Children's Hospital of Pittsburgh of UPMC

Department of Pediatrics

Division of Pulmonology Medicine, Allergy and Immunology
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CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY
Chronic Lung Disease Subject

TITLE: Inhaled nitrite for CF

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SOURCE OF SUPPORT: The Cystic Fibrosis Foundation (CFF)

Why is this research being done?
This study will evaluate whether nebulized sodium nitrite is safe to use for adults with cystic fibrosis and airway infection with Pseudomonas aeruginosa. Sodium nitrite is a compound that appears to have effects on the growth of bacteria. It has been used as a food additive for many decades.

Sodium nitrite may present a new bacteria fighting approach to treating lung infection. Inhaling sodium nitrite can prevent the growth of Pseudomonas aeruginosa in CF lungs. Inhaling nitrite has been tested on animals, and is well tolerated by people with pulmonary arterial hypertension (another form of lung disease). This is a dosing/escalation study. This means you will receive an initial dose of sodium nitrite and then a higher concentration of the study drug at the next visits. We anticipate this study will provide important safety and effectiveness information that will aid in future

development of inhaled sodium nitrite therapy. The study drug, sodium nitrite, is considered experimental and is not FDA approved for general marketing.

Why do I have the option of joining the study?
You are being asked to participate in this study because you have cystic fibrosis (CF) and have had at least 2 sputum cultures that were positive for a strain of bacteria known as Pseudomonas aeruginosa in the past year. About 35 subjects with cystic fibrosis will be enrolled in this study at UPMC.

What procedures will be performed for research purposes?
If you agree to take part in the study, you will come to Children's Hospital of Pittsburgh of UPMC and/or the Clinical Translational Research Center (CTRC) at UPMC Montefiore Hospital for a total of 5 study visits over 2 ½ months. You will be asked to not take any of your routine inhaled medications other than Albuterol on the mornings of your study visit. You will undergo a brief medical history and review of your medical record to determine eligibility for the study at your screening visit. You will also have a physical exam and a blood draw for laboratory testing. If you are eligible for the study, at your scheduled study visits you will have some additional tests and procedures as noted below. These tests and procedures will help us find out if being in this study causes any effects that are important to know about.

Explanation of Tests and Procedures:

Nebulization of sodium nitrite: On study visits 1 and 2 you will be asked to inhale sodium nitrite for 10-15 minutes through a nebulizer under direct observation in the Montefiore CTRC. During the nebulization of sodium nitrite you blood pressure will be checked using a blood pressure cuff on your arm every 15 minutes. You blood pressure will be monitored for a total of two hours on visits 1 and 2. If there is a $\leq$ 20% drop in your blood pressure during the study drug will be stopped and the next higher dose of inhaled nitrite will not be administered.

If you tolerate the nebulized sodium nitrite on study visit 1, you will be given a 7-day supply with instructions for use and discharged from the CTRC. When you return for study visit 2, you will be given a higher dose of sodium nitrate and observed in the CTRC as noted above. If you tolerate the higher dose of nebulized sodium nitrite, you will be given a 7-day supply with instructions for use and discharged from the CTRC. If you do not tolerate the higher dose, you will be given the original dose from visit 1 and continue with blood pressure, spirometry and oxygen saturation measurements.

Oxygen saturation and methemoglobin (blood that is not carrying oxygen) level measurement: A small clip will be placed on your finger prior to starting the sodium nitrite nebulizer. This clip will be used to monitor the level of oxygen in your blood. This clip will let the study staff know the amount of your blood that is carrying oxygen and the amount of your blood that is unable to carry oxygen. This clip will remain on your finger through the nebulization of sodium nitrite and for 4 hours after the dose has

ended on visits 1 and 2. Your oxygen saturation will also be measured at your screening visit and visit 5

Pulmonary function testing: spirometry will be performed at each of the study visits in the pulmonary clinic or in the CTRC. Each spirometry test typically takes 3-5 minutes and the test will be repeated at least 3 times or until an acceptable spirometry test is obtained. To do the spirometry test, you will sit upright in a chair and be asked to breathe through a tube connected to the spirometer machine. While wearing nose clips, you will be asked to take as deep a breath in as you can and then blow all the air out as hard and fast as you can.

Exhaled nitric oxide measurement: Nitric oxide is a gas that is released from inflammatory cells in the lung. For this measurement, you will be asked to gently blow air out into a machine for a 10-second period of time. Exhaled nitric oxide will be measured at your visits 1, 2, and 4.

Sputum collection: If you are able to cough up sputum (mucus), you will be asked to perform a huff cough and then spit any sputum into a cup. If you are unable to cough up sputum on your own, a sputum induction will be performed to collect your sputum. During the sputum induction, you will be asked to breathe in a salty mist for up to 12 minutes and will be asked to cough deeply and vigorously every two minutes in order to bring up a sample of sputum (mucus) from your lungs. Your sputum will be collected at study visits 1, 2, and 4.

Blood draw: We will draw about 5 ml or 1 teaspoon of blood per blood draw. This procedure will be done at your screening visit, Visits 1, 2, and 4. You will have blood drawn from a vein in your arm by a physician involved in the study, a nurse, or a person trained in drawing blood. The blood draw procedure takes about 10-15 minutes. Blood will be used to confirm methemoglobin levels, as well as to evaluate your complete blood count, platelets, electrolytes, glucose, BUN, serum creatinine, and liver function tests. At any time during the study, a blood draw may need to be repeated in case a sample is lost or unusable for study purposes.

CF Questionnaire: You will be asked to complete a brief CF questionnaire at each of your study visits prior to performing any of the above noted procedures. Completing the questionnaire should take about 10-15 minutes.

Urine Pregnancy Test: Urine pregnancy test may be performed only on female subjects of child-bearing potential at the screening visit. Pregnant women will not be allowed to participate in this study.

Oral Washes: You will be asked to brush your teeth with a clean, single use toothbrush. You will then be given 10 ml of 0.9% salt water solution and instructed to swish and

gargle for 1 full minute before spitting the salt water solution into a sterile specimen cup. Oral washes will be done at study visits 1 and 4.

Specimen Banking: After this study is completed, any unused specimens may be stored permanently by the researchers. This is called banking. The banked specimens may be used by the researchers for future research in cystic fibrosis.

These specimens will be de-identified and placed in a secured facility at the University of Pittsburgh. If the blood or sputum samples are shared with investigators at another institution, he/she will not have access to any identifying information. The blood and sputum samples will be stored indefinitely with only an ID number as identification.

Any requests for use of banked specimens must be approved by the principal investigator and Institutional Review Board (IRB). It is unknown at this time what types of research may be done on the banked blood and sputum samples. It is possible that a commercial product could be developed by researchers. No compensation will be provided to you in the event that a commercial product results from this research. You must give your specific permission for your blood and sputum samples to be banked.

Optional Consent for Specimen Banking:
Please read each statement below. Think about your choice. Initial the line next to your choice. If you have any questions, please talk to your doctor or nurse or member of the research team.

_____ I give permission for permanent storage or banking of my specimen. I understand that the blood and sputum will be banked at a secure facility at the University of Pittsburgh. I understand the specimens may be used by other researchers in the future for research. Any additional research must be reviewed and approved by the IRB before specimens are given to the researchers.

_____ I do not give my permission for specimen banking.

What are the possible risks, side effects, and discomforts of this research study?
As with any experimental procedure, there may be adverse events or side effects that are currently unknown and certain of these unknown risks could be permanent, severe or life threatening.

This study might involve the following risks and/or discomforts to you:

Risk of nebulization of sodium nitrite: You may experience airway irritation, coughing, bronchospasm, decline in your lung function, or decrease in your blood pressure during and after the inhalation of sodium nitrite. You will be monitored as noted above and a physician, medications and equipment will be available in the CTRC to treat and manage any difficulty breathing or decrease in blood pressure if necessary.

Risks of blood draw: The risk of collecting blood includes soreness, bruising, mild pain, mild bleeding at the site. Some people experience feelings of or light-headedness or dizziness after having blood drawn. Rarely people have experienced infection and fainting.

Risk of induced sputum collection: You may experience a salty after taste in the mouth, coughing, a feeling of needing to swallow, a sore throat, shortness of breath, wheezing, chest tightness, lightheadedness, nausea or headache. In rare cases, some patients have had a severe asthma attack or a reaction to the salty water that they breathe in. Bronchodilator treatment will be available if this occurs.
There are no know risks associates with the collection of a spontaneous sputum sample.

Risk of withholding inhaled medications: The brief period of hold is very unlikely to result in any change in your health. You may continue to use your routine inhaled Albuterol treatment on the mornings of your study visits. If you feel at any time you can not safely withhold your inhaled medication, you should contact Dr. Pilewski and the research coordinator so that your study visit can be rescheduled.

_____ Initial here to confirm you have withheld your nebulized antibiotics for the past 14 days.

Risk of oxygen saturation and methemoglobin level measurement: There are no known risks associated with the oxygen saturation and methemoglobin measurement.

Risk of pulmonary function testing: There is a small risk of wheezing and shortness of breath and increased cough or lightheadedness when performing spirometry. If you have recently had an air leak from the lungs (pneumothorax) or you are coughing up blood, you should tell your research doctor or nurse to help them to decide if you should do spirometry.

Risk of exhaled nitric oxide measurement: Exhaled nitric oxide measurement is a breathing test that may cause you to have some mild coughing.

Risk of CF questionnaire: There are no known risks associated with completing the CF questionnaire. Some questions may feel too personal or make you feel uncomfortable. You may skip any questions you do not want to answer.

Review of medical records: Investigators will screen medical records in person for determining study eligibility. There is a very minimal risk that confidentiality may be breached with investigators reviewing that information.

Risks of breach of confidentiality: Your research samples and data will not be labeled with your name or other items that might identify you. All data will be stored in a password protected, study specific database and will be labeled with a code number.

There will be very limited access to the link between your name or other personal information and the study code. Because this link will exist, there is a small risk that your name may become known in association with this research study.

Reproductive Risks: It is not known if the study drug can affect an unborn baby. Therefore, you should not become pregnant or father a baby while on this study. If you are physically able to father a baby or become pregnant, you must use an effective method of birth control while on this study. If you become aware that you or your sexual partner is pregnant during the course of your participation in this research study, you must contact the study investigator as soon as possible. If you become pregnant during the study we will ask you to stop taking the study drug. Your research doctor would follow up with you after your child is born and ask you some questions.

Risks of Specimen banking: There is a rare risk that there might be a breach of confidentiality. Your specimens will be de-identified and placed in a secured facility at the University of Pittsburgh. If the blood or sputum samples are shared with investigators at another institution, he/she will not have access to any identifying information. The blood and sputum samples will be stored indefinitely with only an ID number as identification.

What are possible benefits from taking part in this study?

We can not guarantee you any direct benefit from participation in this research study. You may or may not experience any improvement in your lung function as a result of participating in this research study. It is expected that the study will lead to increased knowledge of infections and inflammation in Cystic Fibrosis.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?

You will be promptly notified if, during the conduct of this research study, any new information develops which may cause you to change your mind about continuing to participate.

Will my insurance provider or I be charged for the costs of any procedures performed as part of this research study?

Neither you, nor your insurance provider, will be charged for the costs of any of the procedures performed for the purposes of this research study. You will be charged, in the standard manner, for any procedures performed for your routine medical care.

Will I be paid if I take part in this research study?

You will be paid for your participation. The amount you receive depends on which parts of the study you complete. If you qualify for the study after screening and complete the study visits outlined in this consent form, you will be paid up to $400. If you stop participating before the end of the study or if the study is discontinued through no fault of yours, you will receive a partial payment based upon your participation in the study.

Visit Description	Approximate Length	Reimbursement
Visit 1	5.0 hrs	$150
Visit 2	5.0 hrs	$75
Visit 3	1.0 hr	$50
Visit 4	1.5.0 hrs	$75
Visit 5	1.0 hr	$50

You will also be reimbursed for your parking and your travel at the standard government rate. If you are currently receiving social security/disability payments, study payments may affect that amount.

Research based on the use of your biological specimens and/or data may result in new products, tests, or discoveries. These may have value to others, but you will not share in any financial or other benefits from these products, tests or discoveries.

What happens if I am injured from being in this study?
If you believe that the research procedures have resulted in an injury to you, immediately contact Principal Investigator who is listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you if this emergency treatment is provided by a UPMC facility. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. At this time, there is not plan for any additional financial compensation. You do not waive any legal rights by signing this form.

Who will know about my participation in this research study?
Members of the research team and, if appropriate, your physicians and nurses will know that you are a research subject. Any information about you obtained from this research will be kept as confidential (private) as possible. Your specimen will be assigned an ID number and only identified by this ID number from that point forward. All records related to your involvement in this research study will be stored in a locked file cabinet. You will not be identified by name in any publication of the research results unless you sign a separate consent form giving your permission (release).

Will this research study involve the use or disclosure of my identifiable medical information?
We are requesting your permission to review your medical records to determine whether you meet the conditions for participation in this study. We will review and record pulmonary function and laboratory results from your medical record. In addition, we will also review and record the presence or absence of clinical exacerbation of disease and current medications you are taking.

Who will have access to identifiable information related to my participation in this research study?

In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study:

Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable research information (which may include your identifiable medical information) for the purpose of monitoring the appropriate conduct of this research study.

In unusual cases, the investigators may be required to release identifiable information (which may include your identifiable medical information) related to your participation in this research study in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies.

Authorized representatives of the sponsor of this research study, the Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT), the Cystic Fibrosis Foundation (CFF) and the CFFT Therapeutics Development Network Coordinating Center (TDNCC) and the investigator-sponsor, Aires Pharmaceuticals, Inc., will review and/or obtain identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of monitoring the accuracy and completeness of the research data and for performing required scientific analyses of the research data.

Authorized representatives of the U.S. Food and Drug Administration may review and/or obtain identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of monitoring the accuracy of the research data. While the U.S. Food and Drug Administration understands the importance of maintaining the confidentiality of your identifiable research and medical information, the University of Pittsburgh and Children's Hospital of Pittsburgh cannot guarantee the confidentiality of this information after it has been obtained by the U.S. Food and Drug Administration.

Authorized representatives of the UPMC hospitals or other affiliated health care providers may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance).

We will protect your privacy and the confidentiality of your records, as described in this document, but cannot guarantee the confidentiality of your research records, including information obtained from your medical records, once your personal information is disclosed to others outside UPMC or the University.

For how long will the investigators be permitted to use and disclose identifiable information related to my participation in this research study?
The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical information) related to your participation in this research for an indefinite period of time.

However, you can always withdraw your authorization to allow the research team to review your medical records by contacting the investigator listed on the first page and making the request in writing. If you do so, you will no longer be permitted to participate in this study. Any information obtained from you up to that point will continue to be used by the research team.

All specimen and data will be stripped of individual identifiers and stored anonymously with a subject ID number. Samples and data, identified with your study ID number only, may eventually be transferred to another protocol or to a specimen repository for future research use. This includes future studies with investigators outside of the institution. These investigators will only have access to samples and data identified by the study ID number and not any identifiable medical information.

Is my participation in this research study voluntary?
This authorization is valid for an indefinite period of time. However, your participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. (Note, however, that if you do not provide your consent for the use and disclosure of your identifiable information for the purposes described above, you will not be allowed, in general, to participate in the research study.) Whether or not you provide your consent for participation in this research study will have no affect on your current or future relationship with the University of Pittsburgh. Whether or not you provide your consent for participation in this research study will have no affect on your current or future medical care at any University of Pittsburgh Medical Center (UPMC) hospital or affiliated health care provider or the University of Pittsburgh or your current or future relationship with a health care insurance provider.

Your doctor is involved as an investigator in this research study. As both your doctor and a research investigator, s/he is interested both in your medical care and the conduct of this research study. Before agreeing to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor.

May I withdraw, at a future date, my consent for participation in this research study?
Yes, to do so, you should provide a written and dated notice of this decision to the principal investigator listed on the first page of this consent form. We will continue to use the information we have collected unless you indicate specifically that you wish to have your study data excluded from the study. In this case, the principal investigator will also destroy any electronic or printed copies of your study data. We will continue to bank the blood and sputum samples we have obtained from you unless you specifically request that your banked samples as well as samples that may have been sent to other researchers be destroyed.

Your decision to withdraw your consent for participation in this research study will have no affect on your current or future relationship with the University of Pittsburgh. Your decision to withdraw your consent for participation in this research study will have no affect on your current or future medical care at any University of Pittsburgh Medical Center (UPMC) hospital or affiliated health care provider or the University of Pittsburgh or your current or future relationship with a health care insurance provider.

If I agree to take part in this research study, can I be removed from the study without my consent?
It is possible that you may be removed from the research study by the researchers if the investigator feels that it is not in your best interest to continue or if there is non-compliance with study procedures.

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VOLUNTARY CONSENT
All of the above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by the researchers listed on the first page of this form.

Any questions which I have about my rights as a research participant will be answered by the Human Subject Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668).

By signing this form, I agree to participate in this research study and provide my authorization to share my medical records with the research team. A signed and dated copy of this consent form will be given to me.

_____ _____
Printed Name of Participant Date/Time

_____
Participant's Signature

INVESTIGATOR'S CERTIFICATION

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have 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.

_____	_____
Printed Name of Person Obtaining Consent	Role in Research Study
_____	_____
Signature of Person Obtaining Consent	Date/Time