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A Phase 3, Multi-center, Multinational, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Levofloxacin Inhalation Solution (APT-1026) in Stable Cystic Fibrosis Patients

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Abstract

Rationale For patients with cystic fibrosis (CF) and chronic *Pseudomonas aeruginosa* airway infection, the use of inhaled antibiotics has become standard of care to suppress the chronic airways infection. There are limited antibiotic options formulated and approved for inhaled use and antibiotic efficacies attenuate over time, making additional inhaled antibiotic classes desirable. Three antibiotic classes are approved for inhaled use: polymyxins, beta-lactams, and aminoglycosides. APT-1026 (levofloxacin inhalation solution, LIS) is a fluoroquinolone in development for management of chronic *P. aeruginosa* airways infection in patients with CF.

Objectives To compare the safety and efficacy of a 28-day course of treatment with LIS 240 mg or placebo BID in persons ≥12 years old with CF and chronic *P. aeruginosa* infection.

Methods A multinational, randomized (2:1), double-blinded study of LIS and placebo over 28 days in CF patients ≥12 yrs with chronic *P. aeruginosa* infection. Time to exacerbation was the primary endpoint. FEV_1 (% predicted) and patient-reported quality of life were among secondary endpoints.

Main results Baseline demographics for 330 subjects (LIS=220) were similar although significantly more patients randomized to LIS had experienced multiple exacerbations in the year prior to study entry. There was no statistically significant difference in protocol-defined pulmonary exacerbations between treatment arms. Relative change in FEV_1 % predicted from baseline was significantly greater for patients randomized to LIS compared to those randomized to placebo (mean difference 1.31%, p=0.01 [95% CI 0.27, 2.34%]). LIS was well-tolerated, with dysguesia the most frequent adverse event.

Conclusions LIS did not demonstrate a difference in time to next exacerbation when compared to placebo. Reasons for this result are discussed but may be due to an imbalance in the frequency of prior pulmonary exacerbations between the two groups. An improvement in FEV_1 (% predicted) at 28 days was observed and LIS was well tolerated. LIS is safe and has a potential role in the management of CF patients with chronic *P. aeruginosa.*

INTRODUCTION

Cystic fibrosis (CF) lung disease is characterized by chronic respiratory tract infection with multiple bacterial species frequently dominated by *Pseudomonas aeruginosa* [1], which has been associated with accelerated lung disease progression, increased morbidity, and decreased survival [2-4]. Chronic *P. aeruginosa* infection is typically treated with chronic inhaled antibiotics to suppress infection, reduce risk of pulmonary exacerbations, improve quality of life, and preserve lung function [5,6].

Despite the availability of several inhaled antimicrobial classes, there is need for additional safe and effective alternative options. The response to aerosolized tobramycin, as assessed by change in spirometry, becomes attenuated after extended exposure, a phenomenon that is not explained by selection of bacterial populations with decreased *in vitro* tobramycin susceptibilities[7,8]. It is likely that a similar attenuation of efficacy will occur for other inhaled antimicrobials with extended exposure[9]. In addition some patients are unable to tolerate particular inhaled antibiotic formulations[10,11] while others may find an inhaled therapy an excessive treatment burden resulting in poor adherence[12]. Thus, there is a need for additional inhaled antibiotic options; including additional antimicrobial classes to allow for greater rotation of therapies and potential for extension of the effective lives of all inhaled antibiotic classes[12].

Antibiotic classes currently approved in many countries for use by inhalation include the aminoglycosides (tobramycin), monobactams (aztreonam) and polymyxins (colistimethate) (see e-supplement for approved product names). A separate antibiotic class with high potency and a broad spectrum of action, fluoroquinolones, is used extensively as oral and intravenous (IV) formulations to treat CF lung disease. Both the uniqueness of mechanistic class and recognized utility of fluoroquinolones in treating CF airway infection make them an attractive candidate for

inhaled CF therapy. APT-1026 (levofloxacin inhalation solution, LIS; also formerly known as MP-376)[13] is a formulation of a fluoroquinolone intended for inhaled use in chronic maintenance therapy. We describe the results of a placebo-controlled study designed to evaluate the efficacy and safety of LIS in individuals with CF and chronic *P. aeruginosa* infection who had previously used inhaled tobramycin.

METHODS

Study Design

This was a randomized, double-blind, placebo-controlled trial conducted at 97 CF centers in USA, Canada, Australia, New Zealand and Israel. Subjects were recruited between October 2010 and May 2012. Eligible patients were randomized 2:1 to receive 28 days of treatment with either LIS 240 mg (2.4 mL of a 100 mg/ml of levofloxacin as AP-1026) BID or a 0.9% saline-based placebo (color matched with riboflavin), with a 28-day follow-up period off therapy (e-supplement Figure 1). LIS or placebo was delivered with a PARI investigational eFlow® nebulizer.

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. Patients provided written consent or parents provided consent for their children prior to undergoing study procedures.

Participants

Eligible patients were ≥ 12 years of age with documented CF diagnosis, a forced expiratory volume in 1 second (FEV_1) between 25 and 85 percent of their predicted values using Hankinson/NHANES III reference equations [14], chronic airways infection with *P. aeruginosa*, and had received at least three 28-day courses (> 84 days) of inhaled tobramycin inhalation solution (TIS) over the 12 months prior to screening. 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. Participants continued their routine respiratory care and medications during the study. Patients were not permitted to use other antipseudomonal antimicrobials 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.

Endpoints

The primary efficacy endpoint was the time to an exacerbation of CF lung disease. To meet the definition of an exacerbation, patients must concurrently have had changes in ≥4 of 12 respiratory signs or symptoms originally described by Fuchs et al [15], independent of an investigator decision to treat with an antibiotic. Utilization of the Fuchs criteria in this manner was a modification of their original use, which was to confirm a clinician's decision to treat with IV antibiotics for a respiratory (as opposed to other) event. In addition to those patients meeting this modified Fuchs endpoint, patients were considered to have experienced an exacerbation if they discontinued from the study early for any reason, died, or received an antipseudomonal antimicrobial agent for an event that did not meet the predefined criteria but was determined to be an exacerbation for the purposes of the primary endpoint by an independent, blinded,

exacerbation adjudication committee. Changes in respiratory signs and symptoms were systematically collected using the Respiratory Signs and Symptoms Questionnaire (RSSQ) [16]. The adjudication committee reviewed all instances in which patients 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).

Additional endpoints included absolute change from baseline in FEV_1 percent predicted, change from baseline in CF Questionnaire-Revised (CFQ-R) respiratory symptom score [17], and change from baseline in sputum *P. aeruginosa* density (log_{10} colony-forming units (CFU) per gram sputum). Adverse events and serious adverse events were captured from baseline to the final visit for each patient. In addition to standard adverse event reporting, all worsening of Fuchs criteria, as captured on the RSSQ, were captured as adverse events.

Respiratory secretions (throat swabs or sputum) were collected at all study visits for selective bacterial culture by central laboratories. Distinct *P. aeruginosa* morphotypes from patients were analyzed separately. Bacterial densities in sputum specimens were determined by dilution plating.

Statistics

Statistical analysis was performed on the intention to treat (ITT) population consisting of all randomized patients. A hierarchical testing procedure was employed; all tests conducted subsequent to one in which statistical significance was not demonstrated were to be considered as exploratory. The primary efficacy analysis compared the distributions of the time to exacerbation in the treatment groups using a 2-sided stratified (geographic region [US, non-US],

age [12 to 18 years, > 18 years], and FEV_1 percent predicted at Baseline [55%, ≥ 55%]) log rank test at the 5% level of significance. The time-to-event distributions in the groups were summarized using the Kaplan-Meier method. Based on the hierarchical testing procedure, if the primary efficacy endpoint did not show a statistically significant difference, the treatment comparisons for the key secondary endpoints were to be considered as exploratory; hence the term "statistical significance" would refer to nominal significance only.

Secondary analyses of change in FEV_1 percent predicted (both absolute and relative changes), change in *P. aeruginosa* sputum density (log_{10} CFU/g sputum), and change in the Respiratory Domain of the CFQ-R from Baseline to Day 28 were each compared between treatment groups using linear mixed models for repeated measurements that included terms for treatment group (LIS, placebo), visit (Day 14, Day 28), treatment-by-visit interaction, geographic region (US, non-US), age (12 to 18 years, > 18 years), and FEV_1 percent predicted at Baseline (< 55%, ≥ 55%). Additional terms included were Baseline *P. aeruginosa* sputum density for change in *P. aeruginosa* sputum density and Baseline score for change in the Respiratory Domain of the CFQ-R.

A *post-hoc* analysis of time to pulmonary exacerbation as defined by either the modified Fuchs endpoint or by administration of antipseudomonal antibiotics was performed among patient subgroups defined by the number of pulmonary exacerbations treated with intravenous antibiotics they had experienced in the prior year. Hazard ratios (LIS/placebo) and log rank P values were determined by Kaplan-Meier survival analysis.

Due to lack of prior experience with the modified Fuchs study endpoint, sample sizes were estimated based upon time-to-need for systemic or inhaled antimicrobials observed for placebo patients of a previous LIS study[18]. In that prior study, an event-free rate of 0.50 at Day 56 was

observed. For the current study, a 2:1 (LIS: placebo) randomization, a maximum follow-up time of 56 days, and use of a 2-sided log rank test at the 5% level of significance was determined to require 261 patients to obtain 90% power to detect a hazard ratio (HR) of 0.52 (ratio of the risk of use of a systemic or inhaled antimicrobial for a pulmonary exacerbation in the LIS arm to the risk of same for a pulmonary exacerbation in the placebo arm). The sample size was subsequently increased to account for a secondary endpoint of interest, relative change in FEV_1 percent predicted, in keeping with the primary endpoint of a Phase 3, open-label, randomized trial to compare the safety and efficacy of LIS with TIS over 3 consecutive cycles[19]. Accordingly, the planned sample size was increased to 330 patients to obtain >90% power to detect an 8.0 percentage point treatment difference in relative change in FEV_1 percent predicted, assuming a 2-sided test at the 5% level of significance, a standard deviation of 20%, and 2:1 randomization to LIS: placebo. Approximately 415 patients were to be screened to enroll approximately 330 patients, assuming a 20% screening failure rate.

RESULTS

Three hundred and thirty patients were randomized in this study; 220 to receive LIS and 110 placebo. Most patients completed the study, 95.5% of LIS and 99.1% of placebo patients. The disposition and the reasons for discontinuing the study were similar between the treatment groups (Figure 1). Baseline characteristics of the two groups were generally similar with the exception of prior year pulmonary exacerbations with the treatment group having a greater proportion of subjects with ≥3 exacerbations compared to the placebo group (p=0.011; Table 1). At the randomization visit, *P. aeruginosa* and *Staphylococcus aureus* were isolated in 96% and 51% of patients, respectively. 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 inhaled antibiotic courses during the previous year was 6, and 58.7% of the enrolled patients had received 6 or more courses.

Efficacy:

Time to exacerbation

During the study period, 55.5% of patients receiving LIS and 47.3% of patients receiving placebo experienced a protocol-defined pulmonary exacerbation (Figure 2). There was no statistically significant difference in time to protocol-defined pulmonary exacerbations between treatment arms (HR= 1.33, 95% CI: 0.96-1.84). Most patients who met the protocol definition of an exacerbation did so as a result of concurrent changes in at least 4 of the 12 Fuchs criteria (86.1% of LIS and 84.6% of placebo patients). The remaining patients considered to have had an exacerbation either discontinued from the study early or received an antipseudomonal agent for an event that did not meet modified Fuchs criteria but was determined to be an exacerbation for the purposes of the primary endpoint by the independent, blinded, exacerbation adjudication committee.

In all, 15.9% of LIS patients and 12.7% of placebo patients met the modified Fuchs endpoint for exacerbation but did not receive antipseudomonal agents within 14 days before or after meeting criteria. Conversely, 15.0% of LIS and 25.5% of placebo patients received an antipseudomonal agent but did not meet the modified Fuchs endpoint for an exacerbation prior to or within 14 days after receiving an antipseudomonal agent (based on Blinded Exacerbation Adjudication Committee Summaries).

Pulmonary function

FEV_1 percent predicted values were similar in the treatment groups at Baseline. The LS means for absolute change in FEV_1 percent predicted from Baseline to Day 28 in the ITT population showed an increase in both treatment groups (Figure 3A). The difference between the treatment groups favored the LIS group, with an LS mean difference of 1.31 (95% CI 0.27, 2.34; Figure 3A). The LS means for relative change in FEV_1 percent predicted from Baseline to Day 28 in the ITT population showed a difference between the treatment groups favoring the LIS group, with an LS mean difference of 2.42 (95% CI 0.53, 4.30, e-supplement Figure 2).

Time to antibiotic requirement and hospitalization.

The median time to administration of systemic and/or inhaled antipseudomonal antimicrobials for patients who met symptoms requirements at the time of administration of the antipseudomonal antimicrobials was 59 days in the LIS and 58 days in the placebo group in the ITT population. There was no difference in the distribution of time to administration of the antipseudomonal antimicrobials between LIS and placebo (HR = 0.85; 95% CI: 0.61, 1.18), and no difference in the time to administration of IV antipseudomonal antimicrobials when symptoms requirements were met between LIS and placebo (HR = 0.90; 95% CI: 0.46, 1.78).

Change in P. aeruginosa Sputum Density

At Day 14, both treatment groups showed a mean reduction in *P. aeruginosa* sputum density. However, at Day 28, the LIS group showed a mean reduction in *P. aeruginosa* sputum density while the placebo group showed a slight mean increase back to baseline (Figure 3B). The

difference in change from baseline to Day 28 between the treatment groups was an LS mean difference of -0.63 log10 CFU/g sputum favoring the LIS group (95% CI -0.95, -0.30; Figure 3B).

CFQ-R Respiratory Domain

Scores on the Respiratory Domain of the CFQ-R were similar in the treatment groups at Baseline and both treatment groups had a similar mean increase in CFQ-R Respiratory Domain score from Baseline to Day 28. The results were similar at all time points (e-supplement Figure 3). The between-group difference was not significant in the ITT population.

Time to Exacerbation or Antimicrobial Treatment by Prior-Year Treatment History

Post-hoc analyses of time to exacerbation and time to treatment with inhaled or systemic antipseudomonal antibiotics showed that patients who had no IV-treated exacerbations in the prior year tended to have worse outcomes with LIS than placebo (hazard ratios of 2.77 and 1.34), although neither hazard ratio was statistically significant by log rank test (Figure 4). Patients receiving LIS with a history of three or more IV-treated exacerbations in the prior year had a significantly reduced hazard of treatment with antipseudomonal antimicrobials relative to patients receiving placebo (hazard ratio 0.56, P=.028), an effect that was not observed for time to exacerbation using the modified Fuchs endpoint (Figure 4).

Safety

The majority of patients in both treatment groups had Treatment Emergent Adverse Events (TEAEs) during the treatment period (Table 2). With the exception of dysgeusia (taste complaint), which was only reported in the LIS group, the TEAE profile was qualitatively similar

between the treatment groups during the treatment period and the entire study. Excluding disease progression of CF pulmonary disease, which represents a pulmonary exacerbation, the other most frequent TEAEs were cough and increased sputum.

Treatment-related dysgeusia was reported during the treatment period for 35.2% of LIS and no placebo patients. Other than dysgeusia, the TEAEs reported for at least 5.0% more LIS patients than placebo patients were cough, hemoptysis, pyrexia, and nausea during the entire study, while respiratory tract congestion was reported for at least 5.0% more placebo patients than LIS patients. The proportions of patients with TEAEs other than dysgeusia during the treatment period that were considered by the Investigator to be treatment-related were 27.9% of LIS and 18.2% of placebo patients. Most of the TEAEs during the study were mild or moderate; no deaths or life-threatening TEAEs were reported.

Excluding disease progression, treatment-emergent serious adverse events (SAEs) were reported for 3.2% of LIS and no placebo patients. TEAEs led to discontinuation of the study for 1.8% of LIS patients and 0.9% of placebo patients; these events were disease progression and dysgeusia. The proportion of patients who discontinued Study Drug due to TEAEs, which included patients who required antimicrobial agents because of worsening respiratory symptoms or exacerbation, was 14.6% in the LIS group (including 9.6% due to disease progression and 2.3% due to dysgeusia) and 12.7% in the placebo group (including 11.8% due to disease progression).

Fluoroquinolone class effects associated with systemic administration were uncommon in this study. No TEAEs were reported in this study that were related to myasthenia gravis, severe cutaneous adverse reactions (e.g., phototoxicity), convulsions, peripheral neuropathy, psychosis/psychotic disorders, ocular toxicity (e.g., retinal detachment), or *Clostridium difficile*-

associated diarrhea/pseudomembranous colitis. The incidence of arthralgia was low and similar between treatment groups (3.2% of LIS patients and 2.7% placebo) and one LIS-treated patient had tendonitis; however, there were no reports of tendon rupture. One LIS-treated patient had prolonged QT interval that occurred on Study Day 53, more than 3 weeks after last LIS treatment. Blood glucose increased or hyperglycemia was reported for 3.2% of LIS and 3.6% of placebo patients, and all of these patients had a prior history of diabetes mellitus. Blood glucose decreased or hypoglycemia was reported for a single patient (0.9%) in each treatment group.

DISCUSSION

The study did not achieve its primary endpoint of demonstrating superiority of LIS over placebo in the time to a pulmonary exacerbation, but did show superiority over placebo in key secondary endpoints including improvement in lung function (FEV_1 % predicted) and reduction in bacterial density in the sputum. These latter observations are consistent with other studies of LIS compared to placebo[18] and tobramycin inhalation solution (TIS)[19] in the treatment of subjects with CF and chronic *P. aeruginosa* infection. The former observation was an unexpected finding given the previous demonstration of a reduction in need for antipseudomonal antibiotics for those treated with LIS compared to those on placebo[18] and the similarity in time to exacerbation in the comparison of LIS to TIS[19].

There are several possibilities that could explain why the primary endpoint of time to exacerbation was not met. These include: the treated patients did not receive sufficient concentrations of the antibiotic (analysis of serum levofloxacin concentrations do not support this, data not provided), the drug lacks efficacy (improvement in the other key endpoints does not support this), the study populations are not actually similar, or that the exacerbation definition

used in the primary endpoint is inappropriate. Further examination of these latter two possibilities were the justification for *post hoc* analyses.

There is general agreement that a validated exacerbation definition does not exist. Previous studies have used clinical criteria (i.e. signs and symptoms) or administration of antibiotics as clinical endpoints [21]. For this study, an unvalidated modification of the Fuchs exacerbation endpoint was used. The original Fuchs exacerbation definition required treatment with IV antibiotics and the presence of at least 4 of 12 signs or symptoms. If study participants were not treated with IV antibiotics, or if they were treated but less than 4 of the 12 sign and symptom criteria were present, the definition of exacerbation was not met[15]. In contrast, our "modified Fuchs endpoint" drops the requirement for antibiotic treatment and limits the definition to meeting at least 4 of the 12 sign or symptom criteria. A previous *post hoc* analysis of the data from this study as well as another comparing LIS to TIS[19] has suggested that the modified Fuchs endpoint is a poor predictor for whether an investigator would ultimately treat with antibiotics, an alternative method for defining exacerbation[22].

Neither the Fuchs nor the modified Fuchs are used clinically in the management of patients with CF. In contrast, although antibiotic treatment may be a more subjective event, it is a direct clinical measure of exacerbation diagnosis. In a separate open-label active comparator study, participants randomized to LIS had a significantly lower risk of treatment with antipseudomonal antibiotics for an exacerbation than did those participants treated with TIS[19]. Although the comparison of LIS to placebo in this blinded, placebo-controlled study slightly favored LIS when time to antibiotic treatment for exacerbation was considered in place of the modified Fuchs definition, the effect was not statistically significant.

One of the strongest predictors of hazard for treatment with IV antibiotics for pulmonary exacerbations among CF patients is the number of such treatments received in the previous year[23,24]. Patients who experienced 3 or more treatments for exacerbation in the prior year have been reported to have a >25 fold increased hazard of future treatment compared to patients who were not treated in the prior year, while patients treated once or twice in the prior year had a >4 fold increased hazard[23]. Although participant characteristics were generally similar across treatment groups in this study, there was a disproportionate allocation of participants with 3 or more exacerbations in the prior year to the LIS group (20% placebo vs. 34.1% LIS, P = 0.011; Table 1). An increased proportion of patients at highest risk for exacerbation in the LIS group presumably created a baseline imbalance for exacerbation hazard between groups. When hazards of modified Fuchs endpoint or treatment with antipseudomonal antibiotics were compared *post hoc* among subgroups of similar exacerbation risk to mitigate this imbalance, an interesting picture emerged, with an LIS treatment effect (as measured by hazard of antibiotic treatment) more likely to be observed among patients at higher risk for exacerbation at study entry (Figure 4). A comparable relationship between prior-year exacerbation group and LIS treatment effect was not observed for the modified Fuchs endpoint, again highlighting a lack of correlation between the modified Fuchs measure and the investigators' decision to treat with antipseudomonal antibiotics.

LIS was generally well tolerated. With the exception of dysgeusia, cough, and hemoptysis, the safety and tolerability profile of LIS in this study was generally similar to that seen with placebo and consistent with the underlying condition. The low frequency of adverse events that are potentially attributable to fluoroquinolone class effects (e.g., tendinopathy, QT prolongation)

is notable, although the overall exposure to LIS was relatively small to reliably detect uncommon adverse events.

LIS demonstrated clinical efficacy by a reduction in bacterial density and an increase in lung function. Although it did not meet its primary outcome of reduction in exacerbations overall, in those patients with a prior history of frequent exacerbations, it may also increase the time to antibiotic treatment for pulmonary exacerbations. Given its proven safety and tolerability record, LIS demonstrates promise as a therapy for some patients with CF and chronic *P aeruginosa* infection of the airways.

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FIGURE LEGENDS

Figure 1. Patient disposition

Figure 2. Time to protocol-defined exacerbation by treatment group. Gray boxes denotes on-treatment period. Solid circles and lines denote LIS, open circles and dashed lines denote TIS. Circles represent times at which patients were censored from the analysis.

Figure 3. Mean absolute change from baseline in FEV_1 % predicted and change from baseline in sputum *P. aeruginosa* density by treatment group. Shaded area denotes on-treatment periods. Solid circles and lines denote LIS, open circles and dashed lines denote placebo. Bars represent standard errors. Panel A: Mean absolute change from baseline in FEV_1% predicted. Panel B: Mean change from baseline in $\log_{10}$ *P. aeruginosa* colony-forming units per gram sputum. Differences between treatment groups were statistically significant at Day 28. LS=least squares.

Figure 4. *Post hoc* hazard ratios (LIS patients/placebo patients) for modified Fuchs exacerbation or treatment with antipseudomonal antibiotics stratified by prior IV-treated exacerbation subgroups. Hazard ratios were derived using the Kaplan-Meier survival method. Closed circles show results for the entire study population. Open circles show results for patient subgroups defined by the number of IV-treated exacerbations patients had experienced in the prior year. Bars show 95% confidence intervals and P values are derived from log rank tests.

FIGURES

Figure 1

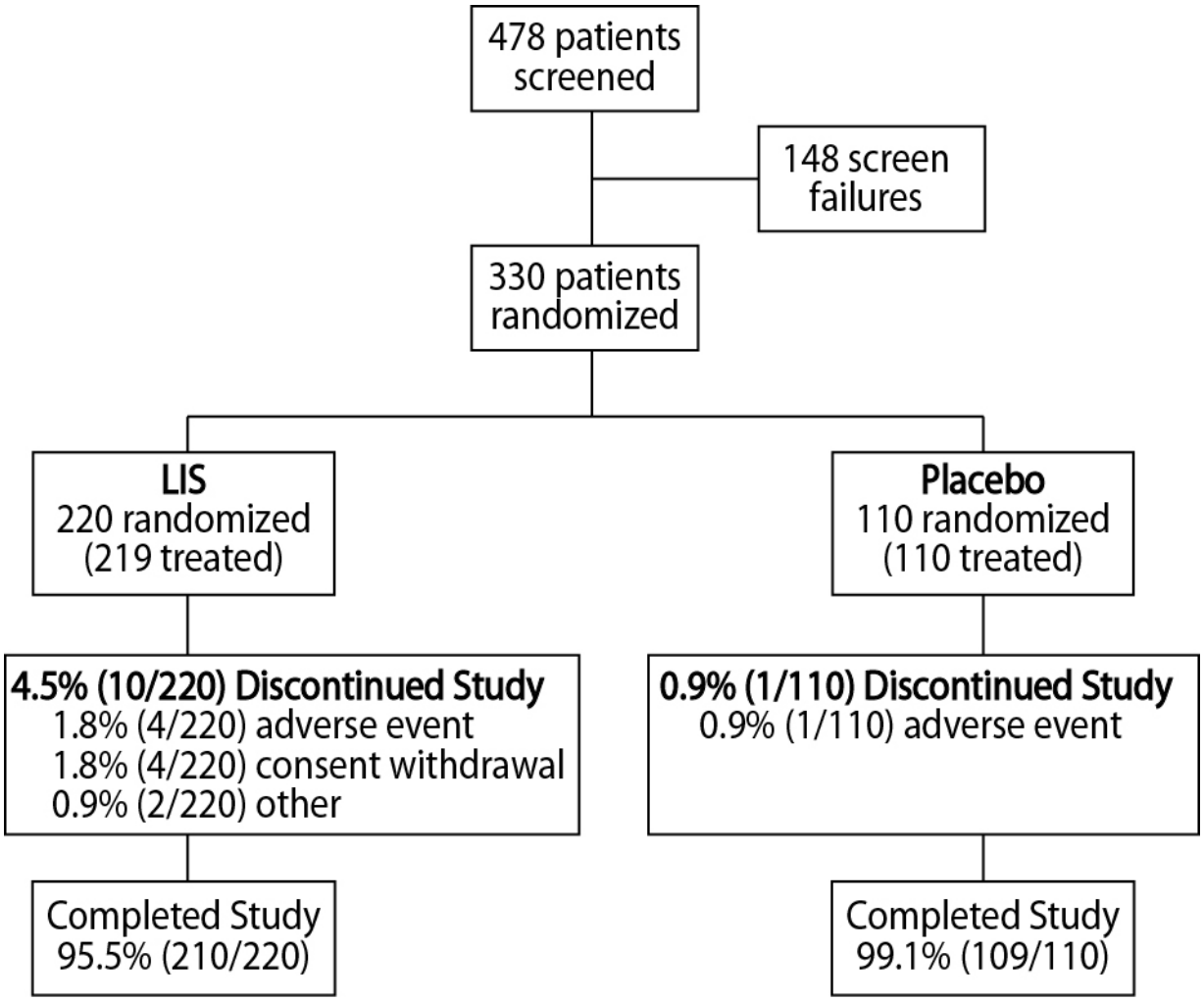
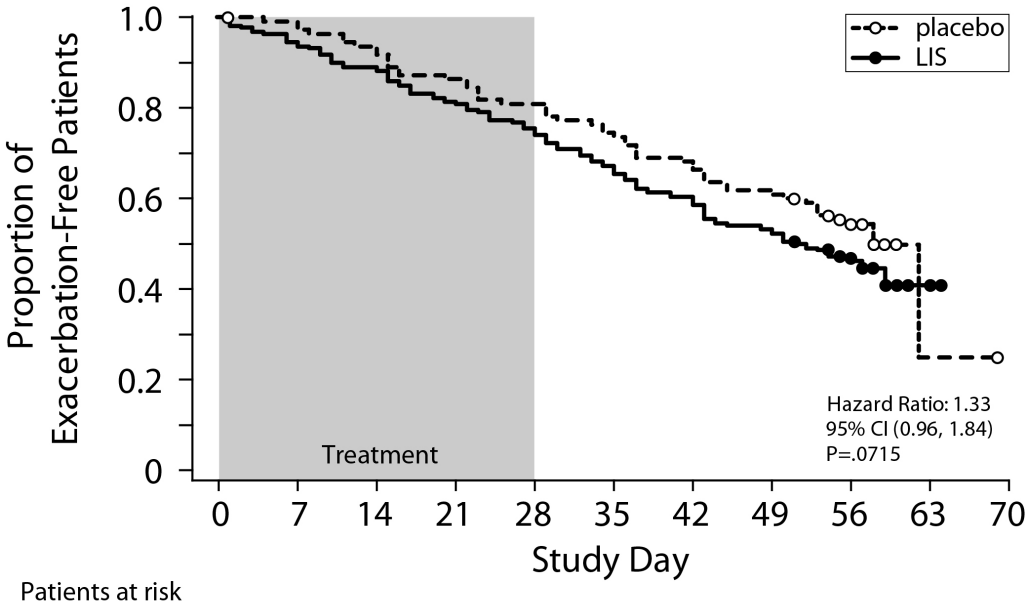


Figure 2



Patients at risk											
Placebo	110	107	101	95	89	81	73	67	47	1	0
LIS	220	206	194	178	163	144	129	115	82	1	0

Figure 3

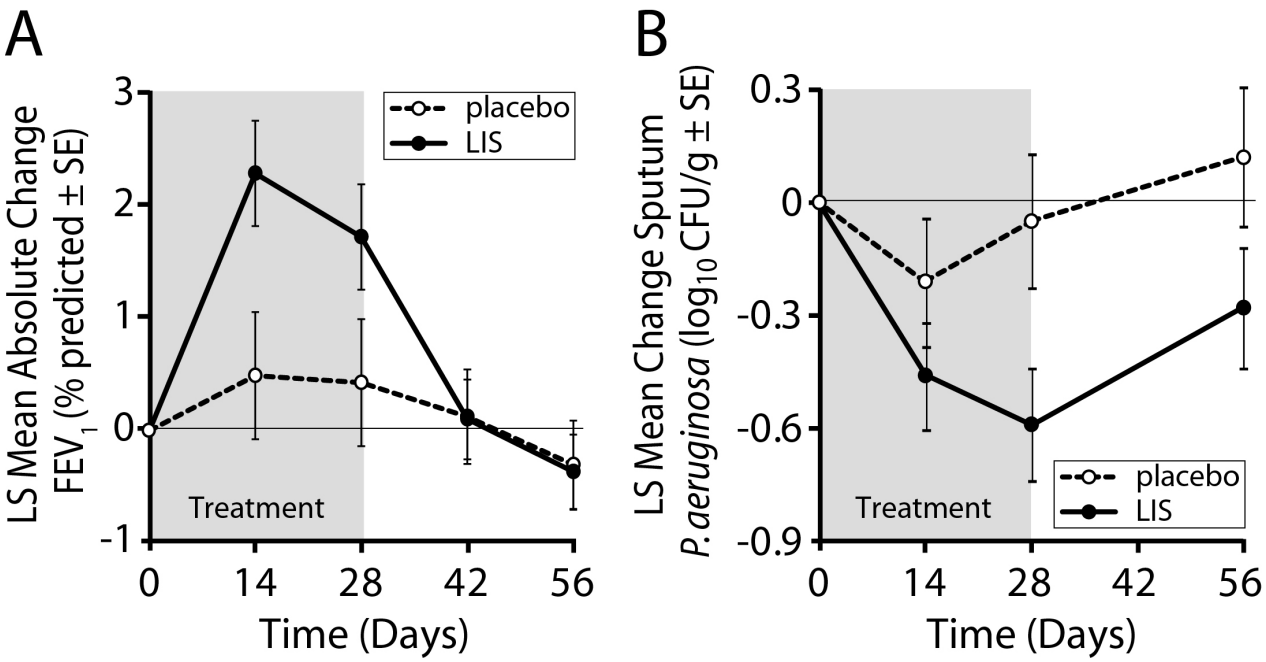
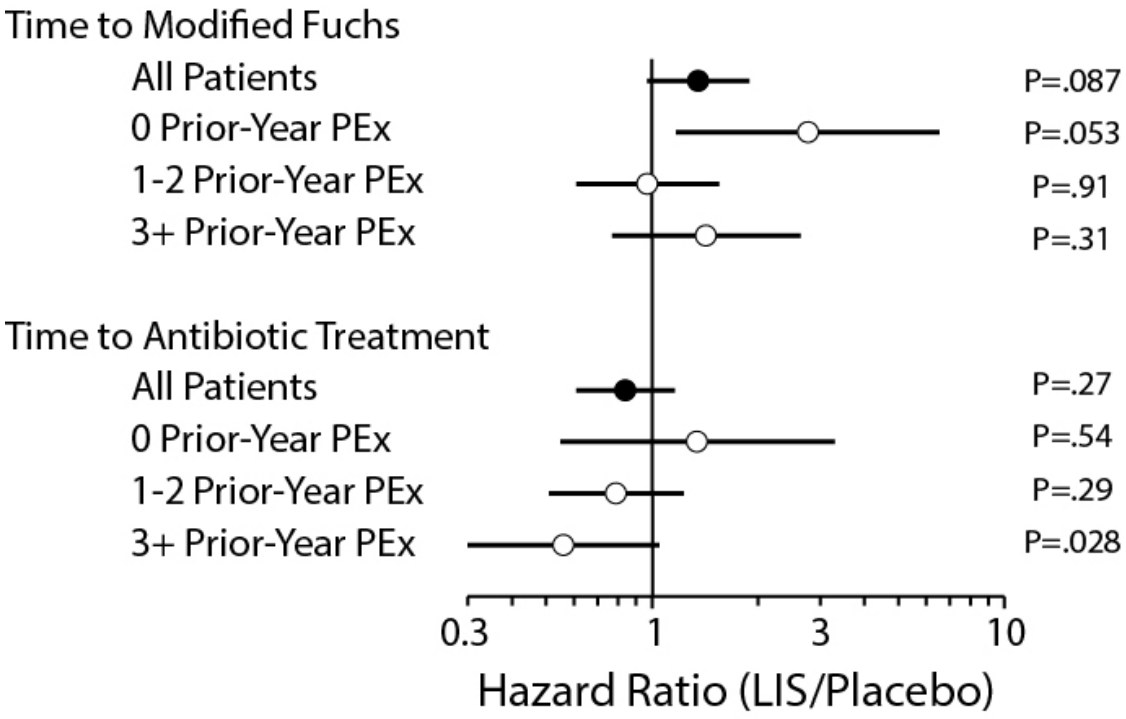

A
LS Mean Absolute Change
FEV1 (% predicted ± SE)
3
2
1
0
-1
placebo
LIS
Treatment
0
14
28
42
56
Time (Days)
B
LS Mean Change Sputum
P.aeruginosa (log10 CFU/g ± SE)
0.3
0
-0.3
-0.6
-0.9
Treatment
placebo
LIS
0
14
28
42
56
Time (Days)

Figure 4.


Time to Modified Fuchs
All Patients
0 Prior-Year PEx
1-2 Prior-Year PEx
3+ Prior-Year PEx
P=.087
P=.053
P=.91
P=.31
Time to Antibiotic Treatment
All Patients
0 Prior-Year PEx
1-2 Prior-Year PEx
3+ Prior-Year PEx
P=.27
P=.54
P=.29
P=.028
0.3
1
3
10
Hazard Ratio (LIS/Placebo)

Tables

Table 1: Demographics at baseline (Safety population)

	Placebo (n=110)	LIS (n=219)
Age, years		
Mean (SD)	28.8 (10.9)	29.4 (10.3)
Median	27.0	28.0
>18 years	94 (85.5%)	184 (84.0%)
Male Sex, N (%)	63 (57.3%)	114 (52.1%)
US Patients, N (%)	98 (89.1%)	193 (88.1%)
FEV_1 percent predicted		
Mean (SD)	56.3 (15.9)	56.6 (15.7)
Median	57.6	57.3
<55, N (%)	52 (47.3%)	100 (45.7%)
BMI, kg/m2		
Mean (SD)	22.1 (3.79)	22.6 (3.95)
Median	21.7	21.8
Inhaled antibiotic courses during previous year		
Mean (SD)	6.0 (2.77)	5.9 (2.65)
Median	6.0	6.0
≤2, N (%)	5 (4.5%)	14 (6.4%)
3, N (%)	13 (11.8%)	26 (11.9%)
4, N (%)	19 (17.3%)	25 (11.4%)
5, N (%)	7 (6.4%)	27 (12.3%)
≥6, N (%)	66 (60.0%)	127 (58.0%)
Prior-year pulmonary exacerbations		
0, N (%)	21 (19.1%)	44 (20.0%)
1-2, N (%)	67 (60.9%)	101 (45.9%)
≥3, N (%)	22 (20.0%)	75 (34.1%)
Baseline pathogen isolation, N (%)		
P aeruginosa	105 (95.5%)	211 (96.3%)
S aureus	58 (52.7%)	110 (50.2%)
Methicillin resistant *S aureus*	22 (20.0%)	56 (25.6%)
S maltophilia	10 (9.1%)	17 (7.8%)
A xylosoxidans	8 (7.3%)	7 (3.2%)
B cepacia complex	3 (2.7%)	4 (1.8%)

Table 2: Treatment Emergent Adverse Events (entire study)

	Placebo N=110	LIS N=219
Patients Reporting at Least 1 Adverse Event	108 (98.2%)	204 (97.7%)
Respiratory, thoracic and mediastinal disorders		
Cough	51 (46.4%)	124 (56.6%)
Sputum increased	42 (38.2%)	91 (41.6%)
Respiratory tract congestion	39 (35.5%)	67 (30.6%)
Increased viscosity of bronchial secretion	21 (19.1%)	44 (20.1%)
Paranasal sinus hypersecretion	18 (16.4%)	37 (16.9%)
Haemoptysis	10 (9.1%)	35 (16.0%)
Sputum discoloured	15 (13.6%)	23 (10.5%)
Dyspnoea exertional	11 (10.0%)	26 (11.9%)
Oropharyngeal pain	7 (6.4%)	10 (4.6%)
Rales	4 (3.6%)	12 (5.5%)
Dyspnoea	5 (5.6%)	8 (4.4%)
General disorders and administration site conditions		
Disease progression	45 (40.9%)	95 (43.4%)
Fatigue	22 (20.0%)	42 (19.2%)
Exercise tolerance decreased	11 (10.0%)	28 (12.8%)
Pyrexia	2 (1.8%)	16 (7.3%)
Investigations		
Weight decreased	21 (19.1%)	36 (16.4%)
Forced expiratory volume decreased	10 (9.1%)	21 (9.6%)
Blood glucose decreased	1 (0.9%)	1 (0.4%)
Nervous system disorders		
Dysgeusia	0	77 (35.2%)
Sinus headache	17 (15.5%)	26 (11.9%)
Headache	3 (2.7%)	14 (6.4%)
Infections and infestations		
Sinusitis	6 (5.5%)	10 (4.6%)
Gastrointestinal disorders		
Nausea	1 (0.9%)	14 (6.4%)
Musculoskeletal and connective tissue disorders		
Arthralgia	3 (2.7%)	7 (3.2%)
Metabolism and nutrition disorders		
Decreased appetite	12 (10.9%)	22 (10.0%)