

(Institution's Name)

Consent Form

**Safety and Tolerability Study of Ascending Single Doses of
Aztreonam for Inhalation (AI) in Patients with Cystic Fibrosis (CP-AI-002)**

(List Investigators)

Researchers' Statement

You are being asked to consider enrolling in a research study because you have cystic fibrosis (CF). Taking part in research is voluntary. Please take time to carefully read and understand the following explanation of the proposed procedures, and consider this request. Feel free to discuss the study with your family and friends.

Why is this research study being done?

People with CF often have lung infections which occur repeatedly or worsen over time. The lung infections are caused by bacteria (germs). Treatment with antibiotics is used to stop or slow down the growth of the bacteria. The antibiotics may be given by mouth, into a vein (IV), or inhaled as a mist. Research has shown that inhaling an antibiotic as a mist is a very effective way to treat lung infections in CF. Aztreonam is one antibiotic which is given IV to treat lung infections in patients with CF. Salus Pharma is developing a new form of aztreonam which can be inhaled, or breathed in, using a nebulizer. A nebulizer is a device used to deliver drugs as a mist to the lungs. The new form of the antibiotic is called Aztreonam for Inhalation (AI).

This research study is being done to evaluate the safety and tolerability of three different doses of AI in patients with cystic fibrosis. In addition, blood and sputum will be collected to study how the antibiotic is broken down, or metabolized, in the body.

AI is an investigational new drug. This means that the U.S. Food and Drug Administration allows the drug to be used only in research. This will be the first study testing AI in patients with CF. AI has been tested in one study with 24 healthy adult volunteers. The subjects received a single dose of either AI (95 mg, 190 mg, or 285 mg) or placebo (an inactive substance). No serious side effects related to AI were reported. The following symptoms were reported one time after dosing: moderate headache, mild dizziness, mild cough, and mild unpleasant taste. Each symptom was reported only one time.

In this study, patients with CF will receive up to three treatments with either AI or placebo. Patients will be assigned to the AI or placebo group by chance, like flipping a coin. After the first treatment, the number of additional treatments and the dose given will depend on how the previous treatment is tolerated. Each study treatment will be breathed in using a new nebulizer, the PARI eFlow™. The PARI eFlow nebulizer is an investigational, reusable electronic device. The nebulizer mixes air with the study drug solution or placebo, so that it becomes a mist which is inhaled with normal breaths. The technology is based on a vibrating membrane technique that assures precise delivery of drug. The amount of drug delivered to the lungs is maximized while the amount of drug deposited in the mouth and throat is minimized. It is expected that treatment time will be shorter than is usual for nebulized treatments.

Are there benefits to taking part in the study?

There is no direct benefit to patients who take part in this study. The information gained may help with the development of AI as a treatment for lung infections for patients with CF. In the future, all

patients with chronic CF lung infections may benefit from having another inhaled antibiotic available for treatment.

How many people will take part in the study?

About 36 patients (18 adults and 18 adolescents) will take part in this study in hospitals and CF clinics across the country. It is expected that X to X patients will take part here at (institution's name). Treatment of the adult group will be completed and the safety information will be reviewed before the adolescent group is treated.

What is involved in this study?

If you agree to take part in this research study, some procedures and tests must be completed to decide if it is safe for you to receive the AI or placebo. Screening tests and procedures will be completed and reviewed by the research doctor. If you are eligible to receive AI or placebo, a treatment visit will be scheduled within 7 days after the Screening visit.

At the first treatment visit, you will be given one dose of study treatment, either AI (75 mg) or placebo. You will be observed for any problems during and after the treatment. If you do not have any problems with the dose on the first day, you will return the next day and the study procedures will be repeated. If you are in the AI group, you will receive a higher dose of AI (150 mg). If you do not have any problems with the dose, you will return for a third and final treatment visit on the following day. Patients in the AI group will receive 225 mg of AI at the third visit. Patients in the placebo group will receive placebo at each treatment visit.

You may receive one, two or three doses of AI or placebo depending on your response to the treatment. Following your last treatment with AI or placebo, you will have two follow-up visits scheduled. A 24 hour follow-up visit will be scheduled for the day after your final treatment. The second visit will be scheduled for 3 days following your final treatment. Study procedures and tests will be completed to determine the safety of AI in patients with CF.

How long will the study last?

You will be in the study for up to 13 days. You will have 4 to 6 study visits depending on the number of treatments with AI or placebo which you receive.

The research doctors may decide to take you off this study at any time. If so, the reasons will be explained to you. For example, the doctors may decide it is in your best interest to stop being in the study because of problems with the treatment or you are not able to complete all the study visits.

You may also decide that you would like to stop taking part in this study at any time. If you decide to stop, talk with the research doctor or nurse so you are taken out of the study in a way that is safe. This will not alter the way you are treated by the doctor. You will be asked by the research doctor to have safety tests (physical exam, heart rate and blood pressure measurements, spirometry, blood sampling) performed before you leave.

Screening (Visit 1)

A screening visit will be scheduled at the Clinical Research Center (CRC). Your medical history and current medications will be reviewed. Your date of birth, race, sex, sweat test results, and CF genotype will be recorded. The following procedures and tests will be completed:

- 1) height and weight
- 2) vital signs-temperature, heart rate, breathing rate and blood pressure
- 3) physical examination by a CF doctor
- 4) oximetry – a small clip will be placed on your finger to measure the amount of oxygen in your blood

- 5) spirometry (PFTs) – you will blow into a machine to check your lung function (if you usually use an inhaled medicine (bronchodilator) to open up your airways, a dose will be given before the spirometry)
- 6) chest X-ray - if you have not had one within the previous 90 days prior to screening or have had a significant illness since your last chest X-ray
- 7) urine collection to check kidney function
- 8) blood collection (2 - 3 teaspoons) to check your blood count, liver and kidney function, and immune response
- 9) pregnancy test (urine or blood) for females of childbearing years.
- 10) sputum collection for aztreonam levels before you begin your study treatment

The screening visit will last 2 – 3 hours. The results of the procedures and tests will be checked by the researchers to decide if it is safe for you to continue in the study. You may not be eligible to take part in the study based on the test results.

Treatment

If all of your test results are satisfactory, you will be eligible to continue in the study and receive treatment with AI or placebo. You will be scheduled for another visit at the CRC within 7 days after the screening visit. You will be assigned to one of two treatment groups: AI or placebo. This will be done by chance, like flipping a coin. You will receive up to three doses of AI or placebo over the next three days. Neither you nor the study doctors will know to which group you are assigned. Your group assignment can be found out quickly, if this information is necessary for your treatment or if a health issue arises during the study.

Treatment Study Visits (Visit 2, Visit 3, and Visit 4)

As long as you are taking part in the study, additional procedures and tests will be done. The results will help the researchers to know if it is safe for you to receive additional doses of the AI or placebo. One treatment of AI or placebo will be given each day for up to three days. The treatments will be given by the PARI eFlow nebulizer and breathed into the lungs as a mist through a mouthpiece. On each treatment day, the following procedures and tests will be completed by the research nurses and doctors:

Before treatment:

- 1) review of medicines and changes in health
- 2) vital signs
- 3) brief physical exam of your heart, lungs and stomach
- 4) oximetry
- 5) spirometry (if you usually use an inhaled medicine (bronchodilator) to open up your airways, a dose will be given before the spirometry)

If you are an adult, on the first day of treatment only, an intravenous line (IV) will be placed in a vein in your arm to collect the blood to be used for determining levels of aztreonam. The IV will be left in your arm so that blood may be taken at different times during the visit. Blood (about 1 teaspoon) will be collected before the treatment.

Treatment:

The research nurse will demonstrate or review the use of the PARI eFlow nebulizer and study drug administration. You will administer the dose of AI or placebo and be observed by a research nurse or CF doctor for any problems. During the treatment and for 30 minutes after completion of the treatment, oximetry will be checked continuously.

After treatment:

- 1) 10 minutes post treatment completion:
 - a. gargle and rinse your mouth 3 times with salt water
 - b. sputum collection to measure the amount of aztreonam
- 2) 30 minutes post treatment completion:
spirometry
- 3) 1 hour post treatment completion:
 - a. brief physical exam
 - b. vital signs
- 4) 2 hours post treatment completion:
 - a. spirometry
 - b. sputum collection for aztreonam levels
- 5) 4 hours post treatment completion:
sputum collection for aztreonam levels

On the first day of treatment, if you are an adult, you will have blood (1 teaspoon) collected from the IV line in your arm 8 more times: within 5 minutes, at 30 minutes, 1 hour, 2 hours, 4 hours, 5 hours, 6 hours and 8 hours after completion of the treatment for aztreonam levels.

If you have not had any problems with the AI or placebo treatment on the first or second day of treatment (Visit 2 or Visit 3), you will be scheduled to come back to the CRC the following morning for the next dose. If you have not tolerated the treatment, as determined by the CF doctor, you will not receive any additional treatments.

Each treatment visit will be about 6 - 7 hours. If you are an adult, the first treatment day will be about 10 hours.

You will have two follow-up visits scheduled. A 24 hour follow-up visit will be scheduled for the day following your final treatment. The second visit will be scheduled for 3 days following your final treatment.

24 hour follow-up (Visit 5)

- 1) review of medicines and changes in health
- 2) vital signs
- 3) physical examination by CF doctor
- 4) oximetry
- 5) spirometry (if you usually use an inhaled medicine (bronchodilator) to open up your airways, a dose will be given before the spirometry)
- 6) urine collection to check kidney function
- 7) blood collection (2 - 3 teaspoons) to check your blood count, liver and kidney function and immune response

This visit will be about 2 - 3 hours.

3 day follow-up (Visit 6)

- 1) review of medicines and changes in health
- 2) vital signs
- 3) physical exam by a CF doctor
- 4) oximetry
- 5) spirometry (if you usually use an inhaled medicine (bronchodilator) to open up your airways, a dose will be given before the spirometry)

If your blood or urine test results were not normal at the 24 hour follow-up visit, additional blood or urine may be collected at this visit. This visit will be about 2 hours.

What are the risks of taking part in this research study?

As with any inhaled medication, the administration of AI or placebo may cause irritation of the airways. You may experience increased cough, shortness of breath, wheezing, chest tightness, decreases in spirometry, decreases in oximetry, or throat irritation. Rarely, a severe and possibly life-threatening allergic reaction or death can occur.

If you usually use a medicine to open your airways (bronchodilator), you will be given a dose before the dose of AI or placebo. You will be asked not to use your bronchodilator at home before your visits as instructed by the research doctor or nurse. If you are assigned to receive AI, you will receive the lowest dose being studied on the first treatment day. On treatment days 2 and 3 (Visits 3 and 4), the dose will be increased. You will be carefully observed for side effects from the AI or placebo and treated if necessary by the CF doctor. If you are not able to tolerate a dose of the AI or placebo, no additional doses will be given.

The blood tests and IV placement may cause discomfort or may occasionally cause some bruising. EMLA (anesthetic) cream can be applied to numb the skin before the blood tests and IV placement if you would like. There is a slight risk of bruising or infection. Spirometry and coughing up sputum may cause a brief mild shortness of breath or an increase in cough.

It is not known if treatment with the study drug will harm an unborn baby. If you are female, you should not become pregnant while taking part in this study. Females who are of childbearing potential will have a pregnancy test before treatment begins and must practice an acceptable form of birth control throughout the study. Acceptable methods of birth control are birth control pills or patch, Depo-provera, diaphragm, intrauterine device (IUD) cervical cap and condom with sponge or foam. Females with a positive pregnancy test will not be able to take part in the study.

You may ask the research doctors any questions you have about the possible side effects and risks from taking part in this research at any time.

What other options are there?

Your alternative to taking part in this study is to continue with your current treatment for CF. You will not be asked to change your CF treatment to take part in the study. If any new therapy becomes available for CF you will be notified.

What about confidentiality?

We will make every effort to keep your personal information confidential. Personal information would be disclosed only if required by law.

Study information which does not identify you by name or medical record number will be given to the sponsors of the research and agencies which supervise the research. These may include [REDACTED]

[REDACTED]

Staff from these agencies have the right to review your medical records only as needed for safety purposes to review the results of this study. Some of these records contain identifying information. These staff are required to keep this information confidential. If results of this research are presented or published, information that identifies you will not be used. Results of your laboratory tests, spirometry, and chest X-ray may be given to your CF doctor to help to prescribe treatment for you in the future.

What are the costs of the research study?

Neither you nor your insurance company will be charged for taking part in this study. The sponsor of this research, [REDACTED] will pay for the costs of the study. This includes the costs of study drugs, procedures, and visits.

If you have a physical injury as a direct result of taking part in this study, you will be treated or referred for treatment at no cost to you. The costs of this treatment will be paid for by the sponsor of the study [REDACTED]. No other form of compensation is available.

What are my rights as a research participant?

Taking part in this research is voluntary. You may decide not to take part. If you do take part, you may withdraw from the study at any time. Your decision will not affect your care by the CF doctors and nurses. There are no penalties or loss of benefits if you choose not to take part or to withdraw early.

It is possible the study sponsor [REDACTED], the FDA, or the Institutional Review Board (IRB) may end the study early. The research doctor could also stop your participation in the study. If this happens, the reasons for doing so will be explained to you. Some examples of why you may be taken out of the study would be for your safety or if you are not able to come to the required study visits.

A Data Monitoring Committee (DMC), an independent group of experts, will review the data from this research study after the adult group has completed treatment and follow-up. The DMC is responsible for reviewing data for the safety of research participants. You will be given any new information that we learn that may affect your health, welfare, or your willingness to continue in the study.

Whom do I call if I have questions or problems?

If you have any questions about the study please call the CF research nurses at XXX-XXX-XXXX

In the event of an emergency or for possible research related injuries call XXX-XXX-XXXX at and ask to page the on-call Pulmonary doctor

For questions about your rights as a research study participant, contact the (Institution's name) IRB. The IRB is responsible for protecting the rights of people taking part in research. They may be reached at XXX-XXX-XXXX.

Signature of Researcher

Date**Participant's Statement****I will be given a copy of this Consent Form after I have signed it.**

The research study described above has been explained to me. I voluntarily agree to take part in this research study. I have had the chance to ask questions. I understand that the persons listed above will answer any future questions I have about the study or about research participants' rights.

Name of Participant

Signature of Participant

Date

Signature of Parent or Legal Representative

Date

Copies to: Participant
Researcher's file

My protected health information is being collected and maintained indefinitely as part of a database or data repository, unless I revoke (take back) my Authorization before the research study ends.

Authorization To Use and Disclose Protected Health Information

I will be given a copy of this Authorization after I have signed it.

Name of Participant

Signature of Participant

Date

Signature of Parent or Legal Representative

Date

