Title: Aztreonam Aerosol to Treat Cystic Fibrosis Nasal Disease

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Aztreonam aerosol to treat cystic fibrosis nasal disease.

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Introduction

P. aeruginosa (PA) is a primary cause of lung infections in persons with cystic fibrosis (CF) (1). Over the past decade, studies have shown that aerosolized antibiotics can reduce lower respiratory bacterial load, decrease exacerbations of pulmonary disease, and in many patients improve pulmonary function. Cayston (aztreonam) oral aerosol using the PARI Altera Nebulizer System was approved by the FDA in February 2010 for CF patients 7 years of age or older with PA (2). In 2011, 35.8% of patients in the National CF Patient Registry used Cayston for treatment (3). Bacterial cultures suggest that the upper airways and lower airways of CF patients are cross-infected by PA and that the paranasal sinuses can act as a bacterial reservoir (4). There is improved post-transplantation patient survival for recipients that undergo sinus surgery and daily nasal washes to reduce bacterial load (2).

Routine CF care does not generally include upper airway assessment. There are no published studies evaluating the effect of aerosol antibiotics to treat nasal and sinus infections in CF in combination with oral inhaled aerosol therapy to treat the lower airway disease. However Mainz and colleagues published a case report that suggested that sinonasal administration of tobramycin using the Pari Sinus nebulizer (Pari Corp, Starnberg, Germany) delayed PA lower respiratory infection in a 12 year-old with CF who had chronic mucopurulent rhinosinusitis (5) and studies in chronic obstructive pulmonary disease suggest that treating upper airways can also improve coexistent lower airway disease (6).

This study is designed to explore the efficacy and safety of nasal aztreonam administered using the Pari Sinus Nebulizer combined with oral Cayston aerosol therapy compared to placebo on clinical and laboratory endpoints such as risk of antibiotic-resistant *Pseudomonas aeruginosa* (PA), time to pulmonary infection exacerbation, nasal quality of life, pulmonary function, nasal and lower airway cultures, and properties of mucus.

Objectives

This is a pilot study to evaluate the effectiveness of treatment with aztreonam by nasal inhalation (Pari Sinus Nebulizer) combined with oral aerosol therapy (PARI Altera Nebulizer System) on chronic PA infection in subjects with CF.

Primary Outcome:

1. Number of protocol-defined pulmonary exacerbations treated with IV anti-pseudomonal antibiotics on day 140

Secondary Outcomes:

1. Time to first protocol-defined pulmonary exacerbation treated with IV anti-pseudomonal antibiotics
2. Change in Sinus and Nasal QoL questionnaire (SNOT-20) on day 140 and day 168
3. Change in Cystic Fibrosis QoL score (CFQ-R) on day 140
4. Change in Pulmonary function (FVC and FEV1 percent predicted) on day 140
5. Change in paired sputum cultures and nasal swabs for bacteria and antibiotic resistance
6. Number of Safety and adverse events including nasal stuffiness, epistaxis, and headache
7. Number of protocol-defined pulmonary exacerbations treated with oral anti-pseudomonal antibiotics

Study Design

This study is designed as a masked, two center, randomized, placebo-controlled pilot study to evaluate the safety and efficacy of nasal and oral inhalation of 75 mg aztreonam in subjects with CF and lung infection due to PA. The study will involve two sites: Virginia Commonwealth University Medical Center (VCU) and Eastern Virginia Medical School (EVMS). Informed consent will be obtained from the eligible participant's parent or legal guardian for subjects 7 to 17 years of age with assent from the child, and consent will be obtained from subjects 18 years of age or older. After informed consent is obtained screening and randomization will occur. Randomization of medication in a 1:1 manner will be carried out by VCU's unmasked study director who is not involved in the direct care of the patient, or by Gilead Sciences. Patients who continue an alternating inhaled antibiotic will be paired 1:1 as the study progresses.

This pilot study is designed to have two arms as shown in Figure 1 with 15 subjects in each arm. Nasal delivery will be achieved by using the PARI Sinus Pulsating Aerosol System (PAS) and oral aerosol administration will use the PARI Altera device. Oral aerosol treatment will be 3 times a day for a 28-day course followed by 28 days off aztreonam therapy. The combination therapy will be administrated based on study assignment. There will be three cycles of therapy over six months. Because of the smaller volume of the nasal and sinus airway and slower paranasal clearance rates, published data suggest that less frequent nasal aerosol dosing may be as effective as more frequent dosing.

Arms	Assigned Intervention
Standard therapy Comparator	Oral Inhalation: Cayston 75 mg three times a day (TID) Nasal Inhalation: Placebo treatment per nostril twice per day (BID)
Experimental	Oral Inhalation: Cayston 75 mg three times a day (TID) Nasal Inhalation: Aztreonam 75 mg per nostril twice per day (BID)

Number of Participants: 30 (15 per arm) – If a patient is on an alternating inhaled antibiotic, they will be randomized in a 1:1 fashion by the unblinded PI

Target Population: Subjects 7 years or older with CF lung disease and at least 2 sputum cultures positive for PA in the previous 24 months.

Main Eligibility Criteria:

Inclusion Criteria

1. Males or females 7 years of age or older and able to perform pulmonary function testing
2. Confirmed diagnosis of CF by the 1997 CF Consensus Conference criteria and followed by the VCU or EVMS CF clinic
3. Presence of PA in 2 lower respiratory tract (sputum) or respiratory swab cultures in the 24 months before baseline (second positive culture can occur at screening)
4. Subjects and/or parent/guardian must be able to give written informed consent prior to any study related procedure
5. All sexually active female subjects who are of childbearing potential must agree to use an effective method of contraception
6. Clinically stable with no significant new respiratory symptoms

Exclusion Criteria

1. Use of oral or IV antibiotics within 30 days of baseline (V2) other than low dose azithromycin
2. Severe pulmonary disease with FEV1<30% predicted or baseline SpO2<0.90
3. ENT surgery within 6 months of screening
4. Allergy or documented adverse reaction to aztreonam
5. Epistaxis or significant (>30 mL) hemoptysis in the past 6 months
6. Frequent or severe headaches
7. Subject is unlikely to comply with the procedures scheduled in the protocol
8. Subject participates in an interventional clinical trial in the 30 days prior to baseline
9. Subjects who have had a lung transplant

Study Procedures & Frequency

The study requires 8 study visits over a period of 6 months. The study procedures to be performed on/by each subject enrolled in the study are outlined in Appendix 1. Study Flow Chart

Test Product, Dose and Mode of Administration

Study medication

Medication will be provided by Gilead Sciences supplied in amber glass vials labeled with inhalation instructions, storage (keep refrigerated), date dispensed, date of expiration, study ID, and a unique barcode for drug tracking. The vials for oral inhalation will be clearly labeled oral and contain 75 mg Cayston. The nasal inhalation vials will be masked and contain either 75 mg aztreonam or placebo solution.

Oral Administration

Gilead Sciences will supply the PARI Altera device for oral administration to all subjects. Subject instructions will be based on the FDA-approved labeling and reconstitution instructions. Oral inhalation will be the recommended dose of a one single-use vial (75 mg of aztreonam) reconstituted with 1 mL of sterile diluent administered 3 times a day for a 28-day course followed by 28 days off Cayston therapy.

Nasal Administration

Gilead Sciences will supply the Pari Sinus Nebulizer and training video to be watched by all subjects under supervision by the study coordinator. Reconstitution instructions will follow the oral reconstitution instructions previously mentioned. Aztreonam or placebo will be aerosolized into one nostril, while the contralateral nostril is occluded and the soft palate elevated. Study medication will be administered into both nostrils for 4 min each side. Clinical trial material will be supplied by the sponsor in sealed, 1 mL vials containing 75 mg of azetreonam or placebo and 2 of these vials will be used for each treatment. With a pump residual volume of 1 mL in the PARI Sinus it is anticipated that half of the 2 mL loading volume will be delivered.

Drug Adherence

The investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition) and patient dispensing records and returned or destroyed study product. Dispensing records document quantities received from Gilead and quantities dispensed to patients, including kit number, lot numbers if applicable, date dispensed, patient identifier number, and the initials of the person dispensing the medication.

Subjects will be asked to complete a Study Medication Dosing Checklist weekly in their diaries to indicate the typical day and time of day each dose of aztreonam was administered during study participation. Subjects will be required to return empty vials to assess medication adherence. Data will be expressed as percent of vials prescribed.

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Appendix 1. Study Flow

Study Flow Chart – Aztreonam Aerosol for CF Nasal Disease								
	Screen		**Treatment Period 3 Cycles (6 Months)**					
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8
		Begin on-month #1		Begin on-month #2		Begin on-month #3		
Time of Visit	7-56 days before V2	Day 1	Day 28 (±3 Days)	Day 56 (±3 Days)	Day 84 (±3 Days)	Day 112 (±3 Days)	Day 140 (±3 Days)	Day 168 (±3 Days)
Eligibility Assessments								
Informed Consent	X							
Obtain Assent (if applicable)	X							
In/Exclusion Criteria	X							
Medical History	X	X						
Procedures								
Physical Exam		X					X	X
Vital Signs	X	X	X	X	X	X	X	X
Pregnancy Test	X	X						
Pulmonary Function Test	X	X	X		X		X	X
SNOT20- Survey		X	X		X		X	X
CFQ-R		X					X	X
Nasal cultures	X	X	X	X	X	X	X	X
Sputum cultures	X	X	X	X	X	X	X	X
Visual scoring of nasal patency		X			X			X
Sinus Swab (Sub-Study Only)	X	**X**						X
General								
Randomize Patient		X						
Handling/Training in product/device use		X						
Diary Instructions/Dispensing		X		X		X		
Diary Collection			X		X		X	
Dispense Study Medication		X		X		X		
Record Concomitant Medications	X	X	X	X	X	X	X	X
Record Adverse Events		X	X	X	X	X	X	X
End of Trial								X

Appendix 2: Detailed study procedure methods.

Power Calculation

No studies have evaluated the effect of upper airway (nasal) and sinus infections in combination with lower (oral) inhaled aerosol therapy to further improve Sino pulmonary symptoms in CF. Thus, the current study is designed as a pilot study that is likely to be underpowered to reach significance.

Protocol-Defined Pulmonary Exacerbation

Protocol-Defined Pulmonary Exacerbation includes events that are characterized by change or worsening pulmonary symptoms (increase cough, increased sputum production, chest congestion, decreased appetite, decreased exercise tolerance, loss of weight, and lung function decline) that prompt initiation of antibiotic therapy.

Demographic & Physical Data

Demographic and baseline measurements will be summarized for the FAS and PP analysis sets using standard descriptive methods (overall and by treatment group). Demographic summaries will include sex, race, ethnicity, and age. Physical Characteristic data will include body weight, height, and body mass index.

The Sino-Nasal Outcome Test questionnaire

The Sino-Nasal Outcome Test 20 (SNOT-20) is a validated health-related QOL questionnaires designed to determine the impact of sinonasal dysfunction [(7).] Patients will assess nasal symptoms, emotion, and activity on a scale of worsening symptoms scored 1 through 7 to provide a quantifiable score capable of disease severity. It has been shown as a responsive measure of health-related quality of life and suitable for use in outcomes studies and routine clinical care [(7)].

Pulmonary function testing

Routine including spirometry will be performed according to American Thoracic Society (ATS) guidelines [(8)]. A minimum of three maneuvers will be performed. The largest FVC and FEV1 will be reported after examining data from all acceptable curves even if they did not originate from the same maneuver. Data will be expressed both in absolute values and as percent (%) predicted based upon NHANES predicted values.

Visual scoring of nasal patency

Nasal patency scores will be based upon direct visualization score of % obstruction by the investigator. Mucosal condition and secretion status, the presence of crusts and polyps will be assessed.

Paired nasal and sputum cultures.

Expectorated sputum and nasal swabs will be cultured at each visit using standardized procedures to identify CF pathogens as well as susceptibility to a standard panel of antibiotics

Electronic Database Capture

Study data for each visit will be collected and managed using REDCap (Research Electronic Data Capture). REDCap is a secure web application designed to support data capture for research studies, providing user- friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (JMP, Stat view, SAS,). REDCap also includes a powerful tool for building and managing online surveys. The database is hosted by VCU under award number UL1RR031990 from the National Center for Research Resources and NIH Roadmap for Medical Research, National Institutes of Health.

OnCore

OnCore a clinical trial management systems (CTMS) will be used for recording and tracking regulatory approvals, staff training, safety management (SAE tracking and IRB reporting) for all sites. The CTMS system was developed by Forte Research and widely used across academic research universities nationwide. The program is a secure web-based system accessible by all affiliate sites. The system is hosted by VCU and MCV health systems.

Data Analysis

Statistical analysis of data will be performed using the JMP Pro 10 statistics package (SAS Institute, Cary, NC). Counts will be compared with Fisher exact tests. Continuous variables will be compared with parametric (t-test) or non-parametric (Wilcoxon Rank-Sum) tests depending upon the normality of data distribution. Time to pulmonary exacerbation will be evaluated using Kaplan-Meier plots and compared using the Mantel-Cox (log-rank) test. A $p< 0.05$ will be considered statistically significant. All results will be presented as means + the standard error of the mean. Because this is a pilot study, there will be no *post hoc* adjustments made for multiplicity

Concomitant Medications

At screening (visit 1), all medications, indications for use, dose (amount, frequency and route of administration) will be recorded. Concomitant medications are classified as any medication, including over the counter, used by subjects during the duration of the study. During each subsequent clinical visit, subjects will be questioned about any changes in their concomitant medications and current therapy.

Adverse Reporting

The frequency, severity and duration of all nasal and pulmonary adverse events, regardless of cause, will be recorded in Redcap as an electronic case report form. Serious adverse events will be captured in OnCore. The frequency and severity of adverse events will be calculated for each patient, with each patient counted once using the most severe grade experienced. The duration of adverse events will be calculated by the number of days each event persisted. Tables will be generated for all adverse events including serious adverse events and withdraws from the study.

Institutional Review Board

This protocol and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigators to an IRB and approval from the IRB must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB approval must also be submitted to the IRB for approval before implementation.