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Original Article

Safety and efficacy of prolonged levofloxacin inhalation solution (APT-1026) treatment for cystic fibrosis and chronic *Pseudomonas aeruginosa* airway infection☆

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Abstract

Background: Levofloxacin inhalation solution (LIS) is the first aerosolized fluoroquinolone licensed for treatment of patients with cystic fibrosis (CF) and chronic *Pseudomonas aeruginosa* lung infection. This study evaluated the safety and efficacy of extended LIS treatment.
Methods: Patients completing a multinational, randomized study comparing LIS and tobramycin inhalation solution (TIS) were enrolled in an open-label extension in which all patients received three additional cycles of 28 days of LIS 240 mg twice daily followed by 28 days off drug. Endpoints included mean relative change in percent predicted forced expiratory volume in 1 s (FEV_1), time to pulmonary exacerbation, and patient-reported quality of life.
Results: Extended treatment with LIS in 88 patients was well tolerated with no new safety signals and evidence of positive effects on FEV_1 and quality of life.
Conclusion: Patients receiving extended LIS treatment continued to show favorable efficacy with no additional safety concerns.

Keywords: Cystic fibrosis; *Pseudomonas*; Antibiotics; Levofloxacin; Fluoroquinolone; Inhalation solution

1. Introduction

Cystic fibrosis (CF) reduces quality of life and life expectancy, and chronic lung infection in persons with CF is associated with increased morbidity and mortality. *Pseudomonas aeruginosa* is the most common bacterial species isolated from respiratory secretions of people with CF, and isolation prevalence increases with advancing age. Chronic *P. aeruginosa* infection is associated with increased pulmonary exacerbations requiring intravenous antibiotics and with acceleration of lung disease progression [1–3]. Aerosolized antibiotic therapy is recommended for the treatment of chronic *P. aeruginosa* infection in patients with CF

Abbreviations: AE, adverse event; CF, cystic fibrosis; CFQ-R, Cystic Fibrosis Questionnaire—Revised; CI, confidence interval; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FEV_1, forced expiratory volume in 1 second; LIS, levofloxacin inhalation solution; MIC, minimum inhibitory concentration; RCT, randomized controlled trial; TEAE, treatment-emergent adverse event; TIS, tobramycin inhalation solution

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[4,5]. Currently approved inhaled antibiotics include tobramycin inhalation solution (TIS), aztreonam inhalation solution, and colistimethate sodium (Table S1). Given the potential for patient intolerance to an inhaled antibiotic class as well as the potential for diminished efficacy with extended treatment with a single inhaled antibiotic class, access to additional classes of inhaled antibiotics that are effective and well tolerated is desirable.

Fluoroquinolones are broad spectrum, high potency antibacterial agents that are delivered systemically to effectively treat a variety of respiratory infections [6]. Practical limits to fluoroquinolone concentrations that can be achieved in respiratory secretions by oral or intravenous delivery can be overcome by topical drug delivery to the lumen of the lung via inhalation. Because of extensive use of systemic fluoroquinolones young children with CF to treat pulmonary exacerbations [6], the prevalence of *P. aeruginosa* isolates resistant *in vitro* to fluoroquinolone concentrations achievable by systemic delivery increases with increasing age [7]. Inhaled delivery of antibiotic results in significantly higher concentrations of drug in the airway that exceed the minimum inhibitory concentration (MIC) for *P. aeruginosa* [8]. Levofloxacin inhalation solution (LIS) is the first aerosolized fluoroquinolone licensed for treatment and maintenance therapy in patients with CF and chronic *P. aeruginosa* lung infections [9,10]. In a phase 3, 24-week, open-label, randomized controlled trial (RCT), the safety and efficacy of LIS 240 mg twice daily (BID) were compared with TIS 300 mg BID over three consecutive 28-day on/off cycles in patients with CF and chronic *P. aeruginosa* lung infection [10]. This study demonstrated that LIS was non-inferior to TIS in relative change in percent predicted forced expiratory volume in 1 second (FEV_1), an accepted surrogate of survival benefit [10]. In addition, LIS had a similar safety profile to TIS with fewer hospitalizations, no difference in pulmonary exacerbations, and similar treatment-emergent adverse events (TEAEs; LIS, 22% vs TIS, 32.2%), with the notable exception of an increased incidence of dysgeusia [10].

Considering that previous safety and efficacy data for LIS were favorable, additional extended treatment data were desired. Therefore, patients completing the RCT at selected sites were offered the opportunity to extend treatment for three additional 28-day on/off cycles of LIS 240 mg BID. Patients previously receiving TIS were thus able to receive LIS for the first time. The objective of this study extension was to extend the initial assessment of safety and efficacy of LIS beyond the RCT comparison with LIS [10].

2. Methods

2.1. Study design

This non-randomized, open-label, single-arm study was an optional 24-week extension of the RCT at specific sites. As previously reported, eligible patients in the RCT were randomized 2:1 to three treatment cycles consisting of 28 days on LIS 240 mg (2.4 mL of LIS 100 mg per mL, as APT-1026) BID or TIS 300 mg (5 mL) BID (Tobi®, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA), followed by 28 days off therapy with seven study visits 28 days apart [10]. Patients in the extension either continued cyclic treatment with LIS 240 mg BID or switched from TIS 300 mg BID to LIS 240 mg BID for three additional cycles (Fig. 1). LIS was delivered with the eFlow® nebulizer (PARI Pharma GmbH, Starnberg, Germany), customized for LIS delivery.

2.2. Participants

Participation in the extension was offered to clinically stable patients who were enrolled in the RCT, had completed treatment up to day 168, and were enrolled at a site that was eligible for the extension (i.e., institutional review board approval was granted before all patients completed the RCT). Inclusion criteria for the RCT were: ≥ 12 years of age with documented CF diagnosis, a FEV_1 between 25% and 85% of predicted values using the third National Health and Nutrition Examination Survey reference equations [11], chronic airway infection with *P. aeruginosa*, and treatment with at least three 28-day courses (≥ 84 days) of inhaled TIS over the 12 months before screening [10]. Chronic *P. aeruginosa* infection was defined as a report of a respiratory secretion culture positive for *P. aeruginosa* in the 12 months immediately before screening and a positive culture obtained at the screening visit 14 days before randomization. Patients continued routine respiratory care and medications [10].

2.3. Safety and efficacy assessments

The endpoints measured in the extension were the same as those in the RCT. Safety was assessed at each study visit via physical examination and vital signs, electrocardiogram, and the collection of blood/urine/sputum samples. All adverse events were

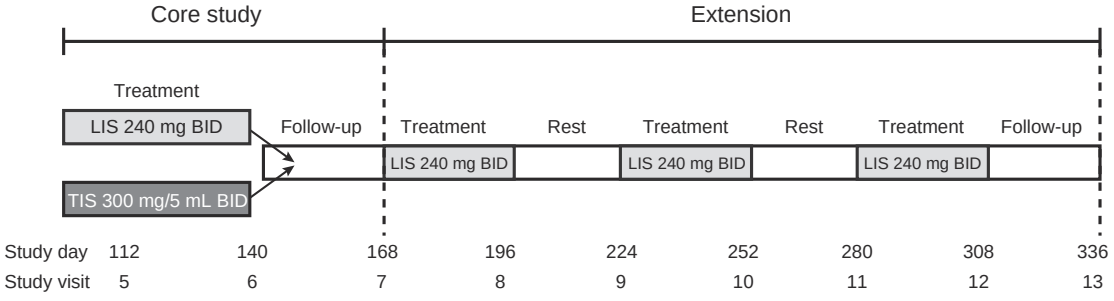

Fig. 1. Study design. Abbreviations: BID, twice daily; LIS, levofloxacin inhaled solution; RCT, randomized control trial [10]; TIS, tobramycin inhalation solution.

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documented and each patient was assessed for pulmonary exacerbation. Sputum microbiology was examined for changes in sputum density (log_{10} colony-forming units per gram sputum) of *P. aeruginosa*, *Staphylococcus aureus*, *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, *Burkholderia cepacia* complex, and methicillin-resistant *S. aureus* from RCT and extension baselines to each visit at which sputum was collected. *In vitro* antibiotic susceptibilities of *P. aeruginosa* isolated from respiratory secretions were studied as minimum inhibitory concentrations (MICs) by microdilution testing.

Efficacy was assessed by spirometry and determined as absolute and relative changes in percent predicted FEV_1 and forced vital capacity from RCT baseline and extension baseline to each visit. Time (in days) to first exacerbation (defined as concurrently having at least four of the 12 Fuchs symptoms/signs or death [12]) from RCT baseline to final visit (day 336) was measured. Unlike the RCT, the extension did not use a blinded adjudication committee to determine if events in which patients received an anti-pseudomonal agent, but did not meet the Fuchs criteria, should be identified as exacerbations. The presence of symptoms/signs consistent with an exacerbation and the start and stop dates of each symptom were captured by the Respiratory and Systemic Symptoms Questionnaire [13] at the beginning of each visit. The Cystic Fibrosis Questionnaire—Revised (CFQ-R) was also completed by patients at each visit and changes in CFQ-R domains from RCT and extension baselines to each visit were determined [12,14].

2.4. Statistical analysis

Descriptive statistics were calculated for each endpoint and included all patients who received at least one dose of LIS in the extension (intention-to-treat population) of the study. Time to first exacerbation was analyzed using Kaplan–Meier methods. No hypothesis tests were defined a priori.

2.5. Study conduct

This study was conducted according to the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice E6 guidelines, the US Food and Drug Administration, and other local regulations and legal requirements. An independent review board and ethics committee at each site approved the study.

3. Results

3.1. Patient disposition

Of 144 eligible patients who participated in the RCT, 88 enrolled in the extension. Including the RCT, 32 patients received TIS followed by LIS (TIS/LIS) and 56 received LIS/LIS; 81.3% completed the study (day 336/week 48) in the TIS/LIS group; 83.9% completed the study in the LIS/LIS group (Fig. 2). There was no difference between the baseline demographics of the extension phase and the RCT population with the exception of a higher proportion of patients aged 12 to 18 years in the extension phase (20.5%) compared with the RCT (13.6%). Baseline characteristics at the start of the RCT were generally comparable between groups except for minor differences in age, FEV_1, and use of azithromycin and hypertonic saline (Table 1). The proportion of patients with an $FEV_1 > 55\%$ predicted was higher among LIS/LIS patients than TIS/LIS patients (50% vs 37.5%). The mean number of exacerbations requiring treatment with antimicrobials in the 12 months prior to the RCT was 1.8 (SD 1.78) among LIS/LIS patients and 1.7 (SD 1.77) among TIS/LIS patients.

3.2. Safety

No new-onset, clinically significant adverse events were observed in the extension (Table 2). LIS was safe and well tolerated among the 88 patients who enrolled in the extension. Presumed TEAEs were reported in 26.1% of patients overall at any time during the extension (TIS/LIS, 37.5%; LIS/LIS, 19.6%); the most common TEAE was dysgeusia (overall, 13.6%; TIS/LIS, 21.9%; LIS/LIS, 8.9%). Most events were mild to moderate in severity. TEAEs that led to permanent discontinuation of LIS occurred in four patients (disease progression [i.e., pulmonary exacerbation]), i.e., two LIS/LIS

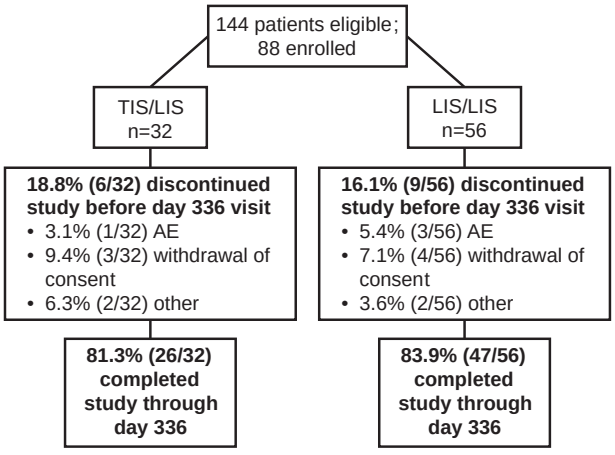

Fig. 2. Patient disposition. Abbreviations: AE, adverse event; LIS, levofloxacin inhaled solution 240 mg twice daily; TIS, tobramycin inhalation solution 300 mg twice daily.

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Table 1
Baseline[a] characteristics in the safety population (extension).

Variable	TIS/LIS	LIS/LIS	Total
	n = 32	n = 56	N = 88
Age in years, mean (SD)	29.5 (11.5)	27.8 (9.8)	28.4 (10.5)
Male, n (%)	18 (56.3)	30 (53.6)	48 (54.5)
United States, n (%)	16 (50.0)	32 (57.1)	48 (54.5)
BMI in kg/m^2, mean (SD)	21.8 (3.9)	21.9 (3.6)	21.9 (3.7)
Extension baseline % predicted FEV_1, mean (SD)	50.9 (16.9)	56.2 (15.7)	54.2 (16.3)
Inhaled antibiotic courses during the previous year, n, mean (SD)	6.0 (3.4)	6.4 (3.1)	6.3 (3.2)
Presence of sputum *P. aeruginosa*, n (%)	30 (93.8)	54 (96.4)	84 (95.5)
Dornase alfa use, n (%)	21 (65.6)	39 (69.6)	60 (68.2)
Azithromycin use, n (%)	21 (65.6)	43 (76.8)	64 (72.7)
Hypertonic saline use, n (%)	17 (53.1)	25 (44.6)	42 (47.7)

Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in 1 s; LIS, levofloxacin inhaled solution 240 mg twice daily; *P. aeruginosa*, *Pseudomonas aeruginosa*; TIS, tobramycin inhalation solution 300 mg twice daily.
[a] Baseline characteristics at the start of the randomized controlled trial.

patients, plantar fasciitis for one LIS/LIS patient with onset during the RCT, and hemoptysis for one TIS/LIS patient.

3.3. Microbiology

Mean sputum *P. aeruginosa* density declined following treatment with LIS and then increased during off-treatment periods, eventually reaching the RCT baseline density (Fig. S1). In the TIS/LIS group, the proportion of patients whose highest *P. aeruginosa* isolate levofloxacin MIC exceeded 1 μg/mL (the European Committee on Antimicrobial Susceptibility Testing [EUCAST] levofloxacin susceptibility breakpoint) was 73.3% at RCT baseline, 75% at extension baseline, and 79.3% at the end of the extension. In the LIS/LIS group, the proportion of patients whose highest *P. aeruginosa* isolate levofloxacin MIC exceeded 1 μg/mL was 77.8% at RCT baseline, 86.3% at extension baseline, and 78.8% at the end of the extension. The prevalence of other sputum bacteria (i.e., *S. aureus* including MRSA, *S. maltophilia*, *A. xylosoxidans*, and *B. cepacia* complex) varied slightly from cycle to cycle during the extension phase and from RCT baseline to the final visit at day 336; however, the number of isolates per bacterial species was too small to detect trends. The prevalence of the nonfermenters *S. maltophilia* and *A. xylosoxidans* decreased from 7.3% to 3.6% and from 8.9% to 3.6%, respectively, from RCT baseline to day 336.

3.4. Lung function and exacerbations

Relative change in percent predicted FEV_1 showed similar mean increases in LIS/LIS patients during cycles 1–3 of the RCT and cycles 4 and 5 of the extension, but this was not apparent during cycle 6 (Fig. 3). Most patients who switched from TIS to LIS experienced an improvement in percent predicted FEV_1 above their post-TIS baselines during cycles 4–6 (77.4% of patients improved at end of cycle 4, 78.6% at end of cycle 5, and 72% at end of cycle 6).

Of the 88 patients who continued into the extension, 65 (TIS/LIS, 24 [75%]; LIS/LIS, 41 [73.2%]) experienced at least one

Table 2
TEAEs first occurring during the extension or during the RCT in ≥5% of patients overall during the extension.

TEAE, n (%)	TIS/LIS		LIS/LIS		Overall	
	n = 32		n = 56		N = 88	
	RCT	Extension	RCT	Extension	RCT	Extension
	TIS	LIS	LIS	LIS		
Weight decreased	15 (46.9)	10 (31.3)	18 (32.1)	12 (21.4)	33 (37.5)	22 (25.0)
Respiratory tract congestion	13 (40.6)	5 (15.6)	20 (35.7)	9 (16.1)	33 (37.5)	14 (15.9)
Disease progression	19 (59.4)	6 (18.8)	30 (53.6)	7 (12.5)	49 (55.7)	13 (14.8)
Cough	15 (46.9)	8 (25.0)	37 (66.1)	3 (5.4)	52 (59.1)	11 (12.5)
Fatigue	12 (37.5)	4 (12.5)	10 (17.9)	7 (12.5)	22 (25.0)	11 (12.5)
Dysgeusia	0 (0.0)	7 (21.9)	9 (16.1)	1 (1.8)	9 (10.2)	8 (9.1)
Hemoptysis	4 (12.5)	1 (3.1)	6 (10.7)	7 (12.5)	10 (11.4)	8 (9.1)
Pulmonary function test decreased[1]	1 (3.1)	3 (9.4)	2 (3.6)	5 (8.9)	3 (3.4)	8 (9.1)
Exercise tolerance decreased	5 (15.6)	2 (6.3)	5 (8.9)	6 (10.7)	10 (11.4)	8 (9.1)
FEV_1 decreased	5 (15.6)	3 (9.4)	6 (10.7)	4 (7.1)	11 (12.5)	7 (8.0)
Nasopharyngitis	6 (18.8)	3 (9.4)	5 (8.9)	5 (8.9)	11 (12.5)	8 (9.1)
Sinus headache	3 (9.4)	4 (12.5)	10 (17.9)	4 (7.1)	13 (14.8)	8 (9.1)
Decreased appetite	2 (6.3)	2 (6.3)	4 (7.1)	5 (8.9)	6 (6.8)	7 (8.0)
Rales	2 (6.3)	1 (3.1)	3 (5.4)	6 (10.7)	5 (5.7)	7 (8.0)
Sputum increased	14 (43.8)	4 (12.5)	31 (55.4)	3 (5.4)	45 (51.1)	7 (8.0)
Exertional dyspnea	6 (18.8)	1 (3.1)	5 (8.9)	6 (10.7)	11 (12.5)	7 (8.0)
Increased viscosity of bronchial secretion	9 (28.1)	3 (9.4)	20 (35.7)	3 (5.4)	29 (33.0)	6 (6.8)
Paranasal sinus hypersecretion	7 (21.9)	1 (3.1)	14 (25.0)	5 (8.9)	21 (23.9)	6 (6.8)
Pyrexia	4 (12.5)	1 (3.1)	6 (10.7)	4 (7.1)	10 (11.4)	5 (5.7)

Abbreviations: FEV_1, forced expiratory volume in 1 s; LIS, levofloxacin inhaled solution 240 mg twice daily; RCT, randomized controlled trial; TEAE, treatment-emergent adverse event; TIS, tobramycin inhalation solution 300 mg twice daily.
[1] Absolute change in FEV_1 percent predicted, FEV_1 (L), FVC (L), FVC percent predicted, and absolute and percent change in FEF25-75.

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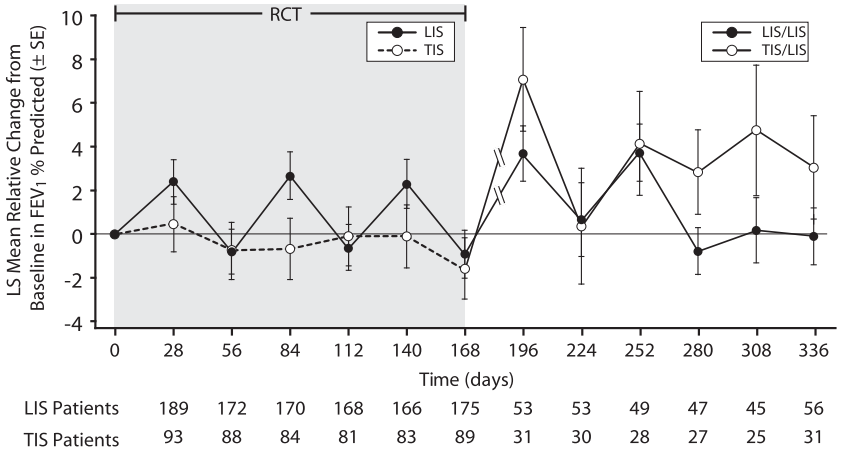

Fig. 3. Relative changes in FEV_1% predicted from RCT baseline to day 336. On the left are data from the intent-to-treat population of the RCT [10]; on the right are those subjects who received ≥ 1 dose of LIS in the extension. Complete data from only those patients who participated in the extension study may be seen in Fig. S2. Error bars indicate standard error. Abbreviations: LIS, levofloxacin inhaled solution 240 mg twice daily; TIS, tobramycin inhalation solution 300 mg twice daily.

exacerbation during the RCT or extension following first dose of study medication. Of these, 12 (21%) LIS/LIS patients and 3 (9%) TIS/LIS patients experienced their first exacerbation during the extension. The median time to first exacerbation from the RCT baseline was 99.5 days among TIS/LIS patients and 153.5 days among LIS/LIS patients (hazard ratio 0.81; 95% confidence interval [CI] 0.48–1.35; Fig. S3). All of the patients in the extension who first experienced an exacerbation met the extension-specified definition of an exacerbation by fulfilling at least four of 12 Fuchs criteria (no patients died). Twenty-three patients in the extension (TIS/LIS, 8 [25%]; LIS/LIS, 15 [26.8%]) remained exacerbation free during the entire study.

3.5. Quality of life

LIS therapy resulted in sustained improvement in CFQ-R respiratory domain compared with RCT baseline (Fig. S3). Patients switched from TIS to LIS also experienced symptomatic benefit assessed by the CFQ-R during the extension similar to those receiving LIS in the RCT for the first on–off cycles. For the second and third cycles, the benefit of LIS to the TIS/LIS patients was less.

4. Discussion

Extended use of LIS at a dose of 240 mg BID for up to six treatment cycles was well tolerated with no clinically relevant new adverse observed in the extension. This study confirms the low frequency of adverse events associated with this drug class, although the small number of patients reduces the chance that an uncommon adverse event would have been observed.

Changes in *P. aeruginosa* sputum density were variable between and within the TIS/LIS and LIS/LIS groups; however, recent research suggests that airway sputum *P. aeruginosa* density changes poorly reflect inhaled antibiotic clinical efficacy as measured by sustained improvement in FEV_1 [15]. The use of cycled LIS over six treatment cycles (48 weeks total observation) was not associated with a clinically relevant decrease in in vitro susceptibility to levofloxacin among *P. aeruginosa* isolates. The relative stability in the proportion of patients with a *P. aeruginosa* isolate with a highest levofloxacin MIC exceeding 1 μg/mL after a year of chronic-intermittent therapy with levofloxacin may be explained by the inability of antibiotics to substantially reduce the burden of *P. aeruginosa* growing in anaerobic biofilms in chronic CF lung infections [16]. The relatively high proportion of patients in this treatment population with at least one *P. aeruginosa* isolate exceeding the EUCAST susceptibility breakpoint for levofloxacin at RCT enrollment suggests that this treatment will have little impact on the use or efficacy of oral and parenteral forms of levofloxacin or other fluoroquinolones in this population with CF. This inference is further supported by the very modest changes in in vitro levofloxacin susceptibility observed among patients receiving chronic intermittent inhaled levofloxacin treatment over 48 weeks, which were similar to levofloxacin susceptibility changes observed among patients treated with LIS during the RCT [10].

LIS has been shown to be effective in the treatment of patients with CF and chronic *P. aeruginosa* lung infection [9,10]. Extended treatment with LIS in this study demonstrated evidence of a sustained benefit. Extended use of LIS has a positive effect on FEV_1 and CFQ-R in this patient population. The mean percent predicted FEV_1 in LIS/LIS patients at the end of six cycles of treatment was similar to that at the beginning of the extension, indicating stabilization of lung function for up to 48 weeks.

Patients originally randomized to TIS who were switched to LIS in the extension had a marked improvement in pulmonary function test in the first cycle of treatment (cycle 4), which was maintained in subsequent treatment cycles, providing additional evidence of benefit with LIS treatment following TIS. Assael et al. observed similar improvements in efficacy after patients switched from TIS to inhaled aztreonam lysine during an extension study [17]. Considering that the present study and the Assael et al. study included TIS-experienced patients, this improvement in pulmonary function test after a change in antibiotic may reflect a diminished effect of inhaled antibiotic

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use over long-periods of continued use supporting the potential benefits of rotating antibiotics [18]. This finding also indicates that patients on cyclical TIS therapy can be switched to LIS without a decrease in efficacy, and possibly experience further improvement in lung function over three cycles of treatment. The lack of improvement in cycle 6 in the current study is likely due to noise associated with the small number of LIS/LIS patients as there is no biologic plausibility for this sudden lack of improvement in cycle 6. The greatest reduction in sputum *P. aeruginosa* density was observed during this cycle, consistent with this being random variation. Importantly, after 6 cycles of LIS, the mean FEV_1 percent predicted at the end of the study for these patients was similar to that at the beginning of the study, indicating the maintenance of lung function over 48 weeks. The long-term maintenance of lung function observed after 6 cycles of LIS therapy is an encouraging observation, as FEV_1 would be expected to decline in this population over time, regardless of therapy [19].

There was a disparity between treatment groups in the number of patients experiencing their first exacerbation during the extension (TIS/LIS, 3 [9%]; LIS/LIS, 12 [21%]). This may have been due, in part, to a larger percentage of patients in the TIS/LIS group having had their first pulmonary exacerbation (based on the extension-specified definition) in the RCT (TIS/LIS, 21 [66%]; LIS/LIS, 29 [52%]). In addition, the time to first exacerbation during the RCT (i.e., cycles 1–3) among participants who later enrolled in the extension was somewhat prolonged relative to that of the entire RCT phase population (Fig. S3). Median time to first exacerbation from RCT baseline was 153.5 days for the LIS/LIS group and 99.5 days for the TIS/LIS group but with a similar hazard ratio for LIS/LIS to TIS/LIS (0.81; 95% CI 0.48–1.35) as observed in the RCT population for TIS to LIS comparison (hazard ratio 0.78; 95% CI 0.57–1.07) [10].

Although there was evidence of sustained clinical benefit in LIS/LIS patients based upon their mean CFQ-R respiratory symptoms domain at the end of cycle 6 (mean improvement from RCT baseline of 4.63), this change was modest. Further, mean CFQ-R respiratory symptom domain scores among TIS/LIS patients were improved at the end of treatment in cycles 4, 5, and 6 in the extension compared with those observed during the RCT (Fig. S4) suggesting an additional indication of LIS treatment benefit.

In open-label extension studies, there is the potential for selection bias with enrichment for patients who had, at best, an overall favorable experience in the RCT or, at worst, did not have substantial problems with treatment tolerability or health outcomes. An additional limitation in this study was the relatively smaller number of patients who participated in the extension compared with the number participating in the RCT; this discrepancy in enrollment was largely due to the timing of the extension protocol approval, which happened too late to allow many RCT-enrolled patients to participate in the extension.

The availability of safe and effective inhaled antibiotics to manage chronic *P. aeruginosa* infection in patients with CF is an ongoing need. Data from this extension augment the evidence that LIS 240 mg BID by inhalation is a safe and effective therapy with some evidence for sustained benefit for the long-term management of chronic lung infection due to *P. aeruginosa*. Inhaled LIS is an important new antibiotic for the treatment of chronic lung infections due to *P. aeruginosa* in patients with CF.

Contributorship

JSE revised the design of the study, implemented the trial in the United Kingdom, interpreted the data, and drafted and revised the paper. He is a guarantor.

PAF revised the design of the study and the statistical analysis plan, implemented the trial in South Carolina, interpreted the data, and drafted and revised the paper. He is a guarantor.

FC revised the design of the study, analyzed the data, and drafted and revised the paper.

JSL designed data collection tools, monitored data collection for the whole trial, wrote the statistical analysis plan, cleaned and analyzed the data, and drafted and revised the paper. He is a guarantor.

DRV cleaned and analyzed the data, and drafted and revised the paper. He is a guarantor.

Additional contributors who implemented the trial in their respective region are listed in the e-supplement.

Conflict of interest

Drs. Elborn and Flume report grants from Aptalis during the conduct of the study. Cohen was an employee of Aptalis during study. Loutit was an employee of the predecessor sponsor to the study and later a consultant to Aptalis. VanDevanter received consultative fees from Aptalis.

Role of the funding source

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcf.2016.01.005.

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