Original Article

Amikacin liposome inhalation suspension for chronic *Pseudomonas aeruginosa* infection in cystic fibrosis

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ABSTRACT

Background: Shortcomings of inhaled antibiotic treatments for *Pseudomonas aeruginosa* infection in patients with cystic fibrosis (CF) include poor drug penetration, inactivation by sputum, poor efficiency due to protective biofilm, and short residence in the lung.

Methods: Eligible patients with forced expiratory volume in 1 s (FEV_1) ≥25% of predicted value at screening and CF with chronic *P. aeruginosa* infection were randomly assigned to receive 3 treatment cycles (28 days on, 28 days off) of amikacin liposome inhalation suspension (ALIS, 590 mg QD) or tobramycin inhalation solution (TIS, 300 mg BID). The primary endpoint was noninferiority of ALIS vs TIS in change from baseline to day 168 in FEV_1 (per-protocol population). Secondary endpoints included change in respiratory symptoms by Cystic Fibrosis Questionnaire-Revised (CFQ-R).

Results: The study was conducted February 2012 to September 2013. ALIS was noninferior to TIS (95% CI, −4.95 to 2.34) for relative change in FEV_1 (L) from baseline. The mean increases in CFQ-R score from baseline on the Respiratory Symptoms scale suggested clinically meaningful improvement in both arms at the end of treatment in cycle 1 and in the ALIS arm at the end of treatment in cycles 2 and 3; however, the changes were not statistically significant between the 2 treatment arms. Treatment-emergent adverse events (TEAEs) were reported in most patients (ALIS, 84.5%; TIS, 78.8%). Serious TEAEs occurred in 17.6% and 19.9% of patients, respectively; most were hospitalisations for infective pulmonary exacerbation of CF.

Conclusions: Cyclical dosing of once-daily ALIS was noninferior to cyclical twice-daily TIS in improving lung function.

ClinicalTrials.gov Identifier: NCT01315678

1. Introduction

Cystic fibrosis (CF) is associated with chronic lung infection that may lead to bronchiectasis, respiratory failure, and death [1,2]. In 2012, *Pseudomonas aeruginosa* infection was reported to occur in approximately 30% of patients with CF aged 6–10 years and 60%

of patients aged 18–24 years [3]. While recent studies suggest that rates are declining, *P. aeruginosa* remains an important pathogen associated with more rapid clinical deterioration than most other CF pathogens, and has proven difficult to eradicate [4–7].

In these patients, the effectiveness of inhaled antibiotics is limited by poor penetration into infection sites, inactivation by sputum, non-penetration of biofilm, emergent resistance, bacterial phenotypic changes, and bacterial retention in mucous plugs [2,5,8–10]. Current approaches for managing chronic *P. aeruginosa* infection in patients with CF include inhaled tobramycin inhalation solution (TIS) or aztreonam solution, combined with non-antibiotic CF treatments [11]. Inhaled antibiotics can reduce bacterial density in sputum and improve clinical outcomes [12–14]. However, alternative antibiotic treatments are needed, especially for patients with intolerance of or non-responsiveness to current inhaled antibiotics [10].

Amikacin liposome inhalation suspension (ALIS)[2] is composed of small (≈0.3 μm), charge-neutral, highly biocompatible liposomes encapsulating amikacin. This formulation facilitates drug penetration into sputum and biofilms [15]; when delivered to the lungs, high amikacin concentrations are achieved with an extended half-life enabling once-daily dosing [16]. In a phase 2 study, once-daily ALIS improved lung function, reduced *P. aeruginosa* sputum density, and improved patient-reported respiratory symptoms over 28 days of treatment [17].

The phase 3 CLEAR-108 study (ClinicalTrials.gov Identifier: NCT01315678) compared the efficacy, safety, and tolerability of 3 treatment cycles of ALIS vs TIS in patients with CF and chronic bronchopulmonary *P. aeruginosa* infection.

2. Methods

CLEAR-108 was a randomised, open-label, active-controlled noninferiority study conducted from February 2012 to September 2013 at 70 sites in Europe and Canada. CLEAR-108 was conducted in accordance with the Institutional Review Board/Ethics Committee–approved protocol and the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements. Written informed consent was obtained from study patients (and their guardian, if applicable) before participation.

2.1. Patient eligibility

Eligible patients were aged ≥6 years with CF, confirmed by a positive sweat test (ie, ≥60 mmol/L) or DNA analysis, and chronic *P. aeruginosa* infection, confirmed by 3 positive cultures within 2 years (≥1 obtained within 6 months) prior to screening, and positive sputum cultures at screening. Key inclusion criteria included forced expiratory volume in 1 s (FEV$_1$) ≥25% of predicted values, oxygen saturation (SaO$_2$) ≥90%, and the ability to expectorate ≥0.4 mL of sputum (see supplementary appendix for complete entry criteria).

Key exclusion criteria included prior exposure to ALIS, major complications of lung disease (eg, atelectasis, pneumothorax, major pleural effusion), haemoptysis ≥60 mL in a 24-hour period, acute pulmonary exacerbation requiring antibiotic treatment, upper respiratory tract infection, clinically significant non-CF pulmonary disease, or use of antipseudomonal antibiotics or initiation of chronic therapy within 4 weeks of day 1.

Inhaled antibiotics other than study drugs, and other parenteral or oral antibiotics unless clinically indicated, were prohibited. Chronic use of anti-inflammatory therapy, including macrolides, was permitted if the patient was on a stable regimen for at least

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2 Previously referred to as liposomal amikacin for inhalation or LAI.

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28 days preceding day 1 and throughout the trial. Use of prohibited antibiotics triggered interruption of study drug until use of the concomitantly prohibited medication ended. Continuation of a stable bronchodilator regimen (consistent use for ≥28 days preceding day 1 and throughout the trial), was permitted.

2.2. Treatment and follow-up

Patients were randomly assigned (1:1) to receive ALIS once daily or TIS twice daily and stratified by age and FEV$_1$% predicted (Fig. 1). ALIS was administered by inhalation using an investigational eFlow® nebulizer (PARI Pharma GmbH, Munich, Germany). ALIS was supplied in single-use vials to deliver amikacin 590 mg/8.4 mL. TIS was provided as a single-use, 5-mL ampule of 300 mg tobramycin administered via the PARI LC PLUS® Reusable Nebulizer and dosed at approximately 12-hour intervals but not <6 h apart. One treatment cycle was defined as 28 days on treatment followed by 28 days off treatment; all patients received 3 treatment cycles. Study drug was discontinued at the investigator's discretion or if a patient withdrew consent, was lost to follow-up, or met predefined criteria for discontinuation.

2.3. Endpoints

The primary endpoint for this 24-week study was relative change from baseline to end of study in FEV$_1$ (L). Secondary endpoints included interim changes from baseline during therapy in FEV$_1$ (L) and FEV$_1$% predicted; change from baseline in Respiratory Symptoms as measured by the Cystic Fibrosis Questionnaire-Revised (CFQ-R); time to first protocol-defined exacerbation (any 4 of 12 signs and symptoms of the Fuchs criteria); change from baseline in log$_{10}$ colony-forming units (CFU) of *P. aeruginosa*; and all-cause hospitalisations. After study initiation, the study sponsor amended the statistical analysis plan (for regulatory purposes in the United States) to define time to first protocol-defined pulmonary exacerbation as the primary endpoint. In this manuscript we retain change in FEV$_1$ (L) as the primary endpoint as defined in the study protocol.

The CFQ-R, which comprises 35 items for children, 44 for parents, and 50 for teens/adults on 12 generic and disease-specific scales, is a reliable and validated self-report instrument [18,19]. CFQ-R scales include Respiratory Symptoms, Treatment Burden, Physical Functioning, Vitality, Health Perceptions, Social Functioning, Role Functioning, and School Functioning scales. The minimal clinically important difference for the Respiratory Symptoms scale of the CFQ-R has been defined as a change of ≥4 points on the 100-point scale [20].

Safety endpoints included acute tolerability measured by treatment-emergent adverse events (TEAEs), AEs leading to discontinuation, serious AEs, laboratory abnormalities, audiology, serum creatinine changes, need for concomitant medications, and predose-to-postdose changes in pulmonary function tests, vital signs, and SaO$_2$. Proportions of patients with emergent pathogens and shift of minimum inhibitory concentrations (MICs) for *P. aeruginosa* were additional endpoints.

Study visits occurred at weeks 2 and 4 and monthly thereafter, with telephone assessments between monthly visits. Patients who discontinued study drug prematurely could remain in the study and were followed up for safety evaluation.

2.4. Statistical methods

A noninferiority margin of 5% was chosen to show that the mean 24-week relative change in FEV$_1$ for ALIS was ≤5% lower vs that for TIS. Sample size was estimated based on prior studies showing that relative change for ALIS would be 2% higher vs that
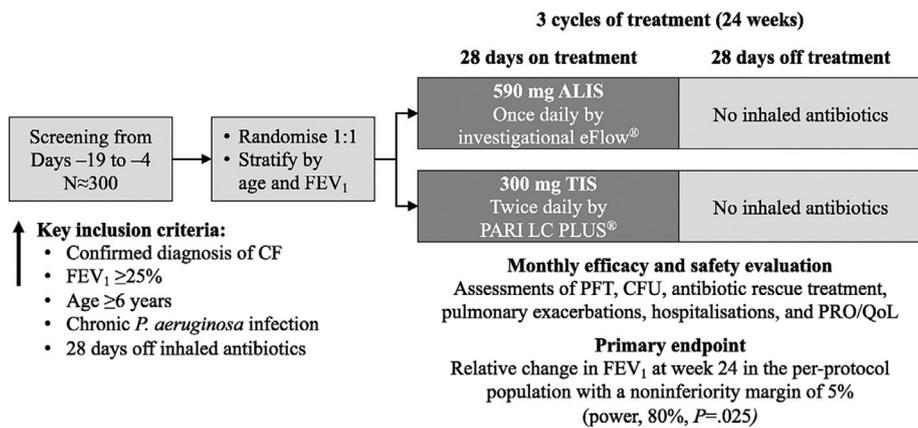
Fig. 1. CLEAR-108 study design.
Patients visited the study site on days 1, 14, 28, 57, 84, 113, 140, and 168; between study visits, patients were followed up by telephone contact (days 7, 21, 42, 63, 70, 77, 98, 119, 126, 133, and 154).
ALIS, amikacin liposome inhalation suspension; CF, cystic fibrosis; CFU, colony-forming units; FEV$_1$, forced expiratory volume in 1 s; HRQoL, health-related quality of life; PFT, pulmonary function testing; PRO, patient-reported outcome; TIS, tobramycin inhalation solution.

for the standard. Therefore, 129 patients were needed per treatment arm to achieve 80% power with a 1-sided significance level of 0.025. Thus, approximately 150 patients were to be enrolled per treatment arm.

Demographics were described using summary statistics. The primary efficacy analysis, a noninferiority test comparing ALIS with TIS, was performed on the per-protocol (PP) population, defined as patients who completed ≥80% of study drug doses without missing >3 consecutive doses in any cycle. Modified intention-to-treat (mITT) and safety populations were defined as all randomised patients who received ≥1 dose of study drug. All secondary efficacy analyses were completed using the mITT population.

Primary endpoint sensitivity analyses were performed on the PP population using a repeated measures linear mixed model and analysis of covariance (ANCOVA), replacing missing values with the worst-observation-carried-forward (WOCF), including baseline, the least favourable group mean or zero (LFGMZ), and the last-observation-carried-forward (LOCF). An ANCOVA model was also used in the primary analysis with factors for treatment and randomisation strata. Additional analyses repeated employing an ANCOVA model, under the assumption of missing at random, with effects for treatment, randomisation, and consistency of bronchodilator use (ie, whether the bronchodilator regimen was changed on or after day 1) using a lower bound of the 95% CI of ≥ −5%.

The Respiratory Symptoms scale of the CFQ-R was a prespecified secondary endpoint, analysed with a random-effects model; additional CFQ-R domains were analysed post hoc. CFQ-R was analysed using an ANCOVA model with effects for treatment, baseline CFQ-R score, and randomisation strata. Missing data were excluded. We used WOCF, LOCF, and mixed-effects models for repeated measures as the sensitivity analyses. A statistical hierarchy for the secondary endpoints was not prespecified; therefore, all effect sizes and P values presented for secondary endpoints cannot be used to infer statistical significance.

3. Results

3.1. Patients

Overall, 302 patients were randomly assigned to study treatments; 152 patients were assigned to ALIS 590 mg once daily and 150 patients to TIS 300 mg twice daily (Fig. S1). Among these, 28 patients (9.3%) did not complete the study (ALIS, 18 (11.8%); TIS, 10 (6.7%)). Four patients in each arm never received study drug and

were not included in the safety population. A total of 274 patients completed the study, and 266 completed per protocol (Fig. S1). The most common reasons for discontinuation of the study drug were protocol-defined safety criteria or AEs (ALIS, 7.2%; TIS, 2.0%) and other reasons (ALIS, 7.2%; TIS, 4.0%) (Table S1).

Demographics and baseline characteristics were comparable between the 2 arms (Table 1); 59.2% of patients were > 18 years of age; 52.7% were male. Baseline FEV$_1$% predicted values of 25%–50%, >50%–75%, and > 75% were reported in 86 (29.3%), 109 (37.1%), and 99 (33.7%) patients, respectively. Most patients reported prior use of inhaled antibiotics (ALIS arm, 86.5%; TIS arm, 87.7%). Similar proportions of patients in each arm received study drug for 3 treatment cycles (ALIS arm, 90.5%; TIS arm, 93.2%).

3.2. Efficacy

In the PP population, the least squares (LS) mean FEV$_1$ (L) improved from baseline to day 168 similarly in the ALIS and TIS arms (1.56% and 2.87%, respectively, P = .48). The difference in LS mean between the 2 arms (ALIS minus TIS) adjusted for treatment and randomisation strata at day 168 was −1.31% (95% CI −4.95 to 2.34) (Fig. 2), indicating noninferiority of improvement in lung function with ALIS vs TIS (ie, lower bound of the 95% CI was ≥ −5%, as per the prespecified analysis plan). In the mITT population, the relative change from baseline in FEV$_1$ (L) at the end of treatment was also comparable in the ALIS and TIS arms in cycle 1 (day 28; LS mean, 4.33% and 7.32%, respectively; P = .08), cycle 2 (day 84; 4.39% and 6.65%, respectively; P = .18), and cycle 3 (day 140; 4.07% and 5.11%, respectively; P = .59) (Fig. S2). Relative change in FEV$_1$ from baseline in the mITT population was generally consistent across subgroups regardless of sex, ethnicity, or age. For FEV$_1$% predicted, comparable improvements were observed between the ALIS and TIS arms in the mITT population at the midpoint of treatment cycle 1 when the peak effect was observed (day 14; LS mean, 5.09% and 7.42%, respectively; P = .15) and at the end of treatment cycle 1 (day 28; 4.14% and 7.00%, respectively; P = .09), cycle 2 (day 84; 3.37% and 5.48%, respectively; P = .20), and cycle 3 (day 140; 2.31% and 3.23%, respectively; P = .63).

Results from the sensitivity analyses for the primary endpoint using a repeated measures linear mixed model and an ANCOVA model that replaced missing values with the WOCF, the LFGMZ, or the LOCF were similar to that of the primary efficacy analysis in both the PP and mITT populations (Fig. S3). Similarly, the results from the ANCOVA model controlling for consistency of bron-

Table 1
Demographics and baseline characteristics (mITT population).

Variable	ALIS 590 mg Once Daily N = 148	TIS 300 mg Twice Daily N = 146	Total N = 294
Race/ethnicity, n (%)			
White (not of Hispanic origin)	139 (93.9)	141 (96.6)	280 (95.2)
Hispanic	5 (3.4)	3 (2.1)	8 (2.7)
African	1 (0.7)	0	1 (0.3)
Asian	0	0	0
Other	3 (2.0)	1 (0.7)	4 (1.4)
Not reported	0	1 (0.7)	1 (0.3)
Sex, n (%)			
Male	79 (53.4)	76 (52.1)	155 (52.7)
Female	69 (46.6)	70 (47.9)	139 (47.3)
Age			
Mean (SD)	22.8 (10.2)	22.0 (10.0)	22.4 (10.1)
6–12 years, n (%)	27 (18.2)	26 (17.8)	53 (18.0)
13–18 years, n (%)	34 (23.0)	33 (22.6)	67 (22.8)
>18 years, n (%)	87 (58.8)	87 (59.6)	174 (59.2)
Height, mean (SD), cm	162.3 (15.0)	162.2 (15.6)	162.3 (15.2)
Weight, mean (SD), kg	54.5 (17.2)	53.1 (15.9)	53.8 (16.5)
BMI, mean (SD), kg/m^2	20.1 (4.0)	19.7 (3.7)	19.9 (3.9)
CF genotype, n (%)			
ΔF508 homozygous	72 (48.6)	70 (47.9)	142 (48.3)
ΔF508 heterozygous	40 (27.0)	43 (29.5)	83 (28.2)
Other	21 (14.2)	25 (17.1)	46 (15.6)
FEV$_1$% predicted			
n	148	144	292
Mean (SD)	64.5 (21.5)	61.9 (22.0)	63.2 (21.7)
FEV$_1$% predicted stratification at screening for randomisation			
25%–50%, n (%)	42 (28.4)	44 (30.1)	86 (29.3)
>50%–75%, n (%)	54 (36.5)	55 (37.7)	109 (37.1)
>75%, n (%)	52 (35.1)	47 (32.2)	99 (33.7)
FEV$_1$ (L)			
n	148	144[a]	292
Mean (SD)	2.142 (0.861)	2.037 (0.846)	2.090 (0.854)
Use of bronchodilator	113 (76.4)	111 (76.0)	224 (76.2)
Use of azithromycin	76 (51.4)	73 (50.0)	149 (50.7)

ALIS, amikacin liposome inhalation suspension; BMI, body mass index; CF, cystic fibrosis; FEV$_1$, forced expiratory volume in 1 s; mITT, modified intention-to-treat; TIS, tobramycin inhalation solution.

[a] Baseline FEV$_1$ data were not available for 2 patients.
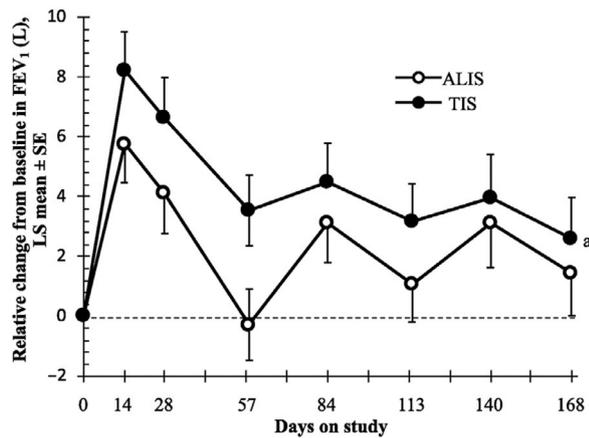
| N, ALIS = | 128 | 126 | 127 | 127 | 125 | 127 | 127 | 128 |
| N, TIS = | 135 | 132 | 135 | 132 | 135 | 135 | 134 | 134 |

Fig. 2. Primary endpoint of relative change from baseline to day 168 in FEV$_1$ (per-protocol population).
[a] LS mean difference (ALIS–TIS) adjusted for treatment and randomisation strata at day 168 was −1.31% (95% CI −4.95 to 2.34; P = .48). The lower bound of the 95% CI was > −5%, indicating noninferiority of ALIS to TIS.
ALIS, amikacin liposome inhalation suspension; FEV$_1$, forced expiratory volume in 1 s; LS, least squares; TIS, tobramycin inhalation solution.

chodilator use was consistent with the primary analysis (Fig. S3). Overall, these analyses confirmed that both treatment groups had improvements in FEV$_1$ from baseline and that the lower bounds of the 95% CIs were ≥ −5%, indicating noninferiority of ALIS vs TIS.

More patients receiving ALIS (63.5%) vs TIS (51.4%) (P = .02) experienced pulmonary exacerbations as defined by the Fuchs criteria. Patients in the ALIS arm had a reduced time to first pulmonary exacerbation (mITT population; hazard ratio 1.51; 95% CI 1.07 to 2.13; P = .03). All-cause hospitalisation was observed in 16.2% (24/148) of patients in the ALIS arm vs 19.9% (29/146) in the TIS arm.

In the mITT population, CFQ-R LS mean scores generally improved in both the ALIS and TIS arms during the treatment in cycle 1 (day 14) and at the end of treatment periods (days 28, 84, and 140); except for a few instances, the differences between the 2 arms on various CFQ-R domains during the study were not statistically significant (Table S2). The scores on CFQ-R Respiratory Symptoms scale improved similarly for both ALIS and TIS arms (Fig. S4). Mean increases on the CFQ-R Respiratory Symptoms scale–adjusted change from baseline suggested clinically meaningful improvement (≥4 points) in both treatment arms during cycle 1 (LS mean at day 14: ALIS, 4.43; TIS, 4.35; P = .96) and at the end of the on-treatment period of cycle 1 (day 28: ALIS, 5.23; TIS, 5.85; P = .72) and in the ALIS arm at the end of the on-treatment period of cycle 2 (LS mean at day 84: ALIS, 4.25; TIS, 3.22; P = .56) and cycle 3 (LS mean at day 140: ALIS, 4.49; TIS, 2.13; P = .15) (Table S2; Fig. S4). In a post hoc analysis, mean improvement in the adjusted change from baseline on the CFQ-R treatment burden score at the end of the cycle 2 on-treatment period (day 84) was 1.69 in the ALIS arm and −2.59 in the TIS arm (P = .03; mITT population). A similar trend was observed at the end of the on-treatment period in cycle 3 (LS mean at day 140: ALIS, 0.739; TIS, −2.826; P = .06). Treatment arms differed regarding reports of CFQ-R Treatment Burden from on- vs off-cycle assessments (estimated

Table 2
Summary of TEAEs.

Variable, n (%)	ALIS 590 mg Once Daily N = 148	TIS 300 mg Twice Daily N = 146	Total N = 294
Patients with TEAEs	125 (84.5)	115 (78.8)	240 (81.6)
Patients with TEAEs by relationship to study drug[a]			
Related	57 (38.5)	21 (14.4)	78 (26.5)
Not related	68 (45.9)	94 (64.4)	162 (55.1)
Patients with TEAEs by maximum severity			
Mild	52 (35.1)	50 (34.2)	102 (34.7)
Moderate	62 (41.9)	59 (40.4)	121 (41.2)
Severe	11 (7.4)	5 (3.4)	16 (5.4)
Life-threatening or disabling	0	1 (0.7)	1 (0.3)
Patients with treatment-emergent SAEs	26 (17.6)	29 (19.9)	55 (18.7)
Patients with treatment-emergent SAEs by strongest relationship to study drug			
Related	1 (0.7)	1 (0.7)	2 (0.7)
Not related	25 (16.9)	28 (19.2)	53 (18.0)
Patients with AEs leading to study drug discontinuation	15 (10.1)	7 (4.8)	22 (7.5)

AE, adverse event; ALIS, amikacin liposome inhalation suspension; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TIS, tobramycin inhaled solution.
[a] Assessed by the investigator. Related events are defined as events with relationships to study procedure of probably, possibly, or unknown. Events not related are defined as events with relationships to study procedures of unlikely or not related.
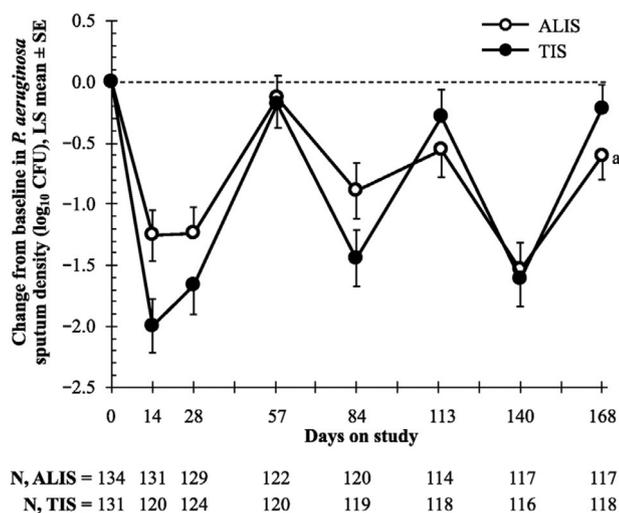
Fig. 3. Change from baseline in sputum density of *Pseudomonas aeruginosa* (mITT population).
[a] LS mean difference (ALIS–TIS) adjusted for treatment and randomisation strata at day 168, $P = .13$. ALIS, amikacin liposome inhalation suspension; CFU, colony-forming units; LS, least squares; mITT, modified intention-to-treat; TIS, tobramycin inhalation solution.

difference, 2.53; SE, 0.97; $P < .01$), with the TIS arm reporting a significant worsening of treatment burden while on cycle (estimate = −2.60, SE = 0.68; $P < .01$) (Table S3).

Mean reductions in *P. aeruginosa* sputum density at the end of treatment in cycle 1 (day 28) and cycle 3 (day 140) were, respectively, 1.2 $\log_{10}$ CFU/g and 1.5 $\log_{10}$ CFU/g in the ALIS arm and 1.7 $\log_{10}$ CFU/g and 1.6 $\log_{10}$ CFU/g in the TIS arm, indicating that the microbiologic effect was maintained across the study (Fig. 3). Mean *P. aeruginosa* sputum densities were below baseline level at day 168 (end of off-treatment period in cycle 3) in both the ALIS and TIS arms. The minimum inhibitory concentrations of amikacin and tobramycin required to inhibit the growth of 50% (MIC_{50}) of *P. aeruginosa* isolates did not increase substantially over treatment cycles.

3.3. Safety

Most patients (ALIS, 84.5%; TIS, 78.8%) experienced ≥1 TEAE, mostly mild or moderate in intensity (Table 2). In the ALIS arm, TEAE incidence decreased from 52.0% during the on-treatment period of cycle 1 to 39.6% during the on-treatment period of cycle 3. In the TIS arm, similar proportions of patients experienced TEAEs

across all cycles, ranging from 34.6% to 37.4%. TEAEs occurring in ≥10.0% of patients in the ALIS arm included infective pulmonary exacerbation of CF (55.4%), nasopharyngitis (16.2%), haemoptysis (16.2%), cough (12.2%), dysphonia (12.2%), and upper respiratory tract infection (10.1%). With TIS, the most common TEAEs were infective pulmonary exacerbation of CF (48.6%) and nasopharyngitis (22.6%). TEAEs considered related to study drug with the most notable differences in frequency between the ALIS and TIS arms, respectively, included dysphonia (10.8% vs 2.7%), cough (8.8% vs 2.1%), haemoptysis (7.4% vs 3.4%), and infective exacerbation of CF (6.8% vs 2.1%). Concomitant therapies for pulmonary exacerbations were used by 49.7% of patients; antibiotics used by ≥10% of patients were fluoroquinolones, third-generation cephalosporins, other aminoglycosides, and carbapenems.

Sixteen patients (ALIS, 7.4%; TIS, 3.4%) experienced ≥1 severe event; only 1 event (severe cough) in the ALIS arm was considered related to study drug. Similar proportions of patients experienced serious AEs in the ALIS (17.6%) and TIS (19.9%) treatment arms; the most serious were hospitalisations for the treatment of infective pulmonary exacerbation of CF. One patient in each arm experienced a serious TEAE considered related to study drug; no deaths were reported.

TEAEs leading to study drug discontinuation were reported in 10.1% and 4.8% of patients in the ALIS and TIS arms, respectively; events were predominantly respiratory. TEAEs requiring antibiotic therapy were reported in 50.0% and 44.5% of patients with pulmonary exacerbations in the ALIS and TIS arms, respectively, and in 23.0% and 28.8% of patients with TEAEs other than pulmonary exacerbations.

No appreciable changes were seen in acute tolerability in vital signs, body weight, SaO_2, and pulmonary function as measured by predose-to-postdose changes over a single day. One moderate and 5 mild AEs of hearing loss were reported in 6 patients receiving ALIS (age, 31–45 years). One adult male patient with a mild AE had moderate 25 dB unilateral loss at the highest frequency and 1 adult male patient with a moderate AE had moderate hearing loss (range 5–30 dB) at multiple frequencies bilaterally. Both patients were aged >35 years. The other 4 patients with mild hearing loss generally had a mixed pattern of loss and improvements. No hearing loss was reported in the TIS arm. No clinically meaningful changes in laboratory values were observed.

4. Discussion

In this open-label, randomised, phase III trial, cyclical dosing of once-daily ALIS or twice-daily TIS in patients with CF and chronic *P. aeruginosa* infection resulted in improvement in FEV_1 (L) from

baseline to day 168; the improvement with ALIS was noninferior to TIS, as determined by the prespecified criterion of the lower bound of 95% CI for ALIS to be ≤5% lower than for TIS. The primary analysis of relative change in FEV_1 at day 168 (PP population) was observed consistently regardless of sex, ethnicity, or age. Relative changes in each pulmonary function test in the mITT population were also similar in ALIS and TIS arms at the end of all 3 on-treatment cycles, suggesting that the effects of ALIS and TIS were maintained over time. Sensitivity analyses confirmed these results.

Both the ALIS and TIS arms demonstrated reductions in *P. aeruginosa* sputum densities during the on-treatment periods, suggesting that both treatments were effective antimicrobials. However, more patients receiving ALIS than TIS experienced protocol-defined pulmonary exacerbations and a shorter time to first pulmonary exacerbation. The observed differences in pulmonary exacerbations in this relatively short study should be evaluated in future studies assessing the efficacy of ALIS for *P. aeruginosa* infection in CF over a longer period, especially given the fact that the definition of exacerbation includes respiratory symptoms that may be short-term adverse effects from the treatment with inhaled study medication. Both arms also demonstrated improvements in CFQ-R Respiratory Symptoms scores; the improvements were clinically meaningful (increased by ≥4 points) in both arms at the end of the on-treatment period of cycle 1 and in only the ALIS arm at the end of the on-treatment period in cycles 2 and 3.

Most AEs in the ALIS group were respiratory in nature, including local respiratory events and infective exacerbation of CF, and were associated with patients' underlying diagnoses. The TEAE incidence in the ALIS arm was higher than in the TIS arm during the on-treatment period of cycle 1, but decreased progressively during the study to proportions similar to that in the TIS arm by cycle 3.

One significant limitation is that this study was of relatively short duration for evaluation of a long-term chronic therapy. The requirement for all patients with prior exposure to be tolerant of TIS may have created a potential selection bias in favour of TIS. Another limitation of the study was that the patients were not blinded as they were aware of being on a once- or twice-daily therapy.

Overall, the results support the hypothesis that ALIS is noninferior to TIS for treatment of chronic *P. aeruginosa* infection in patients with CF. Improvements in FEV_1% predicted and reductions in *P. aeruginosa* sputum density were similar in the 2 arms, and although acute pulmonary exacerbations were more common in the ALIS arm, some patient-reported outcomes tended to favour ALIS. ALIS administered once daily was comparable to TIS administered twice daily in improving lung function. At study completion, patients reported improvement in their respiratory symptoms and had a lower treatment burden as measured by CFQ-R, with trends in favour of ALIS compared with TIS despite a higher frequency of pulmonary exacerbations reported in the ALIS arm.

Appendix. CLEAR-108 Study Group

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Supplementary materials

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References

[1] Elborn JS. Cystic fibrosis. Lancet 2016;388:2519–31. doi:10.1016/S0140-6736(16)00576-6.

[2] Mayer-Hamblett N, Rosenfeld M, Gibson RL, Ramsey BW, Kulasekara HD, Retsch-Bogart GZ, et al. *Pseudomonas aeruginosa* in vitro phenotypes distinguish cystic fibrosis infection stages and outcomes. Am J Respir Crit Care Med 2014;190:289–97. doi:10.1164/rccm.201404-0681OC.

[3] Cystic Fibrosis Foundation. Patient registry 2012 annual data report. [accessed 12 December 2018] www.cysticfibrosisdata.org/LiteratureRetrieve.aspx?ID=149756 .

[4] Strausbaugh SD, Davis PB. Cystic fibrosis: a review of epidemiology and pathobiology. Clin Chest Med 2007;28:279–88. doi:10.1016/j.ccm.2007.02.011.

[5] Gibson RL, Burns JL, Ramsey BW. Pathophysiology and management of pulmonary infections in cystic fibrosis. Am J Respir Crit Care Med 2003;168:918–51. doi:10.1164/rccm.200304-505SO.

[6] Crull MR, Ramos KJ, Caldwell E, Mayer-Hamblett N, Aitken ML, Goss CH. Change in *Pseudomonas aeruginosa* prevalence in cystic fibrosis adults over time. BMC Pulm Med 2016;16:176. doi:10.1186/s12890-016-0333-y.

[7] Crull MR, Somayaji R, Ramos KJ, Caldwell E, Mayer-Hamblett N, Aitken ML, et al. Changing rates of chronic *Pseudomonas aeruginosa* infections in cystic fibrosis: a population-based cohort study. Clin Infect Dis 2018;67:1089–95. doi:10.1093/cid/ciy215.

[8] Quittner AL, Zhang J, Marynchenko M, Chopra PA, Signorovitch J, Yushkina Y, et al. Pulmonary medication adherence and health-care use in cystic fibrosis. Chest 2014;146:142–51. doi:10.1378/chest.13-1926.

[9] Sawicki GS, Ren CL, Konstan MW, Millar SJ, Pasta DJ, Quittner AL. Treatment complexity in cystic fibrosis: trends over time and associations with site-specific outcomes. J Cyst Fibros 2013;12:461–7. doi:10.1016/j.jcf.2012.12.009.

[10] Høiby N. Recent advances in the treatment of *Pseudomonas aeruginosa* infections in cystic fibrosis. BMC Med 2011;9:32. doi:10.1186/1741-7015-9-32.

[11] Mogayzel PJ Jr, Naureckas ET, Robinson KA, Mueller G, Hadjiliadis D, Hoag JB. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Am J Respir Crit Care Med 2013;187:680–9.

[12] Sheinberg M, Elborn JS. Use of inhaled tobramycin in cystic fibrosis. Adv Ther 2015;32:1–9. doi:10.1007/s12325-015-0179-3.

[13] Stuart Elborn J, Geller DE, Conrad D, Aaron SD, Smyth AR, Fischer R. A phase 3, open-label, randomized trial to evaluate the safety and efficacy of levofloxacin inhalation solution (APT-1026) versus tobramycin inhalation solution in stable cystic fibrosis patients, 14; 2015. p. 507–14. doi:10.1016/j.jcf.2014.12.013.

[14] Ramsey BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams-Warren J. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. N Engl J Med 1999;340:23–30.

[15] Meers P, Neville M, Malinin V, Scotto AW, Sardaryan G, Kurumunda R, et al. Biofilm penetration, triggered release and in vivo activity of inhaled liposomal amikacin in chronic *Pseudomonas aeruginosa* lung infections. J Antimicrob Chemother 2008;61:859–68. doi:10.1093/jac/dkn059.

[16] Weers J, Metzheiser B, Taylor G, Warren S, Meers P, Perkins WR. A gamma scintigraphy study to investigate lung deposition and clearance of inhaled amikacin-loaded liposomes in healthy male volunteers. J Aerosol Med Pulm Drug Deliv 2009;22:131–8. doi:10.1089/jamp.2008.0693.

[17] Clancy JP, Dupont L, Konstan MW, Billings J, Fustik S, Goss CH, et al. Phase II studies of nebulised arikace in CF patients with *Pseudomonas aeruginosa* infection. Thorax 2013;68:818–25. doi:10.1136/thoraxjnl-2012-202230.

[18] Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of the cystic fibrosis questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. Chest 2005;128:2347–54. doi:10.1378/chest.128.4.2347.

[19] Quittner AL, Sawicki GS, McMullen A, Rasouliyan L, Pasta DJ, Yegin A, et al. Psychometric evaluation of the cystic fibrosis questionnaire-revised in a national sample. Qual Life Res 2012;21:1267–78. doi:10.1007/s11136-011-0036-z.

[20] Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara 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;135:1610–18. doi:10.1378/chest.08-1190.