Official Title: Safety of Sildenafil in Premature Infants with Severe Bronchopulmonary Dysplasia (SILDI-SAFE)

NCT: NCT04447989

IRB Document Date: 03/27/2024

Institutional Review Board
Informed Consent Document for Research
MASTER CONSENT

Study Title: Sildi-Safe: Safety of Sildenafil in Premature Infants with Severe Bronchopulmonary Dysplasia (BPD)
Version Date: 04/20/2023

Part 1 of 2: MASTER CONSENT

Name of participant: _____

You are being asked to take part in a research study. This study is a multi-site study, meaning it will take place at several different locations. Because this is a multi-site study, this consent form includes two parts. Part 1 of this consent form is the Master Consent and includes information that applies to all study sites. Part 2 of the consent form is the Study Site Information and includes information specific to the study site where you are being asked to enroll. Both parts together are the consent form and must be provided to you.

Key information about this study:
You are being asked to allow your baby to take part in this research study. Before you decide, it is important for you to understand why the research is being done and what it means to be in the research study.

Your baby's participation is voluntary, which means you are free to decide if you want your baby to be in the study. The purpose of the study is to evaluate the safety of sildenafil, when compared to a placebo (fluid with no drugs in it) in premature babies with bronchopulmonary dysplasia (BPD). We are asking you to allow your baby to participate in this study because they have BPD.

Sildenafil is an approved drug available by prescription for use in adult patients and pediatric patients (age 1-17) with pulmonary hypertension, but is not approved for use in patients less than 1 year of age.

Throughout this document, "study drug" means either sildenafil or placebo.

About 120 patients will be in the study. Your baby will be in the study for about 62 days (up to 34 days of study drug plus 28 days of safety follow-up). In addition, a review of your baby's medical records and end of study physical exam will be done when your baby is ready to leave the hospital.

Your baby will be screened to find out if they should be in the study. There will be a review of your baby's medical record and a physical exam. Blood will be drawn from your baby for some blood tests. Your baby will receive either sildenafil or the placebo (fluid with no drugs in it). If your baby joins the study, he/she might not get sildenafil. Approximately 75% of the participants will randomly receive sildenafil and 25% will randomly receive the placebo. We will not tell you, the study doctors or nurses

Study Title: Sildi-Safe: Safety of Sildenafil in Premature Infants with Severe Bronchopulmonary Dysplasia (BPD)
Version Date: 04/20/2023

which group your baby is in. If you have multiple babies participating in this study (e.g., twins or triplets), each baby will be assigned separately and may not receive the same study drug. Your baby's study drug assignment will be available to your study doctor in the event of a medical emergency.

Side-effects (bad reactions to the drug) may occur from taking the study drug. The study team does not know all of the effects that the study drug may have on your baby. These effects may be mild or serious. In some cases, these effects might be long lasting, or permanent, and may even be life threatening. The risks are explained in detail later in this document. There may not be a benefit to your baby for being in this study. We hope the information learned from this study will help other children in the future.

Why is this study being done?
Your baby was born prematurely and has a form of lung disease called bronchopulmonary dysplasia (BPD). Because of BPD, your baby may develop an additional problem called pulmonary hypertension. Pulmonary hypertension may worsen the lung disease. There are no medicines that prevent pulmonary hypertension. It is very important to find new ways to prevent long-term problems such as pulmonary hypertension in babies with BPD, because babies with BPD and pulmonary hypertension are at a higher risk of dying.

The study will learn more about the safety of a drug called sildenafil. We want to learn more about the drug's side effects, how well it works to prevent long-term problems of BPD, and the best amount (dose) to give in premature babies with BPD. Some doctors already use sildenafil to prevent long-term problems in babies with BPD and pulmonary hypertension. The Food and Drug Administration (FDA) has not approved sildenafil to treat or prevent BPD-related long-term problems. This study could help doctors better understand the best doses of sildenafil to give to premature babies with BPD.

This study is paid for by a grant from the National Institute of Health, National Heart, Lung, and Blood Institute (NHLBI), a part of the National Institutes of Health (NIH). Christoph Hornik, MD of Duke University is the study sponsor (Principal Investigator). Duke University is using funds from the grant to pay your baby's study doctor and his or her research staff to conduct the study. Pfizer, Inc. is the maker of sildenafil. Pfizer or the study grant funds will provide the study drug for your child. You or your insurance company will not be charged for the study drug.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want your baby to be in this study.

Study Title: Sildi-Safe: Safety of Sildenafil in Premature Infants with Severe Bronchopulmonary Dysplasia (BPD)
Version Date: 04/20/2023

Side effects and risks that you can expect if your infant takes part in this study:
Risks of Sildenafil:
Lower doses may have fewer side effects than higher doses.

Low blood pressure might occur after receiving sildenafil. Your baby's blood pressure will be checked closely during the study. In adults, reddening of the skin, nose bleeds, headaches, stomach upset, and loss of vision have also been reported with the use of sildenafil. However, it is not clear if these problems occur with use in premature babies.

The FDA has approved the use of sildenafil for pulmonary arterial hypertension in children 1 to 17 years of age. The patient population in the study that led to the FDA's recommendation were older than the babies in this study (ages 1-17 years old), weighed more (greater than or equal to 8 kilograms) and were being treated for a blood vessel disease.

Our research focuses on premature babies with severe BPD, a lung disease.

The placebo (salt water or sugar water) has no known risks. If your baby is included in the placebo arm, s/he will be receiving the usual care given to prematurely born babies.

Risks of Drawing Blood:
There are small risks with blood draws. This may include some momentary discomfort and/or bruising, and risk of infection. We will do our best to collect the samples at the same time as blood tests ordered by your baby's doctor.

Risks that are not known:
Because this treatment is investigational, meaning non-FDA approved, there may be risks that we do not know about at this time. If your baby suffers from allergies to medications, food products, or environmental elements, please tell the study doctor now.

Good effects that might result from this study:
It is possible that babies with BPD who get sildenafil will have improved breathing and a lower risk for pulmonary hypertension. However, it is possible that there will be no benefit. We hope the information that we learn from this study will help us to take care of premature babies in the future.

Procedures to be followed:
Screening/Baseline:

Your baby will have the following tests and procedures done to make sure that your baby is eligible:

- Review your baby's medical history, including their date of birth, weight, eye disorders or other infections, and current medical condition.
- Review the mother's demographics (for example, age, ethnicity, and length of pregnancy).
- Review of all other assessments (lab, heart procedures) and non-medicine related treatments used as routine medical care for your baby.
- Physical exam, including breathing status, blood pressure, heart rate
- Blood draws totaling about 1½ teaspoons to measure the following (if not done as part of routine medical care):
    - Your baby's blood cell counts
    - How your baby's liver and kidneys are working
- Review all medicines your baby may have taken 24 hours prior to starting study drug
- Echocardiogram: if not done per standard of care within the 14 days prior to the start of study drug

Group Assignment:

This study has three dosing groups. Group 1 uses the lowest dose of sildenafil and Group 3 uses the highest dose of sildenafil. Approximately 40 babies will be enrolled into each group – 30 will get sildenafil and 10 will get placebo. Before any baby is enrolled into Group 2, the safety data from Group 1 will need to be reviewed to make sure it's safe to continue. Before any baby is enrolled into Group 3, the safety data from Group 2 must be reviewed to make sure it is safe to continue.

The dose your baby will get depends on the dosing group they are enrolled into and how much they weigh. Your baby may receive the study drug by an intravenous (IV) line (if they have one) or with feedings. If study drug will be given with feedings, it can be given directly into your baby's stomach with a tube or given by mouth. Babies who receive the study drug by feeding tube or by mouth require twice as much study drug as babies who receive study drug into the vein. This is because the study drug is not absorbed as well when given into the stomach.

If your baby is getting placebo they will receive the same volume (amount) of salt water (if given in a vein) or sugar water (if given by mouth) instead.

Treatment Visits (Day 1 up to 28):

- Study drug or placebo will be given for up to 34 days, intravenously (IV) through a small plastic tube that is placed in your baby's vein, or by mouth with their feedings

- The following information will be recorded throughout the study:
  - the time and the amount of study drug your baby receives
  - blood pressures, weights, breathing status
  - medicines your baby is taking since the Screening/Baseline visit
  - all other assessments: labs, heart procedure reports (echocardiogram, heart catheterization)
  - any changes in your baby's medical condition or any problems your baby may be having
- Up to 8 blood draws, totaling about 1½ teaspoons, will be done to show how well the body processes and eliminates the study drug or placebo.

Weaning Off Study Drug:
Sildenafil is commonly used at higher doses to treat pulmonary hypertension in infants. In clinical practice, doctors generally lower the dose of sildenafil over time to prevent side effects that may happen if sildenafil is stopped immediately. If your baby is enrolled in Group 1, study drug will not require stopping over time because the dose is low. If your baby is enrolled in Group 2 or 3, they will be gradually taken off (weaned off) the drug over approximately 6 days. Weaning will occur if they complete 28 days of treatment or are withdrawn from the study drug early but received a high dose. Your baby's doctor may modify the weaning dosing schedule if it is in your baby's best interest (for example, if there is a safety concern).

LAB SAMPLE COLLECTIONS:

Clinical Laboratory Tests
Sildenafil is removed from the body by the liver, so we will monitor how well your baby's liver is working. To do this we will need to collect blood samples from your baby. We will try to collect the blood when your baby is already having blood draws to reduce needle sticks.

We will collect blood for the purpose of checking how well your baby's liver is working before starting the study drug. We will check the liver tests at least every other week while on study drug and, if ordered by your doctor as part of your baby's care, during the follow up period as well. Blood for these tests may be collected specifically for this study, if they are not already ordered by your baby's doctor.

Pharmacokinetic (PK) Tests
PK tests are done to see how much of the drug is in the blood. These tests show how the body processes the drug. All study participants will have blood samples collected. Blood collected from babies who

receive placebo will be tested for inflammation related to BPD instead of measurements of drug amounts.

After your baby has received at least one week of study drug, we will collect up to 8 PK blood samples at different times. We will try to only collect blood during times of routine blood draws to avoid extra "sticks" for this study. About 1/10th of a teaspoon of blood will be collected each time. The maximum possible amount of blood for all blood tests will be about 1½ teaspoons for the duration of the study.

All study samples will be labeled with a unique code but not with your baby's name, initials, or any other information that could identify your baby.

Additional Use of Samples

Leftover blood samples will be sent from the PK testing lab to a central lab for genotype analysis and to a National Institutes of Health (NIH) storage facility. Genotype analysis means looking at the DNA sequence of an individual to see if differences in sequences can be linked to specific traits or diseases. The samples and data will be sent with only a research code number attached. Your baby's name or other directly identifiable information will not be given to the lab or storage facility. There are many safeguards in place to protect your privacy.

Future Use of Stored Samples

Your baby's samples may be used to make new products or tests. These may have value and may be developed and owned by the study staff, Duke University, and/or others. If this happens, there are no plans to provide money to you.

You will not receive any benefit as a result of the tests done on your baby's samples. These tests may help us or other researchers learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Reasons why the study doctor may take your baby out of this study:

The study doctor may decide to take your baby out of this study at any time if:

- Your baby's condition changes and the study is no longer in his/her best interest
- The entire study is stopped, by the study doctor or the sponsor.

If this occurs, you will be told and your study doctor will talk to you about other options.

What will happen if you decide to stop being in this study?

If you decide to stop being part of the study, you should tell your study doctor. Deciding to not be part of the study will not change your baby's regular medical care in any way.

If you change your mind, you can withdraw your baby at any time. If you withdraw your baby from the study, no new data about your baby will be collected for study purposes unless your baby has a side effect related to the study drug. If a side effect occurs, we may need to review your baby's medical record. Any data collected before you withdraw will remain a part of the study records and will be retained for analysis in order to protect the integrity of the research, which may benefit future research participants and patients.

Because samples are also collected for this study, if you decide to withdraw your baby from the study, no new samples will be collected for study purposes. Any samples collected before you withdraw will be utilized for the study.

Clinical Trials Registry.
A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Privacy:
Information about your baby may be made available to others to use for research, including your study doctors, the Federal Drug Administration (FDA), National Heart, Lung, and Blood Institute (NHLBI), Pfizer, Inc. and its Affiliates, and Duke Clinical Research Institute (DCRI) at Duke University. These entities may have access to your baby's medical records (including this consent form) for the purpose of confirming the study data and that the study was run appropriately. Information that could identify you or your baby may be transmitted electronically to the DCRI for this purpose. A secure, cloud-based system will be used to transmit the information. To protect your confidentiality, we will not release your or your baby's name to anyone other than DCRI.

Potential Risks and the Genetic Information Non-Discrimination Act (GINA): There is a potential risk of loss of confidentiality. Every effort will be made to protect your confidential information, but this cannot be guaranteed. The genetic information obtained as a result of your participation in this research will not be included in your medical record. Information from which you may be personally identified will be maintained in a confidential, secure location at DUHS, accessible only by authorized members of the study team, and will not be disclosed to third parties except as described in this consent form, with your permission, or as may be required by law.

The Genetic Information Nondiscrimination Act (GINA) is a Federal law that will protect you in the following ways:

- Health insurance companies and group plans may not request genetic information from this research;
- Health insurance companies and group plans may not use your genetic information when making decisions regarding your eligibility or premiums;
- Employers with 15 or more employees may not use your genetic information when making a decision to hire, promote, or fire you or when setting the terms of your employment.

GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

Study Results:
You may be contacted by the team conducting this research in the future to be provided with overall study results (summary results from all participants). This means you will not know the results as they relate to your baby specifically.

Institutional Review Board
Informed Consent Document for Research
STUDY SITE INFORMATION

Study Title: Sildi-Safe: Safety of Sildenafil in Premature Infants with Severe Bronchopulmonary Dysplasia (BPD)
Version Date: 8/10/2022

Part 2 of 2: STUDY SITE INFORMATION

Site Name:	University of North Carolina at Chapel Hill
UNC IRB Number	UNC IRB# 20-1222
Site Principal Investigator:	Wesley Jackson, MD
Site Principal Investigator Contact:	(P) 984-215-3449 (E) wesley.jackson@unc.edu
Site Study Coordinator *(if applicable)*:	
Site Study Coordinator Contact *(if applicable)*:	

This study is being done at multiple sites. This part of the consent form includes information about your site that is asking you to participate in this study and is specific to participation at your site only. Before making your decision, both the site-specific information and the general study information should be reviewed with you. You will have the opportunity to discuss any questions about this portion of the consent document with your site's study team. Your medical record will contain a note saying you are in a research study and may contain some research information about you. Anyone you authorize to receive your medical record will also get this information.

Payments for your time spent taking part in this study or expenses:
You will not receive any money for your baby's participation in this study.

Costs to you if you take part in this study:
There will be no cost to you or your insurance, for any care that is done as part of this study. The study will pay for all of your baby's care that are done only for the study. All usual care for your baby will be billed to your insurance.

Payment in case you are injured because of this research study:
All research involves a chance that something bad might happen. This may include the risk of personal injury. In spite of all safety measures, your baby might develop a reaction or injury from being in this study. If such problems occur, the researchers will help your baby get medical care, but any costs for the medical care will be billed to you and/or your insurance company. The University of North Carolina at Chapel Hill has not set aside funds to pay you for any such reactions or injuries, or for the related medical care. Further, there is no commitment by Duke University or the study sponsor to provide monetary compensation or free medical care to you in the event of a study-related injury. However, by signing this form, you and your baby do not give up any of your legal rights.

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Who to call for any questions or in case you are injured:
If your baby gets injured or has a medical problem from being in this study, tell your study doctor right away. For questions about the study or research-related injury, contact Dr. Wesley Jackson at 984-215-3449 during regular business hours, after hours, and on weekends and holidays.

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the Vanderbilt University Medical Center Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

Additional information about your local site:
By signing this informed consent document, you agree that some of the information generated by your child participating in this study and/or a copy of the consent form may be included in your child's medical record and that this information may be viewed by other physicians or caregivers who provide healthcare services to you or your child. This will allow doctors caring for your child to know what study medications or tests they may be receiving as a part of the study and know how to take care of your child if they have other health problems or needs during the study. Additionally, the information may be shared with your child's medical insurance plan if the research services provided are billed to insurance.

Under North Carolina law, researchers are required to report information about the abuse or neglect of a child or disabled adult to local or state authorities.

Under North Carolina law, confidentiality does not extend to certain communicable diseases, such as TB, HIV, hepatitis. Or other illnesses that put others at risk. If the researchers become aware that subjects have such an illness, they are required to report it to state authorities.

The University of North Carolina at Chapel Hill requires that you sign a separate authorization form related to the use of your child's protected health information for this research study. This is required for participation in this study.

Confidentiality:

This research is covered by a Certificate of Confidentiality. With this Certificate, the researchers may not disclose or use information, documents or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings in the United States, for example, if there is a court subpoena, unless you have consented for this use.

The Certificate cannot be used to refuse a request for information from personnel of a federal or state agency that is sponsoring the study for auditing or evaluation purposes or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law, such as mandatory reporting requirements for child abuse or neglect, disabled adult abuse or neglect, communicable diseases, injuries caused by suspected criminal violence, cancer diagnosis or benign brain or central nervous system tumors or other mandatory reporting requirement under applicable law. The Certificate of Confidentiality will not be used if disclosure is for other scientific research, as allowed by federal regulations protecting research subjects or for any purpose you have consented to in this informed consent document.

You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

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STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

_____
Printed Name of Research Participant (Child)

_____ Date_____ Time: _____
Signature of Parent/Guardian

_____
Printed Name of Parent/Guardian

I certify that I have explained the nature and purpose of this research study to the above-named individual and I have discussed the potential benefits and possible risks of study participation. Any questions the individual has about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____ _____ Time: _____
Signature of Research Team Member Obtaining Permission Date