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Original Article

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☆

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Abstract

Background: Inhaled antibiotics are standard of care for persons with cystic fibrosis (CF) and chronic *Pseudomonas aeruginosa* airway infection. APT-1026 (levofloxacin inhalation solution, LIS) is fluoroquinolone in development. We compared the safety and efficacy of LIS to tobramycin inhalation solution (TIS) in persons ≥12 years old with CF and chronic *P. aeruginosa* infection.
Methods: This multinational, randomized (2:1), non-inferiority study compared LIS and TIS over three 28-day on/off cycles. Day 28 FEV_1 % predicted relative change was the primary endpoint. Time to exacerbation and patient-reported quality of life were among secondary endpoints.
Results: Baseline demographics for 282 subjects were comparable. Non-inferiority was demonstrated (1.86% predicted mean FEV_1 difference [95% CI −0.66 to 4.39%]). LIS was well-tolerated, with dysgeusia (taste distortion) as the most frequent adverse event.
Conclusions: LIS is a safe and effective therapy for the management of CF patients with chronic *P. aeruginosa* infection.

Keywords: Cystic fibrosis; Antibiotics; *Pseudomonas*; Aerosol; Fluoroquinolone

1. Introduction

Cystic fibrosis (CF) is characterized by chronic respiratory tract infection with multiple bacterial species, including *Pseudomonas aeruginosa* [1]. Chronic *P. aeruginosa* infection

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is associated with accelerated progression of lung disease, increased morbidity, and decreased survival [2–4].

Inhaled antipseudomonal antibiotics are standard therapy to suppress infection, reduce risk of pulmonary exacerbations, improve quality of life, and preserve lung function in CF patients chronically infected with *P. aeruginosa* [5,6]. Approved inhalational antibiotics for use in people with CF and chronic *P. aeruginosa* infection in the EU are tobramycin, colistimethate, and aztreonam, and in the USA are tobramycin and aztreonam (e-supplement for approved product names).

There is a need for additional safe and effective inhaled antibiotics. The prevalence of chronic *P. aeruginosa* infection increases about 3% per year of age [7], with >70% chronically infected by adulthood [8]. As median predicted survival for CF has exceeded 40 years of age [8], adherence to consensus treatment guidelines [5,6] will result in many patients being treated for decades with inhaled antibiotics.

There is evidence that the lung function response to aerosolized tobramycin becomes attenuated in individuals with CF after exposure of more than 6 months [9,10], a phenomenon that cannot be fully accounted for by selection of bacterial populations with decreased in vitro tobramycin susceptibilities [9]. Similar attenuation of efficacy may occur for other inhaled antibiotics [11]. In addition, patient intolerance to some inhaled antibiotic formulations can be substantial [12,13]. Thus, there is a need for additional options, including alternate classes of antibiotics, to treat patients who are intolerant or have developed attenuated response and to allow for rotation of therapies to reduce the emergence of antimicrobial ineffectiveness [14].

Fluoroquinolones have high potency and a broad spectrum of bactericidal activity and so are attractive to develop as inhaled therapy for CF. APT-1026 (levofloxacin inhalation solution, LIS; also formerly known as MP-376) [15] is the first inhaled solution form of a fluoroquinolone intended for use in chronic maintenance therapy. We describe the results of a phase 3 study designed to compare the efficacy and safety of LIS with tobramycin inhalation solution (TIS) when administered over multiple cycles in individuals with CF and chronic *P. aeruginosa* infection who had previously used inhaled tobramycin.

2. Methods

2.1. Study design

This was a randomized, open-label, parallel group, active comparator trial conducted at 125 CF centers in Europe, USA, and Israel. Subjects were recruited between Feb 2011 and Aug 2012. Eligible subjects were randomized 2:1 to three 28 days on/28 days off treatment cycles of LIS 240 mg (2.4 mL of a 100 mg of levofloxacin per mL as APT-1026) twice daily (BID) or TIS 300 mg (5 mL) BID (TOBI®, Novartis Pharmaceuticals Corp.), with seven study visits 28 days apart (Fig. 1). TIS was delivered with a PARI LC® Plus nebulizer with compressor as indicated in the prescribing information, and LIS was delivered with the PARI investigational eFlow® nebulizer.

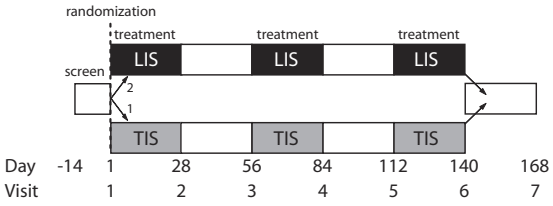

Fig. 1. Study design. Patients were randomized 2:1 to receive LIS or TIS. Three cycles of 28 day BID treatment followed by 28 days off treatment were studied.

Comparison to the approved licensed therapy and delivery device is mandated by the European Medicine Agency (EMA) for approval of a new inhaled antibiotic for CF [16]. Subjects and study coordinators were aware of the treatment assignment, but the site investigators and medical monitors remained blinded in order to minimize treatment bias during the study.

The study was conducted in accordance with Good Clinical Practice, as recommended by the Declaration of Helsinki and the International Congress of Harmonization Guidelines, and the laws and regulations of each study site. Institutional Review Boards and/or Ethics Committees approved the study for each site. Subjects provided written consent and/or parents provided consent for their children prior to undergoing study procedures.

2.2. Participants

Eligible subjects were ≥12 years of age with documented CF diagnosis, a forced expiratory volume in 1 s (FEV_1) between 25 and 85% of their predicted values using the Hankinson/NHANES III reference equations [17], chronic airway infection with *P. aeruginosa*, and had received at least three 28-day courses (≥84 days) of inhaled TIS over the 12 months prior to screening. Prior TIS use was obtained by subject report and verified in the subjects' medical record. Chronic *P. aeruginosa* infection was defined as report of a respiratory secretion culture positive for *P. aeruginosa* in the 12 months immediately prior to screening and a positive culture obtained at the screening visit 2–4 weeks prior to randomization. Subjects continued their routine respiratory care and medications. Subjects were not permitted to use other antipseudomonal antibiotics other than Study Drug unless deemed necessary by the investigator to treat a suspected exacerbation. Detailed inclusion and exclusion criteria and randomization schema can be found in the e-supplement.

2.3. Endpoints

The primary efficacy endpoint was the relative change in FEV_1 percent predicted from baseline to day 28. The trial was designed as a non-inferiority study in accordance with guidance published by the EMA [16]. Additional endpoints included change in other spirometry parameters (FEV_1 [L], $FEF_{25–75}$ [L/s], FVC [L]) from baseline, time to pulmonary exacerbation, time to administration of antipseudomonal antibiotics other than Study Drug, change from baseline in CF Questionnaire-Revised (CFQ-R) respiratory symptom score [18], and change from baseline in sputum *P. aeruginosa* density (log_{10} colony-forming

units (CFU) per gram sputum). Lung function was compared between treatment groups after only 28 days to reduce the probability that concomitant antibiotic treatment for pulmonary exacerbation would confound analyses. A pulmonary exacerbation was defined per protocol as a subject experiencing change in ≥4 of 12 concurrent signs or symptoms [19] regardless of decision to treat with an antibiotic. An independent blinded adjudication board reviewed all instances in which subjects received additional antipseudomonal antibiotics but did not meet the protocol definition of an acute exacerbation to determine if these treatments were associated with exacerbation (further description in e-supplement). Adverse events and serious adverse events (SAEs) were captured from baseline to the final visit for each subject.

Throat swabs or sputum was collected at all study visits (except visit 4/day 84) for selective bacterial culture and in vitro susceptibility testing by central laboratories. Distinct *P. aeruginosa* morphotypes from subjects were analyzed separately. Bacterial densities in sputum specimens were determined by dilution plating.

2.4. Statistics

Statistical analysis was performed on the intention to treat (ITT) population consisting of all randomized subjects. The primary non-inferiority endpoint of relative change in FEV_1 percent predicted from baseline to day 28 was assessed with an analysis of variance (ANOVA) model including fixed effects for the treatment group and the stratification binary variables of geographic region, age and baseline FEV_1 percent predicted. If the lower boundary of the 2-sided 95% confidence interval (CI) for the treatment difference (LIS–TIS) was >−4% (pre-specified non-inferiority margin), non-inferiority of LIS to TIS was concluded. The prospective analysis plan dictated that if non-inferiority of LIS to TIS was demonstrated, a subsequent assessment of superiority was to be performed using a 2-sided test for difference at a 5% level of significance.

The sample size was based on a 4% non-inferiority margin, an 18% standard deviation (SD) in relative change from baseline in FEV_1 percent predicted, and a 10% discontinuation rate over the first 28 days of the study. A sample size of 267 subjects randomized 2:1 to LIS and TIS, respectively, was selected to provide 90% power with a 2-sided 5% significance level based on an assumption that LIS was 4 percentage points better than TIS.

Time to pulmonary exacerbation and time to antibiotic treatment were analyzed by the Cox proportional hazards regression method, with statistical significance of the difference between LIS and TIS determined by a stratified log-rank test. Changes in CFQ-R respiratory symptom score and in sputum *P. aeruginosa* density were assessed using analysis of covariance (ANCOVA) with the same fixed effects as in the ANOVA for the primary efficacy endpoint and with the baseline value included as a covariate. Levofloxacin and tobramycin minimum inhibitory concentrations (MICs) were determined using broth dilution reference methods as published by the Clinical and Laboratory Standards Institute (CLSI; REF-M100). Changes in the levofloxacin MIC were evaluated as the proportion of subjects for which the levofloxacin MIC of their most resistant *P. aeruginosa* isolate changed by >4-fold (the limit of sensitivity of dilution testing) from baseline to the end of the study using a 2-sided Fisher's exact test with a 5% significance level [20]. There was no alpha adjustment for multiple testing for the other efficacy variables. p-Values from these tests were considered to be descriptive only and were evaluated for nominal significance only (i.e., whether ≤0.05).

3. Results

Two hundred and eighty two subjects were randomized in this study; 189 to receive LIS and 93 TIS, with 272 available for safety evaluation (Fig. 2). Baseline characteristics of the groups were similar (Table 1). At the randomization visit, *P. aeruginosa* and *Staphylococcus aureus* were isolated in 93% and 47% of subjects, respectively (*P. aeruginosa* was isolated from all subjects at the screening visit as per inclusion criterion). There were no differences in baseline *P. aeruginosa* antibiotic susceptibility patterns between the two groups (e-supplement Table 1). Concomitant medications were also similar between the two groups at baseline (e-supplement Table 2). The median number of the inhaled antibiotic courses during the previous year was 5 and 44% of the enrolled subjects had received 6 or more courses.

3.1. Efficacy

The study met the primary endpoint of non-inferiority in relative change in FEV_1 percent predicted from baseline to day 28; that is, the lower limit was > the −4% non-inferiority margin. The least squares (LS) mean between-group difference (LIS minus TIS) in FEV_1 was 1.86% [95% CI −0.66 to 4.39%]. As non-inferiority of LIS was demonstrated, a subsequent assessment of superiority was performed, but the difference was not statistically significant (1.86%, p = 0.15; Fig. 3; e-supplement Table 3). A pre-planned analysis of categorical change in FEV_1 percent predicted from baseline to day 28 showed improvement for 70% of subjects receiving LIS compared to 53% of subjects receiving TIS (p = 0.02 by the Cochran–Mantel–Haenszel mean score test). Similar trends were seen for FVC and $FEF_{25–75}$ (e-supplement Tables 4 and 5).

3.2. Time to exacerbation, additional antibiotic requirement and hospitalization

The time to first exacerbation was not significantly different in the LIS group (median 131 days) compared to the TIS group (median 90.5 days) (HR = 0.78; 95% CI: 0.57 to 1.07, p = 0.15; Fig. 4). The median time to administration of antibiotics was 141 days for LIS and 110 days for TIS (HR = 0.73; 95% CI: 0.53 to 1.01; p = 0.04). The proportion of subjects hospitalized for a respiratory exacerbation over the 168 day study period was significantly lower in the LIS group than the TIS group (17.5% versus 28.0%, p = 0.04 by the stratified Mantel–Haenszel test).

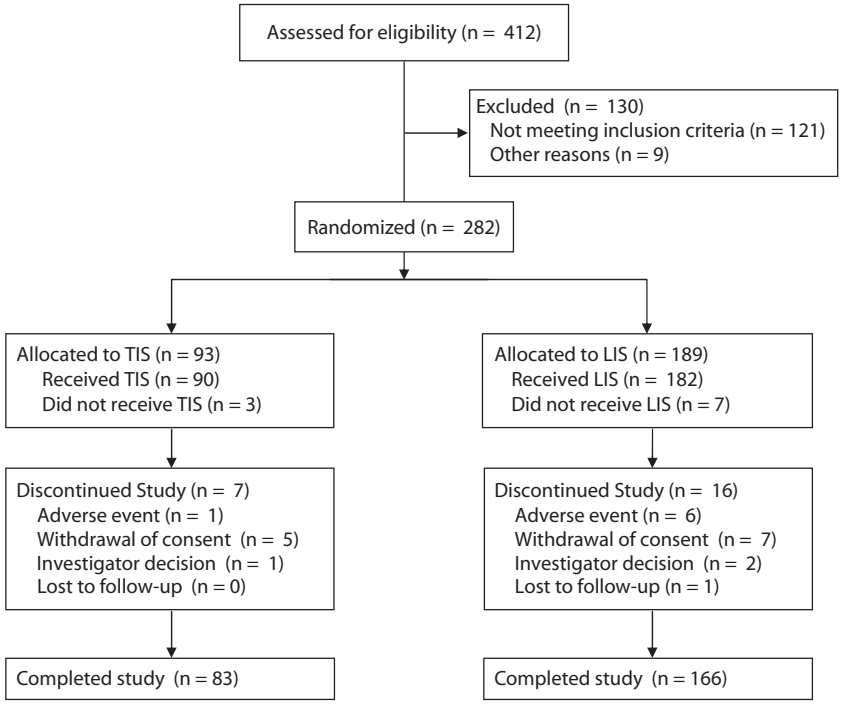

Fig. 2. Patient disposition.

3.3. CFQ-R respiratory domain

Scores in the respiratory domain of the CFQ-R were similar at baseline. The LS means increased (i.e. improvement) in the LIS group and decreased in the TIS group at day 28 (difference of 3.19 units, p = 0.05; e-supplement Fig. 1). The results are similar between the two groups at the end of the study.

Table 1
Demographics at baseline.

	TIS (N = 93)	LIS (N = 189)
Age, years		
Mean (SD)	28.8 (10.94)	28.1 (8.96)
Median	26.0	27.0
>18 years	80 (86.0%)	163 (86.2%)
Male sex, N (%)	56 (60.2%)	103 (54.5%)
US patients, N (%)	63 (67.7%)	128 (67.7%)
FEV_1 percent predicted		
Mean (SD)	53.2 (15.70)	54.8 (16.96)
Median	51.9	54.0
<55, N (%)	52 (55.9%)	100 (52.9%)
BMI, kg/m^2		
Mean (SD)	21.5 (3.30)	21.8 (3.57)
Median	20.8	21.0
Inhaled antibiotic courses during previous year		
Mean (SD)	6.0 (2.79)	6.0 (2.83)
Median	5.0	5.0
≤2, N (%)	3 (3.2%)	8 (4.2%)
3, N (%)	8 (8.6%)	23 (12.2%)
4, N (%)	17 (18.3%)	28 (14.8%)
5, N (%)	25 (26.9%)	44 (23.3%)
≥6, N (%)	40 (43.0%)	85 (45.0%)
Baseline pathogen isolation, N (%)		
P. aeruginosa	86 (92.5%)	175 (92.6%)
S. aureus	35 (37.6%)	96 (50.8%)
Methicillin resistant *S. aureus*	12 (12.9%)	38 (20.1%)
S. maltophilia	8 (8.6%)	20 (10.6%)
A. xylosoxidans	6 (6.5%)	14 (7.4%)
B. cepacia complex	1 (1.1%)	0 (0.0%)

3.4. Microbiology

Both treatments reduced sputum *P. aeruginosa* density, with the magnitude of reduction greater for TIS than LIS, although the difference in change from baseline to day 28 was not significantly different (LS mean difference 0.44 $\log_{10}$ CFU/g; 95% CI −0.01 to 0.88). *P. aeruginosa* densities increased during the subsequent period off treatment. Over the course of the study, the proportion of subjects who experienced a >4-fold increase in the levofloxacin MIC of their most levofloxacin-resistant *P. aeruginosa* isolate was similar in the two treatment groups (21% for LIS versus 17% for TIS; p = 0.5) (e-supplement Fig. 2). No significant emergence of other bacterial opportunists was observed in either treatment group during the study.

3.5. Safety

Discontinuations from the study (Fig. 2) and the occurrence of treatment emergent adverse events (TEAEs; Table 2) were similar between the two groups. Treatment emergent SAEs were reported for 22.0% of LIS and 32.2% of TIS subjects. Excluding disease progression, treatment emergent SAEs were reported for 7.7% of LIS subjects and for 14.4% of TIS subjects during the entire study. There was a higher incidence of dysgeusia (taste distortion) in subjects treated with LIS which accounted for the higher incidence of TEAEs reported in >5% of subjects (Table 2). During the treatment periods, the TEAEs

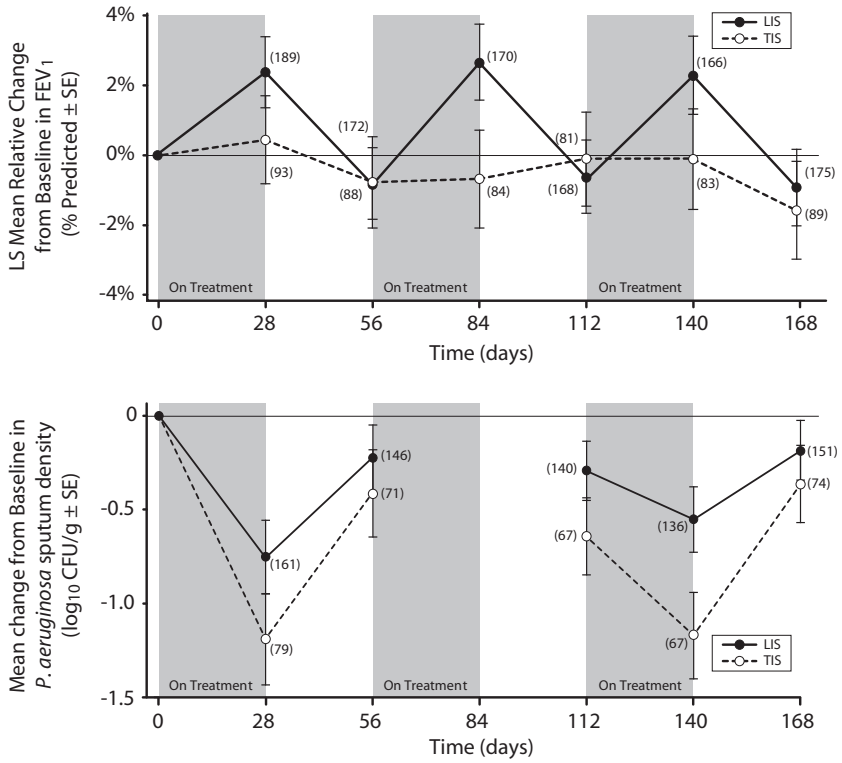

Fig. 3. Mean changes from baseline in FEV_1 % predicted and sputum *P. aeruginosa* density across the study by treatment group. Gray boxes denote on-treatment periods. Solid circles and lines denote LIS, and open circles and dashed lines denote TIS. Bars represent standard errors. Upper panel: Mean relative change from baseline in FEV_1 % predicted. The LS mean for relative change in FEV_1 percent predicted at day 28 was in favor of LIS, but the difference was not statistically significant (2.24%, p = 0.15). Lower panel: Mean change from baseline in $\log_{10}$ *P. aeruginosa* colony-forming units per gram sputum.

other than dysgeusia that were reported for at least 5% more LIS subjects than TIS subjects were cough, increased sputum, paranasal sinus hypersecretion, and sinus headache. Fluoroquinolone class effects associated with systemic administration, such as nausea, arthralgia and tendonitis were uncommon in this study. The incidence of arthralgia during the entire study was low and similar between treatment groups (5.5% LIS, 5.6% TIS), and there were few cases of arthropathy and arthritis/osteoarthritis in the LIS group. One LIS subject had an SAE of costochondritis that led to discontinuation of Study Drug and resolved after treatment. One LIS subject had symptoms consistent with tendonitis but there were no reports of tendon rupture.

4. Discussion

The study demonstrates that LIS is not inferior to TIS in the treatment of subjects with CF and chronic *P. aeruginosa*

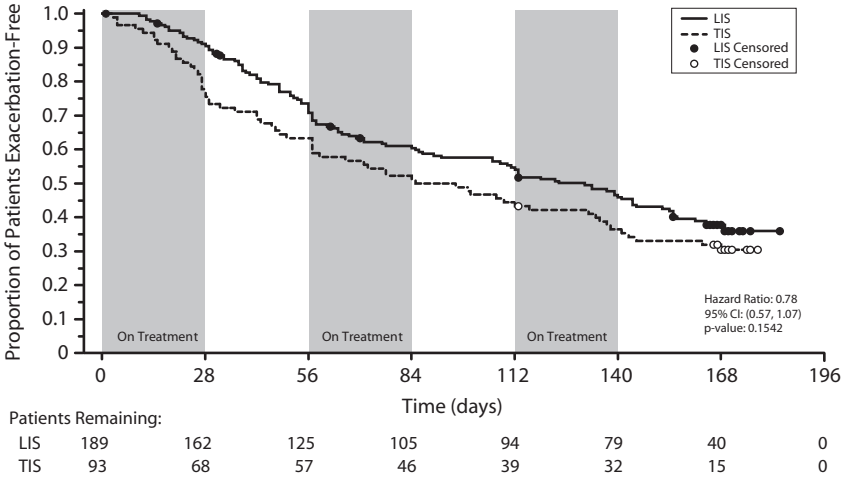

Fig. 4. Time to exacerbation by treatment group. Gray boxes denote on-treatment periods. Solid circles and lines denote LIS, and open circles and dashed lines denote TIS. Circles represent times at which patients were censored from the analysis.

Table 2
Treatment emergent adverse events in >5% of subjects in either treatment group (entire study).

	TIS N = 90	LIS N = 182
System organ class/preferred term		
Patients reporting at least 1 adverse event	90 (100.0%)	180 (98.9%)
Respiratory, thoracic and mediastinal disorders		
Cough	48 (53.3%)	106 (58.2%)
Sputum increased	40 (44.4%)	95 (52.2%)
Respiratory tract congestion	32 (35.6%)	68 (37.4%)
Increased viscosity of bronchial secretion	28 (31.1%)	59 (32.4%)
Paranasal sinus hypersecretion	18 (20.0%)	49 (26.9%)
Hemoptysis	18 (20.0%)	29 (15.9%)
Sputum discolored	16 (17.8%)	26 (14.3%)
Dyspnea exertional	15 (16.7%)	21 (11.5%)
Rales	8 (8.9%)	8 (4.4%)
Dyspnea	5 (5.6%)	8 (4.4%)
Oropharyngeal pain	2 (2.2%)	12 (6.6%)
Epistaxis	5 (5.6%)	2 (1.1%)
General disorders and administration site conditions		
Disease progression	59 (65.6%)	103 (56.6%)
Fatigue	25 (27.8%)	58 (31.9%)
Exercise tolerance decreased	14 (15.6%)	23 (12.6%)
Pyrexia	10 (11.1%)	17 (9.3%)
Malaise	5 (5.6%)	1 (0.5%)
Investigations		
Weight decreased	36 (40.0%)	57 (31.3%)
Forced expiratory volume decreased	15 (16.7%)	17 (9.3%)
Pulmonary function test decreased	8 (8.9%)	14 (7.7%)
Blood glucose increased	7 (7.8%)	4 (2.2%)
Nervous system disorders		
Dysgeusia	0 (0.0%)	46 (25.3%)
Sinus headache	13 (14.4%)	35 (19.2%)
Headache	6 (6.7%)	11 (6.0%)
Infections and infestations		
Nasopharyngitis	11 (12.2%)	17 (9.3%)
Sinusitis	8 (8.9%)	8 (4.4%)
Upper respiratory tract infection	5 (5.6%)	5 (2.7%)
Gastrointestinal disorders		
Abdominal pain	7 (7.8%)	8 (4.4%)
Nausea	7 (7.8%)	11 (6.0%)
Musculoskeletal and connective tissue disorders		
Arthralgia	5 (5.6%)	10 (5.5%)
Metabolism and nutrition disorders		
Decreased appetite	16 (17.8%)	23 (12.6%)
Skin and subcutaneous tissue disorders		
Rash	7 (7.8%)	6 (3.3%)

infection over 28 days. Although the relative change in FEV_1 percent predicted at the end of each treatment period and the median time to first exacerbation favored LIS compared to TIS (Fig. 4), the differences between treatments were not significant. Additionally, respiratory symptoms measured by the CFQ-R respiratory domain improved for LIS subjects compared to those receiving TIS (e-supplement Fig. 1).

TIS and LIS both reduced the sputum density of *P. aeruginosa*. In addition, there were no clinically relevant changes in MICs to either drug during the study. Previous placebo-controlled studies of inhaled antibiotics have noted an association between mean antimicrobial effect (measured by change in bacterial density) and mean lung function benefit [9,21]. However, while there was a numerically greater mean antimicrobial effect among subjects treated with TIS (Fig. 3), there was a numerically greater change in FEV_1 for those treated with LIS, suggesting that there is not a simple relationship between the two measures.

Pulmonary exacerbations are frequent and important events for patients with CF [22]. In this study, no difference was observed between the two groups in the occurrence of pulmonary exacerbations, even when including the adjudicated results of those subjects treated with systemic antimicrobial agents but not meeting the protocol-defined signs or symptoms of an exacerbation. There was a significantly different incidence of hospitalizations between groups, which was lower in the LIS group compared to TIS. Taken together these suggest a benefit in the reduction of exacerbations from treatment with LIS (as has previously been shown for TIS [9]).

There was a significant benefit in CFQ-R respiratory domain scores for subjects treated with LIS compared to TIS. However the patterns of response in this measure were unusual compared to other inhaled antibiotic studies. In previous trials, mean improvements in CFQ-R respiratory domain scores during treatment waned when off therapy. In this study, there was a general improvement in the CFQ-R score in the LIS group throughout the trial, whereas there was little effect in the TIS group. The explanation for these changes is not clear from our data, but may reflect the higher incidence of hospitalizations in the TIS treated group.

One of the objectives of this study was to assess the safety of LIS compared to TIS, a therapy recommended in pulmonary guidelines [5,6] and used over many years [23]. Overall the safety profile of LIS was similar to that of TIS. The most notable difference in safety profiles was the higher incidence of taste distortion in subjects receiving LIS, but this did not appear to have an impact on adherence to the regimen. The inclusion criterion requiring a history of TIS use offers a distinct advantage to TIS with respect to tolerability; subjects who could not tolerate TIS would not have participated. The previously reported rate of taste perversion for TIS was 6.6%.

There are some limitations to the design and interpretation of this study. The first is that the subjects were not blinded to treatment assignment because of differences in nebulizers used for LIS and TIS administration. Despite an effort to reduce bias by attempting to keep the investigators blinded to treatment assignment, it was not possible to do this for study participants. An active comparator was employed to study LIS because of the regulatory requirements to provide data on the non-inferiority of LIS compared to the current standard of care for inhaled antibiotic therapy, TIS, over an extended period [16]. The regulatory requirements also necessitated the use of different delivery devices. Whereas it might be perceived that the faster nebulizer might be preferable (i.e. favoring LIS), the choice of the nebulizer would not favor one drug over the other for the primary endpoint (i.e. FEV_1). It is acknowledged that subjects, and possibly investigators, were aware of the treatment allocation in this study, and perhaps this may have influenced patient care and the assessment of subjective outcomes, such as the diagnosis and treatment of pulmonary exacerbations or subject quality of life. Such biases might have

an impact on the subjective endpoints, but we believe are unlikely to have affected objective endpoints (e.g. FEV_1) in this study.

An additional limitation was that subjects had a substantial treatment experience with inhaled tobramycin. On the one hand this might favor the efficacy findings toward LIS, given the possibility of an attenuated response to TIS over time. On the other hand, there was a likely selection for pre-existing TIS tolerance in this population, so we might expect fewer discontinuations in the TIS group. However, we can also presume a considerable treatment experience with systemic fluoroquinolones in this population, given the substantial use of fluoroquinolones for the treatment of CF pulmonary exacerbations [24] and the levofloxacin susceptibilities of *P. aeruginosa* isolated from subjects at baseline of this study (e-supplement Table 1).

In conclusion, LIS has been shown to be non-inferior to TIS in people with CF chronically infected with *P. aeruginosa*. There was no significant difference in time to first exacerbation between the two groups but there was significant improvement in quality of life assessed by CFQ-R respiratory scores, and a nominally significant reduction in respiratory-associated hospitalizations. No major safety concerns were seen in either group, and changes in airway microbiology were not dissimilar from what is observed in this patient population over the course of time. LIS is as safe and as effective as the standard of care inhaled antibiotic, TIS, and offers an alternative class of antibiotics for use in the long term treatment of people with CF who are chronically infected with *P. aeruginosa*.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcf.2014.12.013.

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.

DEG revised the design of the study, implemented the trial in Florida, interpreted the data, and revised the paper.

DC revised the design of the study, implemented the trial in California, interpreted the data, and revised the paper.

SDA revised the design of the study, implemented the trial in Canada, interpreted the data, and revised the paper.

ARS revised the design of the study, implemented the trial in the United Kingdom, interpreted the data, and revised the paper.

RF revised the design of the study, implemented the trial in Germany, interpreted the data, and revised the paper.

EK revised the design of the study, implemented the trial in Israel, interpreted the data, and revised the paper.

SCB 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.

MND designed data collection tools, monitored data collection for the whole trial, wrote the statistical analysis plan, cleaned and analyzed the data, and revised the paper.

EEM designed data collection tools, monitored data collection for the whole trial, wrote the statistical analysis plan, cleaned and analyzed the data, and revised the paper.

DRV cleaned and analyzed 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.

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

Conflict of interest

Dr. Flume reports grants from Forest Laboratories during the conduct of the study. Authors who also have grant support from Forest include Elborn, Geller, Conrad, Aaron, Smyth, Fischer, Kerem, and Bell. Loutit, Dudley, and Morgan were employees of Forest during study. VanDevanter received consultative fees from Forest.

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