form (e-CRF). The investigator will provide the date of onset and resolution, intensity, frequency, action(s) taken, changes in study drug dosing, relationship to study drug, and outcome.

Follow-up of Adverse Events

All events (study-related or not) must be followed until resolution. Events that cannot be resolved by 30 days after the safety monitoring period will have the status of the ongoing event entered in the EDC system at that time.

All serious suspected adverse reactions and severe adverse events will be followed until resolution or until the patient is medically stable. Any adverse event beginning more than 14 days after the last dose of study drug and any serious adverse event beginning more than 28 days after the last dose of study drug will not be captured.

In cases when the baby has been transferred to another facility or discharged home researchers may access test, treatment and outcome information related to the event from the new treating facility and/or to contact the participant/guardian.

Guidelines for Assessing Intensity of an Adverse Event

The investigator should use the following definitions when assessing intensity of an adverse event:

1. MILD: Participant is aware of symptoms or has minor findings but tolerates them well, and no or minimal intervention required
2. MODERATE: Participant experiences enough symptoms or findings to require intervention
3. SEVERE: Participant experiences symptoms or findings that require significant intervention

Guidelines for Determining Causality

The investigator will use the following question when assessing causality of an adverse event to study drug, where an affirmative answer designates the event as a suspected adverse reaction: Is there a reasonable possibility that the drug caused the event? ‘‘Reasonable possibility’’ means that there is evidence to suggest a causal relationship between the drug and the adverse event.

Discontinuation of a Participant Due to Adverse Events

Participants may be withdrawn from the study at any time. Participants withdrawn from the study due to an AE, whether serious or non-serious, must be followed by the investigator until the clinical outcome from the AE is determined. Any participant who experiences an AE may be withdrawn at any time from the study at the discretion of the investigator. The AE(s) should be noted on the appropriate CRFs, and the participant’s progress should be followed until the AE is resolved or considered stable. The medical monitor or project manager must be notified. If the AE may relate to overdose of study treatment, the package insert should be consulted for details of any specific actions to be taken.

Investigator Reporting Procedures

Serious events will be entered into the data system immediately and no later than within 24 hours of identification. Non-serious adverse events will be entered into the safety data system within 7 days of identification. If there are any technical difficulties, the SAE will be reported by direct communication with the medical monitor.

Serious Adverse Events

Any serious adverse event entered in the safety database will generate an automatic email notification to the IND sponsor or the in-country designee and funding sponsor. The DCC medical monitor will review all SAEs at the time that they are reported. Investigators must also submit safety reports locally as required by their IRB/REB.

Regulatory Reporting

Any event that requires reporting to Regulatory Authorities (i.e. Serious Unexpected Suspected Adverse Reactions or SUSARS) based on applicable national regulations will be forwarded to the sponsor in time to meet reporting requirements, (e.g. 7 days for fatal and life-threatening (expedited) initial reports, with follow up reports within another 8 days, 15 days for all other SUSARs). The sponsor or the in-country representative will submit safety reports (e.g. IND safety reports) to the regulatory agencies as necessary, and will inform the investigators of such regulatory reports. Site investigators must submit safety reports as required by their IRB/REB. Documentation of the submission and receipt by the IRB/REB must be retained for each expedited safety report.

Halting Criteria

An unscheduled DMC review of safety data will be triggered if: (a) ≥3 patients in a cohort have treatment completely stopped due to the same AE with a causal relationship to study treatment, or (b) if ≥3 patients in a cohort have the same SAE, or (c) ≥3 patients in a cohort have a Serious Adverse Reaction. Enrollment will be suspended during DMC review, though study activities will be allowed to proceed on previously enrolled subjects if applicable. If there are 3 or more Serious Adverse Reactions in a cohort, then we will also inform the NICHD, FDA and Health Canada, and the DMC may choose to be unmasked to treatment assignment. The DMC may receive unmasked safety data if safety concerns are identified at any point during the study.

Appendix E. Clinical Monitoring and Data management

Site monitoring will be conducted to ensure that human participant protection, study procedures, laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, GCP/ICH, and regulatory guidelines, and that the study is conducted in accordance with the protocol and DCRI sponsor standard operating procedures. The IND/CTA sponsor, or as detailed in the Transfer of Regulatory Obligations (TORO), the BPCA DCC, NIH, or its designee will conduct site-monitoring visits as detailed in the monitoring plan or in the Manual of Procedures (MOP).

Site visits will be conducted at standard intervals as defined by the site monitoring plans and may be made more frequently as directed by the IND sponsor. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, CRFs, informed consent forms, medical and laboratory reports, and protocol compliance. Study monitors will meet with investigators to discuss any problems and actions to be taken and document visit findings and discussions.

Site monitoring will be conducted to ensure that human participant protection, study procedures, laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, GCP/ICH, and regulatory guidelines, and that the study is conducted in accordance with the protocol and DCRI sponsor standard operating procedures. The IND/CTA sponsor, or as detailed in the Transfer of Regulatory Obligations (TORO), the BPCA DCC, NIH, or its designee will conduct site-monitoring visits as detailed in the monitoring plan or in the Manual of Procedures (MOP).

Participant confidentiality is held strictly in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests, in addition to the clinical information relating to participating

participants. Participants will be assigned unique code numbers and will not be identifiable. Birth dates and date of death or discharge are collected in this study.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The clinical study site will permit access to all documents and records that may require inspection by the sponsor, Regulatory Authorities or its authorized representatives, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study.

This study is covered by a Certificate of Confidentiality (CoC) from the NIH. The CoC prevents U.S. courts and other U.S. agencies from forcing the study team to share information that may identify the participants during a legal or legislative action unless the participant allows this. The CoC does not keep the participants from sharing information about their participation in this study.

For Canadian participants, the NIH CoC may protect data housed in the United States from legal proceedings, but disclosure may still occur if required by Federal, State, or local laws, which may be different from Canadian law. Canadian federal and provincial regulations will govern the confidentiality of data maintained at the Canadian sites.

After the study is completed, information about the study, including study data, will be submitted to the NIH data repository (https://dash.nichd.nih.gov; referred to below as “DASH” (Data and Specimen Hub). With NIH approval, the data submitted to DASH may be used by other researchers for future research. The study data submitted to DASH will be de-identified. When de-identified study data are provided to other researchers for the purposes of future research, it may be done without obtaining additional permission from the participant. Canadian participants must consent to this arrangement before their data is provided.

The principal investigator will ensure that the use and disclosure of personal health information obtained during this research study complies with the Federal Privacy Regulations.

For Canadian sites, privacy requirements are described in several Federal and Provincial laws and regulations. Examples include, but are not limited to the Federal Personal Information Protection and Electronic Documents Act, Genetic Non-Discrimination Act, the Ontario Personal Health Information Protection Act, Quebec's Act Respecting the Protection of Personal Information in the Private Sector, the BC Personal Information Protection Act, Alberta's Personal Information Protection Act and Health Information Act. Note that for several provinces more than one act may apply.

In the U.S., the Health Insurance and Portability and Accountability (HIPAA) Privacy Rule applies. The rule provides U.S. federal protection for the privacy of protected health information sent to or collected in the U.S. for the purposes of this research by implementing standards to protect and guard against the misuse of individually identifiable health information of participants participating in clinical trials. "Authorization" is required from each research participant (i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual's protected health information). A valid authorization must meet the implementation specifications under Canadian Federal and Provincial laws or the HIPAA Privacy rule, whichever applies.

The IND/CTA sponsor or designee will provide the investigator, in writing, any new information that bears significantly on the participants' risk to receive the study drug. This new information will be communicated by the investigator to participants' parents/legal guardians/LARs in accordance with IRB/REB requirements. The informed permission document will be updated, and, if necessary, the informed permission process will be repeated and participants' parents/legal guardians/LARs asked to sign updated permission documents.

Site staff may employ IRB/REB-approved recruitment efforts prior to parent/legal guardian/LAR permission; however, before any protocol-specific procedures are performed to determine protocol eligibility, informed permission must be obtained and properly executed.

By signing the permission form, the participant's parent/legal guardian/LAR agrees that the participant will complete all evaluations required by the trial, unless the participant's parent/legal guardian/LAR withdraws the participant voluntarily or the participant is withdrawn from the trial for any reason.

Biological samples collected as part of this study may be shipped periodically to the PTN central laboratory(s) for protocol defined testing (e.g., drug concentration measurements of PK samples).

After the study is completed, all leftover biological samples (e.g. plasma) from this study will be submitted to an NIH storage facility in accordance with applicable privacy laws and/or IRB/REB determinations. These samples will not include any personal identifiers. They will be labeled with a unique code. The NIH repository will not have access to any personally identifying information of the participant. With NIH approval, the de-identified study samples may be made available to other researchers.

Parents/legal guardians/LARs are asked to provide informed consent/permission for the biological sample collection process, specimens repository, and potential for future research prior to the child's participation in the study.