Common Drug Review
Clinical Review Report

November 2016

Drug	Levofloxacin inhalation solution (Quinsair)
Indication	The management of cystic fibrosis in patients 18 years or older with chronic pulmonary *Pseudomonas aeruginosa* infections
Reimbursement request	As per indication
Dosage form (s)	Inhalation solution 240 mg/2.4 mL (100 mg/mL)
NOC date	09-06-2015 (initial NOC) 05-01-2016 (transfer of DIN)
Manufacturer	Raptor Pharmaceuticals Inc.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

TABLE OF CONTENTS

Tables

Figures

ABBREVIATIONS

AE	adverse event
b.i.d.	twice daily
BMI	body mass index
CDR	CADTH Common Drug Review
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire–Revised
CI	confidence interval
DB	double blind
eCRF	electronic case report form
EMEA	European Medicines Agency
FEF	Forced expiratory flow
FEV_1	forced expiratory volume in one second
HRQoL	health-related quality of life
ITC	indirect treatment comparison
ITT	intention to treat
LIS	levofloxacin inhalation solution
MD	mean difference
MIC	minimum inhibitory concentration
PM	product monograph
PP	per protocol
QoL	quality of life
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SE	standard error
TEAE	treatment-emergent adverse event
TIS	tobramycin inhalation solution
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Chronic endobronchial infection of the airways with bacterial pathogens, such as *Pseudomonas aeruginosa (P. aeruginosa)*, occurs in almost half of individuals with cystic fibrosis (CF) by 18 years of age. Chronic infection with *P. aeruginosa* is associated with a more rapid loss of lung function. The primary cause of increased morbidity and mortality in CF patients is due to chronic *P. aeruginosa* infection. It is estimated that 1 in every 3,600 children born in Canada has CF. More than 4,000 Canadian children, adolescents, and adults with CF attend specialized CF clinics. The prevalence of *P. aeruginosa* infection among Canadian CF patients was estimated to be approximately 43% in 2013.[1]

Inhaled antibiotics, such as tobramycin and aztreonam, are used as chronic suppressive therapy to decrease *P. aeruginosa* load and inflammation. Levofloxacin inhalation solution (LIS) (Quinsair) is a fluoroquinolone antibiotic that has anti-*P. aeruginosa* activity. The objective of this report was to perform a systematic review of the beneficial and harmful effects of LIS for the treatment of CF in patients 18 years or older with chronic pulmonary *P. aeruginosa* infections.

Indication under review
The management of cystic fibrosis in patients 18 years or older with chronic pulmonary *Pseudomonas aeruginosa* infections
Listing criteria requested by sponsor
As per indication

Results and Interpretation

Included Studies

Three randomized controlled trials (RCTs) met the inclusion criteria for this review: MPEX-204 (N = 151),[2] MPEX-207 (N = 330),[3] and MPEX-209 (N = 282).[4] MPEX-204 and 207 were double-blind superiority studies, while MPEX-209 was an open-label non-inferiority trial. MPEX-204 was a phase II dose-finding trial that compared the efficacy, safety, and tolerability of three dosage regimens of LIS (120 mg once daily, 240 mg once daily, and 240 mg twice daily) administered over 28 days, with placebo. MPEX-207 (N = 330) was a phase III trial designed to evaluate the efficacy and safety of LIS 240mg twice daily (N = 220) administered over 28 days compared with placebo (N = 110). MPEX-209 (N = 282) compared the safety and efficacy of LIS 240mg twice daily (N = 189) and tobramycin inhalation solution (TIS) 300 mg twice daily (N = 93) when administered over three cycles of on/off treatment.

Primary outcomes of the included trials included sputum microbiology in MPEX-204, time to pulmonary exacerbation in MPEX-207, and change in FEV_1 from baseline in MPEX-209. Secondary outcomes included: administration of systemic and/or inhaled antipseudomonal antimicrobials, Cystic Fibrosis Questionnaire–Revised (CFQ-R), hospitalization and missed daily activities, and change in weight. The primary efficacy analyses were based on 28 days of treatment in the three included trials.

Efficacy

There were no deaths reported in the included trials.

For the purposes of the CADTH CDR review, disease progression was assessed based on changes from baseline in per cent predicted FEV_1. LIS was associated with a higher increase in percent predicted FEV_1

from baseline to day 28 than placebo in MPEX-204 and 207: the least squares (LS) mean differences (95% CI) were 10.9% (4.6% to 17.3%; relative change; absolute change was not analyzed) in MPEX-204, and 1.31% (0.27% to 2.34%; absolute change) and 2.42% (0.53% to 4.31%; relative change) in MPEX-207. However, the findings for MPEX-207 should be interpreted with caution because the hierarchical statistical analysis plan failed at a higher order comparison; no hierarchical analysis was applied to adjust for potentially inflated type 1 error in MPEX-204. When adult patients were analyzed in a separate subgroup in MPEX-207, the difference between LIS and placebo became not statistically significant. In MPEX-209, the primary analysis (relative change from baseline) and secondary analysis (absolute change from baseline) showed that LIS was non-inferior compared with TIS based on –4% non-inferiority margin; the LSs mean difference between groups after 28 days of treatment was (relative increase) 1.86% (95% CI, –0.66% to 4.39%) and (absolute increase) 1.04% (95% CI, –0.21% to 2.30%). Subgroup analyses for adult patients showed consistent results similar to the primary analysis. No published information on the minimal clinically important difference for the change in percent predicted FEV_1 (absolute or relative) in CF was identified by the CADTH Common Drug Review. The clinical expert consulted for this review indicated that a change in percent predicted FEV_1 of the magnitude observed in the three LIS studies was of uncertain clinical benefit.

Pulmonary exacerbations were reported in MPEX-207 and MPEX-209. In MPEX-207, LIS was associated with more events of exacerbations than placebo, but the difference was not statistically significant. Given this result, all secondary analyses in MPEX-207 were considered exploratory based on the pre-specified hierarchical statistical analysis plan to control for inflated type 1 error with multiple comparisons. Subgroup analyses for adult patients showed that TIS was associated with statistically significant more exacerbations than placebo; the hazard ratio was 1.62 (1.12 to 2.33). In MPEX-209 however, LIS was associated with fewer exacerbation events than TIS, but the difference between treatments was not statistically significant in either the primary analysis or the subgroup for adult patients.

Changes in CFQ-R scores showed that LIS-treated patients had a numerically higher increase in scores, from baseline to day 28, than placebo patients, but the difference between LIS and placebo was not statistically significant. In MPEX-209 however, LIS-treated patients showed statistically significant improvement in CFQ-R scores from baseline to day 28 compared with TIS (1.88 versus –1.31) LS mean difference (95% CI) was 3.19 points (0.05 to 6.32).

MPEX-207 and 209 reported hospitalizations and missed days of school/work/scheduled activities. The results showed that there were no statistically significant differences between LIS and placebo or TIS.

A manufacturer–provided indirect comparison (network meta-analysis [NMA]) evaluated the comparative efficacy and safety of LIS versus tobramycin, aztreonam, and colistin for several outcomes (not pulmonary exacerbations) at 4 week and 24 week end points from RCTs. The consulted clinical expert considered that the 24-week analysis is more relevant than the 4-week one; both NMAs were summarized in this report. The indirect evidence suggested that LIS is not statistically significantly different with respect to efficacy or safety relative to inhaled tobramycin, aztreonam, and colistin in treating patients with CF and chronic *P. aeruginosa* lung infection. However, there are a number of important limitations that make it difficult to conclude no difference in treatment effects between the inhaled antibiotics, including the fact that the three major assumptions of NMA — homogeneity, transitivity, and consistency — were not clearly and explicitly met or addressed and analyses were limited by the available data.

Harms

Overall, there were 84.6% versus 75.7% patients reporting adverse events (AEs) in MPEX-204 in LIS and placebo groups respectively. In MPEX-207, 97.7% of the LIS group reported AEs compared with 98.2% of the placebo group. In MPEX-209, 98.2% of the LIS group reported AEs compared with 96.9% in the TIS group.

Serious adverse events (SAEs) were comparable between LIS and placebo; 8% versus 10.8% in MPEX-204 and 9.6% versus 10% in MPEX-207. In MPEX-209, a lower rate of SAEs was reported by LIS patients (22%) compared with TIS patients (32.2%). In the three trials, the most common SAE was disease progression.

In MPEX-204, fewer LIS patients who discontinued the study drug due to AEs than placebo (5.1% versus 10.8%). In MPEX-207 and 209 however, there was a higher rate of treatment discontinuation due to AEs in the LIS groups than placebo (5% versus 1.8%) and TIS (6.3% versus 1.1%).

Potential Place in Therapy[1]

Levofloxacin provides an alternative therapeutic drug option to treat chronic *P. aeruginosa* pulmonary infection in adults with CF. The clinical expert consulted by the CADTH CDR noted that although there are no data indicating which line of therapy levofloxacin fits in, in practice it will likely be used in adults with CF and chronic pulmonary *P. aeruginosa* infection in whom tobramycin is not effective at maintaining symptom control and or pulmonary function, particularly where resistance to tobramycin on in vitro sputum cultures has been demonstrated. This population, according to the expert, will be easily identified by clinicians based on symptoms, pulmonary function and sputum cultures, which are routinely measured at clinic visits several times per year. As such, levofloxacin will address an unmet need in the clinical care of adults with CF and *P. aeruginosa* infection, in whom maintenance of pulmonary function is paramount for longevity.

Conclusions

The CDR systematic review included two placebo-controlled RCTs and one TIS-controlled RCT that investigated the comparative safety and efficacy of LIS in CF patients with chronic *P. aeruginosa* infections. LIS was associated with a higher increase in per cent predicted FEV_1 from baseline to day 28 than placebo in the two placebo-controlled trials, and it was shown to be non-inferior to TIS after 28-days of treatment. However, LIS was associated with numerically more frequent pulmonary exacerbations than placebo, but it was associated with numerically less frequent events than TIS. LIS was not statistically different from placebo or TIS in terms of changes in CFQ-R, hospitalization, or missed days of school/work/ or scheduled activities when measured 28 days and 56 days after treatment initiation.

LIS was generally well-tolerated in the study populations with more than 88% of LIS-treated patients completing the trial period. LIS was associated with an increased frequency of cough, sputum increase, paranasal sinus hypersecretion, and dysgeusia than TIS and placebo.

A manufacturer–provided indirect treatment comparison (ITC) suggested that little to no difference exists between levofloxacin and other antipseudomonal inhaled antibiotics based on a lack of statistical significance in most of the comparisons; several important limitations make it difficult to be certain in this conclusion.

[1] This information is based on information provided in draft form by the clinical expert consulted by CADTH CDR reviewers for the purpose of this review.

TABLE 1: SUMMARY OF KEY RESULTS

	MPEX-204		MPEX-207		MPEX-209	
	Placebo	**LIS 240 mg b.i.d.**	**Placebo**	**LIS 240 mg b.i.d.**	**TIS 300 mg b.i.d.**	**LIS 240 mg b.i.d.**
N	37	39	110	220	93	189
Relative change from baseline to day 28 in FEV_1 per cent predicted						
• N	37	37	109	218	93	189
• LS mean (SE)	–2.39 (2.370)[a]	8.55 (2.358) [a]	0.43 (0.568)[b]	1.73 (0.471)[b]	0.38 (1.262)[a]	2.24 (1.019)[a]
• LS MD [95% CI]; *P* value	10.94[a] [4.63. 17.25]; 0.0008		1.31[b] [0.27, 2.34]; 0.0137		1.86[a] [–0.66, 4.39]; 0.1481	
Time to first acute exacerbations during 28 days of treatment						
• N (%)	Not reported		52 (47.3%)	122 (55.5%)	62 (66.7%)	111 (58.7%)
• [95% CI]; *P* value			1.33 [0.96, 1.84]; 0.0715		0.78 [0.57, 1.07]; 0.1542	
Change from baseline to day 28 on CFQ-R scale						
• N	37	37	108	218	92	186
• LS Mean (SE)[a]	–0.44 (2.72)	4.06 (2.69)	4.66 (1.37)	4.94 (1.12)	–1.31 (1.58)	1.88 (1.28)
• LS MD (95% CI); *P* value	4.50 [–2.68 to 11.67]; 0.2174		0.28 [–2.30 to 2.85]; 0.8335		3.19 [0.05 to 6.32]; 0.0463	
Time to first missed day of school/work/scheduled activity secondary to worsening respiratory status						
• N (%)	Not reported		18 (16.4%)	28 (12.7%)	5 (5.4%)	14 (7.4%)
• HR [95% CI]; *P* value			0.77 [0.43 to 1.40]; 0.4042		1.54 [0.55 to 4.32]; 0.3969	
Time to Hospitalization secondary to worsening respiratory status						
• N (%)	Not reported		10 (9.1%)	16 (7.3%)	10 (10.8%)	13 (6.9%)
• HR [95% CI]; *P* value			0.82 [0.37 to 1.81]; 0.4902		0.82 [0.35 to 1.93]; 0.6823	
Subjects with > 0 TEAEs						
• N (%)	28 (75.7%)	33 (84.6%)	108 (98.2%)	214 (97.7%)	31 (96.9%)	55 (98.2%)
Most common TEAEs, N (%)						
• Cough	3 (8.1%)	0	51 (46.4%)	124 (56.6%)	15 (46.9%)	37 (66.1%)
• Disease progression	0	0	45 (40.9%)	95 (43.4%)	19 (59.4%)	30 (53.6%)
• Sputum increased	Not reported		42 (35.2%)	91 (41.6%)	14 (43.5%)	31 (55.4%)
• Respiratory tract congestion	2 (5.4%)	2 (5.1%)	39 (35.5%)	67 (30.6%)	13 (40.6%)	20 (35.7%)
• Dysgeusia	18 (48.6%)	13 (33.3%)	0 (0%)	77 (35.2%)	0 (0.0%)	9 (16.1%)
Subjects with > 0 SAEs						
• N (%)	4 (10.8%)	9 (8%)	11 (10.0%)	21 (9.6%)	29 (32.2%)	40 (22.0%)
Most common SAE						
• Disease progression	3 (8%)	7 (6%)	11 (10.0%)	15 (6.8%)	24 (26.7%)	31 (17.0%)
WDAEs, N (%)	4 (10.8%)	2 (5.1%)	2 (1.8%)	11 (5.0%)	1 (1.1%)	12 (6.3%)
Number of deaths, N (%)	0	0	0	0	0	0

CFQ-R = Cystic fibrosis quality of life–respiratory domain; HR = hazard ratio; LIS = levofloxacin inhalation solution; LS = least squares; MD = mean difference; SAE = serious adverse event; SD = standard deviation; SE = standard error; TEAE = treatment-emergent adverse event; TIS = tobramycin inhalation solution; WDAE = withdrawal due to adverse event.

[a] Relative change from baseline.

[b] Absolute change from baseline.

Source: Clinical Study Reports.[2-4]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Cystic fibrosis (CF) is an autosomal recessive inherited disorder caused by mutations in the CF transmembrane regulator gene.[5] In patients with CF, secretions become tenacious and sticky, resulting in pathology in multiple organ systems including the digestive tract and lungs. In the lungs, CF results in airway obstruction, chronic endobronchial infection, and inflammation, which ultimately lead to the destruction of lung tissue with the development of bronchiectasis and loss of lung function.[6] Chronic endobronchial infection of the airways with bacterial pathogens, such as *Pseudomonas aeruginosa (P. aeruginosa)*, which occurs in almost half of individuals with CF by 18 years of age,[6,7] is associated with a more rapid loss of lung function.[8] The primary cause of increased pulmonary exacerbations and mortality in patients with CF is due to chronic *P. aeruginosa* infection.[9] It was reported that CF patients 1 to 5 years old who are infected with *P. aeruginosa* had a 2.6 times higher risk of death than those who are not infected.[10]

In Canada, CF is the most common fatal genetic disease affecting children and young adults for which there is no cure. It is estimated that 1 in every 3,600 children born in Canada has CF. More than 4,000 Canadian children, adolescents, and adults with CF attend specialized CF clinics.[11] The prevalence of *P. aeruginosa* infection among Canadian CF patients was estimated to be approximately 43% in 2013.[1] The prevalence increases with age; *P. aeruginosa* infection is most common among adult patients with CF.[1]

Two patient groups provided input to this submission and were summarized in APPENDIX 1. Patients described having a significant burden of medical therapy and being frequently hospitalized due to acute infections and pulmonary exacerbations. Patients reported they are often too ill to work or maintain daily activities of living, which leads to reduced quality of life. Patients also expressed concerns about the risk of acquiring resistant bacteria that would require the use of more aggressive antibiotics.

1.2 Standards of Therapy

One of the key goals of therapy for CF is preservation of lung function by minimizing pulmonary infection and inflammation. The American Thoracic Society CF guidelines recommend inhaled antibiotic therapy for the treatment and chronic suppression of *P. aeruginosa* infection.[12]

Inhaled tobramycin (Tobi), an aminoglycoside antibiotic, has a Health Canada–approved indication for the management of CF in patients with chronic pulmonary *P. aeruginosa* infections. Tobramycin is recommended by the American Thoracic Society as a first-line inhaled antibiotic for the management of *P. aeruginosa* lung infection in patients with CF.[12] Inhaled tobramycin is available as a solution and as a dry powder for inhalation, both of which are administered in 28 day on and off-treatment cycles (Table 2). Aztreonam lysine inhalation (Cayston) is a monobactam antibiotic that is also indicated for the management of CF in patients with chronic pulmonary *P. aeruginosa* infection. Colistimethate (or colistin) is an injectable polypeptide antibiotic with bactericidal activity against many gram-negative bacteria, including *P. aeruginosa*. The drug, however, is not formulated for inhalation and does not have a Health Canada indication specifically to treat patients with CF and pulmonary infections with *P. aeruginosa.* According to the clinical expert consulted for this review, colistimethate is used for this purpose in clinical practice, particularly for more resistant strains of *P. aeruginosa*.

1.3 Drug

Levofloxacin solution for inhalation, 240 mg, is a fluoroquinolone antibiotic. It is administered through nebulization at a dose of 240 mg twice daily using the included PARI eFlow Nebulizer System. Each dose can be administered in approximately five minutes with the nebulizer. Levofloxacin solution for inhalation is approved in Canada for the management of chronic pulmonary *P. aeruginosa* infections in patients 18 years or older who have CF.

Indication under review
The management of cystic fibrosis in patients 18 years or older with chronic pulmonary *Pseudomonas aeruginosa* infections
Listing criteria requested by sponsor
As per indication

TABLE 2: KEY CHARACTERISTICS OF INHALED LEVOFLOXACIN, TOBRAMYCIN, AND AZTREONAM

	Levofloxacin (Quinsair)	Tobramycin (Tobi)	Aztreonam (Cayston)
Mechanism of Action	Inhibition of bacterial DNA gyrase and topoisomerase IV enzymes	Disrupts bacterial protein synthesis through interaction of 30S ribosomal subunit	Inhibition of bacterial cell wall synthesis
Indication[a]	Management of CF in patients 18 years or older with chronic pulmonary *P. aeruginosa* infections	Management of CF in patients with chronic pulmonary *P. aeruginosa* infections[b]	Management of CF patients with chronic pulmonary *P. aeruginosa* infections[b]
Route of Administration	Inhalation via nebulizer	Oral inhalation via nebulizer (TIS) or dry-powder formulation in capsules (TIP)	Inhalation via nebulizer
Recommended Dose	240 mg (1 ampule) administered by inhalation twice daily Alternating cycles of 28 days on therapy, and 28 days off therapy.	TIS: 300 mg (1 ampule) administered via inhalation twice daily TIP: 112 mg (4 capsules) administered via inhalation twice daily Both: Alternating cycles of 28 days on therapy, and 28 days off therapy.	75 mg (1 vial) administered by inhalation three times daily Alternating cycles of 28 days on therapy, and 28 days off therapy
Serious Side Effects / Safety Issues	• Contraindicated in hypersensitivity to levofloxacin or quinolone antibiotics, and history of tendinitis or tendon rupture associated with use of any quinolone • Caution: QTc prolonging drug, may exacerbate muscle weakness in myasthenia gravis, tendinitis or tendon rupture (especially in patients > 60 years old, with concomitant corticosteroid use, and in patients with kidney, lung or heart transplants), dysglycemia, pregnancy • Caution: Increased coagulation tests and bleeding with concomitant warfarin use	• Contraindicated in hypersensitivity to aminoglycosides • Caution: Associated with ototoxicity (hearing loss, tinnitus) and nephrotoxicity, may exacerbate muscle weakness in myasthenia gravis or Parkinson disease	• Contraindicated in hypersensitivity to aztreonam • Caution: avoid concurrent use with beta-lactamase inducing antibiotics (e.g., imipenem, cefoxitin) due to increased risk for resistance against aztreonam

	Levofloxacin (Quinsair)	Tobramycin (Tobi)	Aztreonam (Cayston)
Other	• Should not be used with any device other than the Zirela Nebulizer System	• TIS should not be used with any other device other than the PARI LC PLUS nebulizer with a DeVilbiss Pulmo-Aide compressor • TIP should not be used with any other device other than the Podhaler device	• Should not be used with any other device other than the Altera Nebulizer System

CF = cystic fibrosis; DNA = deoxyribonucleic acid; *P. aeruginosa* = *Pseudomonas aeruginosa*; QTc = time between the start of the Q wave and the end of the T wave in the electrical cycle of the heart; TIP = tobramycin inhaled powder; TIS = tobramycin inhalation solution.

[a]Health Canada indication.

[b]Product monographs state that the safety and efficacy have not been demonstrated in patients younger than six years of age, in patients with FEV_1 < 25% or > 75% predicted, or in patients infected with *Burkholderia cepacia* complex.

Source: Product monographs for LIS,[13] TIS,[14] TIP,[15] and aztreonam inhaled solution.[16]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of levofloxacin for the treatment of chronic pulmonary *P. aeruginosa* infections in patients 18 years of age and older who have CF.

2.2 Methods

All manufacturer–provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients with CF who have chronic pulmonary *Pseudomonas aeruginosa* infections **Subgroups of interest:** • CF severity (based on baseline FEV_1)
Intervention[a]	Levofloxacin 240 mg twice daily • inhalation over a 5-minute period using a specific nebulizer handset (Zirela) • used in alternating cycles of 28 days on treatment followed by 28 days off treatment • used for a maximum of 3 consecutive cycles (6 months).
Comparators[a]	**Inhaled antibiotics**: aztreonam lysine, tobramycin (powder/solution) **Oral antibiotics**
Outcomes	**Key efficacy outcomes:** • mortality/survival • disease progression (based on FEV_1) • acute exacerbations or infection[b] • health-related quality of life[b] • missed work/school days[b] **Other efficacy outcomes:** • hospitalization[b] • weight/BMI • development of antibiotic resistance[b] **Harms outcomes:** AEs, SAEs, WDAEs, AEs of interest: QTc interval prolongation, anaphylactic reactions, seizures, symptomatic bronchospasm, chondritis, and tendon rupture.
Study Design	Published and unpublished Phase 3 RCTs

AE = adverse event; CF = cystic fibrosis; BMI = body mass index; DB = double blind; FEV_1 = forced expiratory volume in one second; QTc = time between the start of the Q wave and the end of the T wave in the electrical cycle of the heart; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Administered alone or in combination with other oral or inhaled medications to treat CF.

[b] These outcomes were identified as being of particular importance to patients in the input CADTH received from patient groups.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates through Ovid; Embase (1974-) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Quinsair (levofloxacin) and cystic fibrosis.

No filters were applied to limit retrieval by study type. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. Appendix 2 contains the detailed search strategies.

The initial search was completed on June 28, 2016. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on October 19, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, databases (free), and an Internet search. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in APPENDIX 3.

3. RESULTS

3.1 Findings from the Literature

A total of three studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

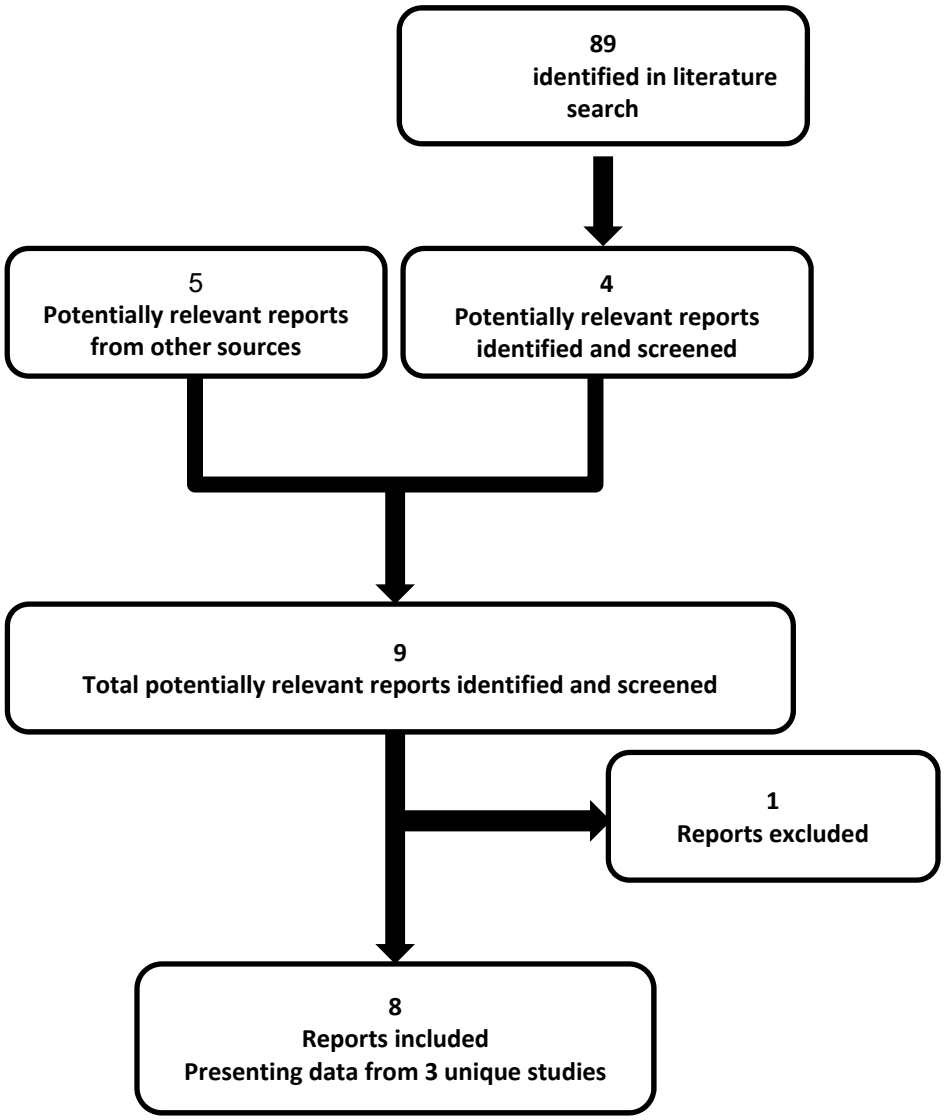


TABLE 4: DETAILS OF INCLUDED STUDIES

		MPEX-204	MPEX-207	MPEX-209
DESIGNS AND POPULATIONS	**Study Design**	Double-bind RCT		Open-label RCT
	Locations	Germany, The Netherlands, and US	Australia, Canada, Israel, and US	Israel, US, Western Europe
	Randomized (N)	151	330	282
	Inclusion Criteria	• Patients with a clinical diagnosis of CF • 25% ≤ FEV_1 ≤ 85% at screening • ≥ 3 inhaled antimicrobial courses over the preceding 12 months, but none in the 28 days before visit 1 (day 1) • Sputum specimen positive for *P. aeruginosa*		
		• ≥ 16 years of age	• ≥ 12 years of age	
	Exclusion Criteria	Acute upper respiratory tract infection within 10 days or lower respiratory tract infection within 30 days		
DRUGS	**Intervention**	Levofloxacin 120 mg q.d. Levofloxacin 240 mg q.d. Levofloxacin 240 mg b.i.d. Administered with PARI eFlow nebulizer	Levofloxacin 240 mg b.i.d. Administered with PARI eFlow nebulizer	Levofloxacin 240 mg b.i.d. Administered with PARI eFlow nebulizer
	Comparator(s)	Placebo (3 doses)	Placebo	Tobramycin inhalation solution 300 mg b.i.d. Administered with PARI LC PLUS nebulizer
DURATION	**Phase**	**Phase II**	**Phase III**	
	Run-in	14 days (screening)		
	Active treatment	28 days (of active double-blind treatment) one cycle		3 cycles of 28 days of treatment followed by 28 days of rest period after cycle 1 and 2 (140 days total)
	Follow-up	28 days		
OUTCOMES	**Primary End Point**	Sputum Microbiology	Exacerbation Assessment (Blinded Exacerbation Adjudication Committee)	Pulmonary Function Tests
	Other End Points	Need for Systemic and/or Inhaled Antipseudomonal Antimicrobials		
		Cystic Fibrosis Questionnaire–Revised		
			Cystic Fibrosis Respiratory Symptoms Weekly Diary Pulmonary Function Tests	Exacerbation Assessment (Blinded Exacerbation Adjudication Committee)
		Pulmonary Function Tests		Sputum Microbiology
NOTES	**Publications**	Geller et al. 2011[17]	Flume et al. 2016[18]	Elborn et al. 2015[19]

CF = cystic fibrosis; b.i.d. = twice daily; DB = double blind; FEV_1 = forced expiratory volume over one second; q.d. = once daily; RCT = randomized controlled trail.
Note: 5 additional reports were included (Health Canada reviewer's reports,[20] 3 Clinical Study Reports,[2-4] and CDR submission[11]).
Source: Clinical Study Reports.[2-4]

3.2 Included Studies

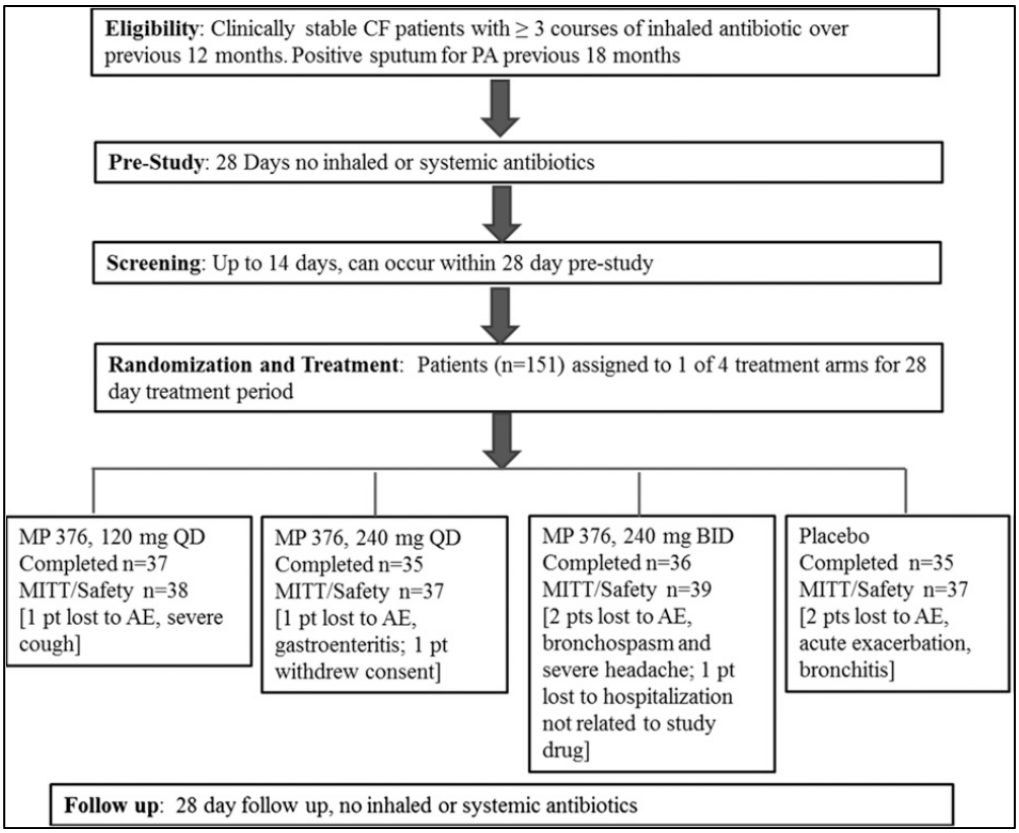
3.2.1 Description of studies

Three RCTs met the inclusion criteria for this review: MPEX-204,[2] MPEX-207,[3] and MPEX-209.[4] MPEX-204 and 207 were double-blind superiority studies, while MPEX-209 was an open-label non-inferiority trial.

MPEX-204 was a phase II dose-finding trial that compared the efficacy, safety, and tolerability of 3 dosage regimens of levofloxacin inhaled solution (LIS) (120 mg once daily, 240 mg once daily, and 240 mg twice daily) administered over 28 days, with placebo (Figure 2). In this report, only data pertaining to the Health Canada–approved dose (240 mg twice daily) will be reported. A total of 151 patients were included in MPEX-204, with 37 patients randomized in the placebo group and 39 patients in LIS 240 mg twice daily group. Patients who were randomized into the study were stratified by geographic region (US and non-US sites).

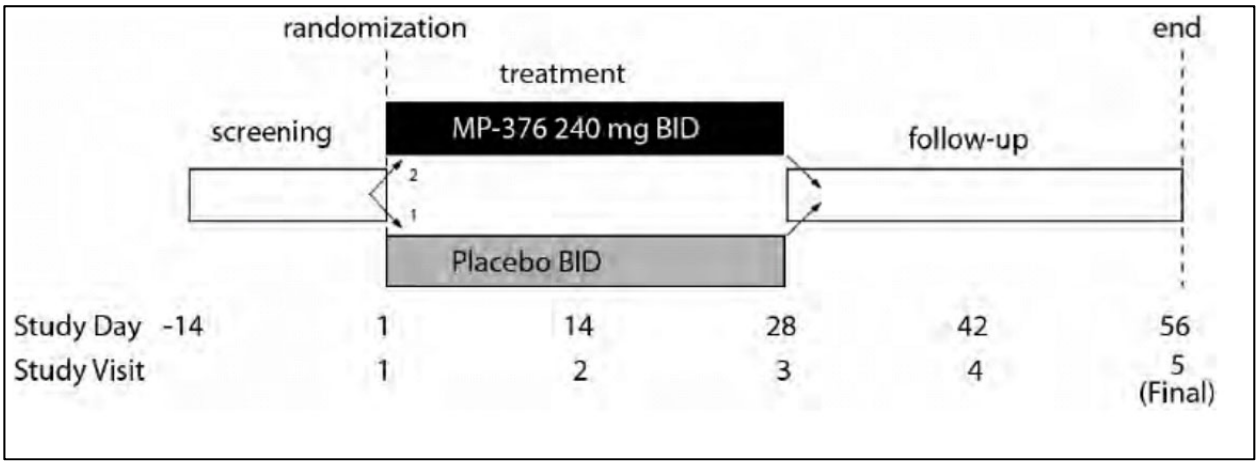
MPEX-207 (N = 330) was a phase III trial designed to evaluate the efficacy and safety of LIS 240 mg twice daily (N = 220) administered over 28 days compared with placebo (N = 110) (Figure 3). MPEX-209 (N = 282) compared the safety and efficacy of LIS 240 mg twice daily (N = 189) and tobramycin inhalation solution (TIS) 300 mg twice daily (N = 93) when administered over three cycles of on and off treatment (Figure 4). In MPEX-209, the primary comparative efficacy evaluation between LIS and TIS was limited to one 28-day cycle of treatment; the trial included an exploratory comparison of efficacy between LIS and TIS when administered over three cycles of on/off treatment. Randomization was stratified by geographic region (US and non-US), age (12 to 18 years and > 18 years), and FEV_1 per cent predicted at baseline (55% and ≥ 55%) in both MPEX-207 and MPEX-209.

FIGURE 2: MPEX-204 STUDY DESIGN



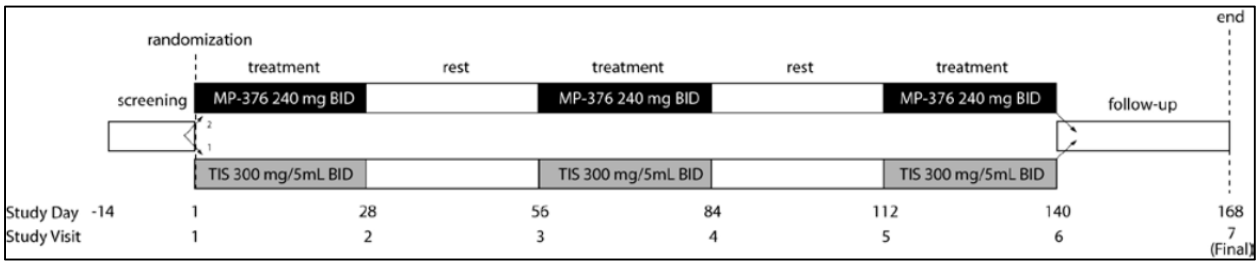
Source: Reprinted with permission of the American Thoracic Society. Copyright© 2016 American Thoracic Society.
Geller DE, Flume PA, Staab D, Fischer R, Loutit JS, Conrad DJ, et al./2011/Levofloxacin inhalation solution (MP-376) in patients with cystic fibrosis with Pseudomonas aeruginosa/The American Journal of Respiratory and Critical Care Medicine/183(11)/1510-6.
The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.[17]

FIGURE 3: MPEX-207 STUDY DESIGN



b.i.d. = twice daily.
Source: Clinical Study Report.[3]

FIGURE 4: MPEX-209 STUDY DESIGN



b.i.d. = twice daily.
Source: Clinical Study Report.[4]

3.2.2 Populations

a) Inclusion and exclusion criteria

In general, the three trials shared similar inclusion criteria except for patients' age; MPEX-204 included patients 16 years and older, while MPEX-207 and 209 included patients 12 years and older. Of note, the Health Canada–approved indication is in patients aged 18 years and older, so this age group is the focus of the CADTH CDR review. However, data were not available for the specific subgroup of patients 18 years and older, and therefore the results are presented in the report for the total populations regardless of age. CF had to be clinically diagnosed based on the following criteria:

- positive sweat chloride ≥ 60 mEq/liter (by pilocarpine iontophoresis) and/or
- a genotype with 2 identifiable mutations consistent with CF
- accompanied by 1 or more clinical features consistent with the CF phenotype.

Disease severity was determined by FEV_1 based on National Health and Nutrition Examination Survey (NHANES) criteria.[21] Patients were included if they were able to elicit an $FEV_1 \geq 25\%$ but $\leq 85\%$ predicted value at screening.

Patients who had a > 15% relative change (increase or decrease) in FEV_1 from screening to visit 1 pre-study drug pulmonary function tests (PFTs) were not to be enrolled but could be rescreened when stable. Changes in the CF medical regimen (i.e., introduction, dose escalation, or elimination of therapies

such as dornase alfa, nonsteroidal anti-inflammatory drugs, azithromycin, hypertonic saline, or inhaled corticosteroids) within 28 days before visit 1(day 1) were exclusionary and were to be avoided during the trial if at all possible.

b) Baseline characteristics

Demographic characteristics at baseline are summarized in Table 5, and baseline medical history is summarized in Table 6.

The three trials included patients of similar mean age, from 28.3 to 30.1 years. MPEX-7 included slightly more patients in the age range of 12 to 18 years compared with MPEX-209 (15.5% versus 13.6% respectively). The majority of the included patients in each study were males; in MPEX-204 however, the LIS group had the highest rate of male participants (64.1%), and the placebo group had the lowest (51.4%) compared with the other trials. The majority of the included patients were Caucasian.

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

	MPEX-204		MPEX-207		MPEX-209	
	Placebo	**LIS 240 mg b.i.d.**	**Placebo**	**LIS 240 mg b.i.d.**	**TIS 300 mg b.i.d.**	**LIS 240 mg b.i.d.**
N	**37**	**39**	**110**	**220**	**90**	**182**
Age (years)						
• N	37	39	110	219	90	182
• Mean (SD)	30.1 (9.94)	29.2 (9.98)	28.8(10.94)	29.4 (10.34)	28.9 (11.05)	28.3 (9.00)
• Median	Not reported		27.0	28.0	27.0	28.0
• Min, Max	16,55	16, 56	12.0, 62.0	12.0. 62.0	12.0, 63.0	12.0, 55.0
• 12 to 18 years	Not reported		16 (14.5%)	35 (16.0%)	12 (13.3%)	25 (13.7%)
• >18 years			94 (85.5%)	184 (84.0%)	78 (86.7%)	157 (86.3%)
Sex						
• Male	19 (51.4%)	25 (64.1%)	63 (57.3%)	114 (52.1%)	53 (58.9%)	101 (55.5%)
• Female	18 (48.6%)	14 (35.9%)	47 (42.7%)	105 (47.9%)	37 (41.1%)	81 (44.5%)
Ethnicity						
• Hispanic or Latino	Not reported		9 (8.2%)	10 (4.6%)	3 (3.3%)	14 (7.7%)
• Not Hispanic or Latino			101 (91.8%)	209 (95.4%)	87 (96.7%)	168 (92.3%)
Race						
• American Indian or Alaska Native	Not reported		0	1 (0.5%)	0 (0.0%)	1 (0.5%)
• Black or African American	1 (2.7%)	0 (0.0%)	5 (4.5%)	3 (1.4%)	1 (1.1%)	2 (1.1%)
• Caucasian	36 (97.3%)	39 (100.0%)	100 (90.9%)	212 (96.8%)	87 (96.7%)	174 (95.6%)
Region						
• US	30 (81.1%)	32 (82.1%)	98 (89.1%)	193 (88.1%)	62 (68.9%)	125 (68.7%)
• Non-US	7 (18.9%)	7 (17.9%)	12 (10.9%)	26 (11.9%)	28 (31.1%)	57 (31.3%)
Weight (kg)						
• N	37	39	110	219	90	182
• Mean (SD)	60.1 (13.26)	63.9 (11.95)	62.4(14.51)	63.4(13.33)	61.7 (13.03))	61.3 (13.68
• Median	Not reported		60.3	61.5	60.2	59.1
• Min, Max	36.8, 90.7	46.1, 86.3	35.6, 120.6	30.2, 116.0	31.5, 103.7	30.2, 124.8

b.i.d. = twice daily; LIS = levofloxacin inhalation solution; SD = standard deviation; TIS = tobramycin inhalation solution.
Source: Clinical Study Reports.[2-4]

Patients included in MPEX-207 and MPEX-209 reported an average of 24 to 25 years since the original CF diagnosis. There were more patients in LIS groups who had ≥ 3 pulmonary exacerbations requiring treatment with antimicrobials in the last 12 months than placebo (33.8% versus 20.0%) or TIS (30.8% versus 27.8%). Furthermore, there were more patients in LIS groups who had used salbutamol in the previous 30 days before the trial than placebo (74% versus 59%) and TIS (62% versus 57%). In MPEX-207, there were more patients in LIS group who used dornase alpha in the previous 30 days before the trial than placebo (81% versus 77%); in MPEX-209, there were fewer LIS patients who had used dornase alpha than TIS patients (73% versus 81%).

The mean FEV_1 ranged from 49 to 57 per cent predicted, and the values were similar between groups in each trial.

TABLE 6: SUMMARY OF BASELINE MEDICAL HISTORY

	MPEX-204		MPEX-207		MPEX-209	
	Placebo	**LIS 240 mg b.i.d.**	**Placebo**	**LIS 240 mg b.i.d.**	**TIS 300 mg b.i.d.**	**LIS 240 mg b.i.d.**
N	**37**	**39**	**110**	**220**	**90**	**182**
Time since original CF diagnosis (years)						
Mean (SD)	Not reported		24.0 (10.77)	25.2 (10.16)	23.8 (10.34)	25.6 (9.06)
Pulmonary exacerbations requiring treatment with antimicrobials in the last 12 months						
Mean (SD)	Not reported		1.6 (1.35)	2.0 (1.65)	1.9 (1.72)	1.8 (1.74)
≤ 2			88 (80.0%)	145 (66.2%)	65 (72.2%)	126 (69.2%)
3			10 (9.1%)	37 (16.9%)	12 (13.3%)	28 (15.4%)
4			7 (6.4%)	19 (8.7%)	7 (7.8%)	17 (9.3%)
5			4 (3.6%)	11 (5.0%)	2 (2.2%)	4 (2.2%)
≥ 6			1 (0.9%)	7 (3.2%)	4 (4.4%)	6 (3.3%)
Time since resolution of most recent pulmonary exacerbation (days)						
Mean (SD)	Not reported		139.9 (98.52)	114.1 (86.95)	129.7 (94.77)	105.4 (72.99)
Inhaled antimicrobial courses during previous year						
Mean (SD)	5.4 (2.28)	4.8 (1.51)	6.0 (2.77)	5.9 (2.65)	6.0 (2.75)	5.9 (2.80)
Use of non-antimicrobial medications up to 30 days before visit 1/day 1						
Drugs for obstructive airway diseases	Not reported				84 (93.3%)	168 (92.3%)
Salbutamol			65 (59.1%)	162 (74.0%)	51 (56.7%)	112 (61.5%)
Cough and cold preparations					85 (94.4%)	157 (86.3%)
Dornase alpha			85 (77.3%)	177 (80.8%)	73 (81.1%)	133 (73.1%)
Baseline Susceptibilities of *P. aeruginosa*[a] to antimicrobials						
Number of isolates			174	335	146	298
Isolates not susceptible to Levofloxacin	Not reported		72 (41.4%)	155 (46.3%)	69 (47.3%)	141 (47.3%)
Isolates not susceptible to Aztreonam			40 (23.0%)	96 (28.7%)	41 (28.1%)	70 (23.5%)
Isolates not susceptible to Tobramycin			48 (27.6%)	93 (27.8%)	50 (34.2%)	106 (35.6%)

	MPEX-204		MPEX-207		MPEX-209	
	Placebo	**LIS 240 mg b.i.d.**	**Placebo**	**LIS 240 mg b.i.d.**	**TIS 300 mg b.i.d.**	**LIS 240 mg b.i.d.**
N	**37**	**39**	**110**	**220**	**90**	**182**
FEV_1 Per cent Predicted						
• Mean (SD)	52.4 (13.42)	48.8 (15.15)	56.3 (15.91)	56.6 (15.71)	52.9 (15.81)	55.3 (16.88)
• < 40, n (%)	7 (18.9%)	12 (30.8%)	Not reported			
• 40 to < 60, n (%)	17 (45.9%)	16 (41.0%)				
• 60 to < 80, n (%)	12 (32.4%)	10 (25.6%)				
• ≥ 80, n (%)	1 (2.7%)	1 (2.6%)				
<55, n (%)	Not reported		52 (47.3%)	100 (45.7%)	52 (57.8%)	95 (52.2%)
• ≥ 55, n (%)			58 (52.7%)	119 (54.3%)	38 (42.2%)	87 (47.8%)

FEV_1 = forced expiratory volume in one second; LIS = levofloxacin inhalation solution; SD = standard deviation; TIS = tobramycin inhalation solution.
Source: Clinical Study Reports.[2-4]
[a] Isolates from sputum; minimum inhibitory concentration (MIC) using breakpoints of > 2 µg/mL for levofloxacin, MIC > 8 µg/mL for aztreonam, MIC > 4 µg/mL for tobramycin.

3.2.2 Interventions and Comparisons

In trial MPEX-204, patients were randomized 1:1:1:1 to receive 1 of 3 LIS treatment regimens or placebo. Patients in the placebo treatment group were further subdivided (0.33:0.33:0.33) to match the number and frequency of ampules in the LIS treatment regimens. The following doses of LIS were administered by the aerosol route using a specialized investigational configuration of a PARI eFlow nebulizer: 120 mg once daily, 240 mg once daily, and 240 mg twice daily. Patients receiving placebo were randomized to 1 of 3 treatment regimens: 2 ampules once daily, 4 ampules once daily, or 4 ampules twice daily to match the LIS treatment regimens. The duration of treatment was 28 days.

At visit 1 (day 1), patients administered study drug in the clinic with guidance from **the unblinded clinic staff**. The clinic staff ensured the patient understood the procedures for administering the study drug and provided the patients with dosing instructions. Patients were advised to withhold one of their doses of study drug on visit 2 (day 7), visit 3 (day 14), and visit 4 (day 28) until they arrived at the clinic and completed study procedures.

MPEX-204 was defined as double blinded. However, due to a difference in colour between LIS and placebo, investigators attempted to minimize identification of the assigned treatment using the following strategies:

- an unblinded staff member (e.g., pharmacist, back-up study coordinator, or other appropriately trained person) dispensed the study drug and associated materials, performed drug accountability, and assisted with study drug administration during clinic visits. **The unblinded staff member agreed to not share treatment** information with the blinded staff members. Specific unblinded staff instructions were included in the Study Operations Manual.
- If a clinic site was unable to assign an unblinded staff member, **at a minimum the Principal Investigator or Sub-investigator was not responsible for dispensing study drug** and associated materials or assisting in administering the study drug. Clinical research associates (CRAs) responsible for monitoring at the clinical sites were not able to perform final drug accountability until after database lock. Drug accountability logs were faxed to an unblinded independent CRA who monitored drug accountability and adherence during the study.

To assess treatment intolerability, **other nebulized products** (with the **exception** of a bronchodilator, dornase alfa, and hypertonic saline) were not to be taken within 4 hours prior to or 30 minutes post-study drug administration on clinic visit days. Antipseudomonal antimicrobial agents were prohibited unless the patient met protocol-specified criteria for their use.

Trial MPEX-207 was reported as a double-blind study and patients were randomized in ratio of 2:1 LIS 240 mg or placebo twice daily. Treatment was self-administered by the patient by the inhalation route using the LIS-customized PARI eFlow nebulizer. The duration of treatment was 28 days.

At visit 1 (day 1) the clinic staff ensured the patient understood the procedures for administering treatment and provided the patient with dosing instructions, a LIS-customized PARI eFlow nebulizer that was used for the course of the study, and enough study drug for 16 days (14 days + 2-day window) of treatment. During visit 2 (day 14) the clinic staff dispensed a new study drug kit to the patient.
Trial MPEX-209 was open-label in which patients were randomized in a ratio of 2:1 LIS 240 mg twice daily or TIS 300 mg twice daily. LIS was self-administered by the patient by the inhalation route using the LIS-customized PARI eFlow nebulizer. TIS was self-administered by the patient by the inhalation route using the PARI LC PLUS nebulizer with compressor or through another nebulizer compatible with country-specific labelling. Patients administered 3 consecutive 56-day cycles (28 days on treatment and 28 days off treatment).

To maintain consistency in MPEX-207 and 209, patients were asked to administer their CF medications (when applicable) at home in the order listed below:

- bronchodilators (e.g., salbutamol)
- dornase alpha or hypertonic saline (or both, one after the other)
- airway clearance techniques (ACTs); based on patient's routine ACTs performed within 30 days of visit 1
- study drug
- inhaled corticosteroids.

3.2.3 Outcomes

Sputum Microbiology was the primary outcome in MPEX-204 and a secondary outcome in MPEX-209. The protocol specified that a sputum sample be collected for microbiological assessment, but a throat swab sample was acceptable for visits when a patient was unable to produce a sputum sample. Predominant colonies were identified using standard microbiological methods and quantitative cultures for *P. aeruginosa* and other organisms were performed. The predominant bacterial isolates from each sample were identified to the species level and quantitative results were expressed on a per species basis as well as by overall bacterial burden. The susceptibility to LIS and comparator antibiotics of the predominant colony types of *P. aeruginosa* and other organisms identified to the species level was determined using Clinical Laboratory and Standards Institute reference methods. In MPEX-204, the primary end point was change in *P. aeruginosa* density in sputum (log10 colony-forming units [CFU] per gram) from visit 1 (day 1) to visit 4 (day 28).

Exacerbation Assessment was the primary outcome used in MPEX-207 and as a secondary outcome in MPEX-209. Modified Fuchs criteria of an exacerbation were applied to define exacerbations. In both 207 and 209, to meet the definition of an exacerbation, patients had to concurrently have had at least 4 of the 12 symptoms/signs as defined by the modified Fuchs criteria,[22] died, or received an antipseudomonal antimicrobial agent for an event that did not meet the Fuchs criteria but was determined to be an by the independent Blinded Exacerbation Adjudication Committee. In MPEX-207,

patients were also counted as having an exacerbation event if they discontinued from the study early for any reason. The 12 symptoms/signs defined by the modified Fuchs criteria were:

1. Change in sputum
2. New or increased hemoptysis
3. Increased cough
4. Increased dyspnea
5. Malaise, fatigue or lethargy
6. Temperature above 38°C
7. Anorexia or weight loss
8. Sinus pain or tenderness
9. Change in sinus discharge
10. Change in physical examination of the chest
11. Decrease in pulmonary function by 10% or more from a previously recorded value
12. Radiographic changes indicative of pulmonary infection

An independent Blinded Exacerbation Adjudication Committee was formed and operated independently under its own charter in MPEX-207 and MPEX-209. The committee reviewed information on patients who did not meet Fuchs criteria for an exacerbation but received treatment with antipseudomonal antimicrobial agents for an exacerbation or worsening respiratory symptoms during the study. The committee also reviewed information on patients who met Fuchs criteria and were not prescribed antipseudomonal antimicrobial agents. The committee determined in a blinded fashion whether the described symptoms, signs, and other information provided in a narrative by the Principal Investigator should have been classified as an exacerbation.

Pulmonary Function Tests (PFTs) comprised the primary outcome in MPEX-209, and were a secondary outcome in MPEX-204 and 207. Patients underwent PFTs to determine their forced vital capacity (FVC), forced expiratory flow (FEF) between 25% and 75% of the FVC (FEF 25 to 75), and FEV_1. Percent predicted FEV_1 and FVC were calculated using NHANES.[21] Up to eight efforts were to be performed to obtain three acceptable and reproducible test results. Pulmonary function testing was performed according to the American Thoracic Society and European Respirator Society Spirometry Standards.[23] Patients were expected to use a short-acting bronchodilator (e.g., albuterol, salbutamol) 10 to 30 minutes before all PFTs.

Patients who had a > 15% relative change (increase or decrease) in FEV_1 from screening to visit 1 pre-study drug PFTs were not to be enrolled, but could be rescreened when stable. Patients who had a > 15% decline in FEV_1 (L) at visit 1 between pre-study drug and post-study drug PFTs were to be asked to administer a short-acting bronchodilator prior to all future dosing of the study drug.

The sponsor recommended that patients who experienced a > 20% decline in FEV_1 between pre-study drug and post-study drug PFTs at visit 1 be evaluated for bronchospasm related to study drug dosing. If symptomatic they were to be discontinued from the study. If the patient was asymptomatic in conjunction with this > 20% decline in FEV_1, the investigator was to contact the medical monitor to determine if the patient could continue in the study. A decline in FEV_1 > 20% at visit 1 was recorded in the electronic case form (eCRF) as an AE.

Administration of Systemic and/or Inhaled Antipseudomonal Antimicrobials was a secondary outcome in the three trials. To meet this end point, patients must have had at least 1 of 4 worsening respiratory symptoms (i.e., increased cough, increased sputum/chest congestion, decreased exercise tolerance, decreased appetite) at the time of administration of the antipseudomonal antimicrobial drug.

In MPEX-209, if patients received antipseudomonal antimicrobials for a pulmonary exacerbation or worsening respiratory status, they discontinued study drug but could be restarted after the completion of the antipseudomonal antimicrobials, as per the original 28-day on/off schedule.

Cystic Fibrosis Questionnaire–Revised (CFQ-R) was a secondary outcome in the three trials. The CFQ-R is a disease-specific instrument that measures health-related quality of life for adolescents and adults with CF.[24] It consists of multiple questions with generic and disease-specific scales. In MPEX-207 and MPEX-209, three versions of the CFQ-R were used based on the age of the patient: patients 14 years and older, patients 12 to 13 years old, and a parent/caregiver questionnaire for patients 6 to 13 years old. The versions are slightly different in that not all of the questions are included in each version and some of the questions are worded differently. The average score of the questions associated with

each domain on each version was calculated and converted to a scale from 0 to 100 so the scores were analyzed the same way across the versions.

3.2.4 Statistical analysis

In MPEX-204, the primary efficacy comparison tested the following hypotheses:

> H0: The average change in log CFU of *P. aeruginosa* per gram of sputum from the start of LIS or placebo (visit 1, day 1) to 4 weeks later (visit 4, day 28) was the same for the combined MP-376 240 mg groups (once daily and twice daily) and the pooled placebo group,
> H1: The average change in log CFU of *P. aeruginosa* per gram of sputum was different between the combined LIS mg groups and the pooled placebo group.

The comparison was performed using a repeated-measures mixed model that included terms for treatment group (LIS 120 mg once daily, LIS 240 mg once daily, LIS 240 mg twice daily, and pooled placebo), visit (visit 2, visit 3, visit 4), treatment LIS by visit interaction, geographical region (US, non-US), baseline value, highest baseline minimum inhibitory concentration (MIC) of LIS against *P. aeruginosa* (log2-transformed), baseline per cent predicted FEV1 (categorized as quartiles), and visit by baseline interaction. The model assumed an unstructured covariance matrix.

Secondary outcomes, except time-to-need for systemic or inhaled antipseudomonal antibiotics, were conducted using the same types of models and methods as for the primary end point, where a repeated-measures model was used for visits during the treatment phase (visit 2, day 7; visit 3, day 14; and visit 4, day 28) and a univariate model was used for follow-up visits (visit 5, day 42, and final/end-of-treatment visit, day 56).

Time-to-need for systemic or inhaled antipseudomonal antibiotics was assessed using a Cox proportional hazards regression model that included the effects of treatment group, geographical region, highest baseline MIC of LIS against *P. aeruginosa* (log2 transformed), and baseline per cent predicted FEV_1 (categorized in quartiles). Patients who did not require antipseudomonal antimicrobials before discontinuation from the study were censored at the date of discontinuation.

For repeated-measures analyses of primary and secondary end points at visit 2 (day 7), visit 3 (day 14), and visit 4 (day 28), when patients received systemic or inhaled antimicrobials other than LIS, the last value before receipt of antipseudomonal antimicrobials was carried forward to subsequent visits whether the patient had missing or non-missing values at the subsequent visits. All other missing values were left as missing. For analyses at visit 5 (day 42) or at the final visit (day 56), values were carried forward only if the patient terminated after the 28-day dosing period.

Subgroups were not examined in MPEX-204, and no multiplicity adjustments were made.

In MPEX-207, the primary efficacy comparison tested the following hypotheses:

- H0: The distributions of time to exacerbation were equal between the LIS and placebo groups
- H1: The distributions of time to exacerbation were different between the LIS and placebo groups.

The analysis of the primary outcome and time to administration of systemic and/or inhaled antipseudomonal antimicrobials and time to hospitalization followed the same method. These analyses compared the distributions of the time to exacerbation in the treatment groups using a two-sided stratified (geographic region [US, non-US], age [12 to 18 years, > 18 years], and FEV_1 per cent 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. Patients who did not achieve any of the exacerbation criteria were censored at the date of their final study visit. The trial had an estimated 90% power to detect an 8.0 percentage point treatment difference in relative change in FEV_1 per cent predicted.

Change in FEV_1 per cent predicted (both absolute and relative), change in *P. aeruginosa* sputum density (log10 CFU/g sputum), and change in the Respiratory Symptom Scale 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 per cent 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 Symptom Scale of the CFQ-R. An unstructured covariance model was used for these analyses.

In MPEX-209, the primary efficacy non-inferiority comparison tested the following hypotheses:

- H0: Mean relative change in FEV_1 per cent predicted from baseline to day 28 was ≥ 4% greater in the TIS group compared with the LIS group (μLIS – μTIS ≤ –4%)
- H1: Mean relative change in FEV_1 per cent predicted from baseline to day 28 was < 4% greater in the TIS group compared with the LIS group (μLIS – μTIS > –4%).

Comparison of relative change in FEV_1 per cent predicted from baseline to day 28 was performed using an analysis of covariance (ANCOVA) model that included terms for: treatment group (LIS, TIS), geographic region (US, non-US), age (12 to 18 years, > 18 years), and baseline FEV_1 per cent predicted (< 55%, ≥ 55%). An unstructured covariance matrix was used in the ANCOVA. The assessment of non-inferiority was based on the lower limit of the 2-sided 95% confidence interval (CI) of the difference in means (LIS minus TIS). If the lower limit of this CI was greater than –4.0, then non-inferiority was demonstrated. If non-inferiority was demonstrated, then assessment of superiority for both relative change and absolute change in FEV_1 per cent predicted from baseline to day 28 would be performed using a 2-sided test at the 5% level of significance.

The distributions of the time to exacerbation, time to administration of systemic and/or inhaled antipseudomonal antimicrobials, and time to first hospitalization in the 2 groups were compared using a 2-sided stratified (geographic region, age, and baseline FEV_1 per cent predicted) log-rank test. The distributions in the 2 groups were summarized using the Kaplan-Meier method. Patients who did not achieve any of the exacerbation criteria were censored at the date of their final study visit. The estimated hazard ratio (HR) and 95% CI were obtained from a Cox proportional hazards regression model including terms for treatment (LIS, TIS), geographic region, age, and baseline FEV_1 per cent predicted.

In MPEX-207 and 209, analyses of the primary end point and key secondary endpoints were performed on the intention to treat (ITT) population using the following subgroups as identified in the statistical analysis plan:

- Geographic region (US, non-US)
- Age (12 to 18 years, > 18 years)
- FEV_1 per cent predicted at baseline (< 55%, ≥ 55%)
- Courses of inhaled antimicrobial in the past year (≤ 5, > 5)
- Number of exacerbations in the past year (≤ 2, > 2)

- Patients co-infected at baseline with: *S. aureus*, methicillin-resistant *S. aureus, Stenotrophomonas maltophilia, Achromobacter xylosoxidans, B cepacia*
- Patients co-infected at baseline with the above organisms, who also had a positive sputum culture for the same organism within the past 12 months.

It was not reported whether tests for interaction between subgroups were performed.

Statistical power estimation was reported for three trials and a sufficient number of patients were enrolled in and completed the studies. The estimation was based on the primary outcome for each study. In MPEX-204, it was estimated that a total of 128 patients would provide 80% power to detect a difference between treatment arms, assuming a standard deviation of 1.5 and a mean log CFU change in *P. aeruginosa* of 0.75 decrease, 0.75 decrease, no change, and 0.25 increase for the LIS 240 mg twice daily, LIS 240 mg once daily, LIS 120 mg once daily, and placebo treatment arms, respectively. In MPEX-207, a total sample size of 261 patients was estimated to have 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 versus placebo). In MPEX-209, the sample size was determined for an assessment of the relative change in FEV_1 expressed as per cent predicted with a non-inferiority margin of 4%. It was estimated that 267 patients randomized 2:1 to LIS and TIS, respectively, would provide 90% power.

No multiplicity adjustments were made in MPEX-204. In MPEX-207 and 209, each of the primary and key secondary efficacy endpoints was tested at the alpha = 0.05 significance level. The overall alpha level of alpha = 0.05 was maintained by hierarchical testing at 0.05 for the primary endpoints, "time to exacerbation" in MPEX-207 and "Non-inferiority comparison of relative change in FEV_1 per cent predicted" in MPEX-209. The hierarchical testing included a limited number of key secondary endpoints for MPEX-207. In MPEX-209 however, the testing included a contingent primary end point (superiority testing of change in FEV_1), but it did not include any secondary endpoints. If one of the endpoints failed to reach statistical significance, the remaining comparisons were to be considered exploratory. Failure to demonstrate statistically significant differences stopped the statistical testing hierarchy at time to exacerbation in MPEX-207 and superiority comparison of relative change in FEV_1 per cent predicted in MPEX-209. Therefore, statistical analyses for the secondary end point should be considered exploratory in the three trials.

a) Analysis populations

In trial MPEX-204, safety analyses included all patients enrolled in the study who received at least one dose of the study drug. MPEX-207 and 209 did not explicitly define safety population.

MPEX-207 and 209 intent-to-treat populations included all patients randomized in the study. All efficacy analyses conducted using the ITT population used the randomized treatment regardless of the treatment the patient actually received. MPEX-204 used a modified intent-to-treat population which included all patients enrolled in the study who received at least 1 dose of study drug.

None of the included trials defined a per-protocol population. The three trials used an "efficacy evaluable" population which included all patients enrolled in the study without major protocol violations who received at least 80% of study drug doses.

3.3 Patient Disposition

Patient disposition is summarized in Table 7.

In general, discontinuation from the studies was greater in LIS groups compared to placebo (7.7% versus 5.4% and 4.5% versus 0.9% in MPEX-204 and 207 respectively) and to TIS (12.2% versus 10.8% in MPEX-209). The primary reason for study drug discontinuation was AEs; these were less frequently reported in LIS group in MPEX-204 compared with placebo (5.1% versus 10.8% respectively). In MPEX-207 and 209 however, patients in LIS groups reported more study discontinuation due to AEs than placebo (5.0% versus 1.8%) and TIS (6.3% versus 1.1%).

TABLE 7: PATIENT DISPOSITION

	MPEX-204		MPEX-207		MPEX-209	
	Placebo	**LIS 240 mg b.i.d.**	**Placebo**	**LIS 240 mg b.i.d.**	**TIS 300 mg b.i.d.**	**LIS 240 mg b.i.d.**
Screened, N	412		478		412	
Randomized, N (%)	37	39	110	220	93	189
Completed Study	35 (94.6%)	36 (92.3%)	109 (99.1%)	210 (95.5%)	83 (89.2%)	166 (87.8%)
Discontinued from Study	2 (5.4%)	3 (7.7%)	1 (0.9%)	10 (4.5%)	10 (10.8%)	23 (12.2%)
Primary Reason for Discontinuation from Study						
• Adverse event	2 (5.4%)	2 (5.1%)	1 (0.9%)	4 (1.8%)	1 (1.1%)	6 (3.2%)
• Withdrawal of consent	0 (0.0%)	0 (0.0%)	0	4 (1.8%)	1 (1.1%)	2 (1.1%)
• Other	0 (0.0%)	1 (2.6%)	0	2 (0.9%)	8 (8.6%)	15 (7.9%)
Study Drug Discontinuation	5 (13.5%)	2 (5.1%)	16 (14.5%)	34 (15.5%)	14 (15.1%)	24 (12.7%)
Primary Reason for Study Drug Discontinuation						
• Adverse event	4 (10.8%)	2 (5.1%)	2 (1.8%)	11 (5.0%)	1 (1.1%)	12 (6.3%)
• Started antimicrobial agents	Not reported		13 (11.8%)	21 (9.5%)	5 (5.4%)	3 (1.6%)
• Patient decision			1 (0.9%)	2 (0.9%)	4 (4.3%)	6 (3.2%)
• Other	1 (2.7%)	0			4 (4.3%)	3 (1.6%)
Data sets						
ITT[a], N	37 (100.0%)	39 (100.0%)	110 (100%)	220 (100%)	93 (100.0%)	189 (100.0%)
Efficacy Evaluable[b], N	32 (86.5%)	34 (87.2%)	88 (80%)	186 (84.5%)	**Day 28:** 77 (82.8%) **Day 140:** 55 (59.1%)	**Day 28:** 158 (83.6%) **Day 140:** 122 (64.6%)
Safety[c], N	37 (100%)	39 (100%)	110 (100%)	219 (99.5%)	90 (96.8%)	182 (96.3%)

b.i.d. = twice daily; ITT = intention to treat; LIS = levofloxacin inhalation solution; PP = per protocol; q.d. = once daily.
[a] All patients enrolled in the study; in MPEX-204 ITT patients included all patients enrolled in the study who received at least one dose of study treatment.
[b] All patients enrolled in the study, without major protocol violations who receive at least 80% of study treatment.
[c] All patients enrolled in the study who received at least one dose of study treatment.
Source: Clinical Study Reports MPEX-204[2] p. 96/533; MPEX-207[3] p. 168-170/1611; MPEX-209[4] p. 169-171/1886.

3.4 Exposure to Study Treatments

Patient exposure to the study treatments is summarized in Table 8. The mean number of days on study drugs was similar between the compared groups in MPEX-207 (27.2 days versus 26.5 days in placebo and LIS groups respectively) and in MPEX-209 (68.5 days versus 70 days in TIS and LIS groups

respectively). Number of days on study drugs was not reported in MPEX-204; however, MPEX-204 was the only included trial to report patient's compliance which was evaluated based on the number of ampules taken and on the number expected. There were more patients who had > 90% compliance in LIS group than placebo (84.6% versus 78.4%).

TABLE 8: SUMMARY OF EXTENT OF EXPOSURE

	MPEX-204		MPEX-207		MPEX-209	
	Placebo	**LIS 240 mg b.i.d.**	**Placebo**	**LIS 240 mg b.i.d.**	**TIS 300 mg b.i.d.**	**LIS 240 mg b.i.d.**
N	37	39	110	220	90	181
Number of days on Study Drug						
• Mean (SD)	Not reported		27.2 (5.31)	26.8 (6.80)	68.4 (18.38)	70.0 (18.40)
• Median			29.0	29.0	76.0	78.0
• Min, Max			8, 31	1, 36	14, 84	1, 84
Compliance						
• < 40%	1 (2.7%)	2 (5.1%)	Not reported		Not reported	
• 40% to < 60%	2 (5.4%)	0 (0.0%)				
• 60% to < 80%	2 (5.4%)	1 (2.6%)				
• 80% to < 90%	3 (8.1%)	3 (7.7%)				
• > 90%	29 (78.4%)	33 (84.6%)				

b.i.d. = twice daily; LIS = levofloxacin inhalation solution; SD = standard deviation; TIS = tobramycin inhalation solution.
Source: Clinical Study Reports.[2-4]

In general, there were more patients in MPEX-209 than MPEX-207 who had concomitant drugs for obstructive airway diseases (92.6% versus 6.1%) or cough and cold preparations (89.3% versus 3.3%) (Table 9). The overall use of drugs for obstructive airway diseases was similar between groups within each trial; however, the use of salbutamol was relatively higher in LIS groups than placebo (5.5% versus 4.5%) and TIS (62.1% versus 57.8%). In MPEX-209, fewer LIS patients used cough and cold preparations during the trial periods than TIS patients (87.4% versus 93.3%).

TABLE 9: USE OF NON-ANTIMICROBIAL MEDICATIONS DURING THE TRIALS

	MPEX-204		MPEX-207		MPEX-209	
	Placebo	LIS 240 mg b.i.d.	Placebo	LIS 240 mg b.i.d.	TIS 300 mg b.i.d.	LIS 240 mg b.i.d.
N	37	39	110	220	90	181
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES						
Overall	Not reported		7 (6.4%)	13 (5.9%)	84 (93.3%)	168 (92.3%)
Salbutamol			5 (4.5%)	12 (5.5%)	52 (57.8%)	113 (62.1%)
COUGH AND COLD PREPARATIONS						
Overall	Not reported		1 (0.9%)	10 (4.6%)	84 (93.3%)	159 (87.4%)
Dornase alpha			0	2 (0.9%)	73 (81.1%)	134 (73.6%)

b.i.d. = twice daily; LIS = levofloxacin inhalation solution; TIS = tobramycin inhalation solution.
Source: Clinical Study Reports.[2-4]

3.5 Critical Appraisal

3.5.1 Internal validity

In the three trials, treatment allocation was randomized using an automated interactive voice response system. In MPEX-204, patients were stratified by geographic region (US and ex-US sites); in addition to geographic region, patients in MPEX-207 and 209 were stratified by age (12 to 18 years, > 18 years), and baseline FEV_1 (< 55%, ≥ 55%). The treatment groups were generally well-balanced with respect to key baseline demographic characteristics. Statistical tests for subgroup analyses were conducted without adjustment for multiple comparisons.

In MPEX-207 and 209, the manufacturer reported that a greater proportion of patients in LIS groups received salbutamol in the 30 days prior the start of trials compared to placebo (74.0% versus 59.1%) and TIS (61.5% versus 56.7%). This unbalanced trend continued during the trials periods, and it was most pronounced in MPEX-209 that reported 62.1% versus 57.8% salbutamol use in LIS and TIS groups respectively. This could potentially bias the treatment effect favouring LIS as the increased use of salbutamol, a short-acting β2 adrenergic receptor agonist, could favour LIS participants for respiratory endpoints. In MPEX-207, there were also more patients in LIS group who used dornase alpha in the 30 days prior the start of trials compared to placebo (80.0% versus 77.3%)In MPEX-209 however, more patients in TIS group who used dornase alpha than LIS patients (81.1% versus 73.1%). The differential use of prior and concomitant treatments was not reported for MPEX-204.

Treatment groups in MPEX-207 and 209 were imbalanced in terms of the number of pulmonary exacerbations requiring treatment with antimicrobials in the year before the trials. More patients in LIS groups had > 2 exacerbations than placebo (33.8% versus 20% in MPEX-207) and TIS (30.8% versus 27.8% in MPEX-209). Furthermore, patients in LIS groups had shorter mean time since the resolution of the most recent pulmonary exacerbation than placebo (114 versus 149 days in MPEX-207) and TIS (105 versus 130 days in MPEX-209). However, pulmonary function, in terms of FEV_1 % predicted, was similar between trials groups.

Based on pulmonary exacerbations in the previous 12 months and use of salbutamol and dornase alpha, it could be suggested that LIS patients might have had more serious disease status or potentially poorer prognosis at baseline versus placebo (in MPEX-207) and TIS (in MPEX-209). However, pulmonary functions at baseline were comparable between groups in each trial, and it did not correlate with discrepancies in previous exacerbations or prior use of salbutamol or dornase alpha.

Although the investigators claim that Studies MPEX-204 and 207 were double blinded, study drugs were not matched in colour (MPEX-204) and taste (MPEX-207). Therefore, patients and investigators may have been aware of the treatment they were randomized to receive. MPEX-209 was an open-label study. Unblinding study treatments might affect subjective outcomes such as the reporting of respiratory symptoms. The reviewed Clinical Study Reports did not include information indicating whether patients were asked if they knew which arm they were randomized to; furthermore, it could not be confirmed that the use of unblinded pharmacist to dispense medication absolutely protected against unblinding. In MPEX-207 and 209, exacerbation was evaluated by an independent Blinded Exacerbation Adjudication Committee; all other outcomes however, were evaluated by the treating investigator or reported by patients.

Patient disposition was well-reported. Percentage of patients who completed each study varied from 88.3 % in MPEX-209 to 96.7% in MPEX-207. The ITT analysis sets included all randomized patients. In MPEX-204, compliance with the study treatments was evaluated based on the number of ampules taken and on the number expected. There were more patients who had >90% compliance in LIS group than placebo (84.6% versus 78.4%). Patient compliance was not reported in MPEX-207 or 209.

The definition for pulmonary exacerbation used in MPEX-207 and 209 slightly differed from each other and from definitions used in RCTs for other approved inhaled antibiotics; this variation would make comparison of results across trials difficult. Nevertheless, the used definitions were considered to be appropriate by regulatory authorities and the clinical expert consulted by CDR. MPEX-207 and 209 had an independent adjudication of pulmonary exacerbation events.

3.5.2 External validity

According to the clinical expert consulted for this review, the diagnostic criteria used in the screening process were consistent with Canadian clinical practice for identifying patients with CF with chronic pulmonary *Pseudomonas aeruginosa* infections. CF patients with wide range of lung disease severity were included in the trials; therefore, the results of the included studies are applicable to patients with severe (i.e., FEV_1 25% to 39%), moderate (i.e., FEV_1 40% to 69%) and mild (i.e., FEV_1 70% to 85%) lung disease. Although the statistical analyses were stratified based on FEV_1% values at baseline of < 55% and ≥ 55%, there were no subgroup analyses based on baseline severity (i.e., mild, moderate, or severe lung disease); this would have been useful to better understand the performance of LIS in CF patients in each severity class.

The majority of participants in the MPEX-204, 207, and 209 trials were from USA (82%, 89%, and 69%, respectively). The study populations were comprised of almost exclusively white patients (98.7%, 94.5%, and 95.6%, in the three trials respectively), which is reflective of the majority of patients who would be eligible for treatment with LIS, though the percentage is slightly higher than the proportion reported for the overall CF population in Canada (92% in 2013).[1]

European Medicines Agency (EMA) reviewers noted that, based on TIS versus placebo studies,[25] there was an early sharp improvement in FEV_1% predicted in the TIS group followed by improvements of lesser magnitude in the sequential cycles.[26] In MPEX-207 and 209, patients had no prior use of inhaled fluoroquinolones. EMA reviewers suggested that a first exposure to LIS could result in an initial response, in terms of FEV_1, that wanes to some extent with longer-term use, similar to TIS. This would bias the comparison of change in FEV_1 between LIS patients and TIS-experienced patients in favour of LIS.

The 28-day trial treatment periods were insufficient for observing treatment differences for a lifelong disease. Furthermore, the occurrence of AEs might be underestimated because the trials' durations may not allow a clear picture of the systemic absorption of the LIS; In MPEX-209, patients were treated with three cycles of LIS; that would provide better understanding of LIS safety than MPEX-204 and 207. However, FEV_1 analyses during this period were exploratory.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 3).

3.6.1 Mortality/survival

There were no deaths reported in the included trials.

3.6.2 Disease progression (based on FEV_1)

Changes from baseline in terms of per cent predicted FEV_1 are summarized in Table 10, Figure 5 and Figure 6.

In MPEX-204, the mean (SD) absolute changes from baseline to day 28 in FEV_1 per cent predicted were 3.11% (7.70%) and –1.51% (4.87%) in the LIS and placebo treatment groups; however, no between group comparative analyses were reported. Patients treated with LIS had a least square (LS) mean increase of 8.55 relative per cent change from baseline to day 28 in predicted FEV_1, while patients treated with placebo had a LS mean decrease of 2.39 per cent predicted from baseline. The LS mean difference in relative change from baseline to day 28 between LIS and placebo showed a statistically significant change favouring LIS: 10.9 per cent predicted (95% CI, 4.6 to 17.3).

In MPEX-207, patients treated with LIS had a statistically significantly higher increase in absolute per cent predicted FEV_1 from baseline compared to placebo (1.73 versus 0.43 per cent predicted). The LS mean difference (95% CI) between LIS and placebo was 1.31 (0.27 to 2.34). Subgroup analyses showed that the difference between LIS and placebo was not statistically significant for adult patients and for both FEV_1 subgroups (< 55% and ≥ 55%). LIS also improved relative change from baseline in per cent predicted FEV_1 to day 28: the LS mean difference versus placebo was 2.42% (95% CI, 0.53% to 4.31%). The results for absolute and relative change need to be interpreted with caution because a higher order comparison in the statistical analysis hierarchy failed and therefore subsequent analyses were considered exploratory.

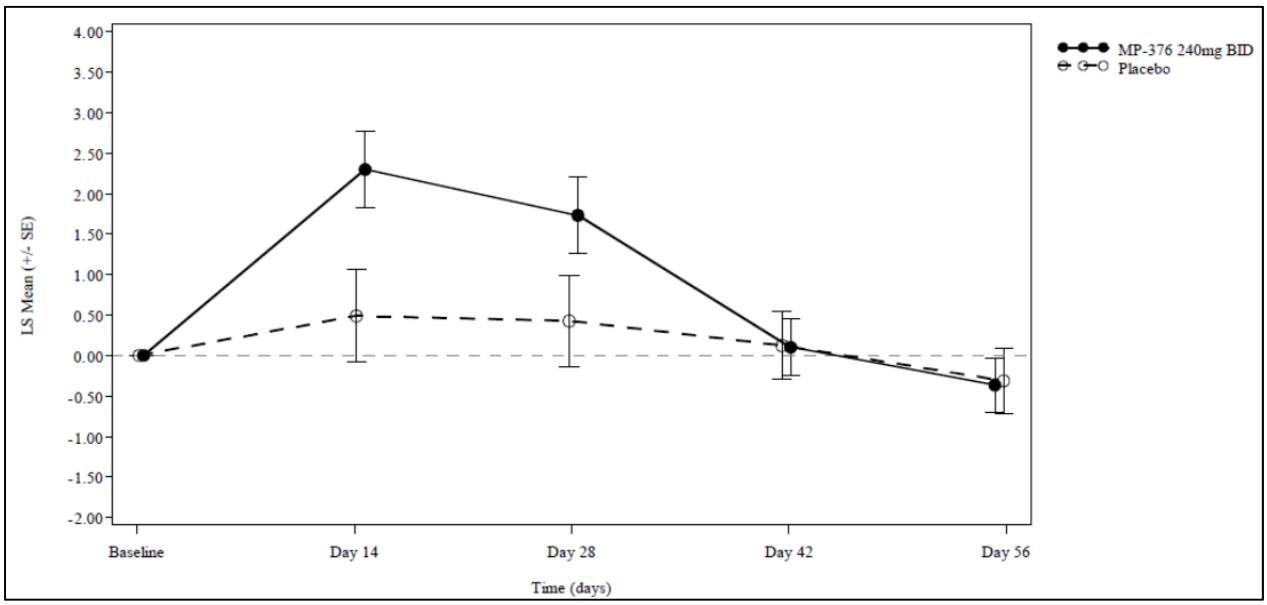
In MPEX-209, the LS mean differences for change from baseline in per cent predicted FEV_1 at day 28 were 1.04% (95% CI, –0.21% to 2.30%) for absolute change and 1.86% (95% CI, –0.66% to 4.39%) for the relative change. The lower limits of the 95% CIs were above the pre-specified non-inferiority margin of -4%, and therefore LIS was considered non-inferior to TIS in terms of absolute and relative changes in FEV_1 per cent predicted. The difference between LIS and TIS was not statistically significant; therefore, superiority of LIS over TIS was not demonstrated. The subgroup analyses based on FEV_1 at baseline showed that LIS did not statistically differ from TIS with respect to absolute change in per cent predicted FEV_1 from baseline to day 28 for patients with baseline FEV_1 < 55%. In patients with baseline FEV_1 ≥ 55%, LIS was associated with higher increase in absolute change in per cent predicted FEV_1 from baseline than TIS (LS mean difference was 2.85 [95% CI, 0.51 to 5.19]. Similar results were reported for these subgroups when examining the relative change from baseline in per cent predicted FEV_1.

TABLE 10: SUMMARY OF PER CENT CHANGE FROM BASELINE IN FEV_1 PER CENT PREDICTED

	MPEX-204		MPEX-207		MPEX-209	
	Placebo	**LIS 240 mg b.i.d.**	**Placebo**	**LIS 240 mg b.i.d.**	**TIS 300 mg b.i.d.**	**LIS 240 mg b.i.d.**
N	37	39	110	220	93	189
Baseline (% predicted)						
• N	37	39	110	220	93	189
• Mean (SD)	52.4(13.42)	48.8(15.15)	56.32 (15.91)	56.53 (15.75)	53.20(15.70)	54.78 (17.02)
• Median	53.0	46.0	57.55	57.30	51.90	54.00
Day 28						
• N	37	37	109	218	93	189
• Mean (SD)	50.9 (14.46)	50.8(15.40)	56.43 (15.80)	57.48 (15.93)	53.32 (16.23)	55.96(17.97)
• Median	52.0	49.0	56.10	58.30	53.50	56.20
Absolute Change from Baseline to Day 28						
• N	37	37	109	218	93	189
• Mean (SD)	–1.51 (4.87)	3.11(7.70)	–0.18 (4.428)	1.15 (4.541)	0.12(5.330)	1.18(4.828)
• Median	–2.00	2.00	–0.18	0.30	0.00	1.00
• LS mean (SE)	Not reported		0.43 (0.568)[b]	1.73 (0.471)[b]	0.20 (0.626)[b]	1.24 (0.505)[b]
• LS mean difference [95% CI]			1.31 [0.27 to 2.34][b]		1.04 [–0.21 to 2.30][b]	
• *P* value			0.0137[b]		0.1015[b]	
Subgroup results based on baseline severity, LS mean difference [95% CI]						
FEV_1 <55%	Not reported		1.24 [-0.04, 2.52]		0.28 [-1.58, 2.14]	
FEV_1 ≥ 55%			1.36 [-0.25, 2.97]		2.05 [0.40, 3.70]	
Relative Per cent Change from Baseline to Day 28						
• N	37	37	109	218	93	189
• Mean (SD)	–3.08 (9.82)	7.97 (19.49)	0.01 (8.03)	2.46 (8.33)	0.39 (11.783)	2.26(9.119)
• Median	–3.77	4.44	0.01	0.62	0.00	2.21
• LS Mean (SE)	–2.39 (2.370)	8.55 (2.358)	1.24 (1.041)[b]	3.66 (0.866)[b]	0.38(1.262)	2.24(1.019)
• LS Mean Diff [95% CI] (minus placebo)	10.94 [4.63 to 17.25][a]		2.42 [0.53 to 4.31][b]		1.86 [–0.66 to 4.39]	
• *P* value	0.0008[a]		0.0122[b]		0.1481	
Subgroup results based on baseline severity, LS mean difference [95% CI]						
FEV_1 <55%	Not reported		Not reported		1.16 [–3.09 to 5.41]	
FEV_1 ≥ 55%					2.85 [0.51 to 5.19]	

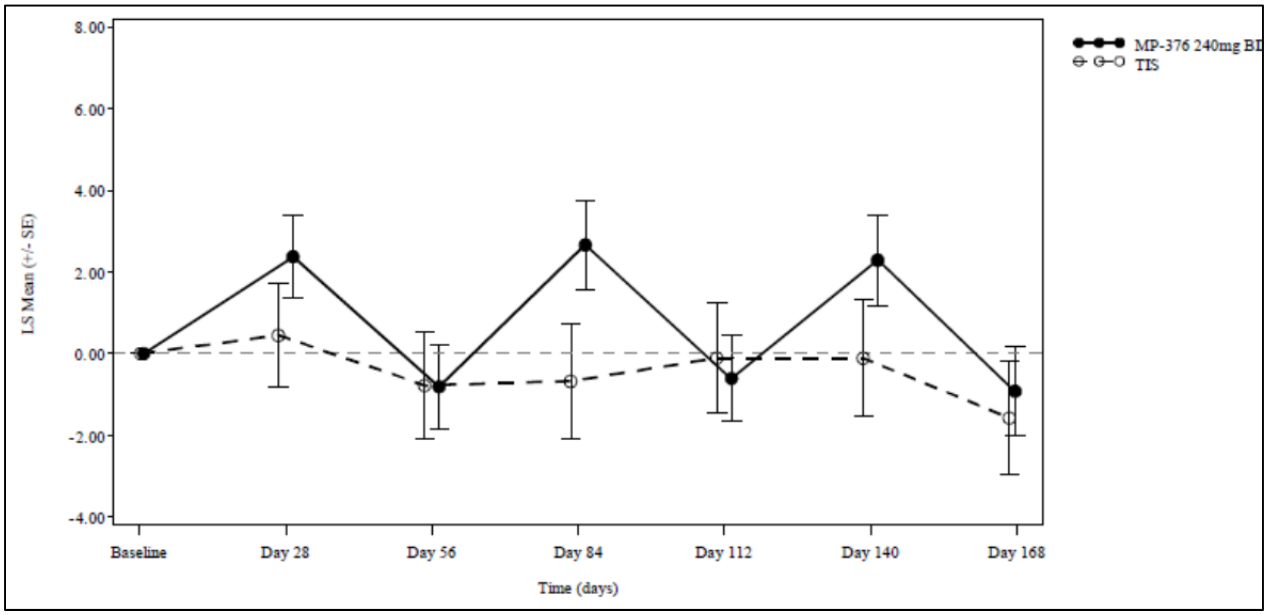
[a] Estimates are obtained from a repeated-measures model with terms for treatment, visit, treatment visit, region, highest baseline MIC of levofloxacin against *P. aeruginosa* (log2), and baseline per cent predicted FEV_1 (quartiles).
[b] Estimates were determined from a repeated-measures model with terms for treatment, visit, treatment*visit, region (US, non-US), age (12 to 18 years, > 18 years), and baseline FEV_1 (< 55%, ≥ 55%).
b.i.d. = twice daily; CI = confidence interval; FEV_1 = forced expiratory volume in one second; LIS = levofloxacin inhalation solution; LS = least squares; SD = standard deviation; SE = standard error; TIS = tobramycin inhalation solution.
Source: Clinical Study Reports.[2-4]

FIGURE 5: ABSOLUTE CHANGE IN PER CENT PREDICTED FEV1 (%) MPEX-207



b.i.d. = twice daily; LS = least squares; MP-376 = levofloxacin inhalation solution.
Source: Clinical Study Report.[3]

FIGURE 6: RELATIVE CHANGE IN PER CENT PREDICTED FEV1 (%) MPEX-209



b.i.d. = twice daily; LS = least squares; MP-376 = levofloxacin inhalation solution.
Source: Clinical Study Report.[4]

In MPEX-209, a categorical analysis of the primary efficacy outcome relative change in per cent predicted FEV_1 was reported and is summarized in Table 11. It was reported that there were more TIS patients, relative to LIS patients, who had moderate decline (14% versus 4.8%), mild decline (33.3% versus 25.4%), and significant improvement (4.3% versus 1.6%). On the other hand, there were fewer

TIS patients, compared with LIS, who had mild or moderate improvements (39.8% versus 54.5% and 8.6% versus 13.8%, respectively).

TABLE 11: CATEGORICAL ANALYSIS OF RELATIVE CHANGE IN FEV_1 PER CENT PREDICTED FROM BASELINE TO DAY 28 IN MPEX-209

	MPEX-209	
	TIS 300 mg b.i.d.	**LIS 240 mg b.i.d.**
Relative change in FEV_1 per cent predicted from baseline to day 28		
N	93	189
• Moderate decline (decline > 10%, death, or lung transplant)	13 (14.0%)	9 (4.8%)
• Mild decline (0% < decline < 10%)	31 (33.3%)	48 (25.4%)
• Mild improvement (0% < improvement < 10%)	37 (39.8%)	103 (54.5%)
• Moderate improvement (5% < improvement < 20%)	8 (8.6%)	26 (13.8%)
• Significant improvement (improvement > 20%)	4 (4.3%)	3 (1.6%)
• *P* value[a]	0.0167	

b.i.d. = twice daily; FEV_1 = forced expiratory volume in one second; LIS = levofloxacin inhalation solution; TIS = tobramycin inhalation solution.
[a] *P* values were determined using the Cochran-Mantel-Haenszel mean score test (assuming equally spaced scores) stratified by region (US, non-US), age (12 to 18 years, > 18 years), and Baseline FEV_1 (< 55%, ≥ 55%).
Source: Clinical Study Reports.[2-4]

3.6.3 Acute exacerbations or infection

Results for acute exacerbations analyses are summarized in Table 12.

In MPEX-207, LIS was associated with more events of exacerbations 122/220 (55.5%) than placebo 52/110 (47.3%), but the difference was not statistically significant. Subgroup analyses reported for patients with baseline FEV_1 < 55% showing higher risk of pulmonary exacerbation with LIS than placebo [HR, 1.76 (95% CI, 1.12 to 2.76)]. The between group difference among patients with baseline FEV_1 ≥ 55% was not statistically significant.

In MPEX-209, LIS was associated with fewer exacerbation events than TIS, 58.7% versus 66.7%; the difference between treatments was not statistically significant. The difference between the two treatments was not statistically significant for both baseline FEV_1 subgroups.

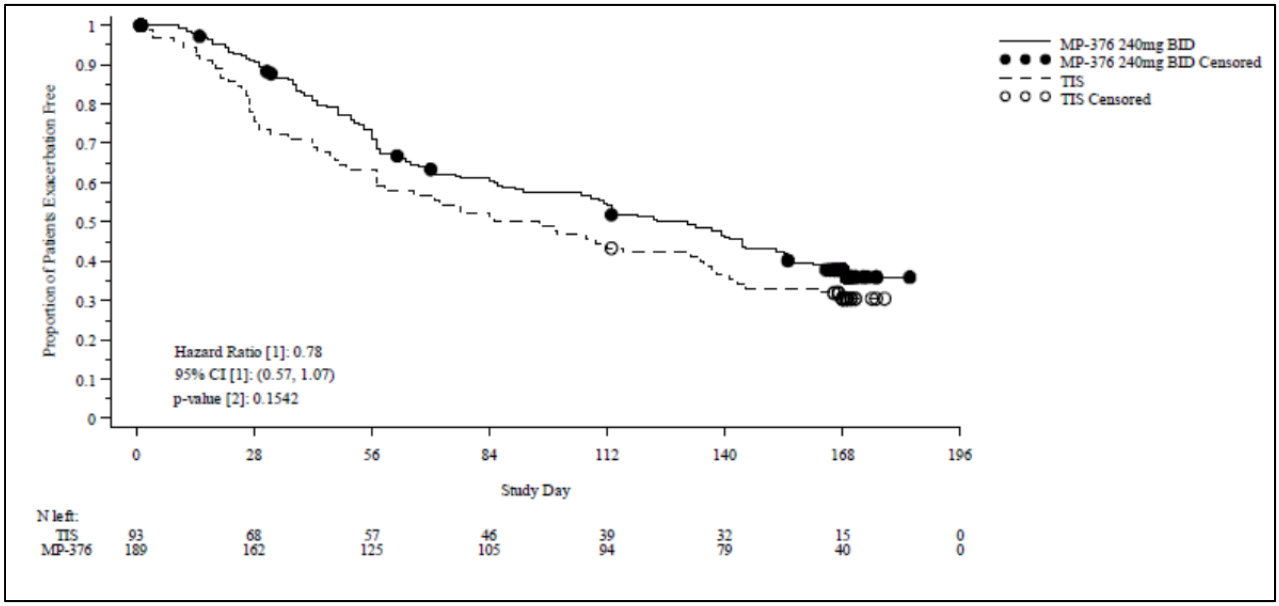
TABLE 12: FREQUENCY OF AND TIME TO EXACERBATION

	MPEX-207		MPEX-209	
	Placebo	**LIS 240 mg b.i.d.**	**TIS 300 mg b.i.d.**	**LIS 240 mg b.i.d.**
N	**110**	**220**	93	189
Number (%) of patients experiencing pulmonary exacerbation	52 (47.3%)	122 (55.5%)	62 (66.7%)	111 (58.7%)
Condition met at first exacerbation event				
• Met at least 4 of 12 Fuchs symptoms	44 (40.0%)	105 (47.7%)	56 (60.2%)	105 (55.6%)
• Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)
• Received an antipseudomonal drug for an event that did not meet Fuchs criteria, but was determined to be an exacerbation for the purposes of the primary end point by the independent blinded exacerbation Adjudication	8 (7.3%)	12 (5.5%)	6 (6.5%)	6 (3.2%)

	MPEX-207		MPEX-209	
	Placebo	**LIS 240 mg b.i.d.**	**TIS 300 mg b.i.d.**	**LIS 240 mg b.i.d.**
committee				
• Number (%) of patients exacerbation free	58 (52.7%)	98 (44.5%)	31 (33.3%)	78 (41.3%)
• Time to exacerbation (days)				
• Minimum, maximum	4, 69	1, 64	1, 178	1, 184
• Minimum, maximum for non-censored patients	4, 62	1, 59	3, 168	10, 169
• Median [95% CI][a]	58 [52, NE]	51.5 [43, NE]	90.5 [57 to 135]	131 [106 to 152]
• HR [95% CI][b]	1.33 [0.96 to 1.84]		0.78 [0.57 to 1.07]	
• *P* value[c]	0.0715		0.1542	
Subgroup results based on baseline severity, HR [95% CI]				
FEV_1 <55%	1.76 [1.12 to 2.76]		0.69 [0.47 to 1.02]	
FEV_1 ≥ 55%	0.96 [0.60 to 1.56]		0.97 [0.57 to 1.65]	

b.i.d. = twice daily; CI = confidence interval; FEV_1 = forced expiratory volume in one second; HR = hazard ratio; LIS = levofloxacin inhalation solution; NE = not estimable; SD = standard deviation; TIS = tobramycin inhalation solution.
[a] Kaplan-Meier estimates.
[b] Estimates were obtained from a Cox proportional hazards regression model including terms for treatment, region (US, non-US), age (12 to 18 years, > 18 years), and Baseline FEV_1 (< 55%, ≥ 55%).
[c] *P* value was determined using a log-rank test stratified by region (US, non-US), age (12 to 18 years, > 18 years), and baseline FEV_1 (< 55%, ≥ 55%).
Source: Clinical Study Reports.[2-4]

FIGURE 7: TIME TO EXACERBATION IN MPEX-209



b.i.d. = twice daily; CI = confidence interval; TIS = tobramycin inhaled solution; MP-376 = levofloxacin inhalation solution.
Source: Clinical Study Reports.[2-4]

3.6.4 Health-related quality of life

Scores on the Respiratory Symptom Scale of the CFQ-R are summarized in Table 13.

In MPEX-204 and MPEX-207, LIS-treated patients had numerically higher increase, from baseline to day 28, in LS mean score than placebo patients (4.0 versus –0.44 and 4.9 versus 4.7 in MPEX-204 and MPEX-

207 respectively). The difference between LIS and placebo was not statistically significant. These findings were maintained during the follow-up at day 56.

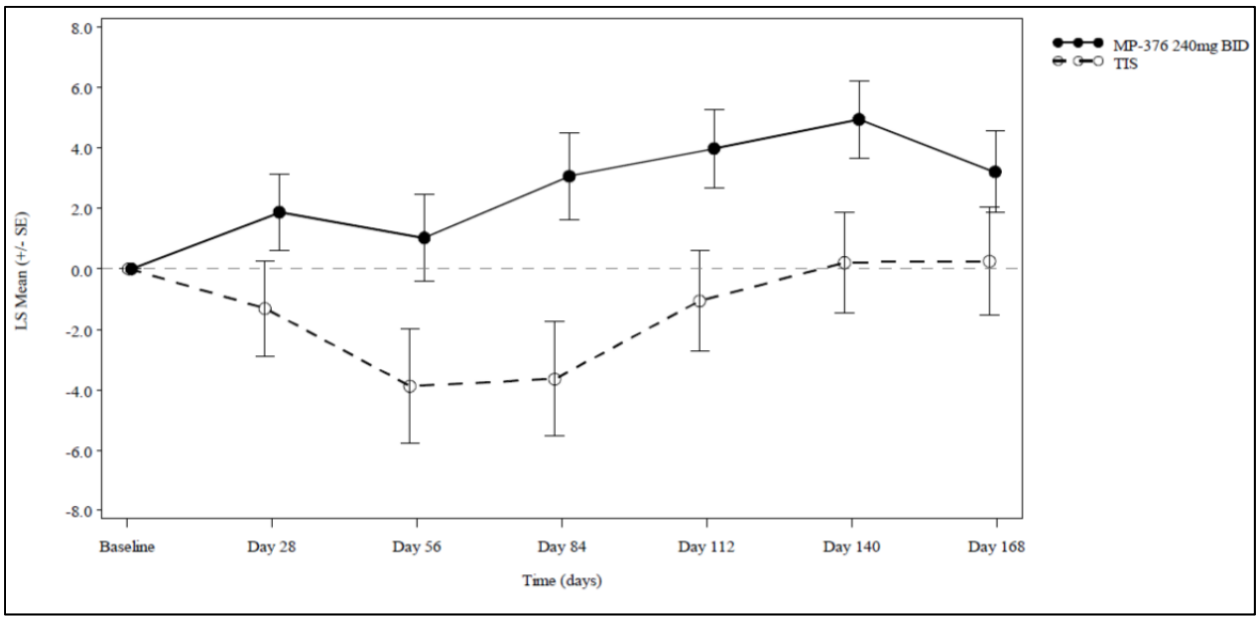
In MPEX-209 however, LIS-treated patients showed statistically significant improvement in Respiratory Symptom Scale CFQ-R scores from baseline to day 28 compared with TIS (1.88 versus –1.31); the LS mean difference (95% CI) was 3.19 points (0.05 to 6.32). These findings were maintained until day 140 (Figure 9). LS mean difference between treatment groups was similar at the end of the final off treatment visit at day 168.

TABLE 13: CHANGE IN RESPIRATORY SYMPTOM SCALE OF THE CFQ-R

	MPEX-204		MPEX-207		MPEX-209	
	Placebo	**LIS 240 mg b.i.d.**	**Placebo**	**LIS 240 mg b.i.d.**	**TIS 300 mg b.i.d.**	**LIS 240 mg b.i.d.**
N	37	39	110	220	93	189
Respiratory symptom scale						
Day 1 (baseline)						
• N	37	39	109	220	91	186
• Mean (SD)	64.9 (14.17)	60.5 (16.31)	63.35 (15.97)	65.64 (16.08)	66.9 (17.4)	67.3 (16.3)
• Median	66.7	61.1	61.11	66.67	66.7	69.5
• Range	39, 89	28, 94	16.67, 100.00	11.11, 100.00	11.11, 94.44	5.56, 100.00
Change at Day 28						
• N	37	37	108	218	92	186
• Mean (SD)	–1.8 (14.11)	3.0 (19.18)	4.42 (11.61)	4.03 (12.37)	–1.71 (13.576)	1.36 (13.097)
• LS Mean (SE)[a]	–0.44 (2.72)	4.06 (2.69)	4.66 (1.37)	4.94 (1.12)	–1.31 (1.58)	1.88 (1.28)
• LS Mean Diff (95% CI)	4.50 [–2.68 to 11.67]		0.28 [-2.30 to 2.85]		3.19 [0.05 to 6.32]	
• *P* value	0.2174		0.8335		0.0463	
Subgroup results based on baseline severity, LS mean difference [95% CI]						
FEV_1 < 55%	Not reported		0.50 [–3.48 to 4.47]		2.60 [–1.39 to 6.59]	
FEV_1 ≥ 55%			–1.09 [–5.07 to 2.90]		4.13 [–1.00 to 9.26]	
Change at Day 56						
• N	37	37	109	220	88	173
• Mean (SD)	–2.6 (15.96)	0.0(15.88)	3.87 (8.054)	2.78 (9.695)	–5.01 (18.342)	–0.53 (15.631)
• LS Mean (SE)[b]	–1.70 (2.931)	–0.43 (2.901)	3.72 (1.166)	2.91 (0.971)	–4.13 (1.857)	0.70 (1.397)
• LS Mean Diff[6] (95% CI)	1.26 [–6.32 to 8.84]		–0.80 [–2.86 to 1.25]		4.83 [0.65 to 9.01]	
• *P* value	0.7424		0.4408		0.0237	

b.i.d. = twice daily; CI = confidence interval; FEV_1 = forced expiratory volume in one second; LIS = levofloxacin inhalation solution; LS = least squares; SD = standard deviation; SE = standard error; TIS = tobramycin inhalation solution.
[a] Estimates were obtained from a repeated-measures model with terms for treatment, visit, treatment-by-visit interaction, geographical region, baseline, age, baseline per cent predicted FEV_1 (quartiles), and visit by baseline interaction.
[b] Estimates were obtained from an ANCOVA model with terms for treatment, geographical region, baseline, age, and baseline per cent predicted FEV_1 (quartiles).
Source: Clinical Study Reports.[2-4]

FIGURE 8: CHANGE IN CFQ-R RESPIRATORY SYMPTOM SCALE IN MPEX-209



b.i.d. = twice daily; CFQ-R = Cystic Fibrosis Questionnaire–Revised; LS = least squares; MP-376 = levofloxacin inhalation solution; TIS = tobramycin inhalation solution.
Source: Clinical Study Report.[4]

3.6.5 Hospitalization and missed school/work/scheduled activity

Results of time to first hospitalization or missed school/work/scheduled activity days and proportions of patients affected are summarized in Table 14.

In general, findings of MPEX-207 and 209 showed that there were no statistical significant differences between LIS-treated patients and placebo- or TIS-treated patients in terms of missed school/work/scheduled activity days or hospitalization.

In MPEX-207, 12.7% of LIS-treated patients had at least one missed day of school/work/scheduled activity due to worsening respiratory status compared to 16.4% of placebo-treated patients. In MPEX-209, there were 26.8% versus 18.8% of patients who missed at least one day of school/work/scheduled activity secondary to worsening respiratory status in LIS and placebo groups respectively. The HR was not statistically significant in either trial.

In terms of hospitalization secondary to worsening respiratory status, there were 7.3% versus 9.1% of LIS- versus placebo-treated patients reporting hospitalization in MPEX-207. In MPEX-209, there were 28.6% versus 34.4% of LIS- versus TIS-treated patients' hospitalization. The differences were not statistically different in both trials.

TABLE 14: SUMMARY OF TIME TO FIRST HOSPITALIZATION OR MISSED SCHOOL/WORK/SCHEDULED ACTIVITY DAYS

	MPEX-204		MPEX-207		MPEX-209	
	Placebo	**LIS 240 mg b.i.d.**	**Placebo**	**LIS 240 mg b.i.d.**	**TIS**	**LIS**
N	**37**	**39**	**110**	**220**	**93**	**189**
Time to first missed day of school/work/scheduled activity secondary to worsening respiratory status (28 days of treatment)						
• Days, Mean (SD)	Not reported		Not reported		2.7 (11.07)	1.7 (5.52)
• Number (%) of Patients with Event			18 (16.4%)	28 (12.7%)	5 (5.4%)	14 (7.4%)
• Number (%) of Patients Censored			92 (83.6%)	192 (87.3%)	88 (94.6%)	175 (92.6%)
• HR [95% CI][a]			0.77 [0.43 to 1.40]		1.54 [0.55 to 4.32]	
• *P* value[b]			0.4042		0.3969	
Time to first missed day of school/work/scheduled activity for any reason (28 days of treatment)						
• Days, Mean (SD)	Not reported		Not reported		1.7 (9.36)	0.9 (4.43)
• Number (%) of Patients with Event			28 (25.5%)	40 (18.2%)	10 (10.8%)	34 (18.0%)
• Number (%) of Patients Censored			82 (74.5%)	180 (81.8%)	83 (89.2%)	155 (82.0%)
• HR [95% CI][a]			0.68 [0.42 to 1.10]		1.87 [0.92 to 3.80]	
• *P* value[b]			0.1500		0.1108	
Time to Hospitalization secondary to worsening respiratory status						
• Number (%) of Patients with Event	Not reported		10 (9.1%)	16 (7.3%)	10 (10.8%)	13 (6.9%)
• Number (%) of Patients Censored			100 (90.9%)	204 (92.7%)	83 (89.2%)	176 (93.1%)
• HR [95% CI][a]			0.82 [0.37 to 1.81]		0.82 [0.35 to 1.93]	
• *P* value[b]			0.4902		0.6823	
Time to Hospitalization for any reason						
• Number (%) of Patients with Event	Not reported		11 (10.0%)	21 (9.5%)	10 (10.8%)	19 (10.1%)
• Number (%) of Patients Censored			99 (90.0%)	199 (90.5%)	83 (89.2%)	170 (89.9%)
• HR [95% CI][a]			0.98 [0.47 to 2.04]		1.30 [0.57 to 2.93]	
• *P* value[b]			0.8670		0.4795	

b.i.d. = twice daily; CI = confidence interval; HR = hazard ratio; LIS = levofloxacin inhalation solution; SD = standard deviation; TIS = tobramycin inhalation solution.

[a] HR is obtained from a Cox proportional hazards regression model adjusting for region (US, non-US), age (12 to 18 years, > 18 years), and baseline FEV_1 (<55%, >55%).

[b] *P* value is determined using a log-rank test stratified by region (US, non-US), age (12 to 18 years, > 18 years), and baseline FEV_1 (<55%, >55%).

Source: Clinical Study Reports.[2-4]

3.6.5 Weight/BMI

Results of weight changes are summarized in Table 15.

In MPEX-207, the LS mean weight change from baseline to day 28 was 0.1 kg versus 0.07 kg in LIS and placebo groups respectively; the LS mean difference between groups was not statistically significant. In MPX-209, it was reported that the mean change from baseline to day 28 was 0.1 kg (LIS) versus no change (0 kg) for TIS; the LS mean difference between groups was not statistically significant.

TABLE 15: SUMMARY OF WEIGHT CHANGE RESULTS

	MPEX-204		MPEX-207		MPEX-209	
	Placebo	**LIS 240 mg b.i.d.**	**Placebo**	**LIS 240 mg b.i.d.**	**TIS**	**LIS**
N	Not reported		110	220	93	189
Baseline (kg)						
• N			110	220	93	189
• Mean (SD)			62.4 (14.51)	63.3 (13.33)	61.6 (12.83)	61.0 (13.56)
• Median			60.3	61.5	60.0	58.9
Change from Baseline to Day 28						
• N	Not reported		109	219	93	189
• Mean (SD)			0.1 (1.17)	0.1 (1.22)	–0.0 (1.02)	0.1 (0.95)
• Median			0.1	0.1	0	0
• LS mean (SE)			0.07 (0.147)	0.10 (0.119)	–0.15 (0.119)	–0.02 (0.096)
• LS mean difference [95% CI]			0.03 [–0.25 to 0.31]		0.13 [–0.11 to 0.37]	
• *P* value			0.8183		0.2859	
Change from Baseline to Day 56						
• N	Not reported		110	220	88	174
• Mean (SD)			0.2 (1.02)	0.1 (1.14)	–0.1 (1.41)	0.1 (1.54)
• Median			0.1	0.1	0.1	0.1
• LS Mean (SE)			0.18 (0.146)	0.05 (0.122)	–0.26 (0.170)	–0.07 (0.129)
• LS Mean Diff [95% CI] (minus placebo)			–0.13 [–0.38 to 0.12]		0.19 [–0.19 to 0.57]	
• *P* value vs. Placebo			Not reported		0.3249	

b.i.d. = twice daily; CI = confidence interval; LIS = levofloxacin inhalation solution; LS = least squares; TIS = tobramycin inhalation solution; SD = standard deviation; SE = standard error.
Source: Clinical Study Reports.[2-4]

3.6.6 Need for antimicrobial therapy

Treatment resistance was not reported in the included trials; however, the use of antipseudomonal antimicrobial therapies was reported and compared between groups. Table 16 shows a summary of patients requiring antimicrobial treatment.

In MPEX-204, it was reported that fewer LIS-treated patients required antimicrobial treatment than in the placebo group (20.5% versus 48.6%). The HR comparing the two treatment groups was statistically significant; 0.21 (95% CI, 0.09 to 0.52). In MPEX-207, there were 49.5% versus 56.4% patients needing antimicrobials in LIS and placebo groups respectively; the difference was not statistically significant.

Results of MPEX-209 showed that 52.4% of LIS-treated patients used antimicrobial therapy compared with 63.4% in TIS group at the end of the first treatment cycle. The HR was not statistically significant; however, the log-rank *P* value was statistically significant (0.0396).

TABLE 16: SUMMARY OF TIME-TO-NEED FOR ANTIPSEUDOMONAL ANTIMICROBIALS TREATMENT

	MPEX-204		MPEX-207		MPEX-209	
	Placebo	**LIS 240 mg b.i.d.**	**Placebo**	**LIS 240 mg b.i.d.**	**TIS**	**LIS**
N	37	39	110	220	93	189
Time to Administration of Antimicrobials and Meeting Symptoms Requirement						
• Number (%) of Patients with Event	Not reported		56 (50.9%)	100 (45.5%)	59 (63.4%)	99 (52.4%)
• Number (%) of Patients Censored			54 (49.1%)	120 (54.5%)	34 (36.6%)	90 (47.6%)
• HR [95% CI][a]			0.85 [0.61 to 1.18]		0.73 [0.53 to 1.01]	
• *P* value[b]			0.4065		0.0396	
Time to Administration of Antimicrobials Regardless of Symptoms Requirements Met						
• Number (%) of Patients with Event	18 (48.6%)	8 (20.5%)	62 (56.4%)	109 (49.5%)	65 (69.9%)	113 (59.8%)
• Number (%) of Patients Censored	19 (51.4%)	31 (79.5%)	48 (43.6%)	111 (50.5%)	28 (30.1%)	76 (40.2%)
• HR [95% CI][a]	0.21 (0.09 to 0.52)		0.82 [0.60 to 1.12]		0.74 [0.54 to 1.00]	
• *P* value[b]	0.0007		0.3000		0.0410	

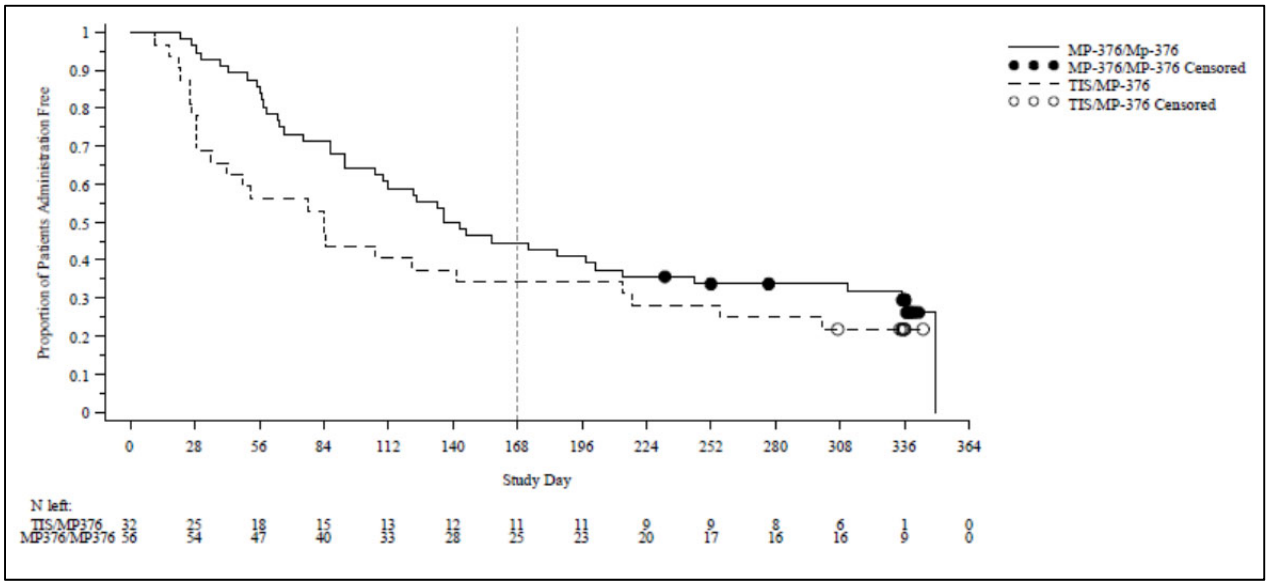
b.i.d. = twice daily; CI = confidence interval; HR = hazard ratio; LIS = levofloxacin inhalation solution; TIS = tobramycin inhalation solution.

[a] HR is obtained from a Cox proportional hazards regression model adjusting for region (US, non-US), age (12 to 18 years, > 18 years), and baseline FEV_1 (< 55%, > 55%).

[b] *P* value is determined using a log-rank test stratified by region (US, non-US), age (12 to 18 years, > 18 years), and baseline. FEV_1 (< 55%, > 55%).

Source: Clinical Study Reports.[2-4]

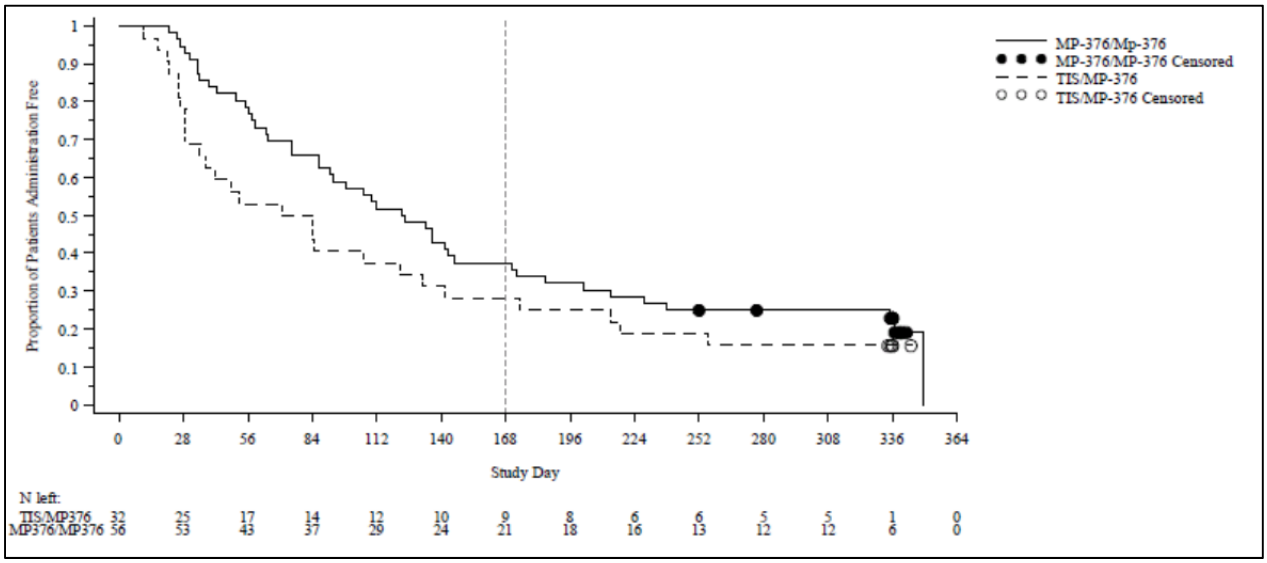
FIGURE 9: TIME TO ADMINISTRATION OF SYSTEMIC AND/OR INHALED ANTIPSEUDOMONAL ANTIMICROBIALS, MEETING SYMPTOMS REQUIREMENT_ MPEX-209



TIS = tobramycin inhalation solution; MP-376 = levofloxacin inhalation solution.

Source: Clinical Study Reports.[2-4]

FIGURE 10: TIME TO ADMINISTRATION OF SYSTEMIC AND/OR INHALED ANTIPSEUDOMONAL ANTIMICROBIALS REGARDLESS OF SYMPTOMS REQUIREMENTS MET, MPEX-209



TIS = tobramycin inhalation solution; MP-376 = levofloxacin inhalation solution.
Source: Clinical Study Reports.[2-4]

TABLE 17: KEY EFFICACY OUTCOMES

	MPEX-204		MPEX-207		MPEX-209	
	Placebo	**LIS 240 mg b.i.d.**	**Placebo**	**LIS 240 mg b.i.d.**	**TIS 300 mg b.i.d.**	**LIS 240 mg b.i.d.**
N	37	39	110	220	93	189
Change from baseline to day 28 in FEV_1 per cent predicted						
• N	37	37	109	218	93	189
• LS mean (SE)	−2.39 (2.370)[a]	8.55 (2.358)[a]	0.43 (0.568)[b]	1.73 (0.471)[b]	0.38 (1.262)[a]	2.24 (1.019)[a]
• LS MD [95% CI]; *P* value	10.94[a] [4.63 to 17.25]; 0.0008		1.31[b] [0.27 to 2.34]; 0.0137		1.86[a] [−0.66 to 4.39]; 0.1481	
Time to first acute exacerbations during 28 days of treatment						
• N (%)	Not reported		52 (47.3%)	122 (55.5%)	62 (66.7%)	111 (58.7%)
• HR [95% CI]; *P* value			1.33 [0.96to 1.84]; 0.0715		0.78 [0.57 to 1.07]; 0.1542	
Change from baseline to day 28 on CFQ-R scale						
• N	37	37	108	218	92	186
• LS Mean (SE)[a]	−0.44 (2.72)	4.06 (2.69)	4.66 (1.37)	4.94 (1.12)	−1.31 (1.58)	1.88 (1.28)
• LS MD (95% CI); *P* value	4.50 [−2.68 to 11.67]; 0.2174		0.28 [−2.30 to 2.85]; 0.8335		3.19 [0.05 to 6.32]; 0.0463	
Time to first missed day of school/work/scheduled activity secondary to worsening respiratory status						
• N (%)	Not reported		18 (16.4%)	28 (12.7%)	5 (5.4%)	14 (7.4%)
• HR [95% CI]; *P* value			0.77 [0.43 to 1.40]; 0.4042		1.54 [0.55 to 4.32]; 0.3969	
Time to Hospitalization secondary to worsening respiratory status						
• N (%)	Not reported		10 (9.1%)	16 (7.3%)	10 (10.8%)	13 (6.9%)
• HR [95% CI]; *P* value			0.82 [0.37 to 1.81]; 0.4902		0.82 [0.35 to 1.93]; 0.6823	

CFQ-R = Cystic Fibrosis Questionnaire–Revised; HR = hazard ratio; LIS = levofloxacin inhalation solution; LS = least squares; MD = mean difference; SD = standard deviation; SE = standard error; TIS = tobramycin inhalation solution.
[a] Relative change from baseline.
[b] Absolute change from baseline.
Source: Clinical Study Reports.[2-4]

3.7 Harms

Only those harms identified in the review protocol are reported below (section 2.2.1, Protocol). Harms results are summarized in Table 18.

3.7.1 Adverse events

Overall, there were 84.6% versus 75.7% patients reporting AEs in MPEX-204 in LIS and placebo groups respectively. In MPEX-207, 97.7% of LIS group reported AEs compared with 98.2% of the placebo group. In MPEX-209, 98.2% of LIS group reported AEs compared with 96.9% in the TIS group.

Cough was reported more frequently in LIS-treated patients than placebo (56.6% versus 46.4% in MPEX-207) and TIS (66.1% versus 46.9% in MPEX-209). In MPEX-204, however, 8.1% of placebo group reported cough, but none in the LIS group. Similarly, there were more LIS-treated patients reporting sputum increase compared with placebo in MPEX-207 (41.6% versus 35.2%) and TIS in MPEX-209 (55.4% versus 43.5%). Furthermore, dysgeusia was reported more frequently in the LIS group than placebo in MPEX-207 (35.2% versus 0.0%) and TIS in MPEX-209 (16.1% versus 0.0%). In MPEX-204, fewer LIS patients reported dysgeusia than placebo (33.3% versus 48.6%).

On the other hand, there were fewer patients in the LIS groups than placebo or TIS groups to report respiratory tract congestion, weight decrease, or discoloured sputum. Respiratory tract congestion was reported by 5.1% and 5.4% in MPEX-204, and 30.6% versus 35.3% in MPEX-207 among LIS and placebo groups respectively. In MPEX-209, 35.7% of LIS patients reported respiratory tract congestion compared with 40.6% for TIS group. Weight loss was reported by 0.0%, 16.4%, and 32.1% for LIS groups in MPEX-204, 207, and 209, respectively, compared with 2.7% and 19.1% for the placebo groups in MPEX-204 and 207; and compared with 46.9% in TIS group in MPEX-209.

3.7.2 Serious adverse events

Similar rates of SAEs were reported for LIS compared with placebo; 8% versus 10.8% in MPEX-204 and 9.6% versus 10% in MPEX-207. In MPEX-209, a lower rate of SAEs was reported by LIS patients (22%) compared with TIS patients (32.2%). In the three trials, the most common SAE was disease progression.

3.7.3 Withdrawal due to adverse events

In MPEX-204, there were fewer LIS patients who discontinued study drug due to AEs than placebo (5.1% versus 10.8%). In MPEX-207 and 209, however, there was a higher rate of treatment discontinuation due to AEs in the LIS groups than placebo (5% versus 1.8%) and TIS (6.3% versus 1.1%).

3.7.4 Mortality

No death events were reported in the included trials.

3.7.5 Notable harms

Of the harms of interest, only one case of costochondritis was reported in MPEX-209 in the LIS group.

TABLE 18: HARMS

	MPEX-204		MPEX-207		MPEX-209	
	Placebo	**LIS 240 mg b.i.d.**	**Placebo**	**LIS 240 mg b.i.d.**	**TIS 300 mg b.i.d.**	**LIS/LIS**
	37	39	110	219	90	182
AEs						
Patients with > 0 AEs, N (%)	28 (75.7%)	33 (84.6%)	108 (98.2%)	214 (97.7%)	90 (100.0%)	180 (98.9%)
Most common AEs[a]						
• Cough	6 (16.2%)	10 (25.6%)	51 (46.4%)	124 (56.6%)	48 (53.3%)	106 (58.2%)
• Disease progression	10 (27.0%)	7 (17.9%)	45 (40.9%)	95 (43.4%)	59 (65.6%)	103 (56.6%)
• Increased sputum	Not reported		42 (38.2%)	91 (41.6%)	14 (43.5%)	40 (44.4%)
• Respiratory tract congestion	2 (5.4%)	2 (5.1%)	39 (35.5%)	67 (30.6%)	32 (35.6%)	68 (37.4%)
• Dysgeusia	1 (2.7%)	13 (33.3%)	0 (0%)	77 (35.2%)	0 (0.0%)	46 (25.3%)
• Fatigue	0	2 (5.1%)	22 (20.0%)	42 (19.2%)	25 (27.8%)	58 (31.9%)
• Increased viscosity of bronchial secretion	Not reported		21 (19.1%)	44(20.1%)	9 (28.1%)	28 (31.1%)
• Weight decreased	1 (2.7%)	0	21 (19.1%)	36 (16.4%)	36 (40.0%)	57 (31.3%)
• Paranasal sinus hypersecretion	0	2 (5.1%)	18 (16.4%)	37 (16.9%)	18 (20.0%)	49 (26.9%)
• Hemoptysis	7 (18.9%)	2 (5.1%)	10 (9.1%)	35 (16.0%)	18 (20.0%)	29 (15.9%)
• Sinus headache	2 (5.4%)	0	17 (15.5%)	26(11.9%)	13 (14.4%)	35 (19.2%)
• Sputum discoloured	Not reported		15 (13.6%)	23 (10.5%)	7 (21.9%)	16 (17.8%)
• Dyspnea exertional	0	1 (2.6%)	11 (10.0%)	26(11.9%)	15 (16.7%)	21 (11.5%)
• Decreased appetite	Not reported		12 (10.9%)	22 (10.0%)	2 (6.3%)	16 (17.8%)
• Forced expiratory volume decreased	1 (2.7%)	1 (2.6%)	10 (9.1%)	21 (9.6%)	15 (16.7%)	17 (9.3%)
• Headache	0 (0.0%)	4 (10.3%)	3 (2.7%)	14 (6.4%)	6 (6.7%)	11 (6.0%)
• Pyrexia	3 (8.1%)	6 (15.4%)	2 (1.8%)	16 (7.3%)	10 (11.1%)	17 (9.3%)
• Nausea	1 (2.7%)	3 (7.7%)	1 (0.9%)	14 (6.4%)	7 (7.8%)	11 (6.0%)
• Rales	3 (8.1%)	2 (5.1%)	4 (3.6%)	12 (5.5%)	8 (8.9%)	8 (4.4%)
• Oropharyngeal pain	Not reported		7 (6.4%)	10 (4.6%)	2 (2.2%)	12 (6.6%)
• Exercise tolerance decreased	0	0	11 (10.0%)	2S (12.8%)	14 (15.6%)	23 (12.6%)
• Nasopharyngitis	3 (8.1%)	3 (7.7)	4 (3.6%)	2 (0.9%)	11 (12.2%)	17 (9.3%)
• Blood glucose increased	Not reported		3 (2.7%)	2 (0.9%)	3 (9.4%)	7 (7.8%)
• Productive cough	4 (10.8%)	2 (5.1%)	0	1 (0.5%)	Not reported	
• Chest discomfort	3 (8.1%)	4 (10.3%)	4 (3.6%)	6 (2.7%)	2 (2.2%)	6 (3.3%)
• Wheezing	2 (5.4%)	1 (2.6%)	4 (3.6%)	7 (3.2%)	3 (3.3%)	5 (2.7%)
SAEs						
Patients with > 0 SAEs, N (%)	4 (10.8%)	4 (10.3%)	11 (10.0%)	21 (9.6%)	29 (32.2%)	40 (22.0%)
Most common SAE						
• Disease progression	3 (8.1%)	3 (7.7%)	11 (10.0%)	15 (6.8%)	24 (26.7%)	31 (17.0%)
WDAEs, N (%)	4 (10.8%)	2 (5.1%)	2 (1.8%)	11 (5.0%)	1 (1.1%)	12 (6.3%)
Number of deaths, N (%)	0	0	0	0	0	0

	MPEX-204		MPEX-207		MPEX-209	
	Placebo	**LIS 240 mg b.i.d.**	**Placebo**	**LIS 240 mg b.i.d.**	**TIS 300 mg b.i.d.**	**LIS/LIS**
NOTABLE HARMS						
• QT interval prolongation	Not reported					
• Anaphylactic reactions						
• Seizures						
• Symptomatic bronchospasm						
• Costochondritis	0	0	Not reported		0	1 (0.5%)
• Tendon rupture	Not reported					

AE = adverse event; b.i.d. = twice daily; LIS = levofloxacin inhalation solution; SAE = serious adverse event; TIS = tobramycin inhalation solution; WDAE = withdrawal due to adverse event; QT = the interval from the beginning of the Q wave to the end of the T wave in the electrical cycle of the heart.
Source: Clinical Study Reports.[2-4]

4. DISCUSSION

4.1 Summary of Available Evidence

The evidence for this review was derived from one phase II dose-response, placebo-controlled RCT (MPEX-204), one phase III placebo-controlled RCT (MPEX-207), and one TIS-controlled, open-label RCT (MPEX-209). The CADTH CDR review focused on the use of LIS at the Health Canada–approved dosage (i.e., 240 mg twice daily). MPEX-204 also included additional LIS dosage regimen (LIS 120 mg once daily and LIS 240 mg once daily), which were excluded from the CDR review as they are not approved LIS dosages in Canada. Comparative efficacy data from the three trials were limited to one cycle of 28-days of treatment followed by 28-days off treatment. MPEX-209 included additional two cycles of 28-days of treatment, but end points were not compared between LIS and TIS. MPEX-209 was followed by an extension study of 3 cycles of LIS treatment (MPEX-209-EXT). The extension study is summarized in APPENDIX 4. The CDR review also included a summary of an indirect treatment comparison (ITC) conducted by the manufacturer and summarized in APPENDIX 6. The ITC compared LIS with TIS, aztreonam and colistimethate sodium inhalation solutions. Lastly, information related to the nebulizer devices used for pulmonary administration of levofloxacin, tobramycin, and aztreonam is described in Appendix 7.

The included trials evaluated a range of different outcomes that are considered to be important in the treatment of CF patients who have chronic *P. aeruginosa* infection. These outcomes include respiratory function (i.e., $ppFEV_1$), health-related quality of life (i.e., CFQ-R), and clinical events (e.g., pulmonary exacerbations).

4.2 Interpretation of Results

4.2.1 Efficacy

Treatment with LIS, when compared with placebo in MPEX-204 and 207, was associated with a statistically significant greater increase in FEV_1 per cent predicted change from baseline to day 28. In MPEX-209, LIS was shown to be non-inferior to TIS in terms of change in FEV_1 per cent predicted from baseline to day 28, but was not superior to TIS. Of note, the positive changes in FEV_1 values while on treatment returned toward baseline at the end of the off-treatment periods. These observations were consistent in MPEX-204 and 207 (Figure 5 and Figure 6).

The manufacturer–provided ITC analyses (Appendix 6) suggested that LIS was not statistically different in terms of change in FEV_1 from baseline to day 28 of treatment when compared with TIS, aztreonam, colistimethate, or placebo (Table 27 and Table 28). However, several serious limitations with the analysis make it difficult to be certain in this conclusion. Moreover, commenting on these results is limited to the statistical interpretation of data because there is no established minimal clinically important difference for absolute and relative change from baseline in per cent predicted FEV_1 in patients with CF (APPENDIX 5).

In terms of time to first exacerbation, there was no statistically significant difference between LIS and placebo or TIS, in MPEX-207 and 209 respectively. The reviewed ITC did not compare rates of exacerbations between LIS and the other interventions. It is known that exacerbations are associated with a faster rate of FEV_1 decline;[27] however, this association was not evaluated in the included trials.

Quality of life and daily life activities were highlighted as important to patients by patient groups who provided input to this submission (APPENDIX 1). Results of the CFQ-R scale was reported in the three

included trials. Compared with placebo, treatment with LIS did not show statistically significant differences in MPEX-204 or MPEX-207. When LIS was compared with TIS in MPEX-209, it showed a statistically significantly higher improvement after 28 days of treatment; this difference continued to be statistically significant after the 28 days off-treatment period. It is unclear why a quality of life difference was observed with LIS versus TIS but not versus placebo. Based on input from the clinical expert consulted by CDR, administration of TIS can be time consuming for patients. However, there is no evidence that differences in administration between LIS and TIS, or other drug-specific factors, had an impact on the observed CFQ-R results. Toward the end of the third off-treatment cycle, the difference between LIS and TIS was no longer statistically significant (Figure 8). Compliance was not assessed in MPEX-209; which would have been helpful to understand the impact of treatment on quality of life as measured by CFQ-R and how this would reflect on adherence to treatment. Nevertheless, a patient's disposition (Table 7) showed that there were more patients in the LIS group, compared with the TIS group, who discontinued study treatment or quit the study due to AEs. This might suggest that the negative impact of TIS seen in terms of CFQ-R Respiratory Symptom Scale scores did not affect patient's willingness to continue treatment. In terms of the ITC, LIS was not statistically different in terms of change in CFQ-R score at 28 days, from TIS, aztreonam or placebo.

4.2.2 Harms

In general, AEs were reported at similar rates for LIS, placebo and TIS with few exceptions. Notably, LIS was associated with higher rates of AEs caused by upper respiratory tract irritation. Of these, cough, sputum increase, and paranasal sinus hypersecretion were reported more frequently with LIS than placebo or TIS. Furthermore, LIS was associated with higher rates of dysgeusia than TIS and placebo. Of note, higher rates of study drug discontinuation due to AEs were reported in MPEX-207 and MPEX-209 for patients treated with LIS than those treated with placebo or TIS, but it is unclear whether or not these discontinuations were related to the above-mentioned AEs.

When compared with placebo, in MPEX-204 and MPEX-207, LIS was associated with higher rates of nausea, headache, and pyrexia. The higher rates of pyrexia were not associated with an increase in infection, low white blood cell (WBC) counts, or high WBCs in the urine.[26]

4.3 Potential Place in Therapy[1]

Tobramycin is the gold standard, most commonly used inhaled antibiotic for the treatment of adults with CF who require treatment for chronic *P. aeruginosa* pulmonary infection.[12] When clinical benefit is no longer demonstrated and/or resistance to tobramycin develops,[8,28,29] alternative inhaled antibiotics such as aztreonam[30-32] or colistin[33,34] are used, particularly in the presence of moderate-to-severe lung disease.[12] These second-line antibiotics are used instead of inhaled tobramycin, or they may be considered for use in alternate 28-day cycles with tobramycin in some cases, in order to maximize treatment benefit.[12] According to the clinical expert consulted, additional antibiotic drugs for treatment in this circumstance are needed to avoid antimicrobial resistance and to provide improvement or maintenance of lung function, without significant side effects or intolerance associated with aztreonam and colistin.

Levofloxacin is an alternative therapeutic drug to treat chronic *P. aeruginosa* pulmonary infection in adults with CF. The clinical expert consulted by CDR noted that although there are no data indicating

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

which line of therapy levofloxacin fits in, in practice it will likely be used in adults with CF and chronic pulmonary *P. aeruginosa* infection in whom tobramycin is not effective at maintaining symptom control and or pulmonary function, particularly where resistance to tobramycin on in vitro sputum cultures has been demonstrated. This population, according to the expert, will be easily identified by clinicians based on symptoms, pulmonary function and sputum cultures, which are routinely measured at clinic visits several times per year. As such, levofloxacin will address an unmet need in the clinical care of adults with CF and *P. aeruginosa* infection, in whom maintenance of pulmonary function is paramount for longevity.

5. CONCLUSIONS

The CDR systematic review included two placebo-controlled RCTs and one TIS-controlled RCT that investigated the comparative safety and efficacy of LIS in CF patients with chronic *P. aeruginosa* infections. LIS was associated with a higher increase in per cent predicted FEV_1 from baseline to day 28 than placebo in the two placebo-controlled trials, and it was shown to be non-inferior to TIS after 28-days of treatment. However, LIS was associated with numerically more frequent pulmonary exacerbations than placebo, but it was associated with numerically less frequent events than TIS. LIS was not statistically different from placebo or TIS in terms of changes in CFQ-R, hospitalization, or missed days of school/work/ or scheduled activities when measured 28 days and 56 days after treatment initiation.

LIS was generally well-tolerated in the study populations with more than 88% of LIS-treated patients completing the trial period. LIS was associated with an increased frequency of cough, sputum increase, paranasal sinus hypersecretion, and dysgeusia than TIS and placebo.

A manufacturer–provided ITC suggested that little to no difference exists between levofloxacin and other antipseudomonal inhaled antibiotics based on a lack of statistical significance in most of the comparisons; several important limitations make it difficult to be certain in this conclusion.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input
Input was received from two patient groups:

Cystic Fibrosis Canada (CF Canada) is a charitable non-profit corporation with a mission to help people with cystic fibrosis (CF). CF Canada funds research toward finding a cure and improving control of CF, supports high-quality CF care, and promotes public awareness of CF. CF Canada has received financial contributions from pharmaceutical companies, including Abbott Laboratories, BPG Pharma, Gilead, Hoffmann-La Roche, Insmed, Merck, Mylan, Novartis, Prometic Life Sciences, PRC, Innovative Medicines Canada, and Vertex. CF Canada declared no conflicts of interest in the preparation of this submission.

The Patient Family Advisory Board (PFAB) is an organization that acts as an advisory resource to St. Michael's Hospital (Toronto, Ontario) CF health care team. The PFAB works collaboratively with the CF team at St. Michael's Hospital, actively participates in the development of new programs, reviews recommendations, provides input for shaping the CF clinic, and promotes improved relationships between patients, families, and staff. PFAB declares no conflicts of interest or financial contributions in the preparation of this submission.

2. Condition Related Information
CF Canada collected information for the following sections from a survey of patient members of CF Canada's Adult CF Advisory Committee. The PFAB reported information was collected through "personal experience." Specifics regarding how information was collected by both patient groups were not provided.

CF is a life-limiting inherited disorder that causes the body to produce thick and sticky mucus that affects many organ systems, particularly the pulmonary and digestive systems. Difficulty in clearing secretions from the lungs leads to persistent cough, shortness of breath, and recurrent infections that result in progressive scarring of the airways and decline in lung function. The main cause of death in CF is respiratory failure. Additionally, the mucus blocks passageways in the pancreas preventing digestive enzymes from getting to the intestine. Many patients with CF in Canada lack pancreatic enzymes and have difficulty digesting and absorbing fats, proteins and other nutrients, like vitamins, leading to difficulties in maintaining a healthy weight.

Patients describe having a significant burden of medical therapy. It requires a daily regimen of administering numerous medications along with other modalities of therapy, such as chest physiotherapy. The medical therapies are complex and time consuming. The routine also includes regular visits to specialized CF clinics, and people with CF are frequently hospitalized due to acute infections and pulmonary exacerbations, often necessitating courses of intravenous antibiotics. Patients report they are often too ill to work to have a steady source of income; and daily activities of living, such as walking, playing with children, household chores, or showering, are often difficult or impossible to complete. Patients also describe a heavy mental burden from having to constantly think of their disease and medical therapies, being unable to do what other people their age would be able to do, and having to experience frequent hospital admissions. One patient describes that during hospital admission she is:

> "secluded from [her] family, [her] friends and [her] life. It's a very lonely time."

Collectively, these factors lead to reduced quality of life for patients with CF.

The impact on caregivers of CF patients is multi-level, including emotional stress from seeing a loved one chronically ill, financial stress from having a dependent that sometimes requires time and attention during work hours, and physical stress from, for example, performing the majority of household duties. These factors negatively impact the health and quality of life of patients' caregivers.

3. Current Therapy Related Information

Patients with CF describe a multi-faceted daily routine to manage their disease, which includes inhaled therapies such as antibiotics and mucolytics, oral antibiotics and digestive enzymes, insulin, and chest physiotherapy. In addition, patients may need intravenous antibiotics to better manage infections. Both patient groups mentioned drug adverse effects, especially with antibiotics, as important concerns. PFAB respondents specifically mentioned ototoxicity, neurotoxicity, steroid-specific adverse drug reactions, and antibiotic resistance as key adverse effects of concern with current therapies. The most significant hardships described were antibiotic resistance secondary to frequent antibiotic exposure, and restricted access to CF medications secondary to financial restrictions. Antibiotic resistance results in limited options to treat lung infections, irreversible damage from chronic infection, and ultimately, lung failure. One patient describes the mental burden of accepting that only a limited number of options exist to treat resistant chronic lung infection. She states that she is:

> "struggling with the realization that [she is] running out of feasible options to treat [her] chronic lung infections," and that "[it] is a terrifying and helpless place to be."

4. Expectations About the Drug Being Reviewed

Patients in Canada do not have experience with the new drug, and as such, neither CF Canada nor the PFAB report information based on patients' experiences with levofloxacin.

Patients hope that levofloxacin will provide an additional option to help reduce the risk for resistant bacteria, manage CF symptoms, defend against chronic lung infections, and prevent the necessity of IV antibiotics and their adverse drug reactions as compared with current alternatives. Patients surveyed by PFAB also expect levofloxacin will result in having fewer hospital admissions, and preventing or delaying the time until a double-lung transplant. The PFAB respondents also expect the drug to help improve quality of life, reduce time off work, reduce financial strain on families and the health care system, and allow for the patient to become a better contributing member of society. With an additional option for therapy, patients describe feeling excited and mentally relieved that they will not be "running out of options" and some expressed a hope of "being less sick, less often."

CF Canada respondents provided information on the expectations for having a drug that is administered through a high-efficiency, portable nebulizer. Patients describe improved convenience, portability, quietness, and less time spent doing inhaled therapies as potential benefits.

Finally, the PFAB respondents noted that the risks and benefits must be weighed individually for each patient.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	June 28, 2016
Alerts:	Bi-weekly (twice monthly) search updates until October 19, 2016
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
Adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
1	Levofloxacin/
2	(6GNT3Y5LMF or 100986-85-4 or 138199-71-0 or 177325-13-2 or 872606-49-0 or 138199-72-1 or 177472-30-9 or 226578-51-4 or 294662-18-3).rn,nm.
3	(quinsair* or levofloxacin* or Levaquin* or quixin* or tavanic* or mp 376 or mp376 or aeroquin* or cravit* or dr 3355 or dr3355 or dynaquin* or elequine* or floxacin* or floxel* or hr 355 or hr355 or iquix* or leroxacin* or lesacin* or levoxacin* or loxof* or mosardal* or nofaxin* or oftaquix* or quixin* or reskuin* or rwj 25213 or rwj25213 or unibiotic* or volequin* or venaxan* or HR 355 or HSDB 8028 or APT-1026 or adlox* or amlevo* or auxxil* or avoxin* or axoflon* or bacflocin* or bactevo* or bredelin* or conlevo* or corvox* or cravox* or evolox* or evoxil* or fenalex* or flexid* or floxacap* or getzlox* or glevo* or hailon* or lamiwin* or lebel* or lecifex* or lecrav* or lectacin* or leflodal* or leflox* or lefloxin* or lefocin* or lemed* or LEO or levo* or levobact* or levocin* or levoflox or levokacin* or levoksa* or levomac* or levomicin* or levoquin* or levores* or levotsyn* or levox* or levoxa* or levoxin* or levoxl* or levunid* or lexacin* or lexlo* or lovequin* or lufi* or matador* or nexquin* or nirliv* or nislev* or olfovel* or omnivox* or pneumocal* or ponaris* or quinomed* or qure* or rinvox* or rozoxin* or truxa* or uroflox* or voLox* or vorotal* or wilovex* or xalecin* or zidalex*).ti,ab,ot,kf,hw,rn,nm.
4	ofloxacin/ and (isomer* or enantiomer*).ti,ab,ot,kf,hw,rn,nm.
5	(Ofloxacin* and (isomer* or enantiomer*)).ti,ab,ot,kf,hw,rn,nm.
6	or/1-5
7	Cystic Fibrosis/
8	((cystic or pancreatic or pancreas) and fibros*).ti,ab,kf.
9	((fibrocystic or fibro-cystic or cystic) adj3 (disease* or illness)).ti,ab,kf.
10	(mucoviscidosis or mucoviscoidosis or mucosis).ti,ab,kf.
11	(CF adj3 (lung* or mucus or respirator*)).ti,ab,kf.
12	or/7-11
13	6 and 12
14	13 use pmez
15	*Levofloxacin/
16	(quinsair* or levofloxacin* or Levaquin* or quixin* or tavanic* or mp 376 or mp376 or aeroquin* or cravat* or dr 3355 or dr3355 or dynaquin* or elequine* or floxacin* or floxel* or hr 355 or hr355 or iquix* or leroxacin* or lesacin* or levoxacin* or loxof* or mosardal* or nofaxin* or oftaquix* or quixin* or reskuin* or rwj 25213 or rwj25213 or unibiotic* or volequin* or venaxan* or HR 355 or HSDB 8028 or APT-1026 or adlox* or amlevo* or auxxil* or avoxin* or axoflon* or bacflocin* or bactevo* or bredelin* or conlevo* or corvox* or cravox* or evolox* or evoxil* or fenalex* or flexid* or floxacap* or getzlox* or glevo* or hailon* or lamiwin* or lebel* or lecifex* or lecrav* or lectacin* or leflodal* or leflox* or lefloxin* or lefocin* or lemed* or LEO or levo* or levobact* or levocin* or levoflox or levokacin* or levoksa* or levomac* or levomicin* or levoquin* or levores* or levotsyn* or levox* or levoxa* or levoxin* or levoxl* or levunid* or lexacin* or lexlo* or lovequin* or lufi* or matador* or nexquin* or nirliv* or nislev* or olfovel* or omnivox* or pneumocal* or ponaris* or quinomed* or qure* or rinvox* or rozoxin* or truxa* or uroflox* or voLox* or vorotal* or wilovex* or xalecin* or zidalex*).ti,ab,kw.
17	*Ofloxacin/ and (isomer* or enantiomer*).ti,ab,kw.
18	(Ofloxacin* and (isomer* or enantiomer*)).ti,ab,kw.

MULTI-DATABASE STRATEGY	
#	**Searches**
19	or/15-18
20	Cystic Fibrosis/
21	((cystic or pancreatic or pancreas) and fibros*).ti,ab,kw.
22	((fibrocystic or fibro-cystic or cystic) adj3 (disease* or illness)).ti,ab,kw.
23	(mucoviscidosis or mucoviscoidosis or mucosis).ti,ab,kw.
24	(CF adj3 (lung* or mucus or respirator*)).ti,ab,kw.
25	or/20-24
26	19 and 25
27	26 use oemezd
28	conference abstract.pt.
29	27 not 28
30	14 or 29
31	remove duplicates from 30

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	June 2016
Keywords:	Quinsair (levofloxacin), cystic fibrosis
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
ELBORN et al. 2016[35]	No study design of interest

APPENDIX 4: SUMMARY OF OTHER STUDIES

1. Objective

To summarize the results from the MPEX-209 extension phase.[35] This review was undertaken to evaluate both the efficacy and safety of levofloxacin inhalation solution (LIS) in patients with cystic fibrosis (CF) and chronic *Pseudomonas aeruginosa* airway infection. The following summary is based on the published[35] and unpublished[36] data from the MPEX-209 extension phase.

2. Findings

This study was an optional, single-arm, open-label extension phase of patients who completed the MPEX-209 study, had clinically stable CF, and whose clinical site was eligible for participation. It consisted of an additional 168-day treatment period, whereby patients were treated with 3 additional 56-day cycles of 28 days on LIS 240 mg twice daily followed by 28 days off treatment. Day 168 constituted the first day of the extension phase (visit seven; including that of the previous RCT) and day 336 (visit 13) was the final/early termination visit; between which cycles 4 through 6 were administered. Patients who were originally randomized to LIS treatment continued to receive the twice daily regimen of LIS, while patients who were originally randomized to the tobramycin inhalation solution (TIS) 300 mg twice daily regimen received LIS upon commencing the extension phase. Both safety and efficacy over multiple cycles were assessed as per the core RCT. Efficacy was evaluated using the following outcomes: pulmonary function tests (forced expiratory volume in one second [FEV_1]), microbiological assessment of sputum samples, time to exacerbation, administration of additional systemic and/or inhaled antipseudomonal antimicrobials, and patient–reported outcomes (Cystic Fibrosis Questionnaire–Revised [CFQ-R]).Safety was assessed by evaluating treatment-emergent adverse events (TEAEs) with regard to severity, duration, and relationship to LIS, adverse events (AEs), serious adverse events (SAEs), and study discontinuations.

Results

Patient Disposition

Of the 144 eligible patients across 45 sites (US and Europe), 88 patients enrolled in the extension phase study. As previously mentioned, patients either continued on LIS (n = 56) or changed to LIS from TIS (n = 32) depending on their randomization group in the original study. The proportion of the patients completing the extension phase (through day 336/final visit) was 81.3% and 83.9% in the TIS/LIS and LIS/LIS groups, respectively. The predominant reason for discontinuation included withdrawal of consent, followed by other reasons (including the commencement of antimicrobial drugs due to symptom worsening or exacerbation, inability to attend specific pre-specfied visits due to life events, sponsor advising that the patient should return for specified visit, and antimicrobial started due to patient no longer being stable), and AEs. The proportion of patients who permanently discontinued LIS treatment was 18.8% compared with 16.1% in the TIS/LIS and LIS/LIS groups, respectively. Disposition results were generally similar between the two groups with the exception of the primary reason for early permanent LIS discontinuation, whereby more patients in the TIS/LIS discontinued for patient reasons when compared with the LIS/LIS group (12.5% versus 7.1%, respectively). The mean (with standard deviation [SD]) number of days on study was 328.6 (26.20) in the TIS/LIS group and 325.6 (39.08), with days ranging from 194 to 425. Detailed patient disposition is presented in the Table 19.

TABLE 19: PATIENT DISPOSITION

	MPEX-209 Extension	
	TIS/LIS	**LIS/LIS**
Patients enrolled	32	56
Patients who completed study through day 336/final visit, n (%)		
• Yes	26 (81.3)	47 (83.9)
• No	6 (18.8)	9 (16.1)
Primary reason for early discontinuation,[a] n (%)		
• AE	1 (3.1)	3 (5.4)
• Consent withdrawal	3 (9.4)	4 (7.1)
• Other	2 (6.3)	2 (3.6)
Permanently discontinued LIS,[b] n (%)		
• Yes	6 (18.8)	9 (16.1)
• No	26 (81.3)	47 (83.9)
Primary Reason for permanent LIS discontinuation, n (%)		
• AE	0	2 (3.6)
• Started antimicrobial drugs	2 (6.3)	2 (3.6)
• Investigator decision	0	1 (1.8)
• Patient decision	4 (12.5)	4 (7.1)
Number of days in study[c]		
• N	32	56
• Mean (SD)	328.6 (26.20)	325.6 (39.08)
• Median	336	337
• Min, Max	224, 358	194, 425

AE = adverse event; LIS = levofloxacin inhalation solution; SD = standard deviation; TIS = tobramycin inhalation solution.
[a] Before day 336 visit.
[b] Before day 308 visit.
[c] Core (original RCT MPEX-209) plus extension.
Source: MPEX-209 Extension Study Clinical Study Report.[36]

Patient Characteristics

The mean age of patients in the TIS/LIS group compared with LIS/LIS group was 29.5 and 27.8 years, respectively, with a larger proportion of patients in the TIS/LIS group being older than 18 year of age (87.5% versus, 75.0, respectively). The proportions were similar across all other characteristics between the two treatment groups. Detailed patient characteristics are provided in Table 20.

TABLE 20: BASELINE[A] PATIENT CHARACTERISTICS (SAFETY POPULATION)

	MPEX-209 Extension Study	
	TIS/LIS	**LIS/LIS**
N	32	56
Age (years)		
• Mean (SD)	29.5 (11.51)	27.8 (9.84)
• Median	27.5	28.0
• Min, Max	12.0, 63.0	12.0, 50.0
• 12 to 18 years, n (%)	4 (12.5)	14 (25.0)
• > 18 years, n (%)	28 (87.5)	42 (75.0)
Sex, n (%)		
• Male	18 (56.3)	30 (53.6)
• Female	14 (43.8)	26 (46.4)
Ethnicity, n (%)		
• Hispanic or Latino	0	2 (3.6)
• Not Hispanic or Latino	32 (100.0)	54 (96.4)

	MPEX-209 Extension Study	
	TIS/LIS	LIS/LIS
Race, n (%)		
• American Indian or Alaska Native	0	1 (1.8)
• Black or African American	0	1 (1.8)
• Caucasian	31 (96.9)	51 (91.1)
• Other	1 (3.1)	2 (3.6)
• Multiple races checked	0	1 (1.8)
Region, n (%)		
• US	16 (50.0)	32 (57.1)
• Non-US[b]	16 (50.0)	24 (42.9)
Weight (kg)		
• Mean (SD)	62.0 (16.81)	59.8 (12.42)
• Median	60.3	58.0
• Min, Max	31.5, 103.7	30.2, 95.8

LIS = levofloxacin inhalation solution; SD = standard deviation; TIS = tobramycin inhalation solution.
[a] Core baseline demographics refers to those demographics observed at the baseline of the original RCT (MPEX-209); however, these are presented for only those entering the extension study.
[b] Includes France, Germany, Ireland, and the United Kingdom.
Source: MPEX-209 Extension Study Clinical Study Report.[36]

Concomitant Medications

While all patients were receiving concomitant medications in all treatment periods of the extension phase, concomitant medications that were started by more than 5% of patients in the extension phase included ciprofloxacin, tobramycin, meropenem, prednisone, aztreonam lysine inhaled solution, trimethoprim/sulfamethoxazole, ibuprofen, and ceftazidime. While proportions were similar between treatment groups with regard to ciprofloxacin and ibuprofen in the treatment periods, a larger proportion of patients commenced tobramycin and ceftazidime in the LIS/LIS group (12.5% and 7.1%, respectively) when compared with the TIS/LIS group (3.1% and 3.1%, respectively). During the off-treatment periods, similar proportions were observed in the commencement of medications between treatment groups with the exception of the commencement of tobramycin and prednisone, whereby the proportions were larger in the TIS/LIS groups compared with the LIS/LIS group (28.1% versus 19.6% and 12.5% versus 3.6%, respectively). Commencement of aztreonam lysine inhaled solution in the off-period was observed in a larger proportion of patients in the LIS/LIS group when compared to TIS/LIS (7.1% versus 3.1%). Details regarding concomitant medications are provided in Table 21.

TABLE 21: CONCOMITANT MEDICATIONS COMMENCING IN EXTENSION PHASE ON AND OFF-TREATMENT PERIODS (DAYS 1 TO 28 OF EACH CYCLE) IN > 5% OF PATIENTS, SAFETY POPULATION

	MPEX-209 Extension Study	
	TIS/LIS	LIS/LIS
N	32	56
Concomitant medications started in the treatment periods, n (%)		
• Ciprofloxacin	4 (12.5)	7 (12.5)
• Tobramycin	1 (3.1)	7 (12.5)
• Ibuprofen	2 (6.3)	5 (8.9)
• Ceftazidime	1 (3.1)	4 (7.1)
Concomitant medications started in the off-treatment periods, n (%)		
• Tobramycin	9 (28.1)	11 (19.6)
• Ciprofloxacin	6 (18.8)	11 (19.6)
• Ceftazidime	4 (12.5)	7 (12.5)
• Meropenem	4 (12.5)	7 (12.5)

	MPEX-209 Extension Study	
	TIS/LIS	LIS/LIS
• Prednisone	4 (12.5)	2 (3.6)
• Aztreonam Lysine inhaled solution	1 (3.1)	4 (7.1)
• Trimethoprim/sulfamethoxazole	2 (6.3)	3 (5.4)

LIS = levofloxacin inhalation solution; TIS = tobramycin inhalation solution.
Source: MPEX-209 Extension Study Clinical Study Report.[36]

Treatment Compliance

A similar rate of LIS treatment compliance was observed in both treatment groups, with greater than 60% of patients having a compliance rate of more than 80% in the extension study. Details regarding treatment compliance are provided in Table 22.

TABLE 22: LIS TREATMENT COMPLIANCE

	MPEX-209 Extension Study	
	TIS/LIS	LIS/LIS
N	32	56
Entire Study, n (%)		
• < 40%	NA	1 (2)
• 40 to < 60%	NA	4 (7)
• 60 to < 80%	NA	10 (18)
• 80 to < 90%	NA	11 (20)
• ≥ 90%	NA	30 (54)
Extension Phase, n (%)		
• < 40%	3 (9)	6 (11)
• 40 to < 60%	2 (6)	4 (7)
• 60 to < 80%	4 (13)	11 (20)
• 80 to < 90%	4 (13)	8 (14)
• ≥ 90%	19 (59)	27 (48)

LIS = levofloxacin inhalation solution; NA = not applicable; TIS = tobramycin inhalation solution.
Source: MPEX-209 Extension Clinical Study Review.[36]

Clinical Efficacy Outcomes

Relative Change from Core Baseline in FEV_1 Percent Predicted

There were discrepancies in the core baseline FEV_1 per cent predicted values between the TIS/LIS and LIS/LIS treatment groups in addition to a similar pattern of differences observed in the extension baseline values. Mean relative improvement in FEV_1 per cent predicted values increased from the core baseline during cycles 1 and 3 of the original RCT, with the improvement being maintained through the end of cycles 4 and 5 in the extension phase. However, this improvement was not observed at the end of cycle 6 of the extension phase in the 45 patients who were analyzed in this group (Table 23). A mean relative improvement above core baseline in FEV_1 per cent predicted was observed in the TIS/LIS patients in cycles 1 through 3 and was maintained or higher in during cycles 4, 5, and 6 (Table 23).

Time to Exacerbation

Pulmonary exacerbation was experienced for the first time in the extension phase in 21% (n = 12) and 9% (n = 3) in the LIS/LIS and TIS/LIS groups, respectively. A total of 23 extension patients remained exacerbation free, with 26.8% (n = 15) in the LIS/LIS group and 25.0% (n = 8) in the TIS/LIS group. The median time to exacerbation from the core baseline was 153.5 days and 99.5 days in the LIS/LIS and TIS/LIS groups, respectively (hazard ratio of 0.81, 95% CIs of 0.48 to 1.35) (Table 23).

Time to Administration of Systemic and/or Inhaled Antipseudomonal Antimicrobials
Patients who received systemic and/or inhaled antipseudomonal antimicrobials along with meeting symptoms requirements (described in the footnotes of Table 23) in the extension phase included 18% (n = 10) and 13% (n = 4) in the LIS/LIS and TIS/LIS groups, respectively. The median time to receive these antipseudomonal antimicrobials was 139.5 days in the LIS/LIS group and 84 days in the TIS/LIS group.

Time to Hospitalization for Worsening Respiratory Status
Hospitalizations secondary to worsening of respiratory status in the extension phase was observed in 16% (n = 9) and 16% (n = 5) of patients in the LIS/LIS and TIS/LIS groups, respectively. As medians could not be estimated, the 25th percentile for the time to hospitalizations due to worsening of respiratory symptoms was 255 days in the LIS/LIS group and 239 days for the TIS/LIS group (Table 23).

School/Work/Scheduled Activity Absence
At least one day of school, work, or scheduled activity was missed due to worsening of respiratory status in the extension phase by 9% (n = 5) and 6% (n = 2) of patients in the LIS/LIS and TIS/LIS groups , respectively (Table 23). The mean number of days missed was lower in the LIS/LIS group compared with TIS/LIS group at 2.2 days (SD of 7.2 days) and 13.7 days (SD of 62.10 days), respectively (Table 23).

Weight
The mean weight change from the core baseline to the final visit was 0.6 kg (SD of 2.49 kg) compared with 1.1 kg (SD of 3.62 kg) in the LIS/LIS and TIS/LIS groups, respectively (Table 23). The mean weight change from the extension baseline to the final visit was –0.4 kg (SD of 2.03 kg) compared with 0.4 kg (SD of 2.53 kg), respectively (Table 23).

TABLE 23: PRIMARY AND SECONDARY EFFICACY OUTCOME MEASURES (ITT POPULATION)

	MPEX-209 Extension Study	
	TIS/LIS	**LIS/LIS**
Relative Change in FEV_1 Per cent Predicted From Core Baseline[a] to Specific Visits		
Core Baseline[a]		
• N	32	56
• Mean (SD)	50.69 (15.218)	55.17 (16.072)
• Median	46.75	55.70
• Min, Max	26.1, 83.3	26.4, 86.5
To day 168 (baseline of extension phase, off treatment at end of cycle 3, end of core phase)		
• N	32	54
• Mean (SD)	–0.13 (13.532)	1.35 (8.406)
• Median	1.29	–0.40
• Min, Max	–33.8, 30.6	–13.1, 20.2
To day 196 (end of treatment during cycle 4)		
• N	31	53
• Mean (SD)	6.91 (13.005)	3.61 (9.084)
• Median	8.09	3.04
• Min, Max	–26.4, 35.5	–14.0, 23.3
To day 252 (end of treatment during cycle 5)		
• N	28	49
• Mean (SD)	4.00 (12.419)	3.64 (9.007)
• Median	2.83	2.51

	MPEX-209 Extension Study	
	TIS/LIS	**LIS/LIS**
• Min, Max	–25.2, 29.7	–17.5, 21.9
To day 308 (end of treatment during cycle 6)		
• N	25	45
• Mean (SD)	4.35 (14.803)	–0.15 (9.884)
• Median	2.68	-0.54
• Min, Max	–22.9, 50.9	–22.5, 21.9
Time to Exacerbation[b] from Core Baseline[a] to Final Visit		
Patients experiencing pulmonary exacerbation, n (%)	24 (75.0)	41 (73.2)
Patients who were exacerbation free, n (%)	8 (25.0)	15 (26.8)
Time to exacerbation (days)		
• Min, Max	4, 344	10, 340
• Percentiles (95% CI)[c]		
○ 25th	32.5 (25 to 77)	54.5 (45 to 131)
○ Median	99.5 (47 to 216)	153.5 (123 to 221)
○ HR (95% CI)	0.81 (0.48 to 1.35)	
○ 75th	337 (116, NE)	NA (206, NE)
Time to Administration of Systemic and/or Inhaled Antipseudomonal Antimicrobials[d] from Core Baseline to Final Visit		
Administration of Antimicrobials		
• Patients with event, n (%)	25 (78.1)	41 (73.2)
• Patients censored	7 (21.9)	15 (26.8)
Time to administration (days)		
• Min, Max	11, 344	22, 349
• Min, Max for non-censored patients	11, 300	22, 349
• Percentiles (95% CI)[c]		
○ 25th	29 (26 to 52)	66 (56 to 110)
○ Median	84 (35 to 214)	139.5 (106 to 214)
○ 75th	278 (106, NE)	349 (202 to 349)
Time to Hospitalization for Worsening Respiratory Status from Core Baseline[a] to Final Visit		
Hospitalization secondary to worsening respiratory status		
• Patients with event	11 (34.4)	16 (28.6)
• Patients censored	21 (65.6)	40 (71.4)
• *P* value[e]	0.6881	
Time to hospitalization (days)		
• Min, Max	41, 344	41, 425
• Min, Max for non-censored patients	41, 302	41, 285
• Percentiles 95% CI)[c]		
○ 25th	239 (101, NE)	255 (172, NE)
○ Median	NE (302, NE)	NE
○ 75th	NE	NE
School/Work/Scheduled Activity Absence		
Missed At Least 1 Day of School, Work, or Scheduled Activity Secondary to Worsening Respiratory Status, n (%)	2 (6)	5 (9)
• Censored for this at end of study (day 336)	26 (81)	41 (73)
Absence, days		
• Mean (SD)	13.7 (62.10)	2.2 (7.72)
• Percentiles 95% CI)[c]		
○ 25th	NE	NE

	MPEX-209 Extension Study	
	TIS/LIS	**LIS/LIS**
○ Median	NE	NE
○ 75th	NE	NE
Weight		
Change in Weight From Core Baseline to Day 336/Final Visit, kg		
• Mean (SD)	1.1 (3.62)	0.6 (2.49)
Change in Weight From Extension Baseline (Day 168) to Day 336/Final Visit, kg		
• Mean (SD)	0.4 (2.53)	–0.4 (2.03)

CI = confidence interval; FEV_1 = forced expiratory volume in one second; HR = hazard ratio; LIS = levofloxacin inhalation solution; NE = not estimable; SD = standard deviation; TIS = tobramycin inhalation solution.
[a] Refers to baseline of original MPEX-209 study.
[b] Met at least 4 of 12 Fuchs symptoms.
[c] Kaplan-Meier estimates.
[d] Meeting symptoms requirements (patients must have had at least 1 of 4 worsening respiratory symptoms [increased cough, increased
sputum/chest congestion, decreased exercise tolerance, decreased appetite] at the time of administration of the antipseudomonal antimicrobial drug).[36]
[e] *P* value was determined using the Mantel-Haenszel test stratified by region (US, non-US), age (12 to 18 years, > 18 years), and baseline FEV_1
(< 55%, ≥ 55%).[36]
Source: MPEX-209 Extension Clinical Study Review.[36]

Safety Outcomes

During the extension phase, 92.9% and 96.9% of patients experienced at least one TEAE in the LIS/LIS and TIS/LIS groups, respectively. The most common TEAEs observed in both treatment groups included cough, disease progression, weight loss, respiratory tract congestion, and fatigue (Table 24). At least one SAE was observed in 25% of patients in both the LIS/LIS and TIS/LIS groups. The most common SAE was disease progression and was observed in both treatment groups (Table 24). No deaths occurred in the extension phase.

TABLE 24: HARMS (SAFETY POPULATION)

	MPEX-209 Extension	
	TIS/LIS	**LIS/LIS**
N	32	56
TEAEs		
• Patients with ≥ 1 TEAE during extension phase, n (%)	31 (96.9)	52 (92.9)
• Patients with ≥ 1 TEAE during extension phase treatment periods[a], n (%)	28 (87.5)	47 (83.9)
TEAEs in ≥ 5%[b] of patients in extension phase, n (%)		
• Cough	8 (25.0)	3 (5.4)
• Decreased appetite	2 (6.3)	5 (8.9)
• Disease progression	6 (18.8)	7 (12.5)
• Dysgeusia	7 (21.9)	1 (1.8)
• Dyspnea exertional	1 (3.1)	6 (10.7)
• Exercise tolerance decreased	2 (6.3)	6 (10.7)
• Fatigue	4 (12.5)	7 (12.5)
• FEV_1 decreased	3 (9.4)	4 (7.1)
• Hemoptysis	(3.1)	7 (12.5)
• Increased viscosity of bronchial secretion	3 (9.4)	3 (5.4)
• Nasopharyngitis	3 (9.4)	5 (8.9)
• Paranasal sinus hypersecretion	1 (3.1)	5 (8.9)

	MPEX-209 Extension	
	TIS/LIS	LIS/LIS
• Pyrexia	1(3.1)	4 (7.1)
• Pulmonary function test decreased	3 (9.4)	5 (8.9)
• Rales	1 (3.1)	6 (10.7)
• Rash	1 (3.1)	3 (5.4)
• Respiratory tract congestion	5 (15.6)	9 (16.1)
• Sinus headache	4 (12.5)	4 (7.1)
• Sputum discoloured	1 (3.1)	3 (5.4)
• Sputum increased	4 (12.5)	3 (5.4)
• Weight decreased	10 (31.3)	12 (21.4)
SAEs		
• Patients reporting ≥ 1 SAE during extension phase, n (%)	8 (25.0)	14 (25.0)
• Patients reporting ≥ 1 SAE during extension phase treatment periods[a], n (%)	2 (6.3)	5 (8.9)
SAEs in ≥ 1% of patients in extension phase, n (%)		
• Arnold-Chiari malformation	0	1 (1.8)
• Chest discomfort	1 (3.1)	0
• Disease progression	6 (18.8)	10 (17.9)
• Dyspnea	1 (3.1)	0
• FEV_1 decreased	1 (3.1)	0
• Nephrolithiasis	0	1 (1.8)
• Pneumonia	0	1 (1.8)
• Pneumothorax	0	1 (1.8)
• Pseudomeningocele	0	1 (1.8)
• Small intestinal obstruction	0	1 (1.8)
• Deaths	0	0

FEV_1 = forced expiratory volume in one second; LIS = levofloxacin inhalation solution; SAE = serious adverse events; TEAE = treatment-emergent adverse event; TIS = tobramycin inhalation solution.
[a] Treatment periods refer to those 28-day periods whereby the patient was receiving LIS.
[b] In at least one of the treatment groups.
Source: Clinical Study Report.[36]

Limitations

The main limitation inherent to this extension study is the lack of a control group. Of the 88 total patients who entered the extension phase, 83.9% of patients in the LIS/LIS group and 81.3% of patients in the TIS/LIS group completed the study; however, this was a small sample size (n = 88; n = 56 and n = 32 for the LIS/LIS and TIS/LIS groups, respectively) from the original cohort entering the core phase. While outcomes specific to CF were assessed in the extension phase, no definitive conclusions can be made due to the small number of patients who entered the extension phase and, most likely, who enriched the study population.

3. Summary

The clinical efficacy and safety results were similar in the LIS/LIS and TIS/LIS treatment groups. CF specific efficacy and safety outcomes were assessed; however, due to the small number of patients entering and potentially enriching the extension phase population, along with the uncontrolled nature of this phase, definitive conclusions regarding efficacy are not appropriate.

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity and minimal clinically important differences (MCID) of the following outcome measures:

- Cystic Fibrosis Questionnaire–Revised (CFQ-R)
- Cystic Fibrosis Respiratory Symptoms Weekly Diary (CFRSD)
- Forced expiratory volume in one second (FEV_1)

Findings

TABLE 25: VALIDITY AND MINIMAL CLINICALLY IMPORTANT DIFFERENCE OF OUTCOME MEASURES

Instrument	Type	Evidence of Validity	MCID	References

CFQ-R	Disease-specific QoL measure for patients with CF. Consists of 3 modules (which contain 12 domains/scales) of which scores are summed for a score between 0 and 100 (higher scores indicating better QoL):
	• General module
	  ○ Generic domain (physical functioning, energy, emotional, social limitations, role limitations)
	  ○ Disease-specific domain (body image, eating disturbances, treatment constraints)
	• Symptoms module with 3 symptom scales (respiratory, digestive, weight)
	• Health perception module
		Yes	• Stable disease = 4
			• Exacerbations = 8.5
				FDA[37]
				Modi et al.[38]
				Quittner et al.[39]
				Quittner et al.[24]
				Retsch-Bogart et al.[32]

CFRSD	16 item disease-specific QoL measure used to assess symptoms and impact of CF. There are 3 groups, of which questions are asked between 5:00 p.m. and bedtime each night and refer to the previous 24 hours:
	• Respiratory
	  ○ Breathing difficulty
	  ○ Cough
	  ○ Cough up mucus
	  ○ Chest tightness
	  ○ Wheeze
	• Presence of tiredness
	• Temperature
	  ○ Feeling feverish
	  ○ Presence of chills or sweats
	• Mood
	  ○ Sleeping difficulties
	  ○ Worried
	  ○ Cranky
	  ○ Sad or depressed
	  ○ Frustrated
		No	Not established	Bennett et al.[40]
				Goss et al.[41]

FEV_1	Establishes the severity of lung disease, converted to a percentage of predicted normal value (adjusted based on age, sex,	Yes	Not established	EMA[42] FDA[43] Miller et al.[23]

Instrument	Type	Evidence of Validity	MCID	References
	and body composition); • Normal or mild pulmonary dysfunction = ≥ 70% predicted • Moderate dysfunction = 40% to 69% predicted • Severe dysfunction = < 40% predicted			

CF = cystic fibrosis; CFQ-R = Cystic Fibrosis Questionnaire–Revised; CFRSD = Cystic Fibrosis Respiratory Symptoms Weekly Diary; EMA = European Medicines Agency; FDA = Food and Drug Administration; FEV_1 = forced expiratory volume in one second; MCID = minimal clinically important difference; QoL = quality of life.

Cystic Fibrosis Questionnaire–Revised (CFQ-R)

The CFQ-R is a disease-specific quality of life instrument designed for patients with CF, comprised of age appropriate versions for children 6 to 13 years old (CFQ-C) and their parents (for those who serve as a proxy for their child; CFQ-P), and individuals ≥ 14 years of age (CFQ-14).[44] It consists of three modules and its respiratory domain is listed in the Food and Drug Administration Clinical Outcome Assessment Compendium for assessing respiratory symptom severity:[37] The modules comprise a QoL module that contains both generic (physical functioning, energy, emotional, social limitations, role limitations) and disease-specific domains (body image, eating disturbances, treatment constraints), a symptoms module that includes three symptom scales (respiratory, digestive, and weight), and a health perception module. Items are summed to generate a domain score and are standardized; scores range from 0 to 100, with higher scores indicating better quality of life. The scales are designed to measure functioning during the two-week period before administration of the CFQ-R.[32] The studies eligible for inclusion in this report included those related to individuals 18 years of age and older; therefore, we have focused our discussion on the validity of the CFQ-14.

Several studies have evaluated the validity and reliability of the CFQ-R.[24,38,39] Quittner et al.[24] examined the psychometric properties of the CFQ-R using data from the Epidemiologic Study of CF, a national US multi-centre longitudinal cohort study containing CFQ-R and health outcomes data from 7,330 patients 6 to 70 years old. They reported adequate internal consistency (Cronbach alpha ≥ 0.70) for most domains and scales for each of the three versions. The CFQ-R was sensitive to changes in QoL associated with increasing disease severity (based on pulmonary function, FEV_1); this analysis was limited, however, since the CFQ-C had less variability in disease severity as few school-age children had a FEV_1 < 70% predicted. Quittner et al.[24] also reported fair to moderate agreement between the child and parent versions on all scales (intraclass correlation coefficient range, 0.26 to 0.56); however, stronger agreement was found on domains that measured more observable signs and symptoms, such as physical functioning, eating problems, and respiratory symptoms. There was fair to moderate convergence between CFQ-R scales and health outcomes, including percent predicted FEV_1 (correlation range, 0.25 to 0.51), number of pulmonary exacerbations treated with intravenous antibiotics (range: −0.23 to −0.35), and BMI (range: 0.22 to 0.44). The strongest correlations were demonstrated for the physical functioning and respiratory domains with percent predicted FEV_1 (range: 0.33 to 0.51 and 0.32 to 0.42, respectively) and for the weight scale and BMI (r = 0.42 and 0.44 on the CFQ-P and CFQ-14, respectively). Overall, the correlations were lower for the CFQ-C and CFQ-P versus the CFQ-14. Test-retest reliability was assessed previously (repeat administration over 14 days) and intraclass correlation coefficients were estimated to range from 0.45 to 0.90 on all scales.[38] The CFQ-R has also been validated in different countries.[45-47]

A previous study[38] also showed the CFQ-R correlated well with the SF-36. Correlations were moderate to strong (r = 0.42 to 0.57) between similar dimensions of the CFQ and SF-36 (physical, health perceptions/general health, vitality, role/role physical, emotional functioning/mental health, and social) and weak to moderate (r = 0.19 to 0.42) between scales not expected to be related (digestion and role scales of the CFQ and general health and mental health scales of the SF-36).

The MCID was estimated using the CFQ-R-Respiratory in two study populations: one of patients with stable cystic fibrosis (CF) and chronic *P. aeruginosa* airway infection; the other of patients with exacerbation of CF and chronic *P. aeruginosa* airway infection.[32] Both anchor-based and distribution-based methods were used. The MCID, based on the smallest change a patient could detect in terms of changes in respiratory symptoms, for patients with stable disease, was determined to be 4.0, and for patients with exacerbation, 8.5.[32]

The main limitations of the CFQ-R are ceiling effects for certain scales (notably the eating problems scale), potential difficulty for patients to understand some of the items (e.g., CFQ-R-Respiratory, item "trouble breathing"), and concerns that a patient may be unable to distinguish between some of the response items on the scale (e.g., response choices such as "somewhat" versus "a little").[24,43]

Cystic Fibrosis Respiratory Symptoms Weekly Diary

The CFRSD is a QoL outcome measure used to assess both the impact and symptoms of CF.[41] It is a daily patient diary that was developed from interviews with patients during times at which the patients were ill and in clinical care outside of their normal CF care.[41]The questionnaire consists of 16 items that assess three main areas of interest, including respiratory symptoms, impact on activity, and impact on emotions.[41] Specific items assessed with regard to symptoms include difficulty breathing, cough, coughing up mucus, chest tightness, wheezing, presence of fever, and presence of chills or sweats. Items assessing emotional impact include sleeping difficulties; if the patient is worried, cranky, sad or depressed, or frustrated; and items assessing impact on activity including how much time the patient spent sitting or lying down, whether the patient reduced their normal activity, and whether the patient missed work or school.[41] Response options include yes/no and, if yes, then it includes the following time aspects: a little bit of the time, some of the time, much of the time, and all of the time. Since there is a 24-hour recall associated with this questionnaire, the patient is instructed to complete it at the same time between 5:00 p.m. and before bed each night,[41] and each question starts with, "During the last 24 hours…."[41]Bennett et al.[40] sought to determine the correlation and concordance between the CFRSD used per indicated (24 hours) versus used at a seven-day time interval. A total of 77 diaries were analyzed, with 47 representing those completed while well and 30 representing those completed while ill. The authors determined that, upon using the weekly questionnaires, the scores were consistently slightly higher than the mean of the daily reports and both versions were comparably able to detect item score differences between periods of ill-health and periods of good-health.[40] However, it should be noted that the full CFRSD was not used in this study, as the three items relating to impact of CF on activity were excluded.[40] Also, the recommended administration of the CFRSD has not changed based on the study results; the CFRSD manual recommends nightly completion of the diary.

As of September 2012, the EMA[48] had deemed the CFRSD unavailable as an outcome parameter for clinical trials. The FDA is awaiting validation from the authors who were assessing the validity of pooled data from five studies (N = 400) of patients with CF.[37,48] Validation studies were not identified in a supplemental search completed in 2016 for this outcome parameter. In addition, no MCID was identified from applicable literature search results.

Forced Expiratory Volume in One Second (FEV_1)

FEV_1 is the maximal amount of air forcefully exhaled in one second, expressed in litres.[23] The measured volume is converted to a percentage of predicted normal value, which is adjusted based on age, sex, and body composition.[23] FEV_1 is used to establish the severity of lung disease (normal or mild pulmonary dysfunction, ≥ 70% predicted; moderate dysfunction, 40% to 69% predicted; and severe dysfunction, < 40% predicted), tracking changes in lung function over time, and in evaluating the effectiveness of therapeutic interventions in lung diseases.[23,42]

FEV_1 is a commonly used end point for clinical trials of obstructive lung diseases including CF[43] and is the preferred end point in the EMA guidance document on the development of therapeutic drugs for CF, based on the fact that the main pulmonary defect in CF is obstructive.[42] The FDA also recommends FEV_1 for assessment of lung function in studies evaluating the treatment of CF.[37] FEV_1 has been shown to relate to morbidity, disease progression, and mortality in CF, making it a meaningful surrogate marker for survival.[43]

However, there are limitations with the use of FEV_1 for patients with CF. These are as follows:

- The manoeuvre required to assess FEV_1 is highly dependent on patient cooperation and effort:
  - The test (spirometry) should be repeated at least three times to ensure reproducibility.[23]
  - Spirometry can only be used on children old enough to comprehend and follow the instructions given (6 years old or older), and only on patients who are able to understand and follow instructions.[42,43]
  - FEV_1 can generally only be underestimated. The only exception in which FEV_1 can be overestimated is in individuals with some diseases where a softer exhalation can reduce the spasm or collapse of lung tissue, thereby artificially elevating the measure.
- FEV_1 decline is only meaningful over time and is subject to seasonal and environmental effects.[43]
- There are no published data on the magnitude of change in FEV_1 that is clinically meaningful.[43]
- CF is a multi-organ disease and FEV_1 only measures lung health.[43]
- FEV_1 improvement has a ceiling effect for patients with mild lung impairment.[43]
- There are no published MCIDs for FEV_1 in patients with CF.

The European Medicines Agency suggests a study duration of six months for the demonstration of efficacy on respiratory function (based on repeated measurements of FEV_1) with a 12-month follow-up for safety.[42]

Conclusion

FEV_1 and CFQ-R are commonly used, validated, and reliable outcome measures in clinical trials of patients with CF. The reported MCID for the CFQ-R-Respiratory symptom scale varies from 4.0 to 8.5, depending on patient disease status (stable versus acute exacerbation, respectively). The CFRSD is an outcome measure reporting on the symptoms and impacts of CF that have yet to be validated. In addition, the CFRSD does not have an established MCID.

APPENDIX 6: SUMMARY OF INDIRECT COMPARISONS

A1.1 Introduction

A1.1.1 Background

There is limited direct evidence on the efficacy of levofloxacin inhalation solution (LIS) versus existing inhaled antimicrobial therapies as the manufacturer only submitted one study that evaluated non-inferiority of LIS 240 mg versus tobramycin inhaled solution (TIS) 300 mg.

The aim of this section is to identify, summarize, and critically appraise indirect treatment comparisons (ITCs) that provide evidence for the efficacy and harms of LIS versus other inhaled antimicrobial therapies for the management of CF patients chronically infected with *Pseudomonas aeruginosa (P. aeruginosa)*.

A1.1.2 Methods

Two network meta-analyses (NMAs) submitted by the manufacturer were reviewed and critically appraised. In addition, a comprehensive literature search was performed by an information specialist to identify published NMAs.

A1.2 Description of ITCs Identified

A supplemental literature search conducted by the CADTH Common Drug Review (CDR) did not identify any published NMAs or any NMAs in the grey literature. Therefore, the following is a summary and critical appraisal of the two manufacturer–provided NMAs.

A1.3 Review and Appraisal of ITCs

A1.1.3 Review of the manufacturer's ITCs

Objectives and rationale for manufacturer's ITCs

Both of the manufacturer's NMAs aimed to determine the relative efficacy and safety of LIS compared with other inhaled antimicrobial therapies for the treatment of patients with CF who were chronically infected with *P. aeruginosa*.

A1.1.4 Methods for manufacturer's ITCs

Study eligibility and selection process

Studies were eligible for inclusion in both NMAs if they had the following characteristics:

- The patient population in the study was patients with CF who were ≥ 6 years old and had chronic *P. aeruginosa* infections.
- The study intervention was any inhaled antibiotic, at any dose, using any method of delivery (i.e., LIS, TIS, colistimethate sodium, or aztreonam).
- The comparators were TIS, colistimethate sodium, aztreonam, or placebo.
- The outcomes measured changes in pulmonary function, pulmonary exacerbations, AEs, and health-related quality of life.
- A published or unpublished randomized controlled trial (RCT).

The 24-week NMA included studies with study duration of ≥ 20 weeks; whereas, the 4-week NMA only included studies with study duration of ≥ 4 weeks. The 4-week study also restricted the eligible population to those with a baseline mean FEV_1% predicted of < 70% among those who had never used an inhaled antibiotic, and a baseline mean FEV_1% predicted of ≥ 70% among patients previously treated by inhaled antibiotics.

The same literature search strategy was used for both of the manufacturer's NMAs. The literature search was restricted to the English language. The search strategy was conducted using two databases: Embase and MEDLINE. In addition to the RCTs identified in the search, systematic reviews identified in the search were retrieved and their lists of references were screened for potential articles for inclusion. Unpublished data from Clinical Study Reports held by the manufacturer (Raptor Pharmaceuticals) were also included for LIS.

The titles and abstracts of retrieved citations were screened against the inclusion and exclusion criteria by two independent reviewers. The full-text citations included after the initial screening were screened again against the inclusion and exclusion criteria by two independent reviewers. Disagreement between reviewers was resolved by consensus as stated in the report.

Data extraction

No information was provided on the number of reviewers conducting the data extraction for both manufacturer–provided NMAs; however, the manufacturer clarified following comments on the review that one reviewer did the initial extraction while a second reviewer performed a quality check of the extraction. Data were extracted into a specifically designed data extraction form, which was validated on three randomly selected included studies. Deviation information was also extracted in order to estimate missing standard deviations.

Comparators

For both manufacturer NMAs, comparators of interest were all available inhaled antibiotic treatments administered by any method of delivery for the management of CF patients chronically infected with *P. aeruginosa,* which are:

- TIS
- colistimethate sodium
- aztreonoam
- levofloxacin.

Outcomes

The following outcomes were collected at 4 weeks and at 24 weeks for the 4-week NMA and the 24-week NMA, respectively:

- relative change in FEV_1% predicted
- absolute change in FEV_1% predicted
- change in sputum *P. aeruginosa* density
- Cystic Fibrosis Questionnaire–Revised respiratory symptoms score
- hospitalization
- additional antibiotic use (any route of administration)
- withdrawal for any reason
- withdrawal for lack of efficacy
- withdrawal for any AEs.

Quality assessment of included studies

In both manufacturer NMAs, quality assessment of individual papers was performed using the Cochrane Risk of Bias Tool by one reviewer. Randomization, blinding, and adequacy of analyses were focused on. A second reviewer reviewed the first reviewer's analysis, and disagreements were resolved by consensus between the two reviewers. It was not reported if and/or how study quality was used in the analysis (e.g., whether poor quality studies were excluded or were sensitivity analyses performed based on study quality). The manufacturer clarified in its comments on CDR report that poor quality studies could not be removed in a sensitivity analysis as this would result in a network that could not include LIS because the MPEX studies would have been removed as they were considered as high risk / unclear risk following the Cochrane risk of bias assessment.

A1.1.5 ITC Methods

For both NMAs, a network meta-analysis was conducted using a Bayesian approach through a Markov Chain Monte Carlo method. In the four-week NMA, certain outcomes did not have enough trials to form a network. For these specific outcomes, no description of the approach for analyzing direct or indirect comparisons was given. However, the results for these outcomes reported a confidence interval instead of a credible interval, so it appears that a frequentist approach was taken. ITC (two trials with a common comparator) was performed when the network did not permit an NMA.

Non-informative priors were chosen for the analysis. The Brooks-Gelman-Rubin diagnostic tool and the inspection of the auto-correlation were used to assess for convergence. An initial burn-in of 100, 000 iterations was discarded, and the results were based on a further 350,000 iterations.

The deviance information criterion and the posterior mean residual deviance were used to assess model fit. A fixed-effects model was used for all outcomes in the 24-week NMA. In the 4-week NMA, all outcomes were analyzed using a fixed-effects model, except for absolute and relative change in FEV_1% predicted, which used a random effects model. Use of a fixed-effects model was rationalized as being due to insufficient trials per comparison in order to establish the random effects model. The transitivity assumption and the similarity assumption were defined but not assessed. Direct and indirect evidence were not compared due to a lack of closed loops involving different studies existing in the NMAs. The authors did not explicitly report comparing the NMA estimates with the results from the individual trials in terms of direction and magnitude. No meta-regression or sensitivity analyses were reported.

A1.1.6 Results

Included studies characteristics

A total of 12 articles describing nine RCTs were included in the 4-week NMA analysis. Six trials included TIS as a treatment comparator, LIS was assessed in 3 trials, aztreonam nebulizer solution in 2 trials, and tobramycin inhalation powder and colistimethate sodium (parenteral powder or solution) in one trial each (Table 26). Tobramycin inhalation solution was the central link for the network. The majority of trials used dosing cycles of 28 days on treatment, followed by 28 days off treatment, except for one trial with colistimethate sodium powder, in which all patients took colistimethate sodium powder daily with no off-treatment period. Only one trial was single-centre; the other 8 trials were multi-centre. The majority of trials were conducted in North America (66.7%) and Europe (55.6%). A small number of included patients were from centres in Israel. None of the trials were conducted in Asia.

TABLE 26: SUMMARY OF THE TRIALS INCLUDED IN THE MANUFACTURER'S NETWORK META-ANALYSES

Trials	Intervention/ Comparator	N	Double Blind/ Open Label	Population Age	Duration (Weeks)	Treatment Schedule
Levofloxacin Trials						
MPEX-204[a]	LIS 120 mg q.d. LIS 240 mg q.d. LIS 240 mg b.i.d. Placebo	151	Double blind	≥ 16 years	8	1 cycle of 28 days on treatment, then 28 days off
MPEX-207[a]	LIS 240 mg b.i.d. Placebo	330	Double blind	≥ 12 years ≥ 18 years (adult subgroup)	8	1 cycle of 28 days on treatment, then 28 days off
MPEX-209[a, b]	LIS 240 mg b.i.d. TIS 300 mg b.i.d.	282	Open label	≥ 12 years ≥ 18 years (adult subgroup)	24	3 cycles of 28 days on treatment, then 28 days off
Tobramycin Trials						
Ramsay, 1999[b]	TIS 300 mg b.i.d. Placebo	520	Double blind	≥ 6 years ≥ 18 years (adult subgroup)	24	3 cycles of 28 days on treatment, then 28 days off
Chuchalin, 2007[b]	TIS 300 mg b.i.d. Placebo	247	Double blind	≥ 6 years	24	3 cycles of 28 days on treatment, then 28 days off
Hodson, 2002[a]	TIS 300 mg b.i.d. CIS 80 mg b.i.d.	126	Open label	≥ 6 years ≥ 18 years (adult subgroup)	8	b.i.d. for 4 weeks, then 4 weeks follow-up
Nasr, 2010[a, b]	TIS 300 mg b.i.d. Placebo	32	Double blind	≥ 6 years	24	3 cycles of 28 days on treatment, then 28 days off
EAGER[a, b]	TIP 112 mg b.i.d. TIS 300 mg b.i.d.	553	Open label	≥ 6 years ≥ 20 years (adult subgroup)	24	3 cycles of 28 days on treatment, then 28 days off
Aztreonam Trials						
McCoy, 2008[a]	AIS 75 mg b.i.d. AIS 75 mg t.i.d. Placebo	246	Double blind	≥ 6 years ≥ 18 years (adult subgroup)	12	b.i.d. or t.i.d. for 4 weeks, then 8 weeks follow-up
Assael, 2013[a, b]	AIS 75 mg t.i.d. TIS 300 mg b.i.d.	273	Open label	≥ 6 years	24	3 cycles of 28 days on treatment, then 28 days off
Colistimethate Trials						
FREEDOM[a, b]	CIP 1,662,500 IU b.i.d. TIS 300 mg b.i.d.	380	Open label	≥ 6 years	24	CIP: continuous TIS: 3 cycles of 28 days on treatment, then 28 days off

b.i.d. = twice daily; CIP = colistimethate sodium inhalation powder; CIS = colistimethate sodium inhalation solution; IU = international units; LIS = levofloxacin inhalation solution; q.d. = once daily; t.i.d. = three times daily; TIP = tobramycin inhalation powder; TIS = tobramycin inhalation solution.

[a] Included in the 4-week NMA.

[b] Included in the 24-week NMA.

Source: Manufacturer's submission.[11]

The manufacturer's NMA stated that the heterogeneity of patient populations in the 4-week NMA was difficult to assess, partially due to unreported data from the individual trials for characteristics such as body mass index (BMI), concomitant medications, and previous antibiotic use. Pooled results of the patient characteristics were not provided. The mean age, FEV_1% predicted, and BMI across trials (with reported characteristics) had a range of approximately 20 to 30 years old, 50% to 55% predicted, and

18.5 kg/m^2 to 22.5 kg/m^2, respectively. One trial had mean age and FEV_1% predicted outside the aforementioned ranges, with a mean age and FEV_1% predicted of 11.81 and 15.86 years old, and 95.73% and 83.71% predicted, respectively, in its two treatment groups.

The risk of bias of the studies was heterogeneous. The majority of the trials had unclear or high risk of bias due to allocation concealment, blinding of participants and personnel, and detection bias for patient–reported outcomes and mortality.

In the 24-week NMA analysis, a total of 9 articles describing 7 RCTs were included. Many of the trials included in the 4-week analysis were also included in the 24-week one. All 7 trials used TIS as a treatment group, and as a result, the central link for the network was TIS. LIS, aztreonam nebulizer solution, tobramycin inhalation powder, and colistimethate sodium inhaler powder were assessed in 1 trial each (Table 26). The majority of trials used dosing cycles of 28 days on treatment, followed by 28 days off treatment, except for one trial with colistimethate sodium powder, in which all patients took colistimethate sodium powder daily with no off-treatment period. Only one trial was single-centre. The majority of studies had centres located in North America (57%), and Europe (57%). No trials were conducted in Asia, and one trial had a small number of patients (4%) from centres in Israel.

Similar to the 4-week NMA, several patient characteristics were not reported from the individual trials included in the 24-week analysis, such as BMI, concomitant medications, and previous antibiotic use. Pooled results of the patient characteristics were not provided. The mean age, BMI, and FEV_1% predicted were similar to those in the 4-week NMA, with the exception of two trials. One of these trials is the same trial as the one exception in the 4-week NMA. The second trial had a younger population (mean age of approximately 14.8 years), lower BMI, (mean of approximately 16.9 kg/m^2), and slightly higher FEV_1% predicted (mean approximately 61.5% predicted).

Relative FEV_1% predicted change from baseline

Seven trials in the 4-week NMA and 4 trials in the 24-week NMA reported the relative FEV_1% predicted change from baseline outcome. At 4 and 24 weeks, when compared with other active comparators, LIS was not associated with a statistically significant improvement in change from baseline of relative FEV_1% (Table 27). The 4-week NMA used a random-effects model, but the 24-week NMA used a fixed-effects model, citing too low trial numbers to use random effects modelling. There were no data comparing LIS with colistimethate inhaled solution at 24 weeks.

TABLE 27: RESULTS OF RELATIVE FEV1% PREDICTED CHANGE FROM BASELINE TO 4 AND 24 WEEKS

Baseline to 4 weeks (random-effects model)		
Comparator (A)	**Treatment (B)**	**Mean Difference (95% CrI)**
TIS	LIS	–1.870 (–9.476 to 5.752)
Aztreonam 75 mg t.i.d.	LIS	5.921 (–4.796 to 16.610)
Colistimethate sodium inhaled solution	LIS	–8.166 (–20.180 to 3.839)
Placebo	LIS	–5.283 (–11.550 to 0.130)
TIP	LIS	–2.660 (–14.470 to 9.068)
Baseline to 24 weeks (fixed-effects model)		
TIS	LIS	–0.553 (–3.906 to 2.799)
Aztreonam 75 mg t.i.d.	LIS	–2.356 (–7.321 to 2.626)
Placebo	LIS	–9.660 (–15.010 to –4.330)
TIP	LIS	–2.951 (–10.44 to 4.507)

CrI = credible interval; FEV_1 = forced expiratory volume in one second; LIS = levofloxacin inhaled solution; t.i.d. = three times a day; TIP = tobramycin inhaled powder; TIS = tobramycin inhaled solution.
Source: Manufacturer's submission.[11]

Absolute FEV_1% predicted change from baseline

In the 4-week NMA, 5 trials assessed the absolute FEV_1% predicted change from baseline. In the 24-week NMA, this outcome was assessed in four trials. Similar to the relative FEV_1% predicted outcome, the 4-week NMA used a random effects model, while the 24-week NMA used a fixed-effects model. There were no data comparing LIS with colistimethate sodium inhalation solution or tobramycin inhalation powder in either NMA. LIS was not associated with a statistically significant benefit over any of the active comparators in either NMA (Table 28).

TABLE 28: RESULTS OF ABSOLUTE FEV_1% PREDICTED CHANGE FROM BASELINE TO 4 AND 24 WEEKS

Baseline to 4 weeks (random-effects model)		
Comparator (A)	**Treatment (B)**	**Mean difference (95% CrI)**
TIS	LIS	–1.039 (–7.387 to 5.291)
Aztreonam 75 mg t.i.d.	LIS	2.241 (–6.936 to 11.440)
Colistimethate sodium inhaler	LIS	–2.456 (–11.440 to 6.511)
Placebo	LIS	–2.680 (–7.487 to 1.756)
Baseline to 24 weeks (fixed-effects model)		
TIS	LIS	0.278 (–1.361 to 1.917)
Aztreonam 75 mg t.i.d.	LIS	–0.653 (–3.117 to 1.819)
Colistimethate Sodium Inhaler	LIS	–1.492 (–3.686 to 0.699)
Placebo	LIS	–6.431 (–8.842 to –4.022)

CrI = credible interval; FEV_1 = forced expiratory volume in one second; LIS = levofloxacin inhaled solution; t.i.d. = three times a day; TIS = tobramycin inhaled solution.
Source: Manufacturer's submission.[11]

P. aeruginosa density change from baseline

In the 4-week and 24-week NMA, 7 and 3 trials, respectively, assessed *P. aeruginosa* sputum density change from baseline. A fixed-effects model was used in both NMAs. There were no statistically significant differences seen between LIS and the other inhaled antibiotics in the 4-week or 24-week NMAs (Table 29). However, the only comparators assessed in the 24-week NMA were placebo and tobramycin inhalation solution and powder.

TABLE 29: RESULTS OF P. AERUGINOSA DENSITY CHANGE FROM BASELINE TO 4 AND 24 WEEKS

Baseline to 4 weeks (fixed-effects model)		
Comparator (A)	**Treatment (B)**	**Mean Difference (95% CrI)**
TIS	LIS	–0.150 (–0.659 to 0.358)
TIP	LIS	–0.610 (–1.562 to 0.336)
Aztreonam 75 mg b.i.d.	LIS	–0.076 (–0.682 to 0.531)
Aztreonam 75 mg t.i.d.	LIS	–0.095 (–0.622 to 0.433)
Colistimethate sodium inhalation solution	LIS	0.111 (–0.672 to 0.894)
Placebo	LIS	0.643 (0.309 to 0.977)
Baseline to 24 weeks (fixed-effects model)		
TIS	LIS	–0.180 (–0.688 to 0.329)
TIP	LIS	–0.589 (–1.41 to 0.231)
Placebo	LIS	0.221 (–0.36 to 0.802)

CrI = credible interval; FEV_1 = forced expiratory volume in one second; LIS = levofloxacin inhaled solution; t.i.d. = three times a day; TIP = tobramycin inhaled powder; TIS = tobramycin inhaled solution.
Source: Manufacturer's submission.[11]

CFQ-R RSS change from baseline

Five trials assessed the change in CFQ-R Respiratory Symptom Scale from baseline in the 4-week NMA, while only one trial assessed this outcome in the 24-week NMA (Table 30). As a result, a NMA was not conducted in the 24-week NMA for this outcome. A fixed-effects model was used. A statistically significant association was not found between LIS and any comparator for the CFQ-R Respiratory Symptom Scale change outcome.

TABLE 30: RESULTS OF CFQ-R RSS CHANGE FROM BASELINE TO 4 AND 24 WEEKS

Baseline to 4 weeks (fixed-effects model)		
Comparator (A)	**Treatment (B)**	**Mean Difference (95% CrI)**
TIS	LIS	–3.107 (–6.646 to 0.418)
Aztreonam 75 mg b.i.d.	LIS	2.599 (–1.745 to 6.949)
Aztreonam 75 mg t.i.d.	LIS	4.658 (–0.213 to 9.541)
Placebo	LIS	–1.070 (-4.003 to 1.870)

b.i.d. = twice daily; CFQ-R RSS = Cystic Fibrosis Questionnaire–Revised Respiratory Symptom Scale; CrI = credible interval; LIS = levofloxacin inhaled solution; t.i.d. = three times a day; TIS = tobramycin inhaled solution.
Source: Manufacturer's submission.[11]

Hospitalization

The 4-week NMA had two trials included in the analysis for hospitalizations. Given the number of trials, an indirect comparison was conducted instead of an NMA with placebo as the common comparator. The 24-week NMA included four trials and an NMA was conducted. The indirect comparison in the 4-week analysis only had results for LIS versus aztreonam (twice daily and three times daily dosing): no statistically significant difference between these treatments in the proportion of patients hospitalized was found (Table 31). The 24-week NMA only had results for placebo and TIS and powder. The 24-week NMA found that the comparators, TIS, tobramycin inhalation powder, and placebo, all had a statistically significant higher odds of hospitalization occurrence than LIS (Table 31).

TABLE 31: RESULTS OF HOSPITALIZATION OCCURRENCE AT 4 AND 24 WEEKS

Baseline to 4 weeks (indirect comparison)		
Comparator (A)	**Treatment (B)**	**RR (95% CI)**
Aztreonam 75 mg b.i.d.	LIS	1.664 (0.081 to 34.299)
Aztreonam 75 mg t.i.d.	LIS	0.955 (0.051 to 18.057)
Baseline to 24 weeks (fixed-effects model)		**OR (95% CrI)**
TIS	LIS	1.920 (1.012 to 3.304)
Tobramycin inhalation powder	LIS	2.247 (1.014 to 4.338)
Placebo	LIS	3.158 (1.531 to 5.784)

b.i.d. = twice daily; CI = confidence interval; CrI = credible interval; LIS = levofloxacin inhaled solution; OR = odds ratio; RR = relative risk; t.i.d. = three times a day; TIS = tobramycin inhaled solution.
Source: Manufacturer's submission.[11]

Additional antibiotic use

Five trials assessed the rate of additional antibiotic use in both the 4-week and 24-week NMAs. The definitions considered as additional antibiotic use were similar between trials, mostly limited to the receipt of additional intravenous or inhaled antipseudomonal antibiotics. A fixed-effects model was used in both NMAs. TIS had a statistically significantly increased odds of 2.187 (95% CrI, 1.034 to 4.077) versus LIS for receiving additional antibiotics at 4 weeks (Table 32). Other comparators were not found to be statistically significantly different compared with LIS, though tobramycin inhalation powder and colistimethate were not assessed (Table 32). At 24 weeks, tobramycin inhalation powder was also associated with a statistically significantly increased OR of requiring additional antibiotics compared with LIS (OR 2.566 [95% CrI, 1.279 to 4.653]) (Table 32).

TABLE 32: RESULTS OF ADDITIONAL ANTIBIOTIC USE AT 4 AND 24 WEEKS

Baseline to 4 weeks (fixed-effects model)		
Comparator (A)	**Treatment (B)**	**OR (95% CrI)**
TIS	LIS	2.187 (1.034 to 4.077)
Aztreonam 75 mg t.i.d.	LIS	0.721 (0.198 to 1.830)
Placebo	LIS	1.043 (0.560 to 1.762)
Baseline to 24 weeks (fixed-effects model)		**OR (95% CrI)**
TIS	LIS	1.632 (0.929 to 2.699)
Tobramycin inhalation powder	LIS	2.566 (1.279 to 4.653)
Aztreonam 75 mg t.i.d.	LIS	0.763 (0.346 to 1.473)
Placebo	LIS	2.859 (1.487 to 5.030)

CrI = credible interval; LIS = levofloxacin inhaled solution; OR = odds ratio; t.i.d. = three times a day; TIS = tobramycin inhaled solution.
Source: Manufacturer's submission.[11]

Withdrawal for any reason

Three trials assessed the proportion of patients who withdrew from the study for any reason in the 4-week NMA, while all 7 trials included in the 24-week NMA assessed the outcome. The three trials eligible for the 4-week analysis compared LIS versus placebo (2 studies) or TIS with colistimethate sodium inhaled solution. A link could not be made between the LIS studies and the TIS and colistimethate study, so the manufacturer conducted a direct pairwise meta-analysis of LIS versus placebo instead of an NMA. The meta-analysis did not find a statistically significant difference between LIS and placebo in the withdrawal rate due to any reason (Table 33).

A NMA, using a fixed-effects model, was conducted in the 24-week NMA. No statistically significant results were found in any of the comparisons between LIS and the other inhaled antibiotics and placebo with respect to withdrawals due to any reason (Table 33).

TABLE 33: RESULTS OF WITHDRAWAL RATE FOR ANY REASONS AT 4 AND 24 WEEKS

Baseline to 4 weeks (direct comparison)		
Comparator (A)	**Treatment (B)**	**RR (95% CI)**
Placebo	LIS	0.416 (0.111 to 1.557)
Baseline to 24 weeks (fixed-effects model)		**OR (95% CrI)**
TIS	LIS	0.921 (0.371 to 1.849)
Tobramycin inhalation powder	LIS	1.576 (0.558 to 3.469)
Aztreonam 75 mg t.i.d.	LIS	0.513 (0.151 to 1.268)
Colistimethate sodium inhaler	LIS	1.656 (0.528 to 3.904)
Placebo	LIS	1.310 (0.448 to 2.946)

CI = confidence interval; CrI = credible interval; LIS = levofloxacin inhaled solution; OR = odds ratio; RR = relative risk; t.i.d. = three times a day; TIS = tobramycin inhaled solution.
Source: Manufacturer's submission.[11]

Withdrawal for lack of efficacy

No trials with LIS as a comparator reported withdrawal rate for lack of efficacy in both 4-week and 24-week NMAs. As a result, no analyses were performed for this outcome.

Withdrawal for any adverse events

As with the analysis for withdrawal due to any reason, only a direct pairwise meta-analysis could be conducted comparing LIS versus placebo in the 4-week NMA set. The meta-analysis did not find a statistically significant difference between LIS and placebo in the withdrawal rate due to any AEs. Five trials were included in the 24-week NMA (fixed-effects model) and no statistically significant differences were found between LIS and the other inhaled antibiotics with respect to withdrawal due to any AEs (Table 34).

TABLE 34: RESULTS OF WITHDRAWAL RATE FOR ADVERSE EVENTS AT 4 AND 24 WEEKS

Baseline to 4 weeks (direct comparison)		
Comparator (A)	**Treatment (B)**	**RR (95% CI)**
Placebo	LIS	0.763 (0.182 to 3.204)
Baseline to 24 weeks (fixed-effects model)		**OR (95% CrI)**
TIS	LIS	0.400 (0.008 to 1.717)
Tobramycin inhalation powder	LIS	0.720 (0.014 to 3.258)
Aztreonam 75 mg t.i.d.	LIS	0.289 (0.003 to 1.591)
Colistimethate sodium inhaler	LIS	4.096 (0.054 to 21.910)
Placebo	LIS	0.258 (0.000 to 1.838)

CI = confidence interval; CrI = credible interval; LIS = levofloxacin inhaled solution; OR = odds ratio; RR = relative risk; t.i.d. = three times a day; TIS = tobramycin inhaled solution.
Source: Manufacturer's submission.[11]

A5.3.5 Critical Appraisal

Multiple databases were searched for eligible trials for inclusion, and search strategies were reported. In addition, the evidence for LIS included in the NMA came from manufacturer reports that have not been peer-reviewed, whereas the other included studies were peer-reviewed publications. As a result, the

information contained in the LIS reports has not received the same amount of scrutiny as the other studies.

Methodological strengths of the NMAs include number of burn-ins, the number of iterations, evaluation of convergence, and using non-informative priors.

There was heterogeneity in the design of the included studies. Almost half of the included trials used open-label designs and are at risk for associated biases, particularly related to withdrawal and quality of life assessments. As well, trials with non-inferiority designs were included. Despite the heterogeneity that existed across the included studies, there was no formal assessment of consistency between direct and indirect comparisons before conducting the NMA, although the absence of closed loops in the network precludes such assessment. In addition, the potential impact of heterogeneity on the results was not assessed through sensitivity or other analyses; however, there may have been an insufficient sample size and such analyses may have led to LIS being excluded. Risk of bias was assessed and reported, and it was found that at least half the trials in both NMAs had unclear or high risk of bias across several categories, including allocation concealment, blinding, and detection bias. Despite measuring risk of bias, the authors did not use this information to examine the potential impact of including lower quality studies in the analysis. The manufacturer clarified in its comments on the CDR report that poor quality studies could not be removed in a sensitivity analysis as this would result in a network that could not include LIS because the MPEX studies would have been removed as they were considered as high or unclear risk following the Cochrane risk of bias assessment. Due to several factors that indicate the included studies had high risk of bias and unclear quality, as well as the lack of evaluation of consistency across direct and indirect comparisons, attempting to draw conclusions from the NMA's results is difficult.

The majority of the included studies enrolled patients ranging from children or adolescents (i.e., ≥ 6 or 12 years old) to adults. Some studies that included mixed-age populations were identified as having adult subgroups. Notably, with the exception of a couple of trials, the range of mean age between the trials was 20 to 30 years old; however, the standard deviations of the means ranged from approximately 5 to 10 years. Levofloxacin is approved by Health Canada for adult patients with CF ≥ 18 years old. Neither of the NMAs assessed the data in terms of subgroups or regression by age, which may act as an effect modifier given the association between age, disease progression, and *P. aeruginosa* lung infection in patients with CF. As mentioned, however, the limited number of studies and sparse network likely precluded sensitivity, subgroup, and meta-regression analyses. The generalizability of the results to the target population for levofloxacin based on the Health Canada indication — adult patients — is also uncertain.

The trials included in the NMAs also had inconsistent reporting of baseline characteristics, in particular previous exposure to antipseudomonal antibiotics and concurrent treatments for CF. As a result, it was not possible to assess whether there were differences in potential effect modifiers. Heterogeneity associated with this incomplete information is likely important and was not accounted for in the NMAs. Moreover, it is difficult to generalize the results of the NMAs to the Canadian CF population.

Two of the included trials used inhaled colistimethate, which is not an approved route of administration for colistimethate in Canada, although it is used in certain patient populations (e.g., those with multi-drug resistant *P. aeruginosa*).

The outcomes assessed in the NMAs were generally clinically relevant; however, pulmonary exacerbations and AEs (serious and non-serious) were not evaluated, but were key outcomes identified for the CDR review of levofloxacin. The manufacturer reported that because of large variations in the definition of pulmonary exacerbation across trials, hospitalizations and need for additional antibiotics were used as surrogates for pulmonary exacerbations. However, the hospitalization and added antibiotic outcome definitions across trials were heterogeneous and, as the manufacturer rightly notes, the comparability of results between trials is "questionable." For example, the definition of hospitalization across included studies included any hospitalization, hospitalization only due to SAEs, and hospitalization only due to worsening of respiratory status. Hence, the degree to which hospitalizations and the addition of antibiotics were appropriate proxies for pulmonary exacerbations and the interpretability of these outcomes from the NMA are highly uncertain.

As for AEs, only withdrawals due to any AEs were analyzed as an outcome. Sparse networks and the aforementioned potential limitation regarding study withdrawal data related to open-label designs means there is uncertainty as to the comparative safety of levofloxacin versus other inhaled antipseudomonal antibiotics.

A fixed-effects model was used for the majority of the analyses in the 4-week NMA, and for all the analyses in the 24-week NMA. This was rationalized as being due to a small number of trials available for analysis. However, using a fixed-effects model, as opposed to a random effects model, makes a key assumption that one true treatment effect exists, and that differences in treatment effect are not due to population characteristic differences (i.e., effect modifiers). As detailed previously, several potential sources for non-negligible heterogeneity were identified. Also, inconsistent reporting of important baseline characteristics from the trials adds to the uncertainty of heterogeneity. These methodological issues raise uncertainty regarding the fixed-effects model comparisons made between LIS and other inhaled antibiotics.

A5.4 Conclusion

Overall, the indirect evidence suggests that LIS is not statistically significantly different with respect to efficacy or safety relative to inhaled tobramycin, aztreonam, and colistin in treating patients with CF and chronic *P. aeruginosa* lung infection. However, there are a number of important limitations that make it difficult to conclude that there is no difference in treatment effects between the inhaled antibiotics. As a result, the three major assumptions of NMA — homogeneity, transitivity, and consistency — have not been clearly and explicitly met or addressed. It is noted that limitations in the available evidence may have precluded analyses to address these key components.

Both manufacturers' NMAs conclude that levofloxacin appears to be equally effective and safe relative to other antipseudomonal antibiotics at 4 and 24 weeks. It is important to note that neither NMA analyzed the results in terms of non-inferiority or equivalence. Though the results imply that little to no difference exists between levofloxacin and other antipseudomonal inhaled antibiotics based on the lack of statistical significance in most of the comparisons, several important limitations make it difficult to be certain of this conclusion.

APPENDIX 7: SUMMARY OF PRODUCT INHALATION DEVICES

Aim

To describe the characteristics regarding ease of use and correct use, as well as patient satisfaction with the Quinsair Zirela Nebulizer Handset, Tobi PARI LC Plus reusable nebulizer with a DeVilbiss Pulmo-Aide compressor, Tobi Podhaler, and Cayston Altera Nebulizer System.

Findings

The characteristics of the product-specific inhalation devices are summarized below:

Characteristics of the Inhalation Devices

Levofloxacin (Quinsair) is delivered with the Zirela Nebulizer Handset device, which is connected to an eBase Controller or an eFlow Rapid Control Unit.[13] One full ampule can be emptied into the Zirela Nebulizer Handset.[13] Each single-use ampule consists of and delivers to the patient 2.4 mL levofloxacin hemihydrate, equivalent to 240 mg of levofloxacin.[13] The solution should be a clear, yellow liquid.[13] In order to administer a dose, the patient must first assemble the Zirela Nebulizer Handset.[13] The device does not need to be plugged into an electrical outlet to operate.[13] Upon turning on the controller, a green light will appear letting the patient know the device is on.[13] A mist should appear in the aerosol chamber to indicate that the device is ready to be used.[13] After 5 to 7 minutes, the medicine should have been fully delivered and the patient will hear two beep sounds.[13] The patient can ensure that the medicine has been fully administered by checking the inside of the medicine cap.[13] If more than a few drops are left, then the patient can restart nebulizer using the same method as described previously until the levofloxacin has been fully administered.[13]

Tobramycin (Tobi) inhalation solution is delivered through the PARI LC Plus reusable nebulizer with a DeVilbiss Pulmo-Aide compressor.[14] One full ampule should be emptied into the nebulizer cup.[14] Each single-use ampule has 5 mL of a clear, slightly yellow liquid, which consists of tobramycin 300 mg.[14] In order to administer a dose, an ampule must first be removed from the foil pouch by gently pulling apart at the bottom tabs.[14] The nebulizer needs to be assembled and connected to an electrical outlet.[14] A steady mist should be observed coming from the mouthpiece after the compressor has been turned on.[14] The mist prompts the patient to start using the device. No other indication is present to let the patient know the device is active. The patient should continue to breathe normally through the tube until all of the medicine is gone and no more mist is being produced, which typically takes 15 minutes.[14] A sputtering sound may be heard once the nebulizer cup is empty.[14]

Tobramycin (Tobi) inhalation powder is delivered through the Podhaler device.[15] Four capsules should be inhaled consecutively as a single dose through the Podhaler device.[15] Each capsule is contained in an aluminum blister-package and consists of 28 mg of tobramycin inhalation powder.[15] The delivered dose from each capsule is 25.5 mg tobramycin.[15] The Podhaler device does not require a nebulizer or compressor. In order to load the Podhaler, the mouthpiece must be unscrewed and then one capsule is inserted into the inhalation chamber, then the mouthpiece is screwed back onto the inhalation chamber.[15] The patient must then press the blue button firmly with their thumb to puncture the capsule.[15] The patient must be able to inhale deeply and hold their breath for approximately 5 seconds to receive an adequate delivery of the drug.[15] After inhaling, the patient must unscrew the mouthpiece and inspect the capsule for a puncture and to ensure there is no remaining powder.[15] The patient may continue to inhale from the same capsule if powder remains.[15] Importantly, if a puncture is present the

patient should not puncture the capsule again.[15] This process needs to be repeated 3 more times for a total for 4 inhaled capsules per dose.[15]
Aztreonam (Cayston) inhalation solution is delivered through the Altera Nebulizer System.[16] One single-use vial, consisting of 72 mg of aztreonam, reconstituted with a 1 mL ampule of sterile diluent, is poured into the Altera Nebulizer Handset for use.[16] In order to administer a dose, the Altera Nebulizer Handset must first be assembled.[49] Upon turning on the nebulizer, a beep sound will be heard and a green light will appear.[49] A mist will be visible in the aerosol chamber when the treatment is ready to be taken.[16,49] If the mouthpiece is not properly level in the patients mouth two beep sounds and two blinks of the green light can be heard and seen, respectively, indicating to the patient to correct the mouthpiece.[49] The patient should breathe normally, and the device will emit 2 beeps, a "DOSE COMPLETE" screen will appear, and the device will automatically shut off when the treatment is complete.[49] Each treatment should take approximately 2 to 3 minutes.[16,49]

More details regarding the characteristics of each inhaler are included in Table 35.

TABLE 35: CHARACTERISTICS OF NEBULIZERS USED TO ADMINISTER INHALED ANTIBIOTICS

Characteristic	Levofloxacin Solution (Quinsair) Zirela Nebulizer Handset	Tobramycin Solution (Tobi) PARI LC Plus Reusable Nebulizer with DeVilbiss Pulmo-Aide compressor	Tobramycin Powder (Tobi Podhaler)	Aztreonam Solution (Cayston) Altera Nebulizer System
Dosage form/packaging	2.4 mL in 3 mL single-use, ready-to-use plastic ampules	5 mL in 5 mL single-use, ready-to-use plastic ampules	28 mg inhalation powder capsule. One dose is 4 capsules, used consecutively. Each capsule is contained within aluminum blister-packs (peel blister pack to remove capsule)	Single-use 2 mL vial of sterile, lyophilized powder, and a 1 mL ampule of sterile diluent. Vial contents must be reconstituted by patient immediately before administration.
Assembly	Assembly of handset required	Assembly of nebulizer and mouthpiece required	Capsules must be placed inside of inhaler by patient	Assembly of handset required
Confirmation dose is ready	Green light on device and mist appears in aerosol chamber	Steady mist from mouthpiece	No confirmation that dose is ready	Beep sound and green light will appear. Mist appears in aerosol chamber
Confirmation of dose delivery	Two beep sounds and manual check of medicine cap	Mist no longer appears, and a sputtering sound may be heard	Manual check of the capsule	Two beep sounds, a "DOSE COMPLETE" screen appears
Treatment duration of a single dose	5 to 7 minutes	15 minutes	No duration provided, but the time it would take to inhale four capsules deeply with 5 second breath-holding period for each capsule	2 to 3 minutes
Cleaning	Zirela handset must be taken apart after each use for disinfecting and	Entire nebulizer must be taken apart after each use for cleaning with soap and water, and disinfecting after each treatment day	Wipe mouthpiece with clean, dry cloth. Inhaler should never be washed with water	Entire nebulizer must be taken apart after each use for cleaning with soap and water, and disinfecting after

Characteristic	Levofloxacin Solution (Quinsair) Zirela Nebulizer Handset	Tobramycin Solution (Tobi) PARI LC Plus Reusable Nebulizer with DeVilbiss Pulmo-Aide compressor	Tobramycin Powder (Tobi Podhaler)	Aztreonam Solution (Cayston) Altera Nebulizer System
	cleaning. Further details were not provided in the levofloxacin monograph	with boiling water		each treatment day with boiling water or a device disinfectant

Source: Drug product monographs[13-16] and Altera nebulizer instructions.[49]

Patient use of Inhalers

No clinical trials were identified that assessed patient adherence to correct administration and cleaning techniques of the inhalation devices. Furthermore, no clinical trials assessed differences in patient preference between the various inhalation devices.

Summary

- The levofloxacin Zirela Nebulizer Handset device and the aztreonam Altera Nebulizer Handset device are similar in that they both use a portable nebulizer device with a product-specific handset.
- The levofloxacin Zirela Nebulizer Handset allows for use of a ready-to-use ampule, while the aztreonam Altera Nebulizer Handset device requires reconstitution of a lyophilized dry powder first.
- The tobramycin inhalation solution (Tobi) uses an older, full nebulizer system that must be assembled for use.
- The tobramycin Podhaler (Tobi Podhaler) mimics inhalers more commonly used with drugs for the treatment of chronic obstructive pulmonary disease (COPD) and does not require the use of nebulizers.

To our knowledge, no clinical studies directly compare differences in administration, adherence to, or the preferences of patients for the various inhaler devices.

REFERENCES

1. The Canadian cystic fibrosis registry: 2013 annual report [Internet]. Toronto (ON): Cystic Fibrosis Canada; 2015. [cited 2016 Aug 26]. Available from: http://www.cysticfibrosis.ca/uploads/cf%20care/Canadian-CF-Registry-2013-FINAL.pdf
2. Clinical Study Report: MPEX-204. A phase 2, multi-center, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability and efficacy of three dosage regimens of MP-376 solution for inhalation given for 28 days to stable cystic fibrosis patients [**CONFIDENTIAL** internal manufacturer's report]. San Diego (CA): Mpex Pharmaceuticals, Inc.; 2010 Mar 19.
3. Clinical Study Report: MPEX-207. A phase 3, multi-center, multinational, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of MP-376 (levofloxacin inhalation solution; Aeroquin™) in stable cystic fibrosis patients [**CONFIDENTIAL** internal manufacturer's report]. Lawrenceville (NJ): Mpex Pharmaceuticals, Inc.; 2013 Jun 20.
4. Clinical Study Report: MPEX-209. A phase 3, open-label, randomized trial to evaluate the safety and efficacy of MP-376 inhalation solution (Aeroquin™) versus tobramycin inhalation solution (TIS) in stable cystic fibrosis patients [**CONFIDENTIAL** internal manufacturer's report]. Lawrenceville (NJ): Mpex Pharmaceuticals, Inc.; 2013 Jun 28.
5. Colin AA, Wohl ME. Cystic fibrosis. Pediatr Rev. 1994 May;15(5):192-200.
6. Ivacaftor (Kalydeco) 150 mg tablet: for treatment of cystic fibrosis with G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or G970R mutation [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2015 Jul. [cited 2016 Aug 24]. (CADTH Common Drug Reviews). Available from: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0085233/
7. Pseudomonas SPP. Pathogen safety data sheet - infectious substances [Internet]. Ottawa: Public Health Agency of Canada; 2011. [cited 2016 Aug 30]. Available from: http://www.phac-aspc.gc.ca/lab-bio/res/psds-ftss/pseudomonas-spp-eng.php
8. Emerson J, Rosenfeld M, McNamara S, Ramsey B, Gibson RL. Pseudomonas aeruginosa and other predictors of mortality and morbidity in young children with cystic fibrosis. Pediatr Pulmonol. 2002 Aug;34(2):91-100.
9. Ratjen F, Munck A, Kho P, Angyalosi G, ELITE Study Group. Treatment of early Pseudomonas aeruginosa infection in patients with cystic fibrosis: the ELITE trial. Thorax. 2010 Apr;65(4):286-91.
10. Silva Filho LV, Ferreira FA, Reis FJ, Britto MC, Levy CE, Clark O, et al. Pseudomonas aeruginosa infection in patients with cystic fibrosis: scientific evidence regarding clinical impact, diagnosis, and treatment. J Bras Pneumol [Internet]. 2013 Jun [cited 2016 Aug 30];39(4):495-512. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4075866
11. CDR submission: Quinsair™ (levofloxacin solution for inhalation), 240 mg/2.4 mL or 100 mg/mL. Company: Raptor Pharmaceuticals [**CONFIDENTIAL** manufacturer's submission]. Oakville (ON): Raptor Pharmaceuticals Inc.; 2016 Jun 30.
12. Mogayzel PJ Jr, Naureckas ET, Robinson KA, Mueller G, Hadjiliadis D, Hoag JB, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2013 Apr 1;187(7):680-9.
13. Quinsair™ (levofloxacin solution for inhalation): 240 mg/2.4 mL (100 mg/mL) (as levofloxacin hemihydrate) [product monograph]. Novato (CA): Raptor Pharmaceuticals Inc.; 2015 Dec 21.

14. Tobi® (tobramycin solution for inhalation): 300 mg/5mL tobramycin (as sulfate) [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2015 Jul 10.
15. Tobi® Podhaler® (tobramycin inhalation powder): 28 mg tobramycin per capsule [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2015 Jul 14.
16. Cayston® (aztreonam for inhalation solution): 75 mg aztreonam/vial [product monograph]. Mississauga (ON): Gilead Sciences Canada, Inc.; 2015 Oct 16.
17. Geller DE, Flume PA, Staab D, Fischer R, Loutit JS, Conrad DJ, et al. Levofloxacin inhalation solution (MP-376) in patients with cystic fibrosis with Pseudomonas aeruginosa. Am J Respir Crit Care Med. 2011 Jun 1;183(11):1510-6.
18. Flume PA, VanDevanter DR, Morgan EE, Dudley MN, Loutit JS, Bell SC, et al. 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. J Cyst Fibros. 2016 Feb 4.
19. Elborn J, Geller DE, Conrad D, Aaron SD, Smyth AR, Fischer R, et al. 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. J Cyst Fibros. 2015 Jul;14(4):507-14.
20. Health Canada reviewer's report: Quinsair (levofloxacin) [**CONFIDENTIAL** internal report]. Ottawa: Therapeutics Products Directorate, Health Canada; 2015 Apr 30.
21. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. 1999 Jan;159(1):179-87.
22. Fuchs HJ, Borowitz DS, Christiansen DH, Morris EM, Nash ML, Ramsey BW, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. N Engl J Med. 1994 Sep 8;331(10):637-42.
23. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005 Aug;26(2):319-38.
24. 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 Sep;21(7):1267-78.
25. Ramsey BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams-Warren J, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. N Engl J Med. 1999 Jan 7;340(1):23-30.
26. Committee for Medicinal Products for Human Use (CHMP). Assessment report: Quinsair [Internet]. London: European Medicines Agency; 2014 Dec 18. [cited 2016 Aug 29]. (EPAR - public assessment report). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002789/WC500187847.pdf
27. Waters V, Stanojevic S, Atenafu EG, Lu A, Yau Y, Tullis E, et al. Effect of pulmonary exacerbations on long-term lung function decline in cystic fibrosis. Eur Respir J. 2012 Jul;40(1):61-6.
28. Langan KM, Kotsimbos T, Peleg AY. Managing Pseudomonas aeruginosa respiratory infections in cystic fibrosis. Curr Opin Infect Dis. 2015 Dec;28(6):547-56.
29. Ryan G, Singh M, Dwan K. Inhaled antibiotics for long-term therapy in cystic fibrosis. Cochrane Database Syst Rev. 2011;(3):CD001021.

30. Oermann CM, Retsch-Bogart GZ, Quittner AL, Gibson RL, McCoy KS, Montgomery AB, et al. An 18-month study of the safety and efficacy of repeated courses of inhaled aztreonam lysine in cystic fibrosis. Pediatr Pulmonol. 2010 Nov;45(11):1121-34.

31. Retsch-Bogart GZ, Burns JL, Otto KL, Liou TG, McCoy K, Oermann C, et al. A phase 2 study of aztreonam lysine for inhalation to treat patients with cystic fibrosis and Pseudomonas aeruginosa infection. Pediatr Pulmonol. 2008 Jan;43(1):47-58.

32. Retsch-Bogart GZ, Quittner AL, Gibson RL, Oermann CM, McCoy KS, Montgomery AB, et al. Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis. Chest. 2009 May;135(5):1223-32.

33. Moskowitz SM, Silva SJ, Mayer-Hamblett N, Pasta DJ, Mink DR, Mabie JA, et al. Shifting patterns of inhaled antibiotic use in cystic fibrosis. Pediatr Pulmonol. 2008 Sep;43(9):874-81.

34. Canton R, Maiz L, Escribano A, Olveira C, Oliver A, Asensio O, et al. Spanish consensus on the prevention and treatment of Pseudomonas aeruginosa bronchial infections in cystic fibrosis patients. Arch Bronconeumol. 2015 Mar;51(3):140-50.

35. Elborn JS, Flume PA, Cohen F, Loutit J, VanDevanter DR. Safety and efficacy of prolonged levofloxacin inhalation solution (APT-1026) treatment for cystic fibrosis and chronic Pseudomonas aeruginosa airway infection. J Cyst Fibros. 2016 Feb 26.

36. Clinical Study Report: MPEX-209 extension phase. A phase 3, open-label, randomized trial to evaluate the safety and efficacy of MP-376 inhalation solution (Aeroquin™) versus tobramycin inhalation solution (TIS) in stable cystic fibrosis patients [**CONFIDENTIAL** internal manufacturer's report]. Lawrenceville (NJ): Mpex Pharmaceuticals, Inc.; 2013 Jun 28.

37. Clinical outcome assessment compendium [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2016. [cited 2016 Aug 29]. Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM459231.htm

38. Modi AC, Quittner AL. Validation of a disease-specific measure of health-related quality of life for children with cystic fibrosis. J Pediatr Psychol. 2003 Dec;28(8):535-45.

39. 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 Oct;128(4):2347-54.

40. Bennett AV, Patrick DL, Lymp JF, Edwards TC, Goss CH. Comparison of 7-day and repeated 24-hour recall of symptoms of cystic fibrosis. J Cyst Fibros. 2010 Dec;9(6):419-24.

41. Goss CH, Edwards TC, Ramsey BW, Aitken ML, Patrick DL. Patient-reported respiratory symptoms in cystic fibrosis. J Cyst Fibros. 2009 Jul;8(4):245-52.

42. Committee for Medicinal Products for Human Use. Guideline on the clinical development of medicinal products for the treatment of cystic fibrosis [Internet]. London: European Medicines Agency; 2008 May 30. [cited 2016 Jul 26]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003507.pdf

43. Issues in the design of clinical trials of aerosolized antimicrobials for the treatment of cystic fibrosis. Day 2: efficacy endpoints for clinical trials of aerolised antimicrobials [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2010 Sep 23. [cited 2016 Jul 26]. Available from: http://www.fda.gov/downloads/Drugs/NewsEvents/UCM231055.pdf Archived document.

44. Henry B, Aussage P, Grosskopf C, Goehrs JM. Development of the Cystic Fibrosis Questionnaire (CFQ) for assessing quality of life in pediatric and adult patients. Qual Life Res. 2003 Feb;12(1):63-76.

45. Yuksel H, Yilmaz O, Dogru D, Karadag B, Unal F, Quittner AL. Reliability and validity of the Cystic Fibrosis Questionnaire-Revised for children and parents in Turkey: cross-sectional study. Qual Life Res. 2013 Mar;22(2):409-14.

46. Montgomery AB, Abuan T, Yeager MA. Regulatory aspects of phase 3 endpoints for new inhaled antibiotics for cystic fibrosis patients with chronic Pseudomonas aeruginosa infections. J Aerosol Med Pulm Drug Deliv. 2012 Aug;25(4):198-203.

47. Bregnballe V, Thastum M, Lund LD, Hansen CR, Preissler T, Schiotz PO. Validation of the Danish version of the revised cystic fibrosis quality of life questionnaire in adolescents and adults (CFQ-R14+). J Cyst Fibros. 2008 Nov;7(6):531-6.

48. Report of the workshop on the endpoints for cystic fibrosis clinical trials [Internet]. London: European Medicines Agency; 2012 Nov 29. [cited 2016 Aug 8]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/12/WC500136159.pdf

49. Instructions for use Altera® nebulizer system [Internet]. Midlothian (VA): PARI Respiratory Equipment, Inc.; 2016. [cited 2016 Jul 20]. Available from: https://www.cayston.com/assets/media/pdfs/Altera_Nebulizer_System_IFU.pdf