CHEST

Original Research

CYSTIC FIBROSIS

Efficacy and Safety of Inhaled Aztreonam Lysine for Airway Pseudomonas in Cystic Fibrosis*

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Background: **We assessed the short-term efficacy and safety of aztreonam lysine for inhalation (AZLI [an aerosolized monobactam antibiotic]) in patients with cystic fibrosis (CF) and *Pseudomonas aeruginosa* (PA) airway infection.**

Methods: **In this randomized, double-blind, placebo-controlled, international study (AIR-CF1 trial; June 2005 to April 2007), patients (n = 164; ≥ 6 years of age) with FEV_1 ≥ 25% and ≤ 75% predicted values, and no recent use of antipseudomonal antibiotics or azithromycin were treated with 75 mg of AZLI (three times daily for 28 days) or placebo (1:1 randomization), then were monitored for 14 days after study drug completion. The primary efficacy end point was change in patient-reported respiratory symptoms (CF-Questionnaire-Revised [CFQ-R] Respiratory Scale). Secondary end points included changes in pulmonary function (FEV_1), sputum PA density, and nonrespiratory CFQ-R scales. Adverse events and minimum inhibitory concentrations of aztreonam for PA were monitored.**

Results: **After 28 days of treatment, AZLI improved the mean CFQ-R respiratory score (9.7 points; $p < 0.001$), FEV_1 (10.3% predicted; $p < 0.001$), and sputum PA density (− 1.453 $\log_{10}$ cfu/g; $p < 0.001$), compared with placebo. Significant improvements in Eating, Emotional Functioning, Health Perceptions, Physical Functioning, Role Limitation/School Performance, and Vitality CFQ-R scales were observed. Adverse events were consistent with symptoms of CF lung disease and were comparable for AZLI and placebo except the incidence of "productive cough" was reduced by half in AZLI-treated patients. PA aztreonam susceptibility at baseline and end of therapy were similar.**

Conclusions: **In patients with CF, PA airway infection, moderate-to-severe lung disease, and no recent use of antipseudomonal antibiotics or azithromycin, 28-day treatment with AZLI significantly improved respiratory symptoms and pulmonary function, and was well tolerated.**

Trial registration: **Clinicaltrials.gov Identifier: NCT00112359** ***(CHEST 2009; 135:1223–1232)***

Key words: aztreonam; cystic fibrosis; inhaled antibiotics; patient-reported outcomes; Pseudomonas; respiratory symptoms

Abbreviations: AZLI = aztreonam lysine for inhalation; CF = cystic fibrosis; CFQ-R = Cystic Fibrosis Questionnaire-revised; CFQ-R-Respiratory = Cystic Fibrosis Questionnaire-Revised Respiratory Symptom Scale; CI = confidence interval; MCID = minimal clinically important difference; MIC = minimum inhibitory concentration; MIC_{50} = minimum inhibitory concentration inhibiting the growth of 50% of *Pseudomonas aeruginosa* isolates; MIC_{90} = minimum inhibitory concentration inhibiting the growth of 90% of *Pseudomonas aeruginosa* isolates; PA = *Pseudomonas aeruginosa*; PRO = patient-reported outcome; TIS = tobramycin inhalation solution

Clinical management of cystic fibrosis (CF) has improved during the past 15 years. Increased standardization of care and a focus on maintenance therapies, including nutrition, combined with the introduction of dornase alfa in 1993, tobramycin inhalation solution (TIS) in 1998, and the widespread long-term use of azithromycin (a macrolide antibiotic) have been associated with an approximate 8-year increase in median predicted survival age (increase from 1990 to 2005 to 36.5 years of age) and

a 10% increase in median FEV_1 percent predicted (from 1990 to 2005).[1–5] However, a sizable proportion of patients with CF do not receive long-term TIS or macrolide therapy. In 2005, among US patients in a national registry who were ≥ 6 years of age with CF and *Pseudomonas aeruginosa* (PA) airway infection, 42% of patients were not receiving long-term TIS therapy, and 46% of patients who were eligible for long-term macrolide therapy were not receiving it.[1] Lack of compliance likely further reduces the number of patients receiving therapy; in one recent study, dosing compliance ranged from 51% (older patients) to 73% (younger patients).[6] The reasons underlying the lack of treatment may include a lack of clinical response or drug availability, patient or physician preference, or drug intolerance. Additional antimicrobial treatment options are needed for treating chronic PA airway infection and may improve the health of these less intensively treated patients.

Aztreonam lysine for inhalation (AZLI) is an aerosolized formulation of the monobactam antibiotic, aztreonam, and lysine.[7] The IV aztreonam formulation contains arginine, which can cause airway inflammation after long-term inhalation in patients with CF.[8,9] In a previous study,[10] AZLI increased the time to the need for additional inhaled or IV antipseudomonal antibiotics to treat symptoms indicative of pulmonary exacerbation; enrolled patients were generally compliant with current guidelines for CF care. In contrast, the study we report herein included patients receiving less maintenance therapy than currently recommended.[11] Patients had not recently received therapy with antipseudomonal antibiotics, azithromycin, or aerosolized hypertonic saline solution. The study hypothesis was that treatment with AZLI, when compared with placebo, would produce a clinically significant improvement in patient-reported respiratory symptoms. The primary efficacy end point was the change in clinical symptoms, measured with the Cystic Fibrosis Questionnaire-Revised Respiratory Symptom Scale (CFQ-R-respiratory). The Cystic Fibrosis Questionnaire-Revised (CFQ-R) is a validated, health-related, quality-of-life measure meeting the most recent US Food and Drug Administration draft guidelines on patient-reported outcomes (PROs).[12–15]

Materials and Methods

Study Design

This randomized, double-blind, placebo-controlled, study was conducted at 53 CF centers (in Australia, Canada, New Zealand, and the United States; June 2005 to April 2007). At baseline (day 0), patients were stratified by CF disease severity (moderate disease, FEV_1 > 50% to ≤ 75% predicted; severe disease, FEV_1 ≥ 25% to ≤ 50% predicted; measured at screening) and randomly assigned to 28 days of treatment with 75 mg of AZLI or placebo (randomized 1:1; administered three times daily). Patients were monitored at midtreatment (day 14), at treatment end (day 28), and at study end (day 42) [Fig 1]. Randomization was accomplished through a Web-based system using a computer-generated randomization schedule. This centralized randomization was stratified by baseline disease severity (FEV_1 ≤ 50% or > 50% predicted) and employed a block size of 4.

A physical examination was performed at screening. Spirometry, using American Thoracic Society standards[16] was performed at every visit, before and 30 min after any treatment. FEV_1 percent predicted values were calculated using the equation of Knudson et al.[17]

AZLI (75 mg of aztreonam, 52.5 mg of lysine monohydrate) or placebo (5 mg of lactose), diluted in 1 mL of a 0.17% NaCl solution, were administered with a nebulizer (eFlow Electronic Nebulizer; PARI Innovative Manufacturers; Midlothian, VA).[18] Patients self-administered a short-acting β_2-agonist 15 min before spirometry measurements were made and study medication was administered at clinic visits, and self-administered a β_2-

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†A list of participating study sites, site investigators, and study research coordinators for the AIR-CF1 Trial is located in the Appendix.

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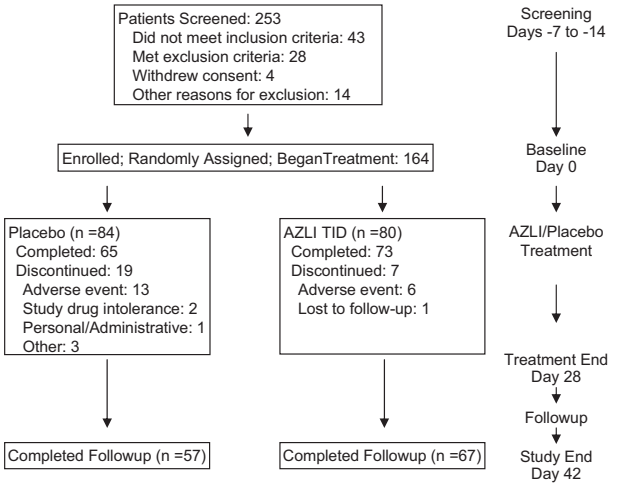

FIGURE 1. Study design and patient disposition.

agonist before administering the study medication at home (within 2 h before dosing for short-acting agents, or 30 min to 8 h before dosing for long-acting agents). Patients continued any prescribed bronchodilator use, excluding a 4-h period before study visits. Study medication was dispensed at baseline; used/unused vials were subsequently collected to assess treatment compliance.

This study was conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonisation guideline for Good Clinical Practices, and the applicable regulations for each participating country. Institutional review boards (in the United States) and ethics committees (in Canada, Australia, and New Zealand) approved the study for each site, and all patients or their guardians provided written informed consent or assent prior to undergoing any study procedures.

Study Population

Patients enrolled into the study were ≥ 6 years of age with a documented CF diagnosis, and had moderate-to-severe lung disease (FEV_1 ≥ 25% to ≤ 75% predicted), arterial oxygen saturation ≥ 90% on room air (at screening), the ability to perform reproducible pulmonary function tests, and PA airway infection (documented at screening or twice within previous year, including once within the previous 3 months) without regard to PA susceptibility to aztreonam. Exclusion criteria included recent (*ie*, day −28 to screening) administration of inhaled, IV, or oral antipseudomonal antibiotics, azithromycin, or aerosolized hypertonic saline solution; current oral corticosteroid use equivalent to > 10 mg of prednisone daily; airway cultures yielding *Burkholderia cepacia* complex (previous 2 years); daily continuous oxygen supplementation or > 2 L/min at night; monobactam antibiotic hypersensitivity; intolerance to inhaled short-acting β_2-agonists; recent changes in antimicrobial, bronchodilator, antiinflammatory, or corticosteroid medications, or physiotherapy technique/schedule; lung transplantation; new findings on chest radiograph at screening or in the previous 90 days; aspartate aminotransferase or alanine aminotransferase levels more than five times the upper limit of normal (at screening), or serum creatinine levels more than two times the upper limit of normal (at screening); pregnancy; lactation; or, in the opinion of the investigator, medical or psychiatric illness interfering with study participation. Patients were not permitted to use other antipseudomonal antibiotics or azithromycin during the study or during the 14-day follow-up period, unless required for the treatment of worsening symptoms.

Efficacy Measures

The CFQ-R was administered at baseline and at every visit thereafter. Unless noted, responses to adult, teen, and child versions were combined for presentation.[14] The primary efficacy end point was change in symptoms, assessed with CFQ-R-Respiratory scores (range, 0 to 100 points; increasing scores indicated improvement). The minimal clinically important difference (MCID) corresponds to the smallest change in symptoms that a patient can detect and is used to interpret responses to PROs.[19,20] An MCID score of 5 was previously determined for the CFQ-R-Respiratory Scale in stable patients.[21] Thus, 5-point changes in scores reflected improved or worsened respiratory symptoms detected by patients.

Secondary end points included changes in pulmonary function, hospitalizations, nonrespiratory CFQ-R scales, sputum PA density (in colony-forming units per gram sputum, $\log_{10}$ transformed), the minimum inhibitory concentration (MIC) of aztreonam for PA, the number of isolates and proportion of patients with an aztreonam MIC > 8 μg/mL for PA (*ie*, the parenteral breakpoint), and the prevalence of other pathogens.[22]

Safety Measures

Adverse events and changes in clinical laboratory values, vital signs, and airway reactivity were monitored. Worsening CF symptoms were treated as adverse events. Patients requiring therapy with nonstudy antipseudomonal antibiotics discontinued their participation in the study.

Statistical Analysis

Efficacy and safety analyses included all randomly assigned patients receiving one or more doses of AZLI/placebo. FEV_1 and CFQ-R analyses used the last-observation-carried-forward convention. Changes in FEV_1 (in liters) and changes in FEV_1 percent predicted were analyzed using relative values; increases and decreases were calculated as percentages of baseline FEV_1 or FEV_1 percent predicted values.

A sample size of 140 was estimated to provide 77% power to detect an 8-point difference for change in CFQ-R-Respiratory scores (assuming an SD of 20) and > 90% power to detect a 9% difference in FEV_1 (assuming an SD of 12), with two-sided $\alpha = 0.05$.

Continuous variables were analyzed using analysis of covariance models with treatment as the fixed effect; disease severity (moderate/severe) and baseline values (except analysis of $\log_{10}$ PA colony-forming units in sputum) were covariates. At day 28, patients were categorized as improved (a ≥ 5-point increase from baseline CFQ-R-Respiratory scores), worse (a ≥ 5-point decrease from baseline), or stable/no change (a < 5-point change). These categories were analyzed with the Cochran-Mantel-Haenszel mean score statistic; disease severity and baseline score were stratification variables.

Hospitalizations were analyzed using the Wilcoxon rank sum test (days) and Fisher exact test (proportion of patients). The aztreonam MIC inhibiting the growth of 50% of PA isolates (MIC_{50}) or the aztreonam MIC inhibiting the growth of 90% of PA isolates (MIC_{90}) and the presence of other pathogenic bacteria were summarized (Covance Central Laboratory Services; Indianapolis, IN) as were plasma and sputum aztreonam concentrations (Alta Analytical Laboratory; El Dorado Hills, CA).[22] A statistical software package (SAS, versions 8.02 and 9.1; SAS Institute Inc; Cary, NC) was used for analyses.

Results

Of the 253 patients screened, 164 began treatment with AZLI or placebo, 138 completed 28 days of treatment, and 124 completed the study (Fig 1). The compliance rate for dosing (≥ 80% of doses) was 92%. The most common reason for discontinuation of participation in the study during the 28-day treatment period was an adverse event (ALZI group, 6 patients [7.5%]; placebo group, 13 patients [15.5%]) [Fig 1]; most of these patients (16 of 19 patients) required treatment with nonstudy antipseudomonal antibiotics and had symptoms indicative of pulmonary exacerbation. The remaining three patients (all randomized to receive placebo) discontinued study participation due to hospitalizations for bowel obstruction (n = 1), for umbilical hernia requiring surgery (n = 1), or for *Staphylococcus aureus* bacteremia, volume depletion, vancomycin-resistant Enterococcus and Pseudomonas septicemia, and deep vein thrombosis of the upper left arm (n = 1).

Patient Characteristics

Demographic characteristics were well balanced between treatment groups (Table 1). The mean age was 29.6 years. Most patients (77.4%) were ≥ 18 years of age. At baseline, mean the FEV_1 was 54.6% predicted. The concomitant medications used by ≥ 40% patients at baseline included pancreatic enzymes (87%), vitamins (87%), salbutamol (79%), dornase alfa (65%), and fluticasone propionate with salmeterol xinafoate (40%).

Efficacy

The adjusted mean CFQ-R-Respiratory scores increased for AZLI-treated patients and decreased for placebo-treated patients (day 28 treatment difference, 9.7 points; 95% confidence interval [CI], 4.3 to 15.1; $p < 0.001$) [Fig 2, *left*, Table 2]. Two weeks after treatment, scores had declined but remained above baseline values for AZLI-treated patients, and had continued to decline for placebo-treated patients (day 42 treatment difference, 6.3 points; 95% CI, 1.2 to 11.4; $p = 0.015$) [Fig 2, *left*].

CFQ-R-Respiratory scores increased for AZLI-treated patients with differing disease severities and ages (Fig 2, *right*). Treatment effects were comparable in magnitude for patients with moderate or severe lung disease and were larger for younger patients (*ie*, those < 18 years of age).

CFQ-R-Respiratory scores improved for more AZLI-treated patients than placebo-treated patients (day 28; ≥ 5-point increase: AZLI group, 45 patients [56%]; placebo group, 31 patients [37%]). Scores also worsened for fewer AZLI-treated patients (≥ 5-point decrease: AZLI group, 20 patients [25%]; placebo group, 37 patients [45%]; $p = 0.006$ for overall comparison).

The adjusted mean FEV_1 increased for AZLI-treated patients and decreased for placebo-treated patients (day 28 treatment difference, 10.3%; 95% CI, 6.3 to 14.3; $p < 0.001$) [Fig 2, *left*]. Two weeks after treatment, the mean FEV_1 had declined but remained above baseline for AZLI-treated patients, and had continued to decline for placebo-treated patients (day 42 treatment difference, 5.7%; 95% CI, 2.1 to 9.4; $p = 0.002$). AZLI treatment improved

Table 1—*Patient Demographics and Baseline Characteristics

Characteristics	Placebo Group (n = 84)	AZLI Group (n = 80)
Country		
United States and Canada	63 (75.0)	62 (77.5)
Australia and New Zealand	21 (25.0)	18 (22.5)
Age,†‡ yr	31.7 (11–74)	27.4 (7–54)
Age group		
< 18 yr§	16 (19.0)	21 (26.3)
≥ 18 yr	68 (81.0)	59 (73.8)
Male gender	45 (53.6)	48 (60.0)
Weight,‖ kg	60.7 (15.2)	59.9 (17.3)
Body mass index,‖ kg/m^2	21.9 (3.9)	21.4 (4.3)
CFTR genotype		
Homozygous for ΔF508	30 (35.7)	38 (47.5)
Heterozygous for ΔF508	22 (26.2)	21 (26.3)
Unidentified or other	32 (38.1)	21 (26.3)
TIS¶		
Courses in previous year	1.7	1.8
Courses in previous year in United States and Canada	2.3	2.3
Dornase alfa use, %	64%	66%
FEV_1,‖ % predicted	54.8 (14.0)	54.4 (13.4)
Patients with $FEV_1 \leq 50\%$ predicted†	30 (35.7)	30 (37.5)
CFQ-R-respiratory score‖	60.9 (18.9)	60.5 (18.1)
MIC of aztreonam for all PA isolates		
MIC_{50}, μg/mL	2	4
MIC_{90}, μg/mL	64	128
Minimum MIC, μg/mL	≤ 1	≤ 1
Maximum MIC, μg/mL	256	> 2048
Isolates tested, No.	140	128

*Values are given as the No. (%) or mean (range), unless otherwise indicated.

†Data were obtained at screening (*ie*, between days − 7 and − 14).

‡The only significant difference ($p < 0.05$) in demographic or baseline characteristics between the two groups was in mean age; patients in the AZLI group were younger. However, the proportion of patients categorized as < 18 vs ≥ 18 years of age was not significantly different between the AZLI and placebo groups.

§Includes 15 children ≥ 6 to ≤ 12 years of age (placebo group, 4 patients; AZLI group, 11 patients).

‖Values are given as the mean (SD).

¶Values are given as the mean. TIS is not commercially available in Australia and New Zealand. Two patients from these countries reported TIS use during the previous year.

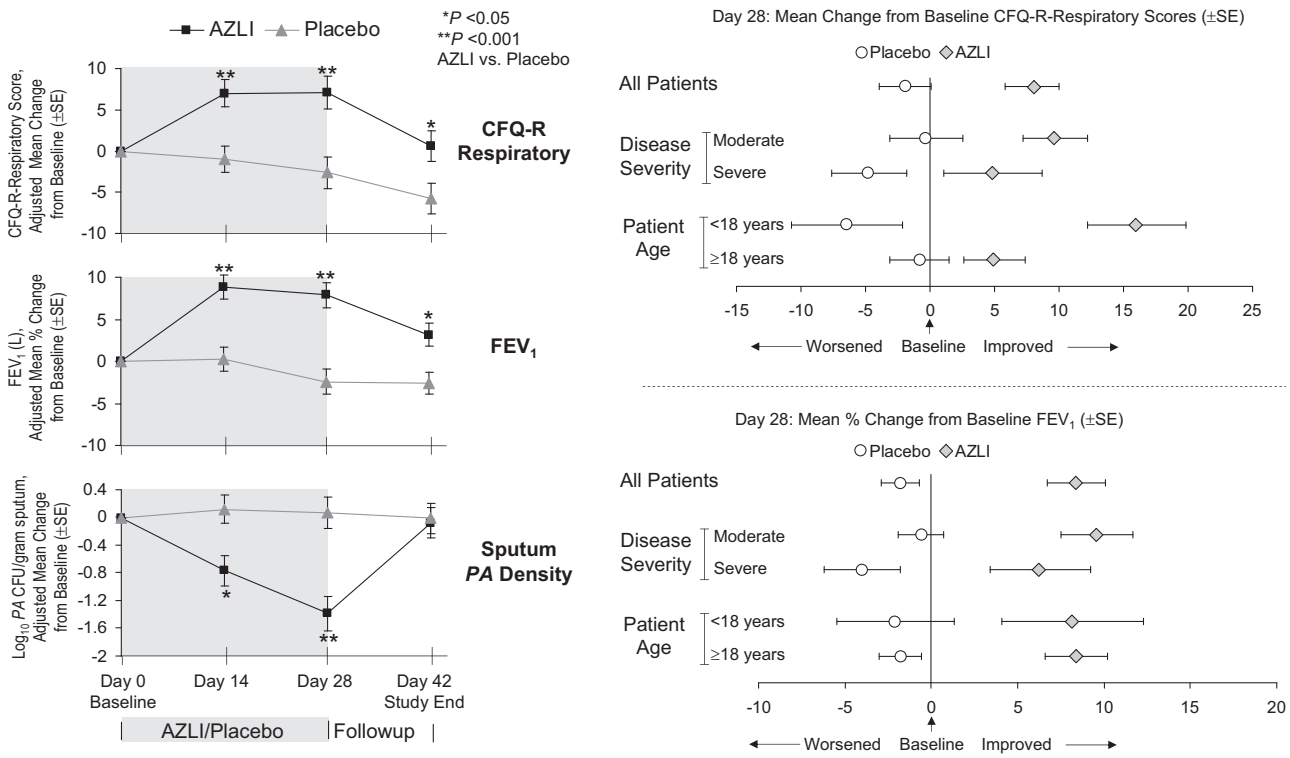

FIGURE 2. *Left*: adjusted mean CFQ-R-respiratory scores, FEV_1, and sputum PA density; change from baseline to study end (days 0 to 42). Child, teen, and adult responses were combined for CFQ-R-Respiratory scores. *Right*: change from baseline to end of treatment for CFQ-R-Respiratory scores and FEV_1; effects of age and baseline CF lung disease severity. Note that the mean change from baseline values improved for all groups treated with AZLI and worsened for all groups treated with placebo. For all patients: AZLI group, n = 80; placebo group, n = 83/84; for disease severity-moderate: AZLI group, n = 50; placebo group, n = 53/54; for disease severity-severe: AZLI group, n = 30; placebo group, n = 30; for patient age < 18 years: AZLI group, n = 21; placebo group, n = 16; for patient age ≥ 18 years: AZLI group, n = 59; placebo group, n = 67/68.

mean FEV_1 values for patients with differing lung disease severities and ages; the subgroups had comparable responses (Fig 2, *right*). At treatment end, changes in CFQ-R-Respiratory scores and FEV_1 were modestly correlated (day 28 Pearson correlation coefficients: AZLI group, 0.32; placebo group, 0.32).

The adjusted mean relative change in FEV_1 percent predicted values also increased for AZLI-treated patients and decreased for placebo-treated patients (day 28 treatment difference, 10.2%; 95% CI, 6.2 to 14.2; $p < 0.001$) and declined for both groups after treatment (day 42 treatment difference, 5.7%; 95% CI, 2.0 to 9.4; $p = 0.003$).

The adjusted mean sputum PA density decreased for AZLI-treated patients and remained near baseline for placebo-treated patients (day 28 treatment difference, -1.453 $\log_{10}$ cfu/g; 95% CI, -2.1 to -0.8; $p < 0.001$) [Fig 2, *left*]. Two weeks after treatment (day 42), values were near baseline values for both treatment groups ($p = 0.822$).

There was a trend toward fewer hospitalized patients in the AZLI group (5%) than in the placebo group (14%; days 0 to 42; $p = 0.064$) and toward fewer mean hospitalization days (AZLI group, 0.5 days; placebo group, 1.5 days; $p = 0.049$). Weight increased 1.1% for the AZLI-treated group and 0.1% for the placebo-treated group (day 28: 95% CI, 0.33 to 1.69; $p = 0.004$).

The responses of AZLI-treated patients were significantly larger than those of placebo-treated patients for 6 of the 11 nonrespiratory CFQ-R scales; these scales included Eating, Emotional Functioning, Health Perceptions, Physical Functioning, Role Limitation/School Performance, and Vitality (Table 2).

Safety

The incidence of adverse events was similar for both groups during the AZLI/placebo treatment period, except "productive cough" was reported by significantly fewer AZLI-treated patients (10 patients; 12.5%) than placebo-treated patients (21 patients; 25%; $p = 0.047$) [Table 3]. Five patients were hospitalized during the treatment period (days 0 to 28); two patients due to respiratory symptoms (AZLI group, one patient; placebo group, one patient), two patients due to bowel obstruction (AZLI group, one patient; placebo group, one patient), and one patient

Table 2—*CFQ-R Scales: Change in Score From Baseline to End of Treatment (Days 0 to 28)*

CFQ-R Scales	Change From Baseline, Adjusted Mean Score		Treatment Difference*	95% CI	p Value
	Placebo	AZLI			
Body Image	1.0	3.2	2.2	− 2.2–6.5	0.327
Digestion	1.9	2.2	0.3	− 3.5–4.0	0.889
Eating	− 4.7	3.6	8.4	4.1–12.7	< 0.001
Emotional Functioning	− 1.3	3.9	5.2	1.6–8.8	0.005
Health Perceptions	− 4.8	5.0	9.8	4.8–14.9	< 0.001
Physical Functioning	− 6.9	2.3	9.2	3.6–14.8	0.001
Respiratory Symptom	− 2.6	7.1	9.7	4.3–15.1	< 0.001
Role/School	− 4.2	2.1	6.4	1.3–11.4	0.014
Social Functioning	− 3.6	− 1.2	2.4	− 1.7–6.5	0.248
Treatment Burden	− 3.1	0.2	3.2	− 1.5–7.9	0.177
Vitality	− 4.4	3.6	8.0	2.5–13.5	0.005
Weight	1.4	4.7	3.3	− 4.0–10.5	0.376

*Comparison is based on type III sum of squares analysis of covariance models including terms for treatment group and disease severity and CFQ-R baseline score as covariates; difference in treatments is defined as AZLI − placebo.

due to umbilical hernia (placebo). Airway reactivity (a ≥ 15% decrease in FEV_1 within 30 min after AZLI/placebo dosing at study visits) occurred in eight patients (AZLI group, three patients; placebo group, five patients); none withdrew for this reason. Clinically significant changes in vital signs or mean clinical laboratory values were not observed, except that AZLI-treated patients trended toward fewer shifts above the reference range for hematology variables; these were all markers of systemic inflammation. From day −14 to day 28, the percentage of patients with shifts above the reference range for WBC count were 11.4% and 5.3%, respectively; for neutrophil counts, 16.5% and 9.6%, respectively; for neutrophil percentage, 13.6% and 7.0%, respectively; and for platelets, 11.7% and 5.6%, respectively, for placebo-treated and AZLI-treated patients. There were no deaths during this study and no reports of anaphylaxis.

Clinical Pharmacology and Microbiology

Sputum and plasma aztreonam concentrations were measured (Table 4). Throughout the study, the aztreonam MIC_{50} and MIC_{90} values for all PA isolates from placebo-treated patients remained unchanged or decreased (Table 5). For AZLI-treated patients, a transient fourfold increase in MIC_{90} was observed (Table 5, day 14). The number of PA isolates with an aztreonam MIC > 8 μg/mL (*ie*, the parenteral breakpoint) and the proportion of patients with such isolates did not increase during AZLI treatment. Throughout the study, MIC_{50} and MIC_{90} values of the other antibiotics tested (tobramycin, gentamicin, amikacin, piperacillin, cefepime, meropenem, ceftazidime, ciprofloxacin, and ticarcillin/clavulanate) for all PA isolates from AZLI-treated patients remained unchanged (*ie*, changes of less than fourfold) or decreased, except for a possible persistent increase in the MIC_{90} value for ticarcillin/clavulanate (increase, 256 to > 256 μg/mL). There was no evidence for persistent increases in the isolation of *Stenotrophomonas maltophilia*, *S aureus*, or *Achromobacter xylosoxidans* resulting from treatment with AZLI (Table 6). *B cepacia* complex was not isolated.

Discussion

Inhaled AZLI was administered at a dose of 75 mg three times daily for 28 days to patients with moderate-to-severe CF lung disease and PA airway infection. These patients were receiving lower levels of maintenance therapy than recommended in published treatment guidelines.[11] Therapy with AZLI significantly improved respiratory symptoms and pulmonary function, and significantly decreased sputum PA density compared with placebo. AZLI was well tolerated; adverse events were generally consistent with symptoms of CF lung disease.

This was the first aerosolized antibiotic clinical study to use a PRO as the primary efficacy end point. Several studies[10,23,24] from the past few years used CFQ-R scales as secondary efficacy end points. In this study, CFQ-R-Respiratory scores measured the benefits of AZLI therapy from the patient's perspective; the 9.7-point treatment response was larger than the 5-point MCID score previously determined for the CFQ-R-Respiratory Scale.[13,21,25]

Respiratory symptom improvements were confirmed by significant improvements in FEV_1 and by the following adverse event measure: compared with placebo, AZLI treatment decreased the number of reports of "productive cough" by half. This demonstrates that

Table 3—*Treatment-Emergent Adverse Events Reported by ≥ 5% Patients in Either Treatment Group During the AZLI/Placebo Treatment Period

TEAEs†	Placebo Group (n = 84)	AZLI Group (n = 80)
Cough	25 (29.8)	28 (35.0)
Productive cough‡	21 (25.0)	10 (12.5)
Pharyngolaryngeal pain	7 (8.3)	10 (12.5)
Nasal congestion	8 (9.5)	8 (10.0)
Pyrexia	4 (4.8)	7 (8.8)
Crackles in lung	6 (7.1)	6 (7.5)
Headache	10 (11.9)	5 (6.3)
Dyspnea	8 (9.5)	5 (6.3)
Wheezing	7 (8.3)	5 (6.3)
Chest discomfort	4 (4.8)	5 (6.3)
Throat irritation	2 (2.4)	5 (6.3)
Fatigue	7 (8.3)	3 (3.8)
Pulmonary function test decreased	6 (7.1)	3 (3.8)
Abdominal pain	6 (7.1)	2 (2.5)
Hemoptysis	6 (7.1)	2 (2.5)

*Values are given as No. (%). TEAE = treatment-emergent adverse event.

†TEAEs were coded using the *Medical Dictionary for Regulatory Activities* (MedDRA, version 8.0) preferred term.

‡Significantly fewer patients in the AZLI group (p = 0.047 [Fisher exact test]); tested whether TEAE incidence was ≥ 10% in either treatment group.

patients with CF can reliably report their symptoms using a standardized measure and provides support for using PROs in clinical studies. However, the modest correlation between patient-reported changes in respiratory symptoms (CFQ-R-respiratory) and measured changes in lung function (FEV_1) suggests that they are measuring different aspects of clinical efficacy; thus, a combination of patient-reported and physiologic measurements may be optimal.

In addition to respiratory symptoms, AZLI-treated patients reported improvements in disease-related symptoms involving eating, emotional and physical functioning, health perceptions, role limitations/school performance, and vitality. These results have particular relevance for patients with a chronic illness, who must adhere to complex, time-consuming medical regimens that affect their normal activities. Their perception of treatment benefit is likely to improve adherence to treatment regimens and influence their long-term health outcomes.[26]

Table 4—*Aztreonam Concentrations in Sputum and Plasma for AZLI-Treated Patients*

Variables	Aztreonam Concentrations		
	Median	Range	No.
Sputum: 10 min after dosing, μg/g sputum			
Day 0 (baseline visit)	530	8–6,010	74
Day 14 (midtreatment visit)	677	2–2,780	67
Day 28 (end-of-treatment visit)	451	1.0–2,800	63
Plasma: 1 h after dosing, ng/mL			
Day 0 (baseline visit)	495	0–1,620	72
Day 14 (midtreatment visit)	595	12–1,660	76
Day 28 (end-of-treatment visit)	603	0–1,740	68

CFQ-R-Respiratory scores and FEV_1 increased for AZLI-treated patients from baseline to midtreatment, with little additional change to treatment end (day 28). However, treatment effects continued to be observed 2 weeks later. Adjusted mean PA density decreased throughout the 28-day AZLI treatment and returned to baseline values 2 weeks later. These results support the 28-day AZLI treatment period, which was extended from the 14-day treatment period utilized in a previous study.[27]

Only 15 patients (9.1%) in this study were children (*ie*, 6 to 12 years of age). For the analyses presented herein, they were combined with adolescent patients to give a group of 37 patients (22.6%) who were < 18 years of age. The mean improvement in the CFQ-R-Respiratory score was larger for these younger patients than for older patients. There was no apparent effect of age on improvement in lung function (FEV_1).

Compared with patients in a previous 28-day AZLI study,[10] patients in this study had received fewer courses of TIS during the previous year (mean number of courses, 1.8 vs 5.3, respectively), and at study entry fewer patients in this study were using dornase alfa (65% vs 85%, respectively) or azithromycin (0% [specified by entry criteria] vs 70%, respectively). Patients in both AZLI studies had comparable lung function (FEV_1, ≥ 25% to ≤ 75% predicted values). The lower levels of maintenance therapy received by patients in the study described herein may reflect a number of factors, as follows: patient intolerance to available therapies; lack of clinical response to specific therapies; clinician and patient preferences; or the difficulty of obtaining TIS in some countries participating in the study (TIS is not commercially available in New Zealand or Australia). The treatment effects observed for these less intensively treated patients were larger than those observed in the previous AZLI study[10] and approached those observed in the original TIS studies[28,29] a decade ago. However, the population in the AZLI study described herein was on average, 8 years older, with a bacterial sputum density approximately 10-fold less, and baseline FEV_1 percent predicted values 4 to 5% higher than those for the population enrolled in the original TIS studies.[28] These baseline differences likely reflect the improved clinical management of CF that has been developed over the past decade.[1–5] Patient compliance with TID dosing was high in the study described herein, it will also be interesting to assess patient compliance and treatment efficacy for the

Table 5—*MIC_{50} and MIC_{90} for All PA Isolates*

Treatment	MIC					Change*	
	MIC_{50}, μg/mL	MIC_{90}, μg/mL	PA Isolates, No.	Minimum MIC, μg/mL	Maximum MIC, μg/mL	MIC_{50}	MIC_{90}
Placebo group (n = 84)							
Day 0	2	64	140	≤ 1	256		
Day 14	2	64	128	≤ 1	512	No	No
Day 28	2	64	116	≤ 1	256	No	No
Day 42	2	32	94	≤ 1	> 2,048	No	No
AZLI group (n = 80)							
Day 0	4	128	128	≤ 1	> 2,048		
Day 14	4	512	118	≤ 1	> 2,048	No	Increased
Day 28	8	128	102	≤ 1	> 2,048	No	No
Day 42	4	128	113	≤ 1	2,048	No	No

*A change of fourfold or more was considered to be an increase/decrease in MIC.

twice-a-day and three-times-a-day dosing groups in the ongoing 18-month AZLI study.

This study was designed to assess the short-term efficacy of AZLI and to provide a rationale for a long-term trial to evaluate its use as suppressive therapy in patients with chronic PA infection. Existing long-term therapies used in patients with CF have typically been assessed in controlled trials with a duration of 6 months.[23,28,30] An open-label, 18-month clinical trial[31] of AZLI (intermittent treatment every other month) is ongoing to address the efficacy and safety of long-term suppressive therapy.

The use of AZLI by clinicians will need to be guided by the results of the two completed phase III studies with regard to the patient's level of lung function, sputum microbiology, and tolerance of inhaled therapy and existing therapies. AZLI may provide an important new therapy for patients with CF who have moderate-to-severe lung disease. Since the improvement in respiratory symptoms and FEV_1 can be easily monitored and measured in a short time period, a 28-day trial of therapy may be an appropriate method of assessing the value of AZLI therapy in an individual patient. Possible clinical strategies may include using AZLI in rotation with other inhaled antibiotics and/or in combination with other nonantibiotic therapies. However, further studies will be needed to define the appropriate strategy for incorporating AZLI use into the long-term treatment of chronic PA airway infection.

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Table 6—*Treatment-Emergent Isolation of Other Organisms

Nature of Isolation	Organism	Placebo Group (n = 84)†	AZLI Group (n = 80)‡
Treatment-emergent intermittent isolation	*S aureus*	7 (8.6)	4 (5.4)
	B cepacia	0	0
	S maltophilia	3 (3.7)	3 (4.1)
	A xylosoxidans	2 (2.5)	0
Treatment-emergent persistent isolation	*S aureus*	5 (6.2)	2 (2.7)
	B cepacia	0	0
	S maltophilia	0	2 (2.7)
	A xylosoxidans	2 (2.5)	1 (1.4)

*Values are given as No. (%). Intermittent isolation = organism not isolated at day 0 but isolated once between days 0 and 42, and not a persistent isolation; persistent isolation = organism not isolated at day 0 but isolated in at least two subsequent specimens or at the early termination visit.
†Data available for 81 of 84 patients.
‡Data available for 74 of 80 patients.

Appendix: Participating Study Sites, Site Investigators, and Study Research Coordinators for the AIR-CF1 Trial

Australia

Alfred Hospital, Melbourne, VIC; Site Investigator (SI): John Wilson; Research Coordinator (RC): Denise Clark.

Princess Margaret Hospital for Children, Perth, WA; SI: Tonia Douglas; RC: Charlotte Allen.

Royal Adelaide Hospital, Adelaide, SA; SI: Hugh Greville; RC: Kirsty Herewane.

Royal Children's Hospital, Herston, Brisbane, QLD; SI: Claire Wainwright; RC: Aaron Buckner.

Sir Charles Gairdner Hospital, Perth, WA; SI: Gerard Ryan; RC: Kerry Boughton.

The Children's Hospital at Westmead, Sydney, NSW; SI: Peter J. Cooper; RC: Karen McKay.

Westmead Hospital, Sydney, NSW; SI: Peter Middleton; RC: Karen Bovington.

Canada

Centre Hospitalier de l'Université de Montreal (CHUM), Montreal, QC; SI: Yves Berthiaume; RC: Nadia Beaudoin.

Children's Hospital of Western Ontario, London, ON; SI: Brian Lyttle; RC: Anne-Marie Lyttle.

Queen Elizabeth II Health Sciences Centre, Halifax, NS; SI: Roger T. Michael; RC: Andrea Dale.

St. Paul's Hospital, Vancouver, BC; SI: Pearce Wilcox; RC: Georgina Lopez.

University of Alberta, Edmonton, AB; SI: Peter Zuberbuhler; RCs: Josette Salgado and Joan Tabak.

New Zealand

Greenlane Clinical Centre and Starship Children's Health Centre, Auckland; SI: John Kolbe; RC: Wendy Fergusson.

United States

Alamo Clinical Research Associates, San Antonio, TX; SI: Peter Fornos; RC: Terri Phillips.

Albany Medical College, Albany, NY; SI: Jonathan Rosen; RC: Katharine Mokhiber.

Baylor Research Institute, Dallas, TX; SI: Mark Millard; RC: Kim Waters.

Capital Allergy and Respiratory Disease Center, Sacramento, CA; SI: Bradley Chipps; RC: Bryce Autret.

Central Maine Pulmonary Associates, Lewiston, ME; SI: Ralph Harder; RC: Rachel Barry.

Children's Hospital Los Angeles, Los Angeles, CA; SI: Marlyn Woo; RC: Lynn Fukushima.

Children's Hospital of Orange County, Orange, CA; SI: Bruce Nickerson; RC: Luis Valdez.

Children's Hospital of Pittsburgh, Pittsburgh, PA; SI: Joseph Pilewski; RCs: Judy Fulton, Elizabeth Hartigan, and Sandra Hurban.

Childrens Lung Specialists, Las Vegas, NV; SI: Craig Nakamura; RC: Tara Brascia.

Children's Memorial Hospital and Northwestern University, Chicago, IL; SI: Susanna McColley; RC: Catherine Powers.

Cincinnati Children's Hospital Medical Center, Cincinnati, OH; SIs: Bruce Trapnell and Cori Daines; RC: Lorrie Duan.

Long Island Jewish Medical Center, New Hyde Park, NY; SI: Rubin Cohen; RC: Maryanne Gannon.

Louisiana State University Health Sciences Center, Shreveport, LA; SI: Kimberly Jones; RC: Antoinette Gardner.

Medical College of Georgia, Augusta, GA; SI: Margaret Guill; RC: Julie C. Hall.

Miller Children's Hospital and Long Beach Memorial Hospital, Long Beach, CA; SI: Terry Chin; RC: Mariam Ischander.

Naval Medical Center, Portsmouth, VA; SI: Rees Lee; RC: Adrienne Espinosa.

Nemours Children's Clinic, Orlando, FL; SI: Mark Weatherly; RC: Sondra Sadler.

Pediatric Breathing Disorders Clinic, Anchorage, AK; SI: Dion Roberts; RC: Vicki Roberts.

Pediatric Pulmonary Associates, Columbia, SC; SI: Daniel Brown; RC: Carolyn Turner.

Phoenix Children's Hospital, Phoenix, AZ; SI: Peggy Radford; RCs: Natalia Argel and Annette Szpiszar Gong.

Riley Hospital for Children, Indianapolis, IN; SI: Michelle Howenstine; RCs: Mary Blagburn and Delana Terrill.

St. Barnabas Healthcare System, Livingston, NJ; SI: Dorothy Bisberg; RC: Carol Epstein.

St. Louis University, St Louis, MO; SI: Ravi Nayak; RC: Jennifer Dizes.

State University of New York (SUNY) Upstate Medical University, Syracuse, NY; SI: Ran Anbar; RC: Donna Lindner.

Tulane University Health Sciences Center, New Orleans, LA; SI: Blesilda Quiniones; RC: Melanie Larrieu.

University of Alabama at Birmingham, Birmingham, AL; SI: JP Clancy; RC: Ginger Reeves.

University of Arkansas for Medical Sciences, Little Rock, AR; SI: Paula Anderson; RC Adam Taggart.

University of Florida Health Sciences Center, Gainesville, FL; SI: L. Terry Spencer; RC: Dawn Baker.

University of Iowa, Iowa City, IA; SI: Richard Ahrens; RC: Mary Teresi.

University of Michigan, Ann Arbor, MI; SI: Samya Nasr; RC: Ermee Sakmar.

University of Missouri, Columbia, MO; SI: Peter Konig; RC: Donna M. Smith.

University of North Carolina at Chapel Hill, Chapel Hill, NC; SI: George Z. Retsch-Bogart; RC: Carol Woody-Barlow.

University of Pennsylvania Health System, Philadelphia, PA; SI: Denis Hadjiliadis; RC: Barbara Finkel.

University of Utah, Salt Lake City, UT; SI: Theodore Liou; RC: Kristyn Packer.

University of Washington Medical Center, Seattle, WA; SI: Moira Aitken; RC: Sharon McNamara.

University of Wisconsin, Madison, WI; SI: James Runo; RC: Sharen Wilson.

University of Mississippi Medical Center, Jackson, MS; SI: Fadel Ruiz; RC: Kim Adcock.

Via Christi Regional Medical Center, St. Francis Campus, Wichita, KS; SI: Maria Riva; RC: Janet Messamore.

Virginia Commonwealth University, Richmond, VA; SI: Greg Elliott; RC: Juellisa Gadd.

Yale-New Haven Hospital, New Haven, CT; SI: John R. McArdle; RC: Kathryn Engle.

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