

Children's Mercy Kansas City

## SHARE @ Children's Mercy

---

Manuscripts, Articles, Book Chapters and Other Papers

---

4-12-2019

### **Aztreonam Lysine Inhalation Solution in Cystic Fibrosis.**

Claire Elson

Joel Mermis

Deepika Polineni

Christopher M. Oermann

Follow this and additional works at: <https://scholarlyexchange.childrensmercy.org/papers>



Part of the [Pharmacy and Pharmaceutical Sciences Commons](#), and the [Pulmonology Commons](#)

---

# Aztreonam Lysine Inhalation Solution in Cystic Fibrosis

Elizabeth Claire Elson<sup>1</sup> , Joel Mermis<sup>2</sup>, Deepika Polineni<sup>2</sup> and Christopher M Oermann<sup>3</sup>

<sup>1</sup>Department of Pharmacy, Children's Mercy – Kansas City, Kansas City, MO, USA. <sup>2</sup>Department of Medicine, University of Kansas Medical Center, Kansas City, KS, USA. <sup>3</sup>Department of Pediatrics, Children's Mercy – Kansas City, Kansas City, MO, USA.

Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine  
Volume 13: 1–10  
© The Author(s) 2019  
Article reuse guidelines:  
sagepub.com/journals-permissions  
DOI: 10.1177/1179548419842822



**ABSTRACT:** Patients with cystic fibrosis (CF) develop pulmonary disease secondary to airway infection and dysregulated inflammation. Therapeutic innovations such as nebulized antimicrobial therapy targeting specific pathogens have resulted in improvements in quality of life and life expectancy. Aztreonam lysine for inhalation (AZLI) solution was initially approved to improve respiratory symptoms in CF patients with *Pseudomonas aeruginosa* (PA) in 2010 by the Food and Drug Administration. Since then, research broadening labeling and clinical application has been developed. In this review, we analyze published and ongoing research regarding AZLI therapy in CF. A search of the Cochrane Database of Systematic Reviews and the PubMed and ClinicalTrials.gov databases was conducted to identify publications about AZLI. Three pre-approval studies were identified and assessed. Two are Phase 3, placebo-controlled trials, assessing a variety of safety and efficacy endpoints, leading to FDA approval. The third is an open-label extension of the two previous trials. An additional seven post-approval, completed trials were identified and are included in this review. They represent a variety of study designs including safety and efficacy in patients with mild lung disease and young patients, an active comparator trial vs inhaled tobramycin, an eradication study, a study among patients with *Burkholderia cepacia*, and a study assessing continuous alternating antibiotic therapy. Finally, five ongoing clinical trials are discussed. Overall, studies demonstrated that inhaled aztreonam is a safe and effective antimicrobial treatment for the eradication of newly acquired *P. aeruginosa* and long-term suppressive therapy of chronic endobronchial infection among people with cystic fibrosis.

**KEYWORDS:** Cystic fibrosis, aztreonam lysine, inhalation, *Pseudomonas*

**RECEIVED:** September 16, 2018. **ACCEPTED:** March 13, 2019.

**TYPE:** Review

**FUNDING:** The author(s) received no financial support for the research, authorship, and/or publication of this article.

**DECLARATION OF CONFLICTING INTERESTS:** The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: ECE disclosed she has served on a pharmacist advisory council for Vertex Pharmaceuticals and Gilead Sciences.

**CORRESPONDING AUTHOR:** Elizabeth Claire Elson, Department of Pharmacy, Children's Mercy – Kansas City, 2401 Gillham Road, Kansas City, MO 64108, USA. Email: ecelson@cmh.edu

## Introduction

Cystic fibrosis (CF) is an autosomal recessive disease that results from mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. This gene codes for the CFTR protein which is located on epithelial membranes throughout several organ systems. CFTR functions directly as a chloride ion channel, allowing efflux of chloride from the intracellular to the extracellular space, and as a controller of other epithelial ion channels.<sup>1</sup> CFTR gene mutations can result in significantly decreased quantities of epithelial CFTR protein and/or severely dysfunctional protein. This leads to abnormal ion transport and decreased water movement into luminal spaces causing viscous, desiccated secretions in the airways, gastrointestinal tract, hepatobiliary structures, and other organ systems.<sup>2</sup> Abnormal airway surface liquid in the lungs causes a cycle of airway obstruction, inflammation, and infection leading to loss of lung function and eventually, death. Chronic airway infection with a variety of pathogens is typical of CF airway disease. *Pseudomonas aeruginosa* (PA) is the primary gram-negative bacterium associated with accelerated decline in lung function and increased morbidity and mortality among CF patients.<sup>3,4</sup> To mitigate the poor outcomes associated with chronic PA infection, several treatment strategies have been recommended as standards of care for CF patients. These include the use of inhaled

anti-pseudomonal antibiotics for both antibiotic eradication therapy (AET) of initial or intermittent PA infection and chronic suppressive therapy (CST). Tobramycin inhaled solution (TIS) was the first inhaled antibiotic approved for use in CF by the US Food and Drug Association (FDA), receiving approval in 1998. Its use has become widespread for both AET and CST.<sup>5–8</sup> More than 10 years after TIS approval, aztreonam lysine inhaled solution (AZLI) was approved by the FDA.<sup>9,10</sup> Since AZLI's approval, review articles focusing on pre-approval data have been published.<sup>11–14</sup> However, these reviews do not cover the clinical pharmacology, safety and efficacy (including pre- and post-approval data), ongoing clinical research, and clinical applications of AZLI. This review provides a comprehensive overview of AZLI across all research studies for healthcare providers responsible for the management of individuals with CF.

## Data Sources, Study Selection, and Data Extraction

A comprehensive literature search using the Cochrane Database of Systematic Reviews and the PubMed and ClinicalTrials.gov databases was conducted to identify publications about AZLI from 1990–2017. Publications including all study designs, retrospective, prospective, randomized and open-label trials, are included in analysis. In addition, this review includes data over currently ongoing clinical trials.



**Table 1.** Pre-approval completed studies.

STUDY	DESIGN	POPULATION	INTERVENTION	CLINICAL OUTCOMES	LIMITATIONS
Retsch-Bogart et al <sup>19</sup> (AIR-CF1)	R, DB, PCT	164 CF patients with PA ≥6years FEV1 25%-75% No recent anti-PA treatment	28 days AZLI TID vs PBO	↑ CFQ-R ↑ FEV1 ↓ Sputum PA density	Short duration Few patients <18years Moderate-severe lung disease with minimal previous treatment
McCoy et al <sup>23</sup> (AIR-CF2)	R, DB, PCT	211 CF patients with PA ≥6years FEV1 25%-75% ≥3 TIS courses within previous year	28 days of TIS then 28 days of AZLI BID or TID vs placebo	↑ Time to treatment with anti-PA antibiotics for PE ↑ CFQ-R ↓ Sputum PA density	Short duration Few patients <18years TIS-treated cohort
Oermann et al <sup>24</sup> (AIR-CF3)	Open-label	274 patients that previously completed AIR-CF1 or AIR-CF2	9 courses of cyclic 28 day AZLI BID or TID	↑ CFQ-R ↑ FEV1 ↓ Sputum PA density ↑ Weight gain	Study design Few patients <18years Potential microbiology resistance Discontinuation rate with extended duration

Abbreviations: AZLI, aztreonam lysine for inhalation; BID, twice daily; CFQ-R, Cystic Fibrosis Questionnaire-Revised; DB, double-blind; FEV1, forced expiratory volume in one second; PA, *Pseudomonas aeruginosa*; PBO, placebo; PCT, placebo-controlled trial; PE, pulmonary exacerbation; R, randomized; TID, three times daily; TIS, tobramycin inhaled solution.

## Clinical Pharmacology

Aztreonam is a monobactam antibiotic with activity against Gram-negative aerobic bacteria including PA. Aztreonam exerts its anti-bacterial activity by binding to penicillin-binding protein-3 (PBP-3), inactivating it, resulting in the disruption of bacterial cell wall synthesis and ultimate cell death.<sup>9,14-17</sup> Aztreonam's monocyclic beta-lactam structure results in resistance to hydrolysis by beta-lactamases.<sup>9,15-17</sup> In clinical trials including 195 CF patients, the mean sputum concentration of aztreonam 10 min after the first inhaled dose was 726 mcg/g.<sup>9</sup> Analyzing pooled data, patient's receiving 28 days of therapy (75 mg three times per day) did not demonstrate accumulation of aztreonam in sputum.<sup>9</sup> In the referenced studies, the mean peak plasma concentration after the first dose was 0.59 mcg/mL. Plasma concentrations following inhalation remained similar for patient's receiving 28 days of therapy.<sup>9</sup> These data indicate that there is minimal systemic absorption of AZLI. Standard AZLI dosing for all patient's ≥7 years of age is 75 mg inhaled three times daily for 28 days.<sup>9,14-17</sup> All doses must be separated by a minimum of 4h. AZLI has only been studied for administration via the Altera® nebulizer system.<sup>3</sup> The Altera system was co-developed with AZLI and has a very rapid nebulization time, approximately 2-3 min.<sup>9,18</sup>

## Clinical Efficacy and Safety

### Pre-approval completed studies

Retsch-Bogart et al<sup>19</sup> conducted AIR-CF1 as a phase 3, double-blind, multi-center, multinational, randomized, placebo-controlled trial to evaluate AZLI three times daily for 28 days in CF patients with PA (Table 1). The study population (N=164) included patients ≥6years of age, with moderate to severe lung disease (percent predicted forced expiratory volume in 1 second (ppFEV1)=25%-75%) and documented PA-positive respiratory culture.

Most patients were receiving concomitant dornase alfa (65%) and few patients had received TIS in the previous 12 months (average courses <2). Comparing the mean baseline demographics between the AZLI vs placebo group, the AZLI group (N=80) was slightly younger (27.4 vs 31.7years) but had similar ppFEV1 (54.4% vs 54.8%) and Cystic Fibrosis Questionnaire-Revised Respiratory Symptom Scores (CFQ-R RSS) (60.5 vs 60.9) scores. CFQ-R RSS is measure of respiratory health using a 0-100 point scale where higher scores indicate better health. There was a significant increase in CFQ-R RSS with an adjusted mean difference between AZLI and placebo patients of 9.71 points ( $P=.0005$ ). Previous studies defined the "minimal clinically important difference" (MCID), the smallest change in patient symptoms that is perceptible to patients, for the CFQ-R RSS as 5 points. An increase in CFQ-R RSS of 9.71 indicates a significant clinical improvement.<sup>20-22</sup> AZLI-treated patients had a significant improvement in ppFEV1 at day 28 (adjusted mean difference of 10.3%,  $P<.001$ ) and decreased PA sputum density (1.45 log<sub>10</sub> cfu/g,  $P<.001$ ). Although not statistically significant, AZLI-treated patients were hospitalized less frequently than placebo patients, 5% vs 14% ( $P=.064$ ). The incidence of adverse events was similar between groups.

This study authors reported that patients ≥6years of age with CF, moderate-to-severe lung disease and PA infection had improved pulmonary function and respiratory symptoms after a single treatment cycle with AZLI. Furthermore, adverse events reported with AZLI therapy was consistent with underlying CF disease.

McCoy et al<sup>23</sup> conducted AIR-CF2 as a phase 3, double-blind, multi-center, randomized, placebo-controlled trial to evaluate the safety and efficacy of AZLI in controlling PA infection in CF patients. Patients received open-label, run-in treatment with TIS 300 mg BID (twice daily) for 28 days prior to AZLI or placebo given either BID or three times daily

(TID) for 28 days. The study population included patients  $\geq 6$  years of age with moderate to severe lung disease (ppFEV1 25%–75%) and chronic PA infection who had received at least 3 courses of TIS in the previous 12 months.

A total of 211 patients were enrolled in the study, 135 patients received AZLI therapy (69 BID and 66 TID) 76 patients received placebo. Patients had received an average of 5.3 courses of TIS in the previous year. The pooled AZLI group was slightly younger (25.3 vs 27.9 years), had slightly better ppFEV1 (55.8% vs 53.9%), and had similar CFQ-R RSS (63.7 vs 62.1). Pooled AZLI-treated patients had a statistically significant increase, 21 days (relative risk reduction = 45%), in time to additional inhaled or intravenous (IV) anti-pseudomonal antibiotics compared with placebo patients ( $P = .007$ ). AZLI-treated vs placebo patients had an increase in adjusted mean CFQ-R RSS (5.01 [ $P = .020$ ]), adjusted mean ppFEV1 (6.3% [ $P = .001$ ]), and a decrease in adjusted mean change in sputum PA density ( $-0.66 \log_{10} \text{cfu/g}$  [ $P = .006$ ]). Treatment-emergent adverse events were similar between groups throughout the study; however, more patients were hospitalized because of serious adverse events (SAE) in the AZLI (8) group, most commonly for pulmonary exacerbation.

The study investigators state AZLI was safe and effective to manage PA infection and a potential therapy for patients previously receiving TIS. Treatment with AZLI increased time to need anti-pseudomonal antibiotics and improved respiratory endpoints including symptom scores and pulmonary function.

Oermann et al<sup>24</sup> conducted AIR-CF3 as an open-label, multi-center, multinational extension trial for all patients participating in AIR-CF1 and AIR-CF2 studies. A total of 274 patients enrolled and continued the same dosing regimen they utilized in either AIR-CF1 or AIR-CF2 (85 BID vs 189 TID) for up to nine courses (28 days on and off AZLI therapy) to assess long-term safety outcomes. Most subjects, 51.5%, received at least one course of TIS over the course of the study for a median duration of 78 days. Although originally designed for patients to receive three treatment courses, the study was extended to up to nine treatment courses to more fully evaluate AZLI's long-term safety and efficacy as well as gain a better understanding of any issues related to long-term AZLI treatment. The extended duration likely led to subject withdrawal as only 195 individuals completed the study (71%).

Patients had a mean age of 28.5 years (range: 8–74), baseline mean ppFEV1 55.6%, and CFQ-R RSS of 61.9. The most common adverse events reported were attributed to underlying disease and included cough (89.4%), productive cough (80.3%), and respiratory tract congestion (49%). Non-respiratory adverse events reported in  $\geq 30\%$  of patients included pyrexia, fatigue, decreased appetite, and headache. Analysis of secondary outcomes (ppFEV1, CFQ-R RSS, weight gain) demonstrated a dose response benefit favoring TID treatment over BID at the end of cycle nine. Throughout the study, MIC<sub>50</sub> and MIC<sub>90</sub> of aztreonam for PA isolates

with the highest MIC remained unchanged for both groups, with most patients demonstrating no change in susceptibility, defined as less than 4-fold increase in MIC. Transient increases in MIC<sub>90</sub> noted for the BID AZLI group favored TID as a dosing regimen. This long-term safety study demonstrated low rates of SAE and no new safety concerns with up to 18 months of AZLI treatment.

This open-label study demonstrated the superiority of AZLI TID vs BID among CF patients  $\geq 6$  years of age with chronic PA infection. In addition, AZLI therapy led to improvement in lung function, respiratory symptoms, and quality of life and increased weight for the 18-month duration of the study, proving sustainability of therapeutic effect. No significant safety concerns were identified during the study. The results of this trial established AZLI as a safe and effective therapy for cycled, suppressive inhaled antibiotic therapy in CF patients with chronic PA infection.

Pre-approval studies for AZLI demonstrate improvement in CFQ-R RSS, ppFEV1, and decreased PA sputum density over 1–18 months of treatment. Most safety concerns were respiratory in nature and attributed to underlying CF disease. Limitations to these pooled studies include a small number of pediatric patients, for Retsch-Bogart et al and McCoy et al a short 28-day treatment duration, and for Oermann et al potential bias secondary to the open-label study design and potential resistance pattern. In addition, the studied population for McCoy et al was primarily a TIS-treated group and there is evidence of a potential “honeymoon” effect with historical treatment of inhaled antibiotics resulting in a decreased magnitude of effect.<sup>23,25,26</sup>

#### *Post-approval completed studies*

Wainwright et al<sup>27</sup> conducted AIR-CF4 with a design similar to AIR-CF1 but included patients with milder CF lung disease (ppFEV1  $> 75\%$ ). It was a phase 3b, double-blind, multi-center, multinational, randomized, placebo-controlled trial to evaluate AZLI in CF patients with PA. The study population (N = 157) included patients  $\geq 6$  years of age with mild lung disease (ppFEV1  $> 75\%$ ) and documented PA-positive respiratory culture.

Most patients were receiving concomitant dornase alfa (82%) and azithromycin (57%); 65% of patients received TIS in the previous 12 months, although the average number of courses was  $< 3$ . The groups were similarly matched for age (19.5 vs 18.9 years), ppFEV1 (95.5% vs 94.7%), and CFQ-R RSS (70.3 vs 73.6). There was a non-significant treatment effect in CFQ-R RSS at day 28 (AZLI improvement = 3.2 vs placebo improvement = 1.4 for a difference of 1.8 [ $P = .443$ ]). A significant mean change in ppFEV1 for AZLI-treated patients (2.75 [ $P = .021$ ]) and decreased sputum PA density ( $-1.2 \log_{10} \text{cfu/g}$  [ $P = .016$ ]) was reported. Post hoc subgroup analysis stratified by ppFEV1, demonstrated for patients with a baseline ppFEV1  $< 90\%$  an improvement in CFQ-R RSS at day 28 (6.7 points [ $P = .072$ ])



and adjusted mean relative change in ppFEV1 (4.8% [ $P=.03$ ]). Most patients experienced at least one mild to moderate adverse event during the study, most commonly cough and productive cough, with similar rates between placebo and treatment groups. SAEs were reported for 11.7% of AZLI-treated patients vs 3.7% of placebo patients, most commonly hospitalization secondary to pulmonary exacerbation (AZLI 2; placebo 2). The authors reported modest improvement in respiratory symptoms in patients with mild CF lung disease and significant improvements in ppFEV1 and decreases in sputum PA density.

Assael et al<sup>28</sup> conducted AZLI-TIS Active Comparator as a phase 3b, open-label, multi-center, randomized, parallel group study to evaluate AZLI 75 mg TID vs TIS 300 mg BID, which is the US CF Foundation guideline recommendation for chronic PA airway infection. The study was a post-approval mandate of the European Medicines Agency, which required the use of mean relative change in ppFEV1 at day 28 as its primary outcome measure and allowed a non-inferiority (NI) analysis with an NI margin of 4% (AZLI vs TIS). The FDA requested an additional co-primary endpoint, mean actual change in ppFEV1 across three 28-day treatment cycles, and use of a superiority analysis. Patients were included if they were  $\geq 6$  years of age, had ppFEV1  $\leq 75\%$ , and had a PA-positive culture within 3 months prior to screening. Most patients (85%) in each group had received TIS for  $\geq 84$  days in the 12 months prior to randomization. Patients were randomized 1:1 to receive either AZLI 75 mg TID or TIS 300 mg BID for three 28-day on/off cycles followed by a 6-month open-label AZLI extension, where patients either continued AZLI or crossed over from previous placebo.

A total of 268 patients were enrolled and had similar mean baseline characteristics including age (25.8 vs 25.1 years), ppFEV1 (52.3% vs 52.2%) and CFQ-R RSS (62.9 vs 58.0). At day 28, AZLI-treated patients had a larger relative and actual improvement from baseline ppFEV1 compared with TIS (8.35% vs 0.55% [ $P<.001$ ], 2.05% vs 0.66% [ $P=.002$ ]). Compared with TIS-treated patients, AZLI patients had improvement in CFQ-R RSS (adjusted mean change of 4.1 points,  $P=.0189$ ), a lower number of respiratory hospitalizations (40 vs 58,  $P=.044$ ), lower number of respiratory events requiring IV and/or inhaled anti-pseudomonal antibiotics (84 vs 121,  $P=.004$ ), and longer duration of time to need IV anti-pseudomonal antibiotics ( $P=.0025$ ). There were similar changes between decreased sputum PA density and a non-statistically significant increase in weight gain favoring AZLI-treated patients (0.58% vs 0.06%,  $P=.289$ ). In the open-label extension period ( $n=133$ ; AZLI/AZLI: 68; TIS/AZLI: 65), AZLI/AZLI patients had sustained improvements in ppFEV1 and body weight, while TIS/AZLI patients had minimal improvement in ppFEV1 and weight loss during the active comparator period but a cross over effect was seen with ppFEV1 improvements and weight gain once patients were switched to AZLI open-label. Similar adverse events were

found between treatment groups, with cough and productive cough being reported most commonly. More patients in the AZLI-treated group experienced both treatment-related adverse events (22.8% vs 12.9%) and SAEs (16.2% vs 8.3%), most of which were respiratory in nature these remained consistent during the open-label extension study. Based on pre-specified definitions (MIC<sub>50</sub> increase of 4-fold or greater), there was no statistically significant increase resistance of PA isolates observed during the study to aztreonam or any other antibiotics. However, a non-significant increase of 15% was noted in the incidence of aztreonam resistance *Pseudomonas* isolates from baseline to the end of the study period.

This authors reported that over three treatment cycles, AZLI was non-inferior regarding the relative change in ppFEV1 and superior regarding actual change in FEV1 compared with TIS treatment. AZLI was statistically superior compared with TIS in terms of lung function and pulmonary exacerbation reduction over a 6-month study period.

Tullis et al<sup>29</sup> conducted AZLI in *Burkholderia* as a phase 3b, multi-center, randomized, placebo-controlled study designed to evaluate the safety and efficacy of 24 weeks of continuous AZLI 75 mg TID in CF patients  $\geq 6$  years of age who had chronic *Burkholderia* spp. infection. The 100 treated patients, continued to receive their usual medical care, determined by their physicians, with no restrictions on additional antibiotic use. Eighty percent of patients received any antibiotic treatment whereas 17% received an additional inhaled antibiotic. Comparing the mean baseline demographics between groups, the AZLI group was slightly older (28.0 vs 24.7 years), had slightly better baseline lung function (ppFEV1 60.7% vs 52.6%) and similar CFQ-R RSS (58.3 vs 59.0). At the end of the study period, there was a small but non-significant change in relative mean ppFEV1 favoring AZLI (0.91% [ $P=.66$ ]) and no significant differences in CFQ-R RSS, respiratory exacerbations, or hospitalization rates. The most common adverse events reported were similar between groups with the exception of increased rates of wheezing (20.8% vs 5.8%) and chills (12.5% vs 3.8%) in the AZLI-treated groups. SAE rates were similar between groups, although treatment-related adverse events, which were all respiratory, were slightly higher in the AZLI-treated group (18.8% vs 5.8%). Analysis of microbiology data found a 4-fold increase in MIC<sub>50</sub> from baseline to week 24 for *Burkholderia* spp. in the AZLI-treated patients at 24 weeks and a no significant change in *Burkholderia* spp. sputum density between groups.

This study is the largest, randomized controlled antimicrobial trial among CF patients with chronic *Burkholderia* infection, an organism which is associated with significant morbidity and mortality. It failed to demonstrate significant differences between ppFEV1, pulmonary exacerbation rates, or antibiotic utilization between treatment and placebo groups.

Flume et al<sup>5</sup> conducted AZLI CAT as a randomized, double-blind, placebo-controlled trial conducted to compare

continuous alternating inhaled antibiotic therapy (CAT) to intermittent inhaled antibiotic treatment regimens in CF patients with chronic PA airway infection. Study patients were randomized to receive TIS 300 mg BID for 28 days alternating with AZLI 75 mg TID or placebo for 28 days for a total of 28 weeks. Study participants were  $\geq 6$  years of age and had a history of PA airway infection, ppFEV1 25%-75%, and  $\geq 1$  hospitalization secondary to pulmonary exacerbation in the year prior to enrollment.

Study enrollment was limited secondary to several barriers, one of which was the early adoption of CAT as a standard clinical practice so only 90 of the 250 subjects necessary for adequate statistical power were randomized. The baseline demographics of aztreonam and placebo groups were similar, with a mean age of 28.4 years and most patients had a single pulmonary exacerbation requiring hospitalization in the previous year (55.7%). CAT reduced rates of pulmonary exacerbation by 25.7% ( $P = .25$ ) and hospitalization by 35.8% ( $P = .14$ ) compared with TIS alone. CAT patients required less additional antibiotics for pulmonary exacerbations (48.8% vs 55.3%) and had an increased median time to pulmonary exacerbation (35 days longer than TIS [ $P = .71$ ]). No significant changes in ppFEV1 or microbiology were identified. The most common treatment-emergent adverse events were cough, increased sputum, and dyspnea but no SAEs were considered treatment related.

AZLI CAT was an attempt to define its roles vs cyclic therapy in the management of CF patients with chronic PA airway infection. Although CAT resulted in decreased exacerbation and hospitalization rates compared with cyclic therapy with TIS, these differences were not statistically significant.

### Combined pediatric experience

The preceding studies excluded children  $< 6$  years of age.<sup>30</sup> However, 23% of the patients in the combined studies by Retsch-Bogart et al, McCoy et al, and Assael et al and 57% of study participants enrolled in Wainwright et al were pediatric patients between 6 and 17 years of age. Therefore, a retrospective analysis to determine the efficacy and safety of AZLI among pooled pediatric patients ( $< 18$  years of age) who participated in these studies was performed.<sup>30</sup> Efficacy data from (1) Retsch-Bogart et al and McCoy et al enrolled patients treated with TID AZLI ( $n = 83$  [55 AZLI]), (2) Wainwright et al enrolled patients with ppFEV1 75%-90% ( $n = 89$  [42 AZLI]), and (3) Assael et al enrolled patients ( $n = 59$  [42 AZLI]) were included in the analysis. Safety data from all patients were combined and included.

In the studies by Retsch-Bogart et al and McCoy et al, pediatric patients demonstrated increased ppFEV1. In all studies, pediatric patients demonstrated improvement in CFQ-R RSS compared with placebo or TIS and decreases in PA sputum density. Other efficacy and safety results in this pediatric subgroup analysis were reportedly similar to those among adults, with pediatric patients demonstrating fewer adverse events.

Tiddens et al<sup>31,32</sup> conducted the Aztreonam Lysine for Pseudomonas Infection Eradication (ALPINE) study as a phase 2, single-arm, multinational, open-label study evaluating the safety and efficacy of a 28-day course of AZLI 75 mg TID for eradication of newly acquired PA infection in pediatric CF patients. The study population included patients between 3 months and  $< 18$  years of age with initial or new onset PA infection.

The average age of the 105 patients enrolled was 6.26 years (range 3 months-16 years) and patients  $\geq 6$  years of age had a baseline ppFEV1  $> 80\%$ . The respiratory culture leading to study enrollment (index culture) was the first PA-positive culture for most patients (70.5%). Analysis of efficacy included 79 clinically evaluable patients who, by definition, completed 28 days of AZLI, did not receive additional anti-pseudomonal antibiotics during treatment, and completed the total 28-week study. Most clinically evaluable patients remained culture negative for PA (58.2%), with more patients achieving this outcome if they were culture negative at baseline (the first culture following the index culture and at the start of AZLI eradication treatment), negative for anti-pseudomonal antibodies, and their index culture was their first PA infection.

Patients who completed 4 weeks of AZLI ( $N = 101$ ) demonstrated PA-negative respiratory cultures rates of 89.1%, 75% at week 8, 63.4% at week 16, and 47.5% at week 28. Eradication rates were similar to other eradication regimens. Patients  $> 6$  years of age not meeting the primary endpoint had greater decreases in ppFEV1 and CFQ-R RSS than patients meeting the endpoint. The most common treatment-emergent adverse events were cough (41%), pyrexia (14.3%), and rhinorrhea (9.5%). The study reports no significant changes in PA susceptibility to AZLI. This study demonstrated that AZLI was safe and effective as an eradication therapy for pediatric patients with new emergence of *Pseudomonas* infection and should be considered for initial antimicrobial eradication therapy.

ClinicalTrials.gov<sup>33</sup> and Accurso et al<sup>34</sup> conducted PA in the lower airways Pediatric Aztreonam Lysine Safety (PALS) as an open-label, single-arm, multi-center, multinational study to evaluate the safety of three courses of AZLI 75 mg TID in pediatric CF patients  $\leq 12$  years of age with chronic PA airway infection. Of the 59 patients who completed the study, the majority were between 6 and 12 years of age ( $N = 52$ , 85%) and had mild lung disease (mean ppFEV1 = 80.31%) and respiratory symptoms (mean CFQ-R RSS = 71.73  $\pm$  17.33). At the end of the study period, no patients had discontinued study participation secondary to safety or tolerability concerns. Patients experienced improvements in ppFEV1 and CFQ-R RSS and decreases in sputum PA density at all time points assessed throughout the study period. During the study period, additional anti-pseudomonal antibiotics were not required by 42.6% of patients, almost 38% of patients experienced at least one pulmonary exacerbation and 18% required hospitalization. The most common adverse events reported were cough, pyrexia,

**Table 2.** Post-approval completed studies.

STUDY	DESIGN	POPULATION	INTERVENTION	CLINICAL OUTCOMES	COMMENTS
Wainwright et al <sup>27</sup> (AIR-CF4)	R, DB, PCT	157 CF patients with PA ≥6 years FEV <sub>1</sub> >75%	28 days AZLI TID vs PBO	No change in CFQ-R ↑ FEV <sub>1</sub> ↓ Sputum PA density	Larger treatment effect FEV <sub>1</sub> 75%-90% Healthier patients Sample size
Assael et al <sup>28</sup> (AZLI-TIS active comparator)	Open-label R, Parallel group	268 CF patients with PA ≥6 years FEV <sub>1</sub> ≤75%	AZLI TID or TIS BID for 3 x28 day on/off cycles	↑ FEV <sub>1</sub> vs TIS ↓ Hospitalizations ↓ PE ↓ Utilization of anti-PA antibiotics	Study design Few pediatric patients Clinical application
Tullis et al <sup>29</sup> (AZLI in <i>Burkholderia</i> )	R, DB, PCT	100 CF patients ≥6 years with chronic <i>Burkholderia</i> spp. infection	AZLI TID continuous for 24 weeks vs PBO then 24 week open-label extension	No change in lung function No change in sputum density	Sample size Variable treatments resulting in confounders Heterogeneous population
Flume et al <sup>5</sup> (AZLI CAT)	R, DB, PCT	90 CF patients with PA ≥6 years	Cyclic AZLI TID vs PBO with open-label TIS for 3 cycles	Non-significant ↓ in hospitalization and PE	Under enrolled with failure to meet power
Retsch-Bogart et al <sup>30</sup> (combined pediatric experience)	Post hoc subset analysis of R, DB, PCT	165 AIR-CF1, AIR-CF2, AIR-CF4, and AZLI-TIS active comparator Pediatric patients ≥6 years to <18 years FEV <sub>1</sub> 25%-75%	28 days AZLI vs PBO or 28 days of TIS then 28 days of AZLI BID or TID vs PBO	↑ FEV <sub>1</sub> similar to adults Slightly less respiratory adverse events than adults	Subgroup analysis Sample size
Tiddens et al <sup>31</sup> (ALPINE)	Single-arm, open-label	105 CF patients with new PA 3 months to <18 years FEV <sub>1</sub> ≥80%	28 days AZLI TID	89.1% PA (-) at end of treatment 75.2% PA (-) 4 weeks post-treatment 58.2% PA (-) at all post-treatment time points	Study design Culture sampling primarily by throat swab Primary outcome measure at the end of the study period High baseline negative culture rates
Accurso et al <sup>34</sup> (PALS)	Single-arm, open-label	61 pediatric CF patients ≤12 years with PA	28 days of AZLI TID for 3 cycles	No discontinuation for safety or tolerability reasons ↑ FEV <sub>1</sub> ↑ CFQ-R	Study design Not powered or designed to assess efficacy outcomes

Abbreviations: AZLI, aztreonam lysine for inhalation; BID, twice daily; CAT, continuous alternating inhaled antibiotic therapy; CFQ-R, Cystic Fibrosis Questionnaire-Revised; DB, double-blind; FEV<sub>1</sub>, forced expiratory volume in one second; PA, *Pseudomonas aeruginosa*; PALS, Pediatric Aztreonam Lysine Safety; PBO, placebo; PCT, placebo-controlled trial; PE, pulmonary exacerbation; R, randomized; TID: three times daily; TIS, tobramycin inhaled solution.

nasal congestion, and rhinorrhea, while 13 patients (21.31%) experienced an SAE most likely associated with underlying disease.

This study provides additional safety and efficacy data for a younger pediatric cohort treated with AZLI for chronic PA infection including improvements in respiratory outcomes and tolerability over three treatment courses (Table 2).

Post-approval studies demonstrate improvement in ppFEV<sub>1</sub> for use of AZLI and the treatment of PA but no significant efficacy found with treatment of *Burkholderia* infection. The Wainwright et al study was limited by short duration of treatment, inadequate sample size estimation limiting power to detect small changes and challenges with symptom scores as the ideal outcome measure for studies including patients with mild lung disease. Assael et al was limited by an open-label study design, small pediatric patients and including a majority of patients receiving TIS >84 days especially given

studies demonstrating waning effects of TIS with chronic therapy.<sup>25,26,28</sup> Tullis et al had a highly heterogeneous patient population and lack of controls for variable standards of care or other treatments, especially additional antibiotics. Analysis of CAT therapy favored hospitalization and decreased pulmonary exacerbation but not significantly. Study enrollment was severely limited by high rates of early adoption of CAT into clinical practice so the study suffered from an insufficient sample size and was inadequately powered to detect significant differences between groups. Questions regarding optimum use of inhaled antibiotics for management of chronic PA infection remain unanswered. Pediatric analysis with AZLI found an increase in ppFEV<sub>1</sub> and efficacy as an eradication strategy of PA. Pediatric subgroup analysis introduced potential bias of a small number of patients and limited data presented only in abstract form without statistical analysis. The Tiddens et al and Accurso et al limitations include study



design (open-label, uncontrolled and single-arm), challenges with comparison to other studies, and limited patient population and duration.

#### *Post-approval ongoing studies*

Gilead Sciences, Inc.<sup>35</sup> completed AIR-CF5 as a prospective, multi-center, longitudinal, 5-year study begun in 2011 as a post-marketing requirement by the FDA. Its objective was to monitor the aztreonam susceptibility of PA isolates taken from the respiratory cultures of a subset of patients from the CF Patient Registry. Specimens for microbiological evaluation were obtained at enrollment then annually for 5 years. The study enrolled 510 participants  $\geq 6$  years of age and was completed in December 2016. Inclusion criteria were ppFEV1  $\geq 25\%$  and  $\leq 90\%$  and a history of PA-positive cultures. Interim data were presented at the North American CF Conference (NACFC) in 2014, 2015, 2016, and 2017. Final results from this study have not yet been published but should provide valuable information regarding resistance patterns during long-term use of inhaled antibiotics.

Co-primary investigators Howenstine and Anderson<sup>36</sup> are conducting a single-center, pilot study of inhaled antibiotic regimens to assess the potential relationship between patients' inhaled antibiotic regimens and clinical and microbiological outcomes. The authors hypothesized that alternating AZLI and TIS would inhibit the development of antibiotic resistance and decrease the prevalence of resistance among bacterial isolates from CF patients. The primary outcome measure was change in an antibiotic resistance profile that included PA resistance, change in PA sputum density, MIC of aztreonam and tobramycin against PA, and changes in other microorganisms identified. Secondary outcome measures include clinical symptoms including changes in CFQ-R RSS, ppFEV1, and hospitalization rates. The targeted enrollment was 27 patients  $> 6$  years old, had a history of PA, and were on an inhaled antibiotic regimen at the time of randomization. Treatment regimens included AZLI only (every other month), TIS only (every other month), or CAT (AZLI and TIS alternating every other month). Results have not been published at this time, but completed in October 2015.

Rubin<sup>37</sup> is conducting a phase 2, two-center, randomized, parallel group, placebo-controlled pilot study evaluating the safety and efficacy of conventional AZLI (75 mg inhaled TID) plus nasal AZLI instillation (75 mg BID) vs conventional AZLI in CF patients with PA infection. The primary outcome measure is the number of pulmonary exacerbations attributed to PA infection. Secondary outcome measures include time to pulmonary exacerbation attributed to PA infection, change in CFQ-R, change in ppFEV1, change in sinus and nasal quality of life questionnaire (SNOT-20), microbiology, and safety analysis. The study aims to enroll 30 patients  $\geq 7$  years and a history of PA infection and started January 2017 with anticipated completion of January 2018.

Frost<sup>38</sup> is conducting a phase 4, single-center, randomized, open-label, cross-over pilot study to assess the use of AZLI (75 mg TID) plus intravenous colistimethate vs standard dual anti-pseudomonal intravenous therapy for the treatment of CF exacerbations. Study patients will receive either AZLI plus intravenous colistimethate or standard dual intravenous anti-pseudomonal therapy for 14 days during their first exacerbation and the alternative regimen for their subsequent exacerbation. The primary outcome measure is the change in ppFEV1 at day 28. Secondary outcome measures include time to subsequent pulmonary exacerbation, CFQ-R RSS, sputum PA density, changes in the patient's microbiome, and the prevalence of antibiotic resistance. The study aims to enroll 16 male patients between 16 and 65 years of age who have a history of PA infection and ppFEV1  $\geq 25\%$  to  $\leq 75\%$  with an anticipated completion of July 2018.

National Jewish Health<sup>39</sup> is conducting an observational, single-center, prospective cohort study evaluating changes in inflammatory biomarkers during treatment with AZLI (75 mg TID). The primary outcome measure is changes from baseline values on a standard genetic biomarker panel which are specific white blood cell compounds that predict decreased infection and inflammation during treatment with intravenous antibiotics. Secondary outcome measures include ppFEV1, sputum PA density, changes in other inflammatory markers (C-reactive protein, interleukin 8), and symptom reports. A total of 30 AZLI-treated patients aged 18-75 years who have a history of PA infection and a ppFEV1  $\geq 25\%$  will be enrolled and the study completed by January 2018 (Table 3).

#### **Availability and Access**

The European Medicines Agent approved AZLI September 21, 2009 for patients  $\geq 6$  years and the FDA approved AZLI to improve respiratory symptoms in CF patients with pulmonary PA infections  $\geq 7$  years on February 23, 2010.<sup>40,41</sup> It is supplied as single-use vials containing 75 mg of lyophilized aztreonam that must be reconstituted with 1 mL of a sterile diluent (0.17% sodium chloride) prior to inhalation.<sup>16,17</sup> It is delivered through the Altera nebulizer system. AZLI is approved to be used as TID therapy in 28-day on/off cycles. A 28-day treatment course based on average wholesale price is approximately USD10,000 but actual cost to patients is variable.<sup>16</sup> Inhaled aztreonam is only available through a small number of specialty pharmacies.<sup>42</sup> For patients with barriers to access, the Cayston Access Program<sup>®</sup> offers assistance with general information, insurance issues, and financial assistance.<sup>42</sup>

#### **Clinical Overview and Application**

Published data from clinical trials demonstrate improvements in lung function, decreased pulmonary exacerbations, and improvement in respiratory symptoms when AZLI is used in 28-day cycles as suppressive therapy.<sup>19,23</sup> Long-term study data show that AZLI use is associated with consistent, sustained weight gain among CF patients.<sup>24</sup> AZLI was found to be safe



Table 3. Post-approval ongoing studies.

STUDY	DESIGN	POPULATION	INTERVENTION	CLINICAL OUTCOMES/ PLANNED	COMMENTS
Gilead Sciences, Inc. <sup>35</sup> (AIR-CF5)	Prospective, observational	CF patients $\geq 6$ years with PA FEV1 25%-90%	Registry data collecting sputum samples for AZLI-treated patients	Annualized proportion of $\geq 4$ -fold MIC $\uparrow$ and above parental breakpoint across 5 years	Sampling techniques Confounders Study duration
Co-PI: Howenstine and Anderson <sup>36</sup>	Prospective, observational, cohort	CF patients $\geq 6$ years with PA	AZLI cohort TIS cohort AZLI-TIS cohort	Antibiotic resistance profiles: microbial resistance, sputum density, MIC of tobramycin and aztreonam microbiome changes every 3 months for 12 months	Sampling techniques Sample size and enrollment challenges Study duration
PI: Rubin <sup>37</sup>	R, PCT Parallel group pilot	CF patients $\geq 7$ years with PA FEV1 $\geq 30\%$	AZLI TID + AZLI Nasal BID or PBO Nasal BID	PE rate Time to exacerbation SNOT-20 CFQ-R Change in FEV1 Microbiology	Sampling techniques Sample size Incorporation into clinical practice
PI: Frost <sup>38</sup>	R, open-label Cross-over	CF patients $\geq 16$ years with PA FEV1 25%-75%	AZLI TID + SOC then SOC or SOC then AZLI TID + SOC SOC: IV colistin + additional anti-PA IV antibiotic	Change in FEV1 Time to exacerbation CFQ-R Microbiology	Sample size Variability in PE treatment externally Utilization of IV colistin
National Jewish Health <sup>39</sup>	Prospective, observational cohort	CF patients $\geq 18$ years with PA FEV1 $\geq 25\%$	New AZLI treatment or no NEB anti-PA antibiotic for 28 days prior to study	Gene biomarker panel Change in FEV1 Sputum density Symptom scores Non-specific inflammatory markers: CRP, IL-8	Study design Small sample size Limited duration Confounding variables

Abbreviations: AZLI, aztreonam lysine for inhalation; BID, twice daily; CFQ-R, Cystic Fibrosis Questionnaire Revised; SNOT-20, Sino-Nasal Outcome Test 20; CRP, C-reactive protein; IL-8, interleukin 8; FEV1, forced expiratory volume in 1 second; MIC, minimum inhibitory concentration; NEB, nebulized; PA, *Pseudomonas aeruginosa*; PBO, placebo; PCT, placebo-controlled trial; PE, pulmonary exacerbation; PI, primary investigator; SOC, standard of care; TID, three times daily; TIS, tobramycin inhaled solution.

across all AZLI trials, with most adverse events classified as mild and respiratory in nature. A specific concern with chronic antibiotic therapy is the development of resistance; however, the clinical trials completed to date have not identified significant or consistent changes in resistance or microbiology. In addition, Cystic Fibrosis Foundation (CFF) Guidelines and National Institute for Health and Care Excellence (NICE) Guidelines support the use of AZLI for chronic PA infection.<sup>43,44</sup> The CFF Guidelines for chronic management of CF lung disease were published prior to the most AZLI publications. Therefore, the recommendations are somewhat limited but do recommend AZLI for patients with CF  $> 6$  years of age with mild, moderate, and severe lung disease and chronic *Pseudomonas* infection to improve lung function and quality of life.<sup>43</sup> The NICE guidelines, published in 2017, stated AZLI was better than placebo with regard to lung function, weight gain, and quality of life, and that AZLI was superior to tobramycin in decreasing pulmonary exacerbations.<sup>44</sup> There were no clinically significant differences between AZLI and TIS in lung function, change in sputum density, quality of life, or weight gain.<sup>26</sup> AZLI has been shown to be safe and effective when used as AET in CF patients with initial or early

*Pseudomonas* infection.<sup>31,32</sup> The eradication trial using AZLI demonstrates eradication rates similar to those reported for inhaled tobramycin and inhaled colistimethate with or without oral ciprofloxacin.<sup>31,32</sup> Therefore, AZLI may be considered as appropriate initial therapy for PA eradication. Based on recommendations from the CF Foundation and guidelines inhaled antibiotics including AZLI should be administered after bronchodilators, mucolytic therapy, and airway clearance.<sup>43</sup> The body of evidence reviewed above supports the safety and efficacy of AZLI as a first-line agent for eradication of initial PA infection and chronic, suppressive therapy. Medication nonadherence is associated with higher costs and healthcare visits including hospitalizations.<sup>45</sup> Clinicians should consider rapid administration of AZLI TID vs longer administration of tobramycin BID in discussions of inhaled PA therapy.

### Ongoing Studies

Questions regarding how to optimally manage chronic suppressive anti-pseudomonal therapy with the available anti-pseudomonal inhaled antibiotics were not answered by the Flume et al<sup>5</sup> study over CAT. Thus, this remains a significant unanswered question requiring additional investigation. A

standardized, evidence based approach to treatment of CF sinus disease associated with PA infection is not well defined and on-going studies attempt to provide guidance including work by Rubin and colleagues.<sup>37</sup> Furthermore, the potential use of AZLI during pulmonary exacerbation and as an adjunct to anti-inflammatory therapy is also being studied by Frost and colleagues<sup>38</sup> as well as National Jewish Health.<sup>39</sup> If the use of AZLI during exacerbations is effective, it may allow for decreased use of other IV antibiotics with known systemic toxicities. There are still important quest to be addressed including the development of resistance over time, eradication of *Pseudomonas* in infants <3 months of age, and the integration of AZLI's into overall care plans as new CFTR modulators are developed and approved. Furthermore, the use of AZLI in pregnancy has not been studied in a systematic fashion but may offer advantages as a pregnancy risk factor B with placenta transmission of minimal systemic concentrations.<sup>9,46,47</sup> Providing answers to all of these questions may allow the CF care community to standardize our approach with evidence-based guidelines to the treatment of chronic PA infection.

## Conclusions

The pharmacologic management of CF has changed dramatically over the past several decades. This, in conjunction with other advances in care, has had a significant role in increasing survival and improving quality of life among people with CF. The development of AZLI has been an important part of this process. CFF and NICE guidelines recommend the use of AZLI for patients with chronic *Pseudomonas* infection. There is less clear guidance regarding antimicrobial eradication therapy but both NICE and the CFF recommend consideration of inhaled antibiotics, which should include AZLI. Despite guideline recommendations, significant questions remain regarding how AZLI and other inhaled antibiotics should be incorporated into routine or standardized CF care. Future research to answer these questions will be critical in continuing to improve the lives of people with CF.

## Author Contributions

All authors conceived the project. ECE designed the outline, collected the published articles and analyzed and completed the manuscript drafts. All authors discussed the drafts, made critical revisions and contributed to the final manuscript.

## Authors' Note

The manuscript is not under review or in press in other medical journals and the content has not been previously presented or published.

## ORCID iD

Elizabeth Claire Elson  <https://orcid.org/0000-0002-1089-7531>

## REFERENCES

1. Elborn JS. Cystic fibrosis. *Lancet*. 2016;388:2519–2531.
2. Rosenstein BJ. Merck manual. 2017. Website. <https://www.merckmanuals.com/professional/pediatrics/cystic-fibrosis-cf/cystic-fibrosis>. Accessed January 17, 2018.
3. Henry RL, Mellis CM, Petrovic L. Mucoid *Pseudomonas aeruginosa* is a marker of poor survival in cystic fibrosis. *Pediatr Pulmonol*. 1992;12:158–161.
4. Emerson J, Rosenfeld M, McNamara S, Ramsey B, Gibson RL. *Pseudomonas aeruginosa* and other predictors of mortality and morbidity in young children with cystic fibrosis. *Pediatr Pulmonol*. 2002;34:91–100.
5. Flume PA, Clancy JP, Retsch-Bogart GZ. Continuous alternating inhaled antibiotics for chronic pseudomonal infection in cystic fibrosis. *J Cyst Fibros*. 2016;15:809–815.
6. Treggiari MM, Rosenfeld M, Mayer-Hamblett N, et al. Early anti-pseudomonal acquisition in young patients with cystic fibrosis: rationale and design of the EPIC clinical trial and observational study. *Contemp Clin Trials*. 2009;30:256–268.
7. Ratjen F, Munck A, Kho P, Angyalosi G. Treatment of early *Pseudomonas aeruginosa* infection in patients with cystic fibrosis: the ELITE trial. *Thorax*. 2010;65:286–291.
8. Van de Kerkhove C, Goeminne PC, Kicinski M, et al. Continuous alternating inhaled antibiotic therapy in CF: a single center retrospective analysis. *J Cyst Fibros*. 2016;15:802–808.
9. Cayston® [Package Insert]. Foster City, CA: Gilead Sciences, Inc.; 2014.
10. U.S. Food And Drug Administration approves Cayston® (aztreonam for inhalation solution) for the improvement of respiratory symptoms in cystic fibrosis patients with pseudomonas aeruginosa. 2010. Website. <http://investors.gilead.com/news-releases/news-release-details/us-food-and-drug-administration-approves-cayston-aztreonam>. Accessed May 21, 2017.
11. Hutchinson D, Barcla M, Prescott WA, Brown J. Inhaled aztreonam lysine: an evidence-based review. *Expert Opin Pharmacother*. 2013;15:2115–2124.
12. Zeidler K, Salvas B, Stevens V, Brown J. Aztreonam lysine for inhalation: new formulation of an old antibiotic. *Am J Health Syst Pharm*. 2012;69:107–115.
13. Plosker GL. Aztreonam lysine for inhalation solution in cystic fibrosis. *Pediatr Drugs*. 2011;13:129–131.
14. Parkins MD, Elborn JS. Aztreonam lysine: a novel inhalational antibiotic for cystic fibrosis. *Expert Rev Respir Med*. 2010;4:435–444.
15. Kim S, Thiessen PA, Bolton EE, et al. PubChem substance and compound databases. *PubChem CID 5742832*. 2016;44:D1202-D1213. Website. <https://pubchem.ncbi.nlm.nih.gov/compound/5742832>. Accessed May 21, 2017.
16. Cayston®. *Lexi-Drugs. Lexicomp*. Riverwoods, IL: Wolters Kluwer Health, Inc. Website. <http://online.lexi.com>. Accessed May 21, 2017.
17. Cayston®. *Micromedex Solutions*. Ann Arbor, MI: Truven Health Analytics, Inc. Website. <http://www.micromedexsolutions.com>. Accessed May 21, 2017.
18. *Altera Nebulizer System Instructions for Use*. Midlothian, VA: PARI Respiratory Equipment; 2014. Website. [https://www.cayston.com/pdfs/Altera\\_Nebulizer\\_System\\_IFU.pdf](https://www.cayston.com/pdfs/Altera_Nebulizer_System_IFU.pdf). Accessed May 21, 2017.
19. Retsch-Bogart GZ, Quittner AL, Gibson RL, et al. Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis. *Chest*. 2009;135:1223–1232.
20. McCoy KS, Quittner AL, Oermann CM, Gibson RL, Retsch-Bogart GZ, Montgomery AB. Inhaled aztreonam lysine for chronic airway *Pseudomonas aeruginosa* in cystic fibrosis. *Am J Respir Crit Care Med*. 2008;178:921–928.
21. Oermann CM, Retsch-Bogart GZ, Quittner AL, et al. An 18-month study of the safety and efficacy of repeated courses of inhaled aztreonam lysine in cystic fibrosis. *Pediatr Pulmonol*. 2010;45:1121–1134.
22. Guyatt GH. Making sense of quality-of-life data. *Med Care*. 2000;38:II175–II179.
23. Jaeschke R, Singer J, Guyatt GH. Measurement of health status: ascertaining the minimal clinically important difference. *Control Clin Trials*. 1989;10:407–415.
24. Quittner AL, Modi AC, Wainwright C, Otto K, Kiriara J, Montgomery AB. Determination of the minimal clinically important difference scores for the cystic fibrosis questionnaire-revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic *Pseudomonas aeruginosa* airway infection. *Chest*. 2009;135:1610–1618.
25. Ramsey BW, Pepe MS, Quan JM, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. *N Engl J Med*. 1999;340:23–30.
26. Bowman CM. The long-term use of inhaled tobramycin in patients with cystic fibrosis. *J Cyst Fibros*. 2002;1:194–198.
27. Wainwright CE, Quittner AL, Geller DE, et al. Aztreonam for inhalation solution (AZLI) in patients with cystic fibrosis, mild lung impairment, and *P. aeruginosa*. *J Cyst Fibros*. 2011;10:234–242.
28. Assael BM, Pressler T, Bilton D, et al. Inhaled aztreonam lysine vs. inhaled tobramycin in cystic fibrosis: a comparative efficacy trial. *J Cyst Fibros*. 2013;12:130–140.
29. Tullis DE, Burns JL, Retsch-Bogart GZ, et al. Inhaled aztreonam for chronic Burkholderia infection in cystic fibrosis: a placebo-controlled trial. *J Cyst Fibros*. 2014;13:296–305.

30. Retsch-Bogart GZ, McCoy KS, Oermann CM, et al. Aztreonam for inhalation solution (AZLI) clinical development program: combined pediatric experience. *Pediatr Pulmonol Suppl.* 2011;46:106–445.
31. Tiddens H, De Boeck K, Clancy JP, et al. Open label study of inhaled aztreonam for *Pseudomonas* eradication in children with cystic fibrosis: the ALPINE study. *J Cyst Fibros.* 2015;14:111–119.
32. Tiddens H, De Boeck C, Clancy JP, et al. Aztreonam for inhalation solution (AZLI) for eradication of new onset *Pseudomonas aeruginosa* (PA) infection in children with cystic fibrosis (CF): initial results from a phase 2 study. *Pediatr Pulmonol Suppl.* 2013;48:103–472.
33. ClinicalTrials.gov. Safety of AZLI in children with cystic fibrosis (CF) and chronic *Pseudomonas aeruginosa* in the lower airways (PALS), (Identifier NCT01404234). Bethesda, MD: National Library of Medicine; July 26, 2011. Website. <https://clinicaltrials.gov/ct2/show/NCT01404234?term=NCT01404234&rank=1>
34. Accurso FJ, Fayon M, Sermet I, Lewis SA. Aztreonam for inhalation solution (AZLI) treatment in children with cystic fibrosis (CF) and chronic *Pseudomonas aeruginosa* (PA) infection. *Pediatr Pulmonol Suppl.* 2013;48:103–472.
35. ClinicalTrials.gov. Registry to monitor the susceptibility to aztreonam of *Pseudomonas aeruginosa* isolates from cystic fibrosis patients (AIR-CF5), (Identifier NCT01375036). Bethesda, MD: National Library of Medicine, June 15, 2011. Website. <https://clinicaltrials.gov/ct2/show/NCT01375036?term=NCT01375036&rank=1>
36. ClinicalTrials.gov. A comparator study evaluating microbiological resistance and effects of alternating inhaled antibiotic therapies, (Identifier NCT01319253). Bethesda, MD: National Library of Medicine, June 15, 2011. Website. <https://clinicaltrials.gov/ct2/show/NCT01319253?term=NCT01319253&rank=1>
37. ClinicalTrials.gov. Aztreonam aerosol to treat cystic fibrosis nasal disease, (Identifier NCT02730793). Bethesda, MD: National Library of Medicine, November 3, 2015. Website. <https://clinicaltrials.gov/ct2/show/NCT02730793?term=NCT02730793&rank=1>
38. ClinicalTrials.gov. Aztreonam for inhalation solution (AZLI) for treatment of exacerbations of cystic fibrosis (AZTEC-CF), (Identifier NCT02894684). Bethesda, MD: National Library of Medicine. September 1, 2015. Website. <https://clinicaltrials.gov/ct2/show/NCT02894684?term=NCT02894684&rank=1>
39. ClinicalTrials.gov. Detection of reductions in cystic fibrosis airway inflammation while using aztreonam lysine solution, (Identifier NCT01736839). Bethesda, MD: National Library of Medicine. November 15, 2012. Website. <https://clinicaltrials.gov/ct2/show/NCT01736839?term=NCT01736839&rank=1>
40. U.S. Food and Drug Administration. Drug approval package. Website. [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2010/050814s000\\_cayston\\_toc.cfm](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/050814s000_cayston_toc.cfm) CAP program. Accessed January 15, 2018.
41. Cayston®. Summary of product characteristics. Website. [https://www.ema.europa.eu/en/documents/product-information/cayston-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/cayston-epar-product-information_en.pdf). Accessed January 15, 2018.
42. Cayston®. Cayston Access Program®. Website. <https://www.cayston.com/programs/cayston-access-program>. Accessed January 15, 2018.
43. Mogayzel PJ, Naureckas ET, Robinson KA, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *Am J Respir Crit Care Med.* 2013;187:680–689.
44. National Institute for Health and Care Excellence. Cystic fibrosis: diagnosis and management (NICE Guideline 78). 2017. Website. <https://www.nice.org.uk/guidance/ng78> Accessed April 4, 2018.
45. Quittner AL, Zhang J, Marynchenko M, et al. Pulmonary medication adherence and health-care use in cystic fibrosis. *Chest.* 2014;146:142–151.
46. Edenborough FP, Borgo G, Knoop C, et al. Guidelines for the management of pregnancy in women with cystic fibrosis. *J Cyst Fibros.* 2008;7:2–32.
47. McArdle J. Pregnancy in cystic fibrosis. *Clin Chest Med.* 2011;32:111–120.