A-PACT: The use of Inhaled **A**ztreonam to eliminate or decrease the bacterial burden of ***P****seudomonas* ***A****eruginosa* in **C**hildren with a **T**racheostomy tube.

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A study to determine if the aerosolized Anti-pseudomonal agent, inhaled Aztreonam, can eliminate or at least decrease the bacterial burden of *Pseudomonas aeruginosa* in children with a tracheostomy tube.

Abstract:

Children with a tracheostomy tube represent a complex group of children that rely on an artificial medical device to help them meet their oxygenation and ventilation needs. The tube may be required to overcome upper airway obstruction and/or for long-term mechanical ventilation.[1,2] There is significant morbidity and mortality in children with a tracheostomy tube, the most common being pneumonia.[3] *Pseudomonas aeruginosa (PsA)* is a common culprit. This bacteria is difficult to treat, and when a patient has a respiratory infection and is colonized with *Pseudomonas*, it requires prolonged use of systemic antibiotics, often intravenous and potentially a hospital admission.[4–8] This leads to a higher cost to society in the number of school days missed by the child and in addition, the number of work days missed by the care provider.[3] Society is constantly attempting to reduce healthcare costs. One such attempt is the use of inhaled aztreonam to eliminate or at least decrease the bacterial load of *PsA* in children with a tracheostomy tube, thereby decreasing the future need for enteral or intravenous antibiotic use and/or hospitalization if the child has a respiratory illness. There are currently no published studies on the use of inhaled antibiotics in children with a tracheostomy tube. Therefore, this proposal has been designed to build upon the anecdotal literature, by studying the efficacy of inhaled aztreonam to decrease the need for systemic (intravenous or enteral) antibiotics for respiratory infections in patients with a tracheostomy tube over a 12-month period.

A. SPECIFIC AIMS

The primary objective of this proposal is to determine in a longitudinal multi-center trial with historical controls whether inhaled aztreonam will decrease the frequency of respiratory infections requiring treatment with systemic antibiotics (IV and enteral) in subjects with a tracheostomy tube over a 12 month period.

Secondary Aims:

1) To determine if inhaled aztreonam can eliminate the colonization or at least decrease the bacterial density of *Pseudomonas aeruginosa* in patients with a tracheostomy tube who are colonized with *Pseudomonas*.
2) To determine if there is a difference in eradication or decrease in bacterial load of *Pseudomonas* in those who have a Bivona vs. a Shiley tracheostomy tube.
3) To determine if there is a decreased number of hospital admissions
4) To determine if there is a shorter duration of hospital stays during the study period

B. BACKGROUND AND SIGNIFICANCE

Tracheostomies became widely used in the treatment of diphtheria in children in the 19th century. It was later used in the early 1950s during the poliomyelitis epidemic.[1] There are several reasons that a tracheotomy is performed: need for long-term mechanical ventilation, upper airway obstruction (from airways malacia, vocal cord paralysis, subglottic stenosis, external compression), brain injury or CNS disorder leading to inability to cough up own secretions, severe head and/or neck trauma that obstructs breathing, and emergent situations when an endotracheal tube (ETT) cannot be placed successfully to ventilate a patient.[9] There is significant morbidity and mortality in patients with a tracheostomy tube. In 2014, a retrospective cohort analysis of the Healthcare Cost and Utilization Project (HCUP) Kid's Inpatient Database (KID) 2009 was conducted. KID is a multistate database of 3.4 million hospital discharges from 4,121 hospitals in 44 states. The most common organ system affected in children with a tracheostomy tube-necessitating hospital admission was the respiratory system (50.8%, n = 10,946), and they also accounted for the largest percentage of hospital charges (45.7%, $652 million U.S.). Therefore, a better understanding of pneumonia prevention and management in children with a tracheostomy would be beneficial.[3]

Bacterial colonization of the tracheobronchial tree almost always follows placement of a tracheostomy tube.[10] Due to ineffective mucociliary transport and cough mechanisms that occur in patients with a tracheostomy, clearing of microorganisms from the upper airway becomes impaired, and thus, bacteria tend to colonize their airways.[4] Gram negative bacterial colonization is common. This is due in part to the fact that children who are chronically ill and/or hospitalized with recurrent lower airway infections may have increased amounts of polymorphonuclear cells (PMNs). The PMNs have an enzyme, salivary elastase, that degrades fibronectin, which plays a role in protecting the airway epithelia from being colonized by gram negative bacteria.[5] Most patients with a tracheostomy, if not all of them, become colonized with *Pseudomonas aeruginosa* (PsA), a gram negative rod, soon after placement of the tracheostomy.[6] A recently published study found that PsA was the most commonly isolated bacteria in tracheostomy tube aspirate cultures in the pediatric population.[11]

PsA is an opportunistic pathogen. Once infection is established, it is highly virulent, therefore it is difficult to eradicate.[7] PsA exists as a biofilm, which is an organized matrix of bacterial colonies. In a study

published in 2002, it was found that there was no difference in susceptibility to biofilm formation among four different tracheostomy tube materials tested: polyvinyl chloride (Mallinckrodt; St. Louis), silicone (Bivona Medical Technologies; Gary Ind.), stainless steel (Pilling Weck; Marckham, Ont.), sterling silver (Pilling Weck).[12] The role of mechanical ventilation in the development of tracheal colonization is still unclear. In the study published in1984, persistent enteric gram negative bacterial (EGNB) tracheal colonization developed in 4 subjects receiving mechanical ventilation, 2 others treated with mechanical ventilation did not become colonized. In addition, 3 subjects developed persistent EGNB tracheal colonization while not being treated with mechanical ventilation.[8] Few studies have been done to look at this.

When treating patients with tracheostomy tubes with antibiotics, most clinicians treat "empirically". The most frequent antibiotics prescribed are trimethoprim-sulfamethoxazole and amoxicillin-clavulanate; only a few use inhaled antibiotics. Of those that treat with inhaled antibiotics, they use inhaled tobramycin and inhaled gentamycin.[4] However, there is no literature to date that supports the use of inhaled antibiotics in children with tracheostomy tubes.

Nebulized antibiotics have the benefit that they can be delivered directly into the airways, therefore, they target the site of infection. As such, they are unlikely to cause adverse side effects due to minimal systemic absorption.[13] In addition, nebulized antibiotics provide sputum concentrations well above the minimum inhibitory concentrations (MICs) necessary (about 10 times the MIC) to allow penetration of antibiotics into biofilms, and therefore achieve a bactericidal effect. When using intravenous antibiotics, there are higher risks of systemic toxicity as higher drug doses are needed to reach the appropriate MIC.[4,14]

Antibiotics have been trialed as an inhaled formulation since the 1940s. However, prior to the late 1990s, these antibiotics were the aerosolized antibiotics designed for parenteral administration. These formulations caused significant bronchial irritation due to added preservatives and non-physiologic chemical composition.[11] In the late 1990s, inhaled antibiotics were just being studied for the use in cystic fibrosis (CF) patients with chronic endobronchial colonization with *PsA*. In 1998, tobramycin inhaled solution (TIS) was the first antibiotic to be developed and approved for use as an aerosolized antibiotic in patients with CF.[15] Multiple clinical trials have been conducted in those with CF assessing the efficacy of inhaled antibiotics. They commonly compared inhalation of an aminoglycoside such as gentamycin or tobramycin or other anti-pseudomonas antibiotics with normal, hypertonic, or hypotonic saline as placebo.[7]

A study published in 1999 in the New England Journal of Medicine suggested the clinical efficacy of inhaled tobramycin given intermittently (28 days on, and 28 days off). It revealed when compared to placebo that inhaled tobramycin was safe, improved lung function, decreased sputum *PsA* density, and lowered the risk of hospitalization and intravenous anti-pseudomonal antibiotic use. The administration of tobramycin in these trials (28 days on drug, 28 days off drug) was used to reduce the emergence of tobramycin resistance.[16] Another study by the same group found no evidence of increased selection for intrinsically tobramycin-resistant bacterial pathogens.[17]

A randomized controlled trial of nebulized gentamicin in non-cystic fibrosis patients with bronchiectasis chronically infected with a variety of pathogens was conducted over a 1-year period and was published in 2011. 65 subjects were randomized to receive twice-daily nebulized gentamicin (80mg) or twice daily nebulized 0.9% saline, 5ml. They found that regular, long-term nebulized gentamicin significantly reduces the bacterial density and airways inflammation, with less sputum purulence. In the total cohort who

received nebulized gentamicin, 21.9% vs. 6% in the saline group reported bronchospasm. No nephrotoxicity or ototoxicity was detected.[13]

Inhalation aztreonam (AZLI) is an aerosolized formulation of the monobactam antibiotic aztreonam with lysine as a synthetic substance in place of arginine. This substitution was made as arginine, which is in the intravenous (IV) formulation of aztreonam, can cause airway inflammation as seen in patients with cystic fibrosis when aerosolized.[18,19] There have been several published studies on the efficacy and adverse effects of aerosolized aztreonam in CF patients. Two placebo-controlled studies of AZLI revealed a benefit in patients with CF and colonization with *PsA*. AIR-CF1 revealed that a 28-day course of AZLI given three times daily (TID) resulted in improved respiratory symptoms. They measured this improvement by using a cystic fibrosis questionnaire (CFQ-R), measuring forced expiratory volume in 1 second (FEV 1), and measuring bacterial density in sputum. AIR-CF2 demonstrated that a 28-day course of AZLI followed by a 28-day course of Tobramycin Inhaled Solution (TIS) delayed the time to the need for additional inhaled or systemic anti-pseudomonal antibiotics. They also used the CFQ-R and measured FEV1 and found improvement in both when compared to placebo. In AIR-CF3, an open-label 18-month study was conducted to evaluate the efficacy of AZLI using a month on/month off cycle, and to observe long-term effects of the drug. This protocol found that AZLI did have a long-term suppressive effect on *PsA* as there was a persistent reduction in *Pseudomonas* CFUs from baseline each month of the study. As expected, the decreases in bacterial density were consistently occurring during on months; and during off months, the density increased toward baseline. Thrice-daily dosing appeared more efficacious than twice-daily dosing. This was attributed to the mode of action of aztreonam, as bacterial killing is dependent on time above the MIC (minimal inhibitory concentration). Adverse events include: cough, respiratory tract congestion, pharyngolaryngeal pain, nasal congestion, dyspnea, hemoptysis, rhinorrhea, wheezing, chest discomfort, crackles lung, pulmonary function testing decreased, non-cardiac chest pain, sinus congestion, sinus headache, dyspnea exacerbated, exertional dyspnea.[19]

Antibiotics currently on the market as inhaled antibiotics include tobramycin (TOBI), polymyxin E (Colistin), and aztreonam (Cayston). Studies of all of these have shown clinical benefits in those with Cystic Fibrosis. Given these findings, there is a growing interest in the use of inhaled antibiotics in other disease processes in which subjects become colonized with bacteria in the lower respiratory tract.

We propose a multi-center longitudinal study with historical controls on the use of inhaled aztreonam (AZLI) in pediatric patients ages 7-21 years with a tracheostomy who, in the last year, have had one of their previous 3 tracheostomy aspirate cultures positive for *PsA.* Their past history if the previous year of requirement for systemic antibiotics will be used for each subject as the historical control. A tracheostomy aspirate culture will be collected upon initiation of the study. We will subsequently start them on AZLI on a one month on/one month off schedule. Tracheal aspirate cultures will continue to be collected quarterly (every 3 months), and the bacterial density will be used for analysis. Goal is to see if there is a decrease need for systemic antibiotics for *PsA* infection.

In addition, we will also be simultaneously performing a retrospective chart review of all patients at UCSF Benioff Children's Hospital Oakland age 0-21 years with a tracheostomy tube to find out the incidence of Pseudomonas acquisition, and their subsequent need for systemic antibiotics and hospitalization. This will give us prevalence data for our population that will help with statistical analysis of the above proposed study.

C. PRELIMINARY STUDIES/PROGRESS REPORTS

None

D. RESEARCH DESIGN AND METHODS

- **Formulations**
  - Lyophilized aztreonam = AZLI (75mg/vial)
  - Diluent (0.17% sodium chloride): 1 mL/ampule
- **Dose, Administration, Duration, and Storage**
  - Administer one dose (one single use vial and one ampule of diluent) 3 times a day for 28 days
  - Use dose immediately after reconstitution
  - Administer only with the Altera® Nebulizer System and a compressor. Do not administer with any other type of nebulizer
  - AZLI will be stored in room temperature
- **Dosage Modification**
  - The dose will not be modified in this study
- **Concomitant Therapy**
  - There is no concomitant therapy that will be given with our study, but the subjects can continue any other therapy they are receiving as determined by their treating physician. If there are any concomitant medications administered to the subjects, it will be recorded on concomitant medication log form by study staff on the Data Collection sheet (see Appendix 3).
- **Schedule of Assessments**
  - Patients are to be assessed every 3 months. A questionnaire will be filled out by the parent or legal guardian regarding concomitant medications and side effects. Please see detailed Study Protocol section on the next page for details.
- **Data Safety Monitoring Committee (DSMC)**
  - A DSMC will be formed to monitor subjects' safety during this study. This committee will be a central committee based here at UBCHO. They will review data from the 2 sites involved in the study.
  - In order to avoid spending alpha, no interim analysis for efficacy will be performed. However, the DSMC will review the unblended data after the first 6 months of data subjects have completed the study for an analysis of safety. They will determine if there is an absolute difference between study groups for the following criteria: days in the ICU, oxygen requirement, and serious adverse events. They will also be responsible for reviewing any adverse event in an unblended fashion as it occurs. If a difference is found, a sequential analysis will be performed to determine if there is a significant difference ($p<0.01$ for the first 3 criteria; $p<0.05$ for SAE). If the DSMC determines on sequential analysis that a significant difference exists, the DSMC will be required to notify the PI, who in turn will be required to stop the study and notify the IRBs, FDA, and Gilead.
- **Treatment Discontinuation**
  - Study medication will be discontinued in subjects that develop respiratory failure (defined as: 1) $pCO2 >60$ mmHg; 2) oxygen requirement > 5 L/min; and 3) Invasive or non-invasive ventilation) and/or worsening of their clinical status (such as refractory coughing) during the trial. These subjects will then be categorized as treatment failures.
- **Follow Up Period**
  - Each subject will go back to their respective institutions and their physicians are to decide if they wish to keep the subject on the inhaled aztreonam. At 3 and 6 months, we will obtain

data on number of exacerbations requiring systemic antibiotics as well as tracheostomy aspirate cultures if one was obtained (culture result, CFUs, MIC, and sensitivities).

- **Compliance with Laws and Regulations**
    - This study will be conducted in accordance with current Good Clinical Practices (GCPs). The Declaration of Helsinki, and local ethical and legal requirements.
- **Institutional Review Board Approval**
    - Institutional Review Board (IRB) approval will be obtained prior to the start of this study at all 3 institutions (UCSF Benioff Children's Hospital Oakland and Children's Hospital Central California).
    - A copy of each institution's IRB approval of this study will be sent to Gilead. The Principal Investigator at each institution is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate. The Principal Investigator at each institution must also keep the IRB informed of any significant adverse events.
- **Study Protocol:**
    - Recruitment:
        - Each institution's designated PI will query their respective institutions' pulmonary and ENT group patient panels who have a tracheostomy tube. (For UBCHO, we will only use the pulmonary group's patients as all tracheostomy patients at this institution are followed by pulmonary as of 11/30/15 and Rachna Wadia will be calling them. She will be performing a retrospective review that has been approved by the UBCHO IRB # 2016-015. Using this review, she will be able to identify UBCHO patients that meet criteria to be recruited in the A-PACT study).
        - If they have had a culture positive for *Pseudomonas aeruginosa*, then each respective institution's designated research coordinator will call the patient's family to recruit them. We will also put out a flyer to recruit patients in each institution that is involved in this study (UCSF Benioff Children's Hospital Oakland, Lucile Packard Children's Hospital at Stanford, and Children's Hospital Central California).
        - We will recruit all subjects ages 7-21 years old with a tracheostomy tube and a history of *Pseudomonas* in one of their tracheostomy tube cultures in the past year. Patient will then be scheduled for an appointment in their respective institution's CTSI or pulmonary/ENT clinic for enrollment.

    - Enrollment:
        - Eligibility Checklist (see Appendix 3 – Eligibility Checklist)
            - Consent/Assent
            - Inclusion/Exclusion Criteria
        - Demographic Data (see Appendix 4- Demographic Sheet)
            - Past Medical History
            - Family History
            - Social History
        - Data Collection (see Appendix 5 – Data Collection)
            - Physical exam
            - Tracheostomy tube information (type, size, cuffed, etc.)
        - Document most recent culture. If + for PsA in the past month, then can start participant on study drug (see Visit 1).

- If has not had a culture in the past month, then obtain a tracheostomy aspirate culture using standardized sterile technique amongst all institutions involved in the study (See Appendix 10 – Obtaining a tracheostomy aspirate culture)
- Once culture results obtained and positive for *Pseudomonas aeruginosa*, the participant will be called to schedule their Visit 1 Study visit

▪ Patient's chart will be reviewed in the previous year. Data collected will include tracheostomy aspirate culture results, number of respiratory illnesses requiring systemic antibiotics and/or hospitalization, duration of antibiotic treatment, and duration of hospitalizations. We will also collect the date they first acquired *Pseudomonas aeruginosa* as seen on a tracheostomy tube aspirate culture.

o Visit 1:
  ▪ Data Collection (see Appendix – 5)
    - Physical exam
    - Tracheostomy tube information (type, size, cuffed, etc.)
    - Study Medication history (return of used vials, currently taking study med?)
    - Systemic Antibiotics and Hospitalization:
      - Has the participant
        - received systemic antibiotics in last 3 months?
        - Had a respiratory infection in last 3 months?
        - Been hospitalized in the last 3 months?
  ▪ Obtain tracheostomy aspirate culture using standardized sterile technique amongst all institutions involved in the study (See Appendix 10 – Obtaining a tracheostomy aspirate culture)
    - Tracheostomy tube cultures will be routinely collected quarterly (every 3 months) starting with the first culture on day of enrollment (total of 5 cultures for each subject). The culture sample will be obtained with a new sterile suction catheter. The specimens will be cultured for aerobic bacteria. Bacterial load/density will be performed on each culture.
  ▪ The patient will then receive the first dose AZLI via e-flow nebulizer system. When giving the first dose of inhaled antibiotics, caution is warranted for bronchospasm. Therefore, it is recommended that the first dose be given while supervised. If they develop audible wheezing on exam, or they have a decrease in oxyhemoglobin desaturation of 3% or more, then they are considered to have bronchospasm. If the subject fails according to the above criteria, then they should receive albuterol (4 puffs via MDI and spacer or 1 nebulizer treatment 2.5mg will be administered). If they return to baseline within 15 minutes, then they will need to take albuterol prior to administration of inhaled antibiotic. If they do not return to baseline, or if they have any other adverse event that leads to an allergic reaction, then they will be taken out of the study.
  ▪ Parent/guardian will be taught how to administer the study drug using the e-flow nebulizer system.
  ▪ They will then be sent home with the study drug to be taken 3x daily on a 28 day on / 28 day off cycle starting the day after Study Visit 1 and wills start on the ON cycle.

- Study Visits #2-5:
  - Data Collection (see Appendix – 5)
    - Physical exam
    - Tracheostomy tube information (type, size, cuffed, etc.)
    - Study Medication history (return of used vials = adherence, currently taking study med?)
      - **Adherence:** Patients are to return the empty vials, and this can be compared to the number of vials prescribed on their quarterly visits for when they have to come in and have a tracheostomy aspirate culture.
        - Each site study coordinator will also call the subjects monthly to ask if they are taking their medication consistently and they are cycling on and off at the appropriate times.
    - Systemic Antibiotics and Hospitalization:
      - Has the participant
        - received systemic antibiotics in last 3 months?
        - Had a respiratory infection in last 3 months?
        - Been hospitalized in the last 3 months?
  - Document last tracheostomy tube aspirate culture on the culture results form (Appendix 6).
  - Adverse events Form filled out by participant's guardian or participant if they are 18 years of age and capable of filling out the form (See Appendix 7a)
    - Symptoms include: cough, respiratory tract congestion, pharyngolaryngeal pain, nasal congestion, dyspnea, hemoptysis, rhinorrhea, wheezing, chest discomfort, crackles lung, pulmonary function testing decreased, non-cardiac chest pain, sinus congestion, sinus headache, dyspnea exacerbated, and exertional dyspnea.
  - Adverse Events Reporting Form filled out by Study Staff if participant or guardian reports an adverse event (See Appendix 7b). If an adverse event is reported, the MEDWATCH form must be filled out and sent to the FDA (see Appendix 7c).
  - Obtain tracheostomy aspirate culture using standardized sterile technique amongst all institutions involved in the study (See Appendix 10 – Obtaining a tracheostomy aspirate culture)
  - They will then be sent home with the study drug to be taken 3x daily to continue on a 28 day on / 28 day off cycle.
  - On Visit 5: the Termination of Study Participation Form will be filled out (See Appendix 8). This form is to be filled out at the last study visit to verify the participant has completed the study and on what date. Or, it is to be used if the parent/guardian or participant if 18 years or older has withdrawn consent and why. The date of withdrawal will be documented on this sheet.
- Follow-up:
  - At 3 and 6 months, each institution's PI or research coordinator at (UCSF Benioff Children's Hospital Oakland, Lucile Packard Children's Hospital at Stanford, and Children's Hospital Central California) will call the participant's primary pulmonologist/ENT physician to obtain follow-up information regarding whether or not the participant continued on the study drug, how many respiratory exacerbations have they had requiring systemic antibiotics and/or hospitalizations,

and tracheostomy aspirate culture results if there are any that were done. (See Appendix 9).

- **If the subject is hospitalized during the study period, the subject may continue on the study drug as planned. However, this decision will be left to the subject's primary physician. This study will not interfere with the standard of care. If the study drug is discontinued during the hospitalization, then they can restart it where they left off once discharged (example: admitted while on day 11 of an "On" month. Day after discharge will be day 12 of the same "On" month. If this were to occur, the Study Drug Break form will be filled out (Appendix 11).

D1. Study Population

Subjects ages 7-21 years old with a tracheostomy tube who have grown *Pseudomonas aeruginosa* in a tracheostomy tube culture in the previous 3 cultures performed.

D2. Population Description

The population eligible will be children who have undergone a tracheotomy in the Bay Area, California at one of the following Children's hospitals: UCSF Benioff Children's Hospital Oakland and Valley Children's Hospital in Madera, California. This population includes, but is not limited to: Caucasians, Hispanics, Native Americans, Asians, and Africans. Caucasian subjects are defined as being of the white race and having parents and grandparents not born in Mexico, other Central/South American or Caribbean countries, Spain and /or Portugal. Non-Caucasian subjects are defined as self-reporting at least one non-Caucasian parent.

D3. Inclusion/Exclusion Criteria

- Inclusion Criteria
  - Age: 7 – 21 years old
  - Currently has a tracheostomy tube
  - One of previous 3 tracheostomy tube aspirate cultures positive for *Pseudomonas aeruginosa*
  - Non-smoker
  - Ability of parent to provide informed consent, as evidenced by signing a copy of the consent form approved by the Institutional Review Board of the subject's respective study institution.
  - Written assent for children 7-17 years of age.
  - Informed consent for children ages 18-21, as evidence by signing a copy of the consent form approved by the Institutional Review Board of the subject's respective study institution.
- Exclusion Criteria
  - History of immunodeficiency
  - History of cystic fibrosis. Primary ciliary dyskinesia, or bronchiectasis
  - History of tuberculosis
  - History of positive culture for *Burkholderia cepacia*
  - Use of inhaled antibiotics in the last 6 months

D4. Drop-Out Criteria/Treatment Failure

- Drop Out
  - When a subject or legal guardian withdraws consent, data collection will stop and the subject will be dropped from the experiment. However, all efforts will be made to have the

subject or legal guardian allow study staff to continue to follow the subjects as this will allow for a more intent-to-treat basis.

- Treatment Failure
    - When a subject experiences adverse effect of treatment, the study medication will be stopped. However, the subject will continue to be followed and data collected as described as all subjects will be analyzed on an intent-to-treat basis.

D5. Sample Size/Power

Due to the paucity of studies performed on children with a tracheostomy tube, it is difficult to perform a sample size calculation. Our study is a pilot study. Depending on the number of patients at the institutions participating in this study, we plan to recruit about 10-15 subjects.

D6. Statistical analysis

- Randomization
    - There will be no randomization. All subjects will receive the study drug.
- Masking
    - All subjects will be receiving the inhaled antibiotic (AZLI), so there will not be any blinding.
- Analysis
    - Standard techniques for the analysis of the data from longitudinal trials with historical controls will be applied. Initial bivariate comparisons using a t-test for continuous data and a chi-square test for categorical comparing the 2 groups. Then, using a longitudinal model for each outcome measure comparing the 2 groups over time while adjusting for demographic characteristics, such as age.
    - We will use the software program STATA to perform data analysis.
- Drop Out/Treatment Failure Status
    - Initial analysis of the data will be completed using an intention-to-treat-model. Therefore, the available data from all randomized subjects will be included in the statistical analyses, regardless of drop out/treatment failure status. Supplemental statistical analyses will be applied in which data collected after the assignment of treatment failure status are excluded.

D7. Data Entry/Management

Data entry and quality control checks will be performed. The data will be kept in an electronic database with access limited by password protection. Hard copy and electronic data will be stored in a locked area accessible only to authorized personnel. Electronic data will be backed-up daily on zip disk and stored in a locked cabinet in a separate room.

D8. Research Time Line

The proposed research should take 20 months to complete + 6 month follow-up period. The first month will be used to train study personnel in the study design. The next 3 months will be used for subject recruitment and data collection. Goal is to have subjects on the study drug or placebo for a total of 12 months. There will then be a 6 month follow-up period. The remaining months will be used for completion of the data analysis and manuscript preparation.

The start of the subject recruitment will be targeted for mid 2016 with a goal of enrollment of 10-15 subjects. Completion of the study will then be late 2017 / early 2018.

D9. Study Design

The general tasks for the contact, interview, and study period will include the following:

- Training of Study Personnel
    - All study personnel will pass the CITI course for human subjects' research or its equivalent
    - All study personnel will undergo HIPAA training and certification
    - All study personnel will undergo training of the proper methods to obtain informed consent and assent.
    - All study personnel will receive training in how to obtain a tracheostomy aspirate culture using sterile techniques
- Identification and Recruitment of Subjects
    - Ascertainment of potential subjects from each pulmonary center's database
    - Interview subject and/or subject's legal guardian regarding participation in clinical study by study personnel.
    - Obtain informed consent from the legal guardian of subjects aged 17 years and younger and either verbal or written informed assent of subject
    - Obtain informed consent from subjects aged 18-21 years
- Study Period
    - Subjects will receive study drug three times a day via nebulized treatment for 1 year alternating 28 days on / 28 days off.
    - Collection of data for primary and secondary outcomes throughout the study period
        - Respiratory Infection necessitating systemic antibiotics will be defined as meeting 3 of the 6 following criteria: fever, hypoxemia ($SpO2 < 92\%$), cough, increased tracheal secretions, change in color of secretions from clear and/or white, and radiographic evidence of pneumonia.
        - If a study subject does have a respiratory infection necessitating systemic antibiotics, then they will have to visit their study coordinator to have a tracheal aspirate culture collected
        - Tracheal aspirate cultures will be collected in a standardized way in all institutions participating in the study
        - Laboratory culture techniques will be standardized in all institutions participating in the study

D10. Preparation of Manuscript

After the completion of data collection, entry, and analysis, manuscript preparation shall be done.
The completed manuscript will then be submitted to an appropriate publication and/or conference such as: *Pediatrics, American Journal of Respiratory and Critical Care Medicine*, and American Thoracic Society's International Conference.

E. HUMAN SUBJECTS RESEARCH

E1. Recruitment and Informed Consent

- Trained study personnel will approach eligible subjects to participate in this proposal once they have been identified to have a tracheostomy tube and a tracheostomy aspirate culture positive for *Pseudomonas*. It will be stressed to the subjects and their legal guardians that their participation in this study is voluntary. They have the right to withdraw from the study at any time, and that choosing not to participate in the study will not adversely affect their medical care or their relationship with any of their medical care providers. Patients and their legal guardians will also be asked to sign an authorization for release of medical information.

E2. Assessment of Safety

- The safety of AZLI will be assessed through the collection of both Adverse Events and Serious Adverse Events (SAEs)
- All adverse events that occur during this study from the initiation of study drug administration until completion of the study, whether attributed to the study drug, that are observed by the Investigator, study staff, subject's physician or reported by the patient and/or guardian will be recorded on an adverse event case report form. In addition to recording the adverse event, attributes of the adverse event will be recorded as well. These attributes will include a description, onset, and resolution date, duration, maximum severity, assessment of relationship to the study agent, other suspect agent(s), treatment procedures, and the patient's pre-existing disease, action taken and outcome.
    - In the event of an adverse event, the first concern will be for the safety of the subject. Investigators are required to report to Gilead, IRB, and FDA any serious adverse event, whether expected or unexpected, and which is assessed by the investigator to be reasonably or possibly related to AZLI. All deaths, regardless of causality, will also be reported. All events meeting these criteria will be reported for the time period beginning with any amount of exposure to AZLI through the protocol-defined follow-up period. Serious criteria, definitions and guidance for reporting follow.
- An Adverse Event (AE) is any untoward medical occurrence (e.g. sign, symptoms, disease, syndrome, intercurrent illness, abnormal lab finding) that emerges during AZLI treatment or is a pre-existing condition that worsens relative to the pretreatment state, regardless of the suspected cause.
- Note: Unchanged, chronic conditions should not be recorded as an adverse event on the FDA safety and adverse event reporting program MedWatch unless there is an exacerbation of the chronic condition.
- Serious Adverse Events (SAE) are adverse events occurring at any dose which meet one or more of the following serious criteria:
    - It resulted in death (i.e., the adverse event caused or led to death)
    - It was life threatening (i.e., the adverse event placed the patient at immediate risk of death: it does not apply to an adverse event that hypothetically might have caused death if it were more severe)
    - It required or prolonged inpatient hospitalization (i.e., the adverse event required any inpatient hospitalization or prolonged a hospitalization beyond the expected length of stay.)
    - It was disabling (i.e., the adverse event resulted in a substantial disruption of the patient's ability to carry out normal life functions)
    - Is a congenital anomaly/birth defect (i.e., an adverse outcome in a child or fetus of a subject exposed to the trial drug prior to conception or during pregnancy)
- Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator Brochure
- Unexpected adverse events are those not listed in the Package Insert (PI) or current Investigator Brochure (IB) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the PI or IB. For example, under this definition, hepatic necrosis would be unexpected if the PI or IB only referred to elevated hepatic enzymes or hepatitis.

E2.1 Methods For Eliciting, Recording and Assessing Adverse Events

- Eliciting Adverse Events

- To elicit adverse events, simple questions with minimal connotations should be used as the initial questions at all evaluation points during the study.
- A questionnaire (adverse events listed are those listed on the Package Insert of AZLI) will be given to the participant if they are 18 years old and capable, or to the guardian. (see Appendix 7b).

- Recording Adverse Events
  - When completing a MedWatch form, investigators should consider the following when assigning a primary event term:
    - Whenever possible, use recognized medical terms when recording adverse events on the adverse event section(s) of the MedWatch form. Do not use colloquialisms and/or abbreviations.
    - If known, record the diagnosis (i.e., disease or syndrome) rather than component signs and symptoms on adverse event section(s) of the MedWatch (e.g., record congestive heart failure rather than dyspnea, rales, and cyanosis). However, signs and symptoms that are considered unrelated to an encountered syndrome or disease should be recorded as individual adverse events on the MedWatch (e.g., if congestive heart failure and gastrointestinal bleed are observed at the same time, each event should be recorded as an individual adverse event)
    - Adverse events occurring secondary to other events (e.g., sequelae) should be identified by the primary cause. A "primary" adverse event, if clearly identifiable, generally represents the most accurate clinical term to record on adverse event pages of the MedWatch and the CRF. Events occurring secondary to the primary event should be described in the narrative description of the case. For example:
      - Orthostatic hypotension → fainting and fall to floor → head trauma → neck pain
        - The primary adverse event is orthostatic hypotension

- Assessing Causality (Trial Drug Relationship to Adverse Event)
  - The investigator will determine which events are associated with the use of the trial drug. Investigators are required to report to Gilead any serious adverse event, whether expected or unexpected, and which is assessed by the investigator to be reasonably or possibly related to AZLI. All deaths, regardless of causality, will also be reported. All events meeting these criteria will be reported for the time period beginning with any amount of exposure to AZLI through the protocol-defined follow-up period. For reporting purposes, an AE should be regarded as related to or not related to the use of investigational product if the investigator believes:
  - Yes (includes possibly or probably) event is related to AZLI
    - There is a clinically plausible time sequence between onset of the adverse event and AZLI administration; and/or
    - There is a biologically plausible mechanism for AZLI causing or contributing to the adverse event;
    - And the adverse event cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures.
  - Event is probably not related to AZLI:
    - A clinically plausible temporal sequence is inconsistent with the onset of the adverse event and AZLI administration; and/or
    - A causal relationship is considered biologically implausible

E2.2 MedWatch 3500 Completion Methods

- In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section B5) of the MedWatch 3500 form:
    - Identification of the primary event term
    - Protocol description (and number, if assigned)
    - Description of event, severity, treatment, and outcome if known
    - Supportive laboratory results and diagnostics
    - Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication
    - If a death occurred, autopsy results if available

E2.3 MedWatch 3500 Follow-up Information Methods

- Additional information may be added to a previously submitted report by any of the following methods:
    - Add to the original MedWatch 3500 report and submit it as follow-up
    - Add documents and submit follow-up with the original MedWatch 3500 form
    - Summarize new information and fax it with a cover letter including subject identifiers (i.e. D.O.B., initial, subject number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted. (Patient identifiers are important so that new information is added to the correct initial report.)
        - Occasionally, Gilead may contact the investigator for additional information, clarification, or current status of the subject for whom an adverse event was reported.

E2.4 REPORTING OF ADVERSE EVENTS

E2.4.1 General Reporting of Serious Adverse Events Associated with AZLI

- The Primary Investigator will report all SAEs to the IRB of the respective institutions involved.
- All SAEs that are serious and reasonably or probably related to AZLI (this applies to both expected and unexpected events) along with all deaths should be recorded on a MedWatch 3500 Form faxed to:
    - Gilead Contact Information:

E2.4.2 ADDITIONAL REPORTING REQUIREMENTS FOR IND HOLDERS FOR INVESTIGATOR SPONSORED IND STUDIES N/A for our study.

E3. Risks/Benefits of Participation

- There should be minimal risk to the subjects associated with participation in this study. Some of the subject may experience adverse effects of the study drug or placebo such as bronchospasm and/or hemoptysis.
- Subjects will be carefully monitored by the medical team (Attending physician, pulmonary fellow, nursing staff, respiratory therapy staff), and the study coordinator for adverse events. If an adverse event occurs, the medical team and/or study coordinator will recognize it and the subject will be treated accordingly. If there is a temporary relationship between the study drug administration and the adverse event is deemed severe/serious by the PI, RSG, Gilead, the FDA, or the IRB, the subject

will be treated as a drop out/treatment failure. The adverse event will be reported to the RSG, Gilead, and the IRB or the participating hospital. If deemed appropriate by any of the aforementioned groups, governmental agencies will also be notified of any adverse event. The reports will be made through telephone calls as well as written reports.

- The data collected from subjects will be stored securely in either a locked storage container (paper data) or password restricted electronic medium (electronically collected/entered and analyzed data). All study personnel associated with this proposal will be reminded prior to the start and at regular intervals as to the necessity for keeping data confidential. Subjects will be identified by code and a code breaker sheet which associates the code to a name will be kept in a separate, locked storage container.
- The benefits of participation in the proposal for the subjects are both direct and indirect. The direct benefits the subjects could potentially experience are an avoidance of intravenous antibiotic therapy due to *Pseudomonas aeruginosa* infection, if needed – a shorter duration of hospital stay due to lower bacterial burden of *Pseudomonas*. The indirect benefits the subjects could potentially experience include: less disruption in the family dynamic, decrease in hospital needs allowing parents to continue work, and collection of this data may provide for furthering of more studies using aztreonam and/or other inhaled antibiotics to eradicate colonization or decrease bacterial burden of lower respiratory tract bacterial infections.

APPENDIX

1) Study Checklist:

Enrollment (Visit 0)

1. Consent	☐
2. Assent	☐
3. HIPAA	☐
4. Demographic Form	☐
5. Eligibility Check list	☐
6. Data Collection Form	☐
7a. + PsA trach cx in last month?	☐ Yes ☐ No
7b. If YES in 7a, then go to Visit 1	☐
7c. If NO in 7a, then obtain tracheal aspirate culture using sterile technique (see guidelines) and send sample for bacterial culture	☐ (check if sent culture during today's visit)
8. Time Sheet	☐
9. Chart review done completed by RW	☐ Yes ☐ No

Visit 1

1. Data Collection Form	☐
2. Obtain tracheostomy aspirate culture using sterile technique (see guidelines) and send sample for bacterial culture	☐
3. AZLI Test Trial	☐
4. Teach guardian how to deliver AZLI	☐
5. Study drug (2 month supply*) given to participant. * 2 month supply as will start on an ON month starting tomorrow (day after Visit 1)	☐
6. Time Sheet	☐

Visit 2

1. Data Collection Form	☐
2. Adverse Events Form	☐
3. Obtain tracheal aspirate culture using sterile technique (see guidelines) and send sample for bacterial culture	☐
4. Document results of Visit 1 culture on the Culture Results Form	☐
5a. Obtain empty vials of the study drug from the participant.	☐
5b. Document how many vials were returned and were used.	_____ (max should be 168)
6. Study drug (1 month supply*) given to participant. * this quarter, will be on study drug once	☐
7. Time Sheet	☐

Visit 3

1. Data Collection Form	☐
2. Adverse Events Form	☐
3. Obtain tracheal aspirate culture using sterile technique (see guidelines) and send sample for bacterial culture	☐
4. Document results of Visit 2 culture on the Culture Results Form	☐
5a. Obtain empty vials of the study drug from the participant.	☐
5b. Document how many vials were returned and were used.	_____(max should be 84)
6. Study drug (2 month supply*) given to participant. * this quarter, will be on study drug twice	☐
7. Time Sheet	☐

Visit 4

1. Data Collection Form	☐
2. Adverse Events Form	☐
3. Obtain tracheal aspirate culture using sterile technique (see guidelines) and send sample for bacterial culture	☐
4. Document results of Visit 2 culture on the Culture Results Form	☐
5a. Obtain empty vials of the study drug from the participant.	☐
5b. Document how many vials were returned and were used.	_____ (max should be 168)
6. Study drug (1 month supply*) given to participant. * this quarter, will be on study drug once	☐
7. Time Sheet	☐

Visit 5

1. Data Collection Form	☐
2. Adverse Events Form	☐
3. Obtain tracheal aspirate culture using sterile technique (see guidelines) and send sample for bacterial culture	☐
4. Document results of Visit 2 culture on the Culture Results Form	☐
5a. Obtain empty vials of the study drug from the participant.	☐
5b. Document how many vials were returned and were used.	_____(max should be 84)
6. Termination (Study Exit) Form*	☐
7. Time Sheet	☐

* termination form to be filled out at the last study visit to verify the participant has completed the study and on what date. Or, it is to be used if the parent/guardian or participant if 18 years or older has withdrawn consent and why.

Follow-up

1. 3 month telephone follow-up Form	☐
2. 6 month telephone follow-up Form	☐

2) Time Sheet Form

VISIT TYPE	DATE	Staff's NAME	Staff's Signature	TIME SPENT (min)
Enrollment				
Study Visit 1				
Study Visit 2				
Study Visit 3				
Study Visit 4				
Study Visit 5*				
			TOTAL:	

* Study visit 5 is not needed in those that had a + tracheostomy aspirate culture + for Pseudomonas in the month preceding enrollment.

3) Eligibility Checklist Form:

Informed Consent and Subject Assent Criteria	
1) Has a parent/legal guardian appropriately signed and dated the informed consent?	☐Yes ☐ No
2) If YES, record the date that the form was signed.	_ _ / _ _ / _ _ _ _ Mo Day Year
3) If the participant is 7-17 years of age, has the participant appropriately given verbal consent?	☐Yes ☐ No
4) If YES, record the date that verbal consent was given.	_ _ / _ _ / _ _ _ _ Mo Day Year
Medical History Criteria	
5) Is the participant 7-21 years old?	☐Yes ☐ No
6) Has the participant had a positive tracheostomy tube aspirate culture positive for Pseudomonas in the past?	☐Yes ☐ No
7) Has the participant been admitted to the hospital for respiratory related problems requiring antibiotics while having a tracheostomy tube?	☐Yes ☐ No
8) Has the participant smoked any type of tobacco products or other products in the last 12 months?	☐Yes ☐ No
9) Has the participant had inhaled antibiotics in the last 6 months?	☐Yes ☐ No
10) Does the patient have any of the following conditions: ☐CF (cystic fibrosis) ☐ PCD (primary ciliary dyskinesia) ☐ Tuberculosis ☐ Bronchiectasis ☐ previous culture positive for *Burkholderia cepacia*	
11) Does the participant have a significant medical illness other than asthma (mark all that apply)? ☐ Congenital heart disease ☐ Neuromuscular disease ☐ Cerebral palsy ☐ Asthma ☐ Other: _____ ☐ N/A	
12) Does the participant have a history of pulmonary edema or hemoptysis in the last 48 hours?	☐Yes ☐ No
13) Does the participant have a history of an adverse reaction to inhaled aztreonam?	☐Yes ☐ No
14) Is the participant in respiratory failure?	☐Yes ☐ No

Other Criteria	
16) Date of Birth _ _ / _ _ / _ _ _ _ Mo Day Year	16) Gender: ☐ Male ☐ Female
17a) Mother's ethnicity: ☐ Caucasian ☐ Hispanic ☐ African Amer. ☐ Native Amer. ☐ Asian Amer. ☐ Other	
17b) Father's ethnicity: ☐ Caucasian ☐ Hispanic ☐ African Amer. ☐ Native Amer. ☐ Asian Amer. ☐ Other	
17c) Participant's ethnicity: ☐ Caucasian ☐ Hispanic ☐ African Amer. ☐ Native Amer. ☐ Asian Amer. ☐ Other	
18a) Mother's Education: _____ years completed	

18b) Father's Education: _____ years completed
19) Does anyone living with the participant smoke? (mark all that apply) ☐ Mother ☐ Father ☐ Other: _____
20a) Is there any other reason why this participant should not be in this study? ☐Yes ☐ No 19b)If YES, please describe: _____

21) Is the participant eligible? If any of the shaded boxes are selected, mark No. ☐Yes ☐ No 21a) If NO, participant is ineligible for the study. STOP HERE, thank participant and family for helping with the study, and complete Termination Form.

4) Demographic Data Form

Participant's Information	
1) Name: _____ _____ _____ First Middle Last	
2) Primary Care Physician / Clinic: _____	
3) Phone #: • Primary: (_____) _____ - _____ (Home/Mobile/Work) • Secondary: (_____) _____ - _____ (Home/Mobile/Work)	
4) Address: • _____ Street Address • _____ _____ _____ City State Zip • _____ Mailing Address (if different from above Street Address) • _____ _____ _____ City State Zip	
Medical History	
5) Does the participant have a tracheostomy tube?	☐Yes ☐ No
6) If YES, when was the tracheostomy tube placed?	_ _ / _ _ / _ _ _ _ Mo Day Year
7) Does the participant require a ventilator? • If YES, does he/she need it 24 hours a day?	☐Yes ☐ No ☐Yes ☐ No
8) Does the participant see a pulmonologist?	☐Yes ☐ No
9) Does the participant take any regular medications for asthma or breathing problems? • If YES, what are the medications: ☐ Albuterol ☐ Xoponex ☐ QVAR ☐ Flovent ☐ Pulmicort ☐ Advair ☐ Symbicort ☐ Dulera ☐ Prednisone ☐ Singulair	☐Yes ☐ No
10) How many times in the last year has the participant received antibiotics for a respiratory infection? ☐ none ☐ 1 ☐ 2 ☐ 3 ☐ 4 or more	
11) How many times in the last year has the participant been hospitalized for a respiratory infection? ☐ none ☐ 1 ☐ 2 ☐ 3 ☐ 4 or more	

12) Has the patient been hospitalized in the past for respiratory problems while having a tracheostomy tube:	☐Yes ☐ No
13) Regarding the tracheostomy tube that the participant has: • What brand is it? ☐ Bivona ☐ Shiley • Cuffed? ☐ Yes ☐ No	
14) How often do you do trach changes • When well:_____ • When sick:_____	
15) Does the patient use the following (check all that apply): • Cool mist: ☐Yes ☐ No • HME: ☐Yes ☐ No • Speaking valve ☐Yes ☐ No - If YES, what type_____ • In-line ventilator humidification ☐Yes ☐ No	
16) Does the participant have a history of an adverse reaction to inhaled aztreonam?	☐Yes ☐ No
17) Does the participant have any allergies?	☐Yes ☐ No
18) What medications does the participant take? (please list all of them)	
19) Does the participant have any other medical problems? (If YES, please list all of them)	
Social History	
20) Are there any pets in the home (mark all that apply): ☐ none ☐ cat ☐ dog ☐ bird ☐ other: _____	

21) Do you know of any mold in the participant's home?	☐Yes	☐ No
22) Are there any smokers in the home?	☐Yes	☐ No
Family History		
23) Please list the medical problems of the family members of the participant in this study:		

5) Data Collection Form:

Physical Exam:	
1. Participant's Height:__ __ __.__ cm	2. Participant's Weight:__ __ __.__ kg
3. O_2 saturation: __ __% in RA / __ __lpm O_2	4. Respiratory rate: __ __ __ bpm
5. Heart rate: __ __ __ bpm	6. Temperature: __ __.__ ^oC
7a. Tracheostomy tube type: ☐ Shiley ☐ Bivona ☐ Other_____	
7b. Tracheostomy tube size: _____ 7c. Tracheostomy tube cuffed? ☐ Yes ☐ No If YES in 7c, how much is it inflated?_____ If YES in 7c, how many hours per day is cuff inflated?_____	
7d. Tracheostomy tube cuff type : ☐ TTS ☐ Air cuff ☐ Fome cuff	
7e. Tracheostomoy tube cannula: ☐ single cannula ☐ dual (inner and outer cannula) ☐ fenestrated	
8a. Ventilator dependent: ☐ Yes ☐ No	
8b. If YES on 8a, when does patient need ventilator: ☐ at all times ☐ with sleep ☐ Other_____	
8c. If YES on 8a, how many hours per day is participant on the ventilator?_____	
9a. Chest auscultation is clear: ☐ Yes ☐ No	
9b. If NO, circle all findings that apply: 1. Expiratory wheeze 2. Inspiratory wheeze 3. Prolonged expiration 4. Decreased breath sounds 5. Retractions 6. Tachypnea 7. Crackles 8. Wet cough 9. Dry cough	
Study Medication: (skip if filling out on Visit 0 = Enrollment)	
10a. Did the participant bring the empty AZLI vials they have used since the last study visit? ☐ Yes ☐ No	
10b. If YES, how many vials did they bring:_____ (should be 84 per cycle = 28 days TID)	
11a. Is the participant currently receiving the study medication (ON cycle)? ☐ Yes ☐ No	
11b. Which week of current cycle is patient on (ie. week 1, 2, 3, or 4): ☐ 1 ☐ 2 ☐ 3 ☐ 4	
Systemic Antibiotics and Hospitalization:	
12a. Has the participant received antibiotics in the last 3 months? ☐ Yes ☐ No	
12b. If YES in 12a, was it for a respiratory infection? ☐ Yes ☐ No **Respiratory infection defined as meeting 3 of the 6 following criteria: fever, hypoxemia (SpO2 < 92%), cough, increased tracheal secretions, change in color of secretions from clear and/or white, and radiographic evidence of pneumonia.	
12c. If YES in 12a, what type of antibiotic did the participant receive? _____	
12d. If YES in 12a, was the drug IV (intravenous) or oral/feeding tube? ☐ IV ☐ Oral or via feeding tube	
13a. Has the patient been hospitalized in the last 3 months for respiratory problems? ☐ Yes ☐ No	
13b. If YES in 13a, please describe length of stay, treatment, oxygen need, respiratory support:_____ _____	
14a. Is the participant currently receiving medications other than the study drug? ☐ Yes ☐ No	
14b. If YES, please list (may continue on the back of this form)	

Drug	Start Date	Dose	Frequency	End Date

6) Culture Results Form

*** PLEASE PRINT CULTURE RESULTS ONCE THEY ARE FINAL, AND SAVE IN STUDY FILE***

Enrollment/Visit 1 culture	Culture collection date: Culture results: CFUs (if applicable): MIC: Sensitivities:
Visit 2 Culture	Culture collection date: Culture results: CFUs (if applicable): MIC: Sensitivities:

Visit 3 Culture	Culture collection date: Culture results: CFUs (if applicable): MIC: Sensitivities:
Visit 4 Culture	Culture collection date: Culture results: CFUs (if applicable): MIC: Sensitivities:
Visit 5 Culture	Culture collection date: Culture results: CFUs (if applicable): MIC: Sensitivities:

Follow-up	Culture collection date: Culture results: CFUs (if applicable): MIC: Sensitivities:

7a) Adverse Events Participant Form

How have you/your child felt sick since your last visit?	☐Yes	☐ No
Have you/your child had any health problems since you were last here?	☐Yes	☐ No
Have you/your child had any unusual or unexpected worsening of your underlying medical condition?	☐Yes	☐ No
Have you/ your child experienced coughing while taking the inhaled medication?	☐Yes	☐ No
Have you or your child experienced or been told by your physician one of the following:		
• Cough	☐Yes	☐ No
• Chest congestion	☐Yes	☐ No
• Throat pain	☐Yes	☐ No
• Throat irritation	☐Yes	☐ No
• Hoarse voice	☐Yes	☐ No
• Nasal congestion	☐Yes	☐ No
• Shortness of breath	☐Yes	☐ No
• Coughing up blood	☐Yes	☐ No
• Runny nose	☐Yes	☐ No
• Wheezing	☐Yes	☐ No
• Chest discomfort	☐Yes	☐ No
• Crackles on lung exam that your physician has told you	☐Yes	☐ No
• Pulmonary function testing decreased (if you had an lung function testing)	☐Yes	☐ No
• Non-cardiac chest pain	☐Yes	☐ No
• Sinus congestion	☐Yes	☐ No
• Sinus headache	☐Yes	☐ No
• Worsening shortness of breath	☐Yes	☐ No
• Shortness of breath on exertion	☐Yes	☐ No
Other (please write response):		

7b) Adverse Event Reporting Form

Adverse Event Time/Date	Visit 2	Visit 3	Visit 4	Visit 5
AE Present at Previous Evaluation? If NO, date of onset: (mo/day/yr) (if actual unknown, list approximate)	☐ Yes ☐ No __ __/__ __/__ __ __ __	☐ Yes ☐ No __ __/__ __/__ __ __ __	☐ Yes ☐ No __ __/__ __/__ __ __ __	☐ Yes ☐ No __ __/__ __/__ __ __ __
Severity – circle only one	Mild Moderate Severe	Mild Moderate Severe	Mild Moderate Severe	Mild Moderate Severe
Action – check all relevant: Study drug was: (circle one)	☐ Not changed ☐ Increased ☐ Reduced ☐ Held ☐ D/C	☐ Not changed ☐ Increased ☐ Reduced ☐ Held ☐ D/C	☐ Not changed ☐ Increased ☐ Reduced ☐ Held ☐ D/C	☐ Not changed ☐ Increased ☐ Reduced ☐ Held ☐ D/C
Subject withdrawn from study:	☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No
Treatment given: (specify details in concomitant treatment section)	☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No
Other: (specify)	☐_____ _____	☐_____ _____	☐_____ _____	☐_____ _____
Observation:	☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No

Enroller Initials:

Do Serious Criteria Apply? Fatal; Life threatening; Inpatient Hospitalization; Persistent or significant disability/incapacity; Congenital anomaly/birth defect; Important medical event (ie. may jeopardize subject and require medical or surgical intervention to prevent above listed outcomes).	☐Yes ☐ No If YES, notify PI (who will notify IRB, FDA, and Sponsor) immediately.	☐Yes ☐ No If YES, notify PI (who will notify IRB, FDA, and Sponsor) immediately.	☐Yes ☐ No If YES, notify PI (who will notify IRB, FDA, and Sponsor) immediately.	☐Yes ☐ No If YES, notify PI (who will notify IRB, FDA, and Sponsor) immediately.
Outcome of AE (to date) Still present? Date:	☐ Yes ☐ No ☐ Unknown __ __/__ __/__ __ __ __	☐ Yes ☐ No ☐ Unknown __ __/__ __/__ __ __ __	☐ Yes ☐ No ☐ Unknown __ __/__ __/__ __ __ __	☐ Yes ☐ No ☐ Unknown __ __/__ __/__ __ __ __
Complete Following Section at AE resolution or at End of Study				
Causality In PI's Judgment, was Study Drug the MOST likely cause of the AE?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
If NO, in PI's Judgment, what was the most likely cause of the AE?(check one only)				
1.Disease Under Study	☐ Yes	☐ Yes	☐ Yes	☐ Yes
2.Other Illness (specify)	☐_____	☐_____	☐_____	☐_____
3.Concomitant Treatment (specify)	☐_____	☐_____	☐_____	☐_____
4.Other (specify)	☐_____	☐_____	☐_____	☐_____

Comments:

7c) FDA MedWatch 3500 Form:
Go to www. Patientsafetyasap.org/pdf/FDA-Voluntary%20Reporting.pdf

8) Termination of Participation (Study Exit) Form:

1) Has the participant completed the study? • If YES, skip to signatures portion of this form	☐Yes ☐ No
2) Participant qualifies for the study based on eligibility criteria (See Eligibility Form). • If NO, skip to signatures portion of this form.	☐Yes ☐ No

3) Parent/guardian or participant if 18 years old or older, has withdrawn consent?
• If YES, why (choose one)?
  • Parent/guardian no longer wishes to participate
  • Participant no longer wises to participate
  • Other_____
  _____
	☐Yes ☐ No

4) Did the participant experience an adverse reaction? • If YES, what (choose one): ☐ cough ☐ chest congestion ☐ throat pain ☐ throat irritation ☐ hoarse voice ☐ nasal congestion ☐ shortness of breath ☐ coughing up blood ☐ runny nose ☐ wheezing ☐ chest discomfort ☐ crackles on lung exam ☐ sinus congestion ☐ decrease on pulmonary function testing ☐ non-cardiac chest pain ☐ sinus headache ☐ worsening shortness of breath ☐ shortness of breath on exertion ☐ respiratory failure: defined as: 1) pCO2 >60 mmHg; 2) oxygen requirement > 5 L/min; and 3) Invasive or non-invasive ventilation) and/or worsening of their clinical status (such as refractory coughing) during the trial. (automatic treatment failure) ☐ other (please write response):_____ _____	☐Yes ☐ No

Signatures

Please complete the following section regardless of the reason for study termination.

I verify that all information collected for this child is correct to the best of my knowledge and has been done so in accordance with the Manual of Procedures.

_____ ___ ___ / ___ ___ / ___ ___ ___ ___
Coordinator/Study Staff Signature Mo Day Year

_____ ___ ___ / ___ ___ / ___ ___ ___ ___
Principal Investigator Signature Mo Day Year

9a and b) 3 and 6 Month Follow-up Form

At Follow Up (Telephone call to primary pulmonologist or ENT physician)

1) Date of completion of study:	_ _ / _ _ / _ _ _ _ Mo Day Year
2) Did the subject continue on inhaled Aztreonam on a 28 days on / 28 days off cycle?	☐Yes ☐ No
3) Has the subject had any respiratory exacerbations requiring systemic (IV or oral) antibiotics?	☐Yes ☐ No
4) Has the subject had any respiratory exacerbations requiring hospitalization?	☐Yes ☐ No
5) Has the subject had a recent tracheostomy aspirate culture?	☐Yes ☐ No
5a) If YES, please provide results including culture results, CFUs, MIC and sensitivities.	Culture collection date: Culture results: CFUs (if applicable): MIC: Sensitivities:

10) Trach Aspirate Protocol:

Obtaining a Sterile Tracheal Aspirate for Culture

Assemble needed equipment:

- Wall suction or portable suction with adjustable suction regulator and manometer, vacuum bottle, connecting tubing.
- Suction catheter kit of appropriate size (new and unused). This will include sterile gloves. The size of the suction catheter should be about half the size of the inner diameter of the tracheostomy tube; or tracheostomy size x 2 = size Fr catheter to use. Too large a catheter will occlude the tracheostomy and transmit the full force of suction to the lungs. Too small a catheter may be ineffective.
- Sterile specimen Trap 40 ml.
- Normal saline, without preservatives.

Clean and sanitize hands.
Gown, glove and mask.
Using the portable or wall suction: attach sterile specimen trap to the 6 foot suction tubing.
Open sterile suction catheter kit and add some sterile saline to the sterile basin.
Don sterile gloves.
Measure the suction catheter based on tracheostomy tube length so you know how far to place the catheter in the tracheostomy tube.
Hold catheter in dominate hand. Using other hand, attach catheter to the rubber tube of the sterile specimen trap.
Ask nurse or parent to temporarily disconnect patient from circuit if they use a ventilator.
Suction patient with correct technique to avoid tracheal trauma.
Ask nurse or parent to re-connect patient to circuit if they use a ventilator.
Use sterile saline (maximum of 5ml) to clear suction catheter and secretions into sterile specimen trap.
Disconnect sterile specimen trap and properly seal (specimen trap comes with a sterile lid to seal specimen) and store specimen in specimen bag.

11) Study Drug Break Form:

1) Was the study drug discontinued or held?	☐Yes ☐ No
2) If yes, please specify the dates study drug was held:	
3) If yes in question 1, was it due to being hospitalized?	☐Yes ☐ No
4) If yes in question 1, was it due to being requiring antibiotics at home?	☐Yes ☐ No
5) If yes in question 1, but not due to hospitalization or need for antibiotics at home, please write down the reason: _____ _____ _____	

Signatures

Please complete the following section regardless of the reason for study deviation.

I verify that all information collected for this child is correct to the best of my knowledge and has been done so in accordance with the Manual of Procedures.

_____ ___ ___ / ___ ___ / ___ ___ ___ ___
Coordinator/Study Staff Signature Mo Day Year

_____ ___ ___ / ___ ___ / ___ ___ ___ ___
Principal Investigator Signature Mo Day Year

REFERENCES

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