

INFORMED CONSENT TO PARTICIPATE IN A RESEARCH STUDY**Approved by Institutional Review Board:****Study #:** CP-AI-003**Title:** A Blinded, Multicenter, Randomized, Placebo-Controlled Trial with Aztreonam for Inhalation (AI) in Cystic Fibrosis Patients with Lung Disease Due to *P. aeruginosa* Infection**Investigator (research doctor):****Sponsor:** [REDACTED]**24-hour emergency telephone number:** (###) ###-####**1. Introduction**

You are being asked to be part of a research study. The purpose of this consent form is to supply you with the information you will need to help you decide whether or not to be in the study. Please read the form carefully. You can ask questions about the purpose of the research, what we might ask you to do, the possible risks and benefits, your rights as a volunteer and anything else about the research or this form that is unclear. When all your questions have been answered, you can decide if you want to be in the study or not. This process is called 'informed consent'. Federal regulations require written informed consent from participants prior to participation in a research study.

This is a double-blind, randomized, placebo-controlled study. "Double-blind" means that the study sponsor [REDACTED] the clinic staff and the patients will not know who is receiving active drug (a substance containing medication) and who is receiving placebo (an inactive substance, containing no medication). Two different doses of the active drug will be tested in this study. "Randomized, placebo-controlled" means that each patient will be randomly assigned to receive one of two doses of active drug or one of two doses of placebo. This is done by chance, like flipping a coin. You have a 1 in 3 chance (33%) of being assigned to placebo, and a 2 in 3 chance (67%) of being assigned to one of the active drug groups.

The active drug being studied is Aztreonam for Inhalation (AI). The effect of AI in patients with cystic fibrosis (CF) will be tested in this study. AI or placebo will be delivered to the lungs with the PARI eFlow™ electronic nebulizer. The PARI eFlow nebulizer, a reusable electronic device, delivers drugs to the lungs as a mist. The nebulizer mixes air with the study drug solution (AI or placebo), so that it becomes a mist you inhale as you breathe in a normal pattern. The technology is based on a vibrating membrane technique that assures precise delivery of drug, maximizing the amount of drug delivered to your lungs within a reasonable time and minimizing the amount of drug deposited in your mouth and throat.

AI and the PARI eFlow nebulizer are investigational products. The US Food and Drug Administration (FDA) allows these products to be used in people for clinical research purposes only.

2. Purpose of This Research Study

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

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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 an effective way to treat lung infections in CF. Aztreonam is one antibiotic which is given IV to treat lung infections in patients with CF. [REDACTED] is developing a new form of aztreonam which can be inhaled using a nebulizer. The new form of the antibiotic is called Aztreonam for Inhalation (AI).

This research study is being done to evaluate how well two different doses of AI treat lung infections in patients with CF.

3. Length of Your Participation

Your participation in the study may last up to 37 days. You will have 5 study visits.

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 if 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 off the study drug 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 [tests of your lung function], blood sampling) performed before you leave.

4. Where the Study is Being Done and Number of People Participating

This study is taking place in approximately 20 clinics throughout the US and about 140 people are expected to take part.

5. Study Procedures

If you usually use a medicine to open your airways (bronchodilator), you will take a dose before you receive a dose of study drug. You will also be given instruction on the timing for use of bronchodilators at home.

If you agree to take part in this study, the following will happen:

Visit 1, Screening: You will undergo an initial screening examination.

Visit 1 Procedures:

- 1) Questions concerning your medical history
- 2) A physical examination
- 3) Height and weight measurements
- 4) Vital signs including temperature, heart rate, breathing rate and blood pressure
- 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) Blood collection (2 - 3 teaspoons) to check your blood count, liver and kidney function, and immune response

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- 7) A 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
- 8) Oximetry – a small clip will be placed on your finger to measure the amount of oxygen in your blood
- 9) Sputum collection—at least 1 gram (two tenths of a teaspoon) will be collected to test for current lung infections
- 10) Pregnancy test (blood) for females of childbearing years

This screening exam will take approximately 2-3 hours to complete. You will be asked to return to the clinic within 7 days.

Visit 2: At visit 2 you will be randomized (put into a treatment group by chance) to receive one of two possible doses of AI or placebo. Neither you nor the clinic staff conducting the study will be told which study drug you will receive. You will inhale your first dose of study drug during this visit.

Visit 2 Procedures:

- 1) Review medications and health
- 2) Sputum collection – at least 1 gram will be collected to test for current lung infections
- 3) You will be shown how to use and clean the eFlow nebulizer by the research coordinator
 - a) You will be shown how to add one ampule of diluent (a salt solution) to one vial of dry study drug before adding it to the nebulizer
- 4) You will watch an instructional video on the eFlow nebulizer

Procedures done before and after your treatment:

- 5) Brief physical exam of your heart, lungs and stomach
- 6) 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 pre-treatment spirometry)
- 7) Aztreonam levels – at least one gram of sputum and 1 teaspoon of blood will be collected
- 8) Vital signs including temperature, heart rate, breathing rate and blood pressure
- 9) Oximetry – a small clip will be placed on your finger to measure the amount of oxygen in your blood

This appointment should last about 4 hours. The next appointment will be in 7 days. If your CF symptoms become worse, you can call the research coordinator or the doctor at (###) ###-####. Worsening symptoms will be treated with standard therapy (bronchodilators and antibiotics) if needed.

You will give yourself your assigned study drug twice a day. You will mix up your study drug solution and administer it with the PARI eFlow nebulizer. You will receive one PARI eFlow nebulizer with instructions for use and cleaning. You must return the PARI eFlow nebulizer to the clinical site at the end of the study.

Visit 3: Since the last visit, you will have used the nebulizer with the study drug solution 2 times a day. You will bring your study drug and PARI eFlow nebulizer to the clinic for this

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visit. You will return all of your study drug vials (used and unused) to the research coordinator. On this day a dose of study drug will be taken at the clinic to make sure your device is working properly.

Visit 3 Procedures:

- 1) Review medications and health
- 2) Sputum collection – at least 1 gram will be collected to test for current lung infections

Procedures done before and after your treatment:

- 3) 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 pre-treatment spirometry)
- 4) Brief physical exam of your heart, lungs and stomach
- 5) Vital signs including temperature, heart rate, breathing rate and blood pressure
- 6) Oximetry – a small clip will be placed on your finger to measure the amount of oxygen in your blood

Procedures done after your treatment only:

- 7) Aztreonam levels – at least one gram of sputum and 1 teaspoon of blood will be collected

This appointment should last about 4 hours. The next appointment will occur in 7 days.

Visit 4: At the end of your treatment period you will return to the clinic for Visit 4. You will return all of your study drug vials (used and unused) and your PARI eFlow to the research coordinator.

Visit 4 Procedures:

- 1) Review medications and health
- 2) A physical examination
- 3) Vital signs including temperature, heart rate, breathing rate and blood pressure
- 4) 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)
- 5) Blood collection (2 - 3 teaspoons) to check your blood count, liver and kidney function, and immune response
- 6) Aztreonam levels – at least one gram of sputum and 1 teaspoon of blood will be collected
- 7) Sputum collection – at least 1 gram will be collected to test for current lung infections
- 8) Oximetry– a small clip will be placed on your finger to measure the amount of oxygen in your blood

This appointment will last 1-2 hours. Your next appointment will occur in 14 days.

Visit 5, Follow-up: Fourteen days after you have ended treatment with the study drug, you will return to the clinic to assess your overall health.

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Visit 5 Procedures

- 1) Review medications and health
- 2) A physical examination
- 3) Vital signs including temperature, heart rate, breathing rate and blood pressure
- 4) 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)
- 5) Blood collection (2 - 3 teaspoons) to check your blood count, liver and kidney function, and immune response if the research doctor feels it is necessary based on your previous blood test
- 6) Sputum collection – at least 1 gram will be collected to test for current lung infections
- 7) Oximetry – a small clip will be placed on your finger to measure the amount of oxygen in your blood

This appointment will last 1-2 hours.

6. What Will Happen When You Complete the Study

When your participation in the study ends, you will no longer have access to the study drug or the PARI eFlow nebulizer.

7. Procedures that are Not Standard Care for Your Condition or are Experimental

Use of a placebo (inactive solution), blinding (one or more groups are unaware of the treatment each patient is assigned), and randomization (study drug selection by chance) are only done for research studies. Sputum and blood sampling for aztreonam levels are only being done for the purposes of the study and may not be part of your routine care.

8. Possible Risks, Stresses or Discomfort from Taking Part in this Study

As with any inhaled drug, 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 lung function, decreases in blood oxygen levels or throat irritation.

Allergic reactions can occur with any drug. Common symptoms may include: rash, itching or skin problems.

Rarely, a severe and possibly life-threatening allergic reaction or death can occur. Symptoms of a severe reaction include swelling of the face, difficulty breathing, and a sudden drop in blood pressure that may cause dizziness. If you have any of these symptoms, call your doctor immediately.

AI is still being tested for the treatment of CF; therefore, you may experience other side effects that have not yet been reported. However, you or your legally authorized representative will be kept informed of any significant new findings that may relate to your willingness to continue to take part in this study.

Drawing blood may cause some discomfort, bleeding or bruising where the needle enters the skin. Rarely, blood draws may cause fainting or infection. Precautions will be taken to avoid these difficulties. Blood samples will be taken during the study. Up to 65 cc (approximately 5 tablespoons) of blood will be drawn during the study.

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You may have some coughing or experience some shortness of breath after spirometry, but there is no pain associated directly with these tests.

A chest x-ray (or chest radiography) provides your doctor with an image of your heart, lungs, and surrounding organs. Getting an x-ray is really just having a picture taken, so the procedure is painless. An x-ray is usually performed in a hospital radiology department or in a doctor's office by a technician. Because the x-ray procedure involves the use of radiation, there is a very low risk of radiation exposure. Pregnant women and children are most susceptible to the risks of radiation exposure. The procedures are strictly regulated, though, to ensure that the minimum amount of radiation necessary to provide an image is used.

9. Important Information for Women

The effect of the study drug on a baby's development is not known. Therefore, you and your sexual partner(s) must use adequate birth control measures while participating in this study. Acceptable methods include birth control pills, Depo-Provera, diaphragm, intrauterine device (IUD), cervical cap, abstinence, or condom with sponge/foam. All women who can become pregnant must have a negative pregnancy test prior to starting treatment with study drug. Pregnancy test results will be made available to you prior to starting the study. If you become pregnant during this study, you must stop taking the study drug and call your doctor immediately.

10. Costs

There is no cost to you for study drug and supplies, study-related clinic visits, study-related procedures or laboratory tests that are part of this study. Treatment will be available if a medical problem results from your participation in this study. This treatment will include any necessary emergency treatment and proper follow-up care. Payment for this treatment will be billed to your insurance. [REDACTED] will pay any charges that your insurance does not cover. Injuries caused by the negligence of any person, or the intentional misconduct of any person outside of [REDACTED] will not be covered by [REDACTED]. No other compensation for such injury is available.

11. Payment

You will be paid as follows: If you complete the study, you will be paid \$X for 5 study visits. If you do not complete the study for any reason, you will be paid \$X for each visit you complete.

12. Possible Benefits to You

No specific health benefits can be guaranteed as a result of participation in this study. However, the study may further the understanding of CF and prove beneficial in treating patients with CF in the future. Results of all physical exams, laboratory testing and breathing tests will be communicated to you.

13. Other Alternative Treatments Available

Your alternative to taking part in this study is to continue with your current treatment for CF. CF treatments may include use of other antibiotics, such as TOBI[®], to treat infection. You may be asked to change your CF treatment to take part in this study if you are currently taking an antibiotic drug for treatment of an infection. If any new therapy becomes available for CF, you will be notified.

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14. About Participating in this Study

Your participation in this study is voluntary. You may stop participating in this study at any time. Your decision not to take part in this study or to stop your participation will not affect your medical care or any benefits to which you are entitled. If you decide to stop taking part in this study, you should tell the research doctor immediately. You will be asked to return for a final study visit so the research doctor can perform safety tests (physical exam, heart rate and blood pressure measurements, spirometry, blood sampling) and to return all used and unused study drug supplies and the device.

Your doctor, the research doctor and/or the [REDACTED] may stop your participation in the study at any time if they decide that it is in your best interest. They may also do this if you do not follow instructions given to you by the research doctor and his/her study staff. If you have other medical problems or side effects, the doctor will decide if you may continue in the research study.

15. Participant Responsibilities

It is your responsibility to complete all of the study visits and procedures, take all of the study drug and follow the instructions given to you by the research doctor and staff. If you are unsure about what you are suppose to do, you must ask the research doctor or coordinator to explain it to you.

You must return all of the used and unused study drug vials to the clinic at Visit 3, day 7 of your treatment, and when your participation in the study ends. You must also return the eFlow nebulizer to the clinic when your participation in the study ends.

16. Reasons not to Participate in this Study

You may not want to participate in this study if you cannot perform any of responsibilities listed above, do not want to be given a random treatment assignment (active drug or placebo) or you have significant safety concerns. Discuss these issues with the research doctor or coordinator.

17. Compensation for Injury

By signing this consent form you will not waive any of your legal rights nor release the parties involved in this study from liability for negligence.

18. Confidentiality of Study Records and Medical Records

Information collected for this study is confidential. However, representatives of [REDACTED] the FDA will receive copies of the study records. Representatives of [REDACTED] the FDA, and the Institutional Review Board may see parts of your medical records related to this study. Data collected and recorded on study forms are the property of [REDACTED]. In the event of any publication regarding this study, your name will not be disclosed.

19. Names of Contacts for Questions About the Study

If you have any questions about taking part in this study or in case of an emergency, call [REDACTED] at [REDACTED]. If you have any questions about your rights as a research subject, you can call the Institutional Review Board at <phone>.

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VOLUNTEER'S STATEMENT

I have been given a chance to ask questions about this research study. These questions have been answered to my satisfaction. If I have any more questions about taking part in this study or about a research-related injury, I may contact _____ at _____.

I understand that my participation in this research project is voluntary. I know that I may quit the study at any time without affecting my future medical care or losing any benefits to which I might be otherwise entitled. I also understand that the research doctor or person(s) in charge of this study may decide at any time that I should no longer participate in this study.

If I have any questions about my rights as a research subject in this study I may contact:

IRB Chairperson Name

Address

Telephone (collect calls will be accepted)

By signing this consent form, I have not waived any of my legal rights or released the parties involved in this study from liability for negligence.

I have read and understand the above information. I agree to participate in this study. I have been given a copy of this form for my own records.

Signature of participant

Date

Name of participant

Signature of legally authorized representative

Date

Title of person who explained the study

Signature of person who explained the study

Date

