# Comparison of Inhaled Antibiotics for the Treatment of Chronic *Pseudomonas aeruginosa* Lung Infection in Patients With Cystic Fibrosis: Systematic Literature Review and Network Meta-Analysis

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## ABSTRACT

**Purpose:** In Europe, 4 inhaled antibiotics (tobramycin, colistimethate sodium, aztreonam, and levofloxacin) are currently approved for the treatment of chronic *Pseudomonas aeruginosa* lung infection in patients with cystic fibrosis (CF). Levofloxacin inhalation solution (LIS) is the most recently approved inhaled antibiotic for adult patients with CF. A systematic literature review and Bayesian network meta-analysis (NMA) was conducted to compare the relative short-term (4 weeks) and long-term (24 weeks) outcomes of these inhaled antibiotics versus LIS.

**Methods:** A systematic literature search was conducted on February 16, 2016, using EMBASE and Medline via OvidSP. All randomized controlled trials comparing any of the aforementioned inhaled antibiotics with 4 or 24 weeks of follow-up were evaluated. NMA was performed for the following outcomes: relative and absolute percent changes from baseline in forced expiratory volume in 1 second (FEV$_1$%) predicted, change in *P aeruginosa* sputum density, respiratory symptoms score from the CF questionnaire–revised, hospitalization, additional antibiotics use, and study withdrawal rates.

**Results:** Of the 685 articles identified, 7 unique studies were included in the 4 weeks' NMA and 9 unique studies were included in the 24 weeks' NMA. Aztreonam was predicted to result in the greatest numerically increase in FEV$_1$% predicted at 4 weeks, whereas LIS were predicted to be numerically greater than colistimethate sodium, tobramycin inhaled solution (TIS), and tobramycin inhaled powder (TIP). However, all of the 95% credibility intervals (CrIs) of these comparisons included zero. At 24 weeks, none of the treatments was significantly more effective than LIS. The estimates for the mean change from baseline to 24 weeks in relative FEV$_1$% versus LIS was –0.55 (95% CrI, –3.91 to 2.80) for TIS, –2.36 (95% CrI, –7.32 to 2.63) for aztreonam, –2.95 (95% CrI, –10.44 to 4.51) for TIP, and –9.66 (95% CrI, –15.01 to –4.33) for placebo. Compared with LIS, the odds ratio for hospitalization at 24 weeks was 1.92 (95% CrI, 1.01–3.30) for TIS, 2.25 (95% CrI, 1.01–4.34) for TIP, and 3.16 (95% CrI, 1.53–5.78) for placebo, all statistically worse than LIS. *P aeruginosa* sputum density scores, additional use of antipseudomonal antibiotics, and study withdrawal rates were comparable among all inhaled antibiotics at all times.

**Implications:** Based on this NMA, the analyses for many of the outcomes did not provide significant

evidence to indicate that the other approved inhaled antibiotics were more effective than LIS for the treatment of chronic *P aeruginosa* lung infection in patients with CF. Study withdrawal rates seemed to be comparable among these inhaled antibiotics. (*Clin Ther.* 2016;■:■■■–■■■) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: cystic fibrosis, levofloxacin inhalation solution, network meta-analysis.

## INTRODUCTION

Chronic lung infection in patients with cystic fibrosis (CF) usually involves multiple bacterial species but is frequently dominated by *Pseudomonas aeruginosa*. Chronic *P aeruginosa* lung infection is the primary cause of progressive lung function decline, increased morbidity, and mortality. Once chronic *P aeruginosa* lung infection occurs, long-term maintenance therapy with inhaled antibiotics is recommended to suppress infection, reduce acute pulmonary exacerbations, and preserve lung function.[1,2]

A variety of inhaled antibiotics in various delivery systems have been approved for the treatment of chronic *P aeruginosa* lung infection, including tobramycin, aztreonam, colistimethate sodium, and (most recently) levofloxacin. The relative efficacy of these inhaled antibiotics has not been well defined because of the lack of direct comparison among these treatments.

In 2012, Littlewood et al[3] conducted a network meta-analysis (NMA) to evaluate the relative efficacy at 4 weeks of tobramycin inhaled powder (TIP), tobramycin inhaled solution (TIS), colistimethate sodium for inhalation, and aztreonam inhalation solution for the treatment of chronic *P aeruginosa* lung infection in patients with CF. They included a total of 7 clinical trials that reported the following outcomes at 4 weeks: percent change from baseline in forced expiratory volume in 1 second ($FEV_1\%$) predicted, *P aeruginosa* sputum density, and acute pulmonary exacerbations. The investigators reported that improvements in efficacy (as measured by changes in $FEV_1\%$ predicted at 4 weeks) were comparable between the tobramycin preparations, colistimethate sodium for inhalation, and aztreonam inhalation solution.

A systematic review of the clinical effectiveness and cost-effectiveness of colistimethate sodium for inhalation and TIP for the treatment of chronic *P aeruginosa* lung infection in CF was conducted by Tappenden et al[4] in 2013. Both colistimethate sodium for inhalation and TIP were reportedly noninferior to TIS as measured by predicted $FEV_1\%$ in the clinical effectiveness review. The investigators also assessed the viability of an NMA with key study characteristic data extracted from an additional 13 trials from 16 publications. They concluded that due to heterogeneity of the subjects' baseline characteristics among these trials and the incompleteness of the evidence network, an NMA could not be performed.

Although the 2 reviews provided some level of evidence that these inhaled antibiotics are comparable in efficacy in the short term (4 weeks), they did not include levofloxacin inhalation solution (LIS), which was recently approved in Europe, as a comparator.[3–6] It was unclear if these inhaled antibiotics have comparable efficacy profiles beyond 4 weeks. Thus, we performed a systematic literature review (SLR) and an NMA to achieve the following: (1) identify the clinical evidence for the most widely used inhaled antibiotics (tobramycin, aztreonam, and colistimethate sodium) for the management of chronic *P aeruginosa* lung infection in patients with CF; and (2) compare the short-term (4 weeks) and long-term (24 weeks) efficacy of LIS versus other inhaled antibiotics in this indication. Although safety was not assessed, study withdrawals (including withdrawals due to adverse events [AEs]) are described.

## MATERIALS AND METHODS
### Systematic Literature Review

The systematic literature review was undertaken according to the Centre for Reviews and Dissemination and the Preferred Reporting Items for Systematic Review and Meta-analysis.[7]

### Search Strategy and Study Selection

A systematic literature search was conducted by using electronic databases EMBASE and Medline via OvidSP on February 16, 2016, to identify relevant randomized controlled trials (RCTs) of inhaled antibiotics meeting the following criteria: RCTs of patients with CF ≥6 years of age, previously treated with inhaled antibiotics, diagnosed with *P aeruginosa*

infections, evaluating the efficacy, safety, or quality of life outcome measures of anti-pseudomonal antibiotics, over a study duration of either 4 or 24 weeks. A detailed overview of inclusion and exclusion criteria is provided in Table I. Unpublished data from clinical study reports (MPEX-204, MPEX-207, and MPEX-209) held by Raptor Pharmaceuticals, Inc were also included.[8–10] The manufacturers of other inhaled antibiotics were not contacted for unpublished data.

The list of unique titles and abstracts were screened by 2 independent reviewers to select relevant articles according to the predefined inclusion and exclusion criteria. Once the selection of chosen publications was finalized, the publications were checked for any possible linking or duplicity. Other published SLRs identified through the search were retrieved and cross-checked against our screening decisions to ensure consistency.[3,4]

## Quality Assessment

We assessed the risk of bias in these clinical trials and evaluated the quality of evidence, by using the Cochrane Risk of Bias Tool. RCTs included in the review were assessed by 1 reviewer for randomization, blinding, and adequacy of analyses. This analysis was then reviewed by another reviewer, and disagreements were resolved by consensus.

## Data Collection and Extraction

Data were extracted into specifically designed data extraction forms that were tested and validated on 3 randomly selected, included studies. Extracted data included information regarding study design, patient characteristics, details of intervention, outcomes description, results for each outcome, and study limitations. Grafula 3 V2.1 (WESik Soft Haus, Moscow, Russia) for a PC was used to extract data from the graphs.

The outcome results were extracted (means, mean change from baseline to final visit, and difference of mean change) with deviation information, such as SEs, significance levels, and CIs, to estimate missing SDs wherever possible. Data for both continuous and binary outcomes were extracted based on the number of patients included in the analysis. Where possible, reported findings were based on the full analysis set. If studies reported the mean adjusted for baseline values (eg, using analyses of covariates), these values were also extracted.

## Network Meta-analysis

An NMA was performed to compare the efficacy of LIS (Quinsair®, Raptor Pharmaceuticals Europe B.V., Amsterdam, The Netherlands) with any methods of inhaled delivery of tobramycin (TOBI®, Novartis Pharmaceuticals UK, Surrey, UK; TOBI™ Podhaler™, Novartis Europharm Ltd, Camberley, UK; Bramitob®, Chiesi Limited, Manchester, UK), colistimethate sodium (ColoBeathe®, Forest Laboratories UK Limited, Devon, UK; Colomycin®, Forest Laboratories Limited, Devon, UK; Promixin®, Profile Pharma Limited, West Sussex, UK), and aztreonam (Cayston®, Gilead Sciences International Limited, Cambridge, UK).

The inclusion and exclusion criteria for the mixed treatment comparison for the NMA were the same as those stated for the SLR with the exception of excluding studies with no estimates of mean changes of key outcomes in the study design. Mixed treatment comparisons were first conducted by using data from trials with 4 weeks of follow-up and then using data from trials with 24 weeks of follow-up.

The following outcomes were compared across the identified RCTs by using a mixed treatment comparison network: changes from baseline to 4 weeks and 24 weeks in relative $FEV_1\%$ predicted and absolute $FEV_1\%$ predicted; change from baseline to 4 weeks and 24 weeks in *P aeruginosa* density; change from baseline to 4 weeks and 24 weeks in CF questionnaire–revised (CFQ-R) respiratory symptoms score (RSS); hospitalization; use of additional inhaled or systemic antipseudomonal antibiotics; and study withdrawal rates for any reason, for lack of efficacy, or AEs. An assessment of safety was not performed given a lack of detailed information across studies.

## Statistical Methods

In an NMA, the efficacy of a particular intervention versus competing interventions can be obtained in the absence of head-to-head comparisons; an indirect treatment comparison of 2 interventions is made via a common comparator. Bayesian NMA models were used to simultaneously synthesize the results of the included studies for each outcome of interest.[11–14]

For the continuous outcomes, a normal likelihood distribution was used; for the binary outcomes, a binomial likelihood was used.[12,14–16] Both fixed effects and random effects models were evaluated. Fixed effects models assume 1 true treatment effect, whereas
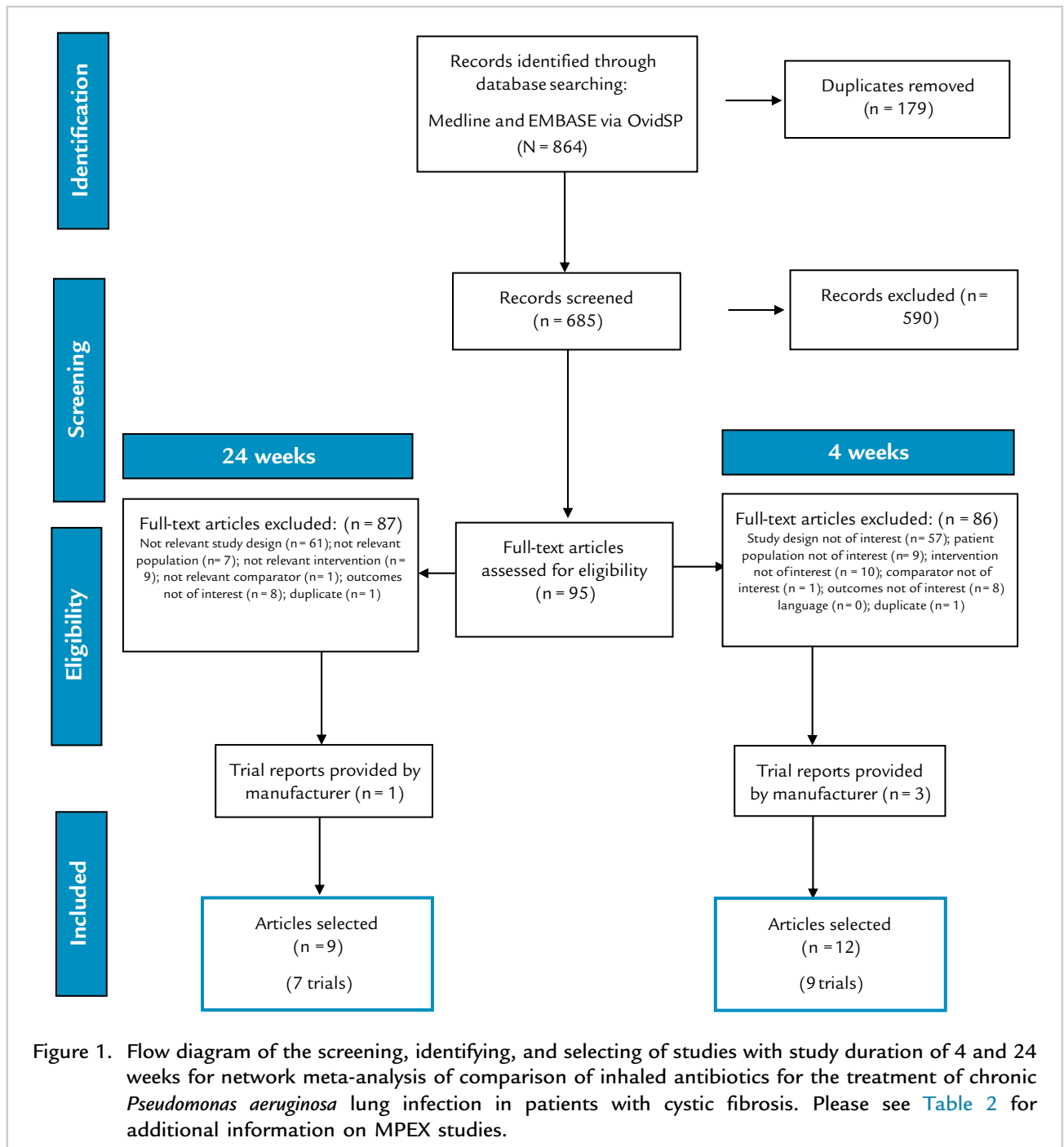
Table I. Patients, intervention, comparator, outcomes, study (PICOS) design inclusion and exclusion criteria.

| PICOS Criteria | | Inclusion | Exclusion |
|---|---|---|---|
| Study design | Abstract selection | Randomized controlled trials | Cost-effectiveness analyses |
| | | Study duration $\geq$4 wk or $\geq$24 wk[*] | Observational studies |
| | Full-text selection | Randomized controlled trials (full-text or abstracts) | Reviews or meta-analyses[†] |
| | | | Methodology studies or protocols |
| | | | "N of 1" trials (ie, sample size of 1 patient) |
| | | | Studies lasting <4 weeks |
| | | | Single-arm studies |
| | | | Opinions, editorials, letters |
| Population | Abstract and full-text selection | CF patients with chronic *Pseudomonas aeruginosa* infection | Studies including only patients aged <6 y |
| | | Patients aged $\geq$6 y | Studies including only patients aged <21 y |
| | | Studies that include adults and children | Study including only patients with first or new *P aeruginosa* infection |
| | | Mean $FEV_1$% predicted of included patients at baseline $\leq$70% predicted | |
| | | $\geq$70% of included patients previously treated by inhaled antibiotics | |
| Treatment/ intervention | Abstract and full-text selection | Any inhaled antibiotic, at any dose, using any method of delivery: | None |
| | | ● Tobramycin (TOBI®, Novartis Pharmaceuticals UK, Surrey, UK; TOBI Podhaler, Novartis Europharm Ltd, Camberley, UK; Bramitob®, Chiesi Limited, Manchester, UK) | |
| | | ● Colistimethate sodium (ColoBreathe®, Forest Laboratories UK Limited, Devon, UK; Colomycin®, Forest Laboratories Limited, Devon, UK; Promixin®, Profile Pharma Limited, West Sussex, UK) | |
| | | ● Aztreonam (Cayston®, Gilead Sciences International Limited, Cambridge, UK) | |
| | | ● Levofloxacin (Quinsair®, Raptor Pharmaceuticals Europe B.V., Amsterdam, The Netherlands) | |
| | | | None |

(continued)

**Table I.** (continued).

| PICOS Criteria | | Inclusion | Exclusion |
|---|---|---|---|
| Comparator | Abstract and full-text selection | All listed above in treatment/intervention, as well as placebo | |
| Outcomes | Abstract selection | No selection on outcomes during the abstract screening | |
| | Full-text selection | Report results for 1 of the following outcomes (for all treatments): | Outcomes not of interest |
| | | ● Relative change in $FEV_1$% predicted | |
| | | ● Absolute change in $FEV_1$% predicted | |
| | | ● Change in *P aeruginosa* density | |
| | | ● CFQ-R respiratory symptoms score | |
| | | ● Hospitalization | |
| | | ● Additional antibiotic use | |
| | | ● Withdrawal for any reason | |
| | | ● Withdrawal for lack of efficacy | |
| | | ● Withdrawals for any AEs | |

AE = adverse events; CF = cystic fibrosis; CFQ-R = cystic fibrosis questionnaire–revised; $FEV_1$ = forced expiratory volume at 1 second.

*Two separate literature searches were conducted using the same inclusion and exclusion criteria, with the exception of duration of follow-up. The first search included studies with ≥4 weeks of follow-up, and the second search included studies with ≥24 weeks of follow-up.

†Reviews and meta-analyses were excluded from data extraction because the pooled results could not be used in our analysis. However, good-quality meta-analyses and reviews (ie, Cochrane reviews) could be used for cross-checking of references if the search did not omit any articles.

Figure 1. Flow diagram of the screening, identifying, and selecting of studies with study duration of 4 and 24 weeks for network meta-analysis of comparison of inhaled antibiotics for the treatment of chronic *Pseudomonas aeruginosa* lung infection in patients with cystic fibrosis. Please see Table 2 for additional information on MPEX studies.

random effects models allow for different true treatment effects across studies, thus taking into account the heterogeneity in relative treatment effects. The deviance information criterion was used to compare the models, which provides a measure of model fit that penalizes model complexity accordingly.[17] All models were based on the NICE Decision Support Unit

research. All WinBUGS codes for continuous and binary outcomes were based on the NICE Decision Support Unit TSDS document.[7] The analyses were performed by using WinBUGS 1.4.1 statistical software.[18]

The results of the NMA are presented in terms of point estimates for the relative treatment effects and

Table II. Characteristics of the studies included in the network meta-analysis.

| Author/Year | Intervention (Upper, Study Drug; Lower, Comparator) | Double-blind/ Open-label | Patient Population | No. of Randomized Patients | Trial Length | Treatment Schedule |
|---|---|---|---|---|---|---|
| Ramsey et al,[28] 1999 | Tobramycin nebulizer solution 300 mg Placebo | Double-blind | ≥6 y | 520 | 24 wk | Intervention and comparator: 3 cycles of 28 d on treatment followed by 28 d off treatment |
| Chuchalin et al,[29] 2007 | Tobramycin nebulizer solution 300 mg BID Placebo | Double-blind | ≥6 y | 247 | 24 wk | Intervention and comparator: 3 cycles of 28 d on treatment followed by 28 d off treatment |
| Hodson et al,[20] 2002 | Tobramycin nebulizer solution 300 mg BID Colistimethate sodium nebulizer solution 80 mg BID | Open-label | ≥6 y | 126 | 8 wk | Intervention and comparator: BID for 4 weeks followed by 4 wk of follow-up |
| McCoy et al,[21] 2008 | Aztreonam nebulizer solution 75 mg BID Aztreonam nebulizer solution 75 mg TID Placebo | Double-blind | ≥6 y | 246 | 12 wk | Intervention and comparator: BID or TID for 4 wk followed by 8 wk of follow-up |
| Nasr et al,[22] 2010 | Tobramycin nebulizer solution 300 mg BID Placebo | Double-blind | ≥6 y | 32 | 24 wk | Intervention and comparator: 3 cycles of 28 d on treatment followed by 28 d off treatment |
| Konstan et al,[23] 2011 | Tobramycin inhaler powder 112 mg BID | Open-label | ≥6 y | 553 | 24 wk | Intervention and comparator: 3 cycles of 28 d on treatment followed by 28 d off treatment |
| Geller et al,[24] 2014 | Tobramycin nebulizer solution 300 mg BID | | | | | |
| Schuster et al,[25] 2013 | Colistimethate sodium inhaler powder 1,662,500 IU BID Tobramycin nebulizer solution 300 mg BID | Open-label | ≥6 y | 380 | 24 wk | Intervention: continuous treatment Comparator: 3 cycles of 28 d on treatment followed by 28 d off treatment |

(continued)

Table II.  (continued).

| Author/Year | Intervention (Upper, Study Drug; Lower, Comparator) | Double-blind/ Open-label | Patient Population | No. of Randomized Patients | Trial Length | Treatment Schedule |
|---|---|---|---|---|---|---|
| Assael et al,[26] 2013 | Aztreonam nebulizer solution 75 mg TID Tobramycin nebulizer solution 300 mg BID | Open-label | ≥6 y | 273 | 24 wk | Intervention and comparator: 3 cycles of 28 d on treatment followed by 28 d off treatment |
| MPEX-204 report[9,27] | Levofloxacin nebulizer solution 120 mg QD Levofloxacin nebulizer solution 240 mg QD Levofloxacin nebulizer solution 240 mg BID Placebo | Double-blind | ≥16 y | 151 | 8 wk | Intervention and comparator: 1 cycle of 28 d on treatment followed by 28 d off treatment |
| MPEX-207 report[10,30] | Levofloxacin nebulizer solution 240 mg BID Placebo | Double-blind | ≥12 | 330 | 8 wk | Intervention and comparator: 1 cycle of 28 d on treatment followed by 28 d off treatment |
| MPEX-209 report[6,8] | Levofloxacin nebulizer solution 240 mg BID Tobramycin nebulizer solution 300 mg BID | Open-label | ≥12 y | 282 | 24 wk | Intervention and comparator: 3 cycles of 28 d on treatment followed by 28 d off treatment |

the 95% credible intervals (95% CrIs). The probability that each treatment is best is also presented; this probability was calculated based on the proportion of Markov chain Monte Carlo cycles in which a specific treatment ranks first out of the total (in which the ranking is based on the treatment effect size).[19]

### Analysis Outputs

A network diagram representing all direct comparisons between treatments included in the analysis was produced for each outcome of interest. Results are presented with summary statistics, including estimates for the mean change in the number of events for the efficacy outcomes and the odds ratio (OR) estimates for the dichotomous outcomes. Mean values, SEs, and 95% CrIs are reported for differences in changes from baseline to end point between LIS and the other treatments. A difference in mean change was considered as statistically significant when the associated 95% CrIs did not include zero. Relative risk (RR) and OR values with corresponding 95% CrIs for other parameters were reported as appropriate. An OR was considered statistically significant when the associated 95% CrI did not include unity. Additional outputs included mean rank for each treatment, probability of being the best treatment, and surface under the cumulative ranking line (SUCRA) for each treatment. SUCRA will be 1 when a treatment is certain of being the best or 0 when a treatment is certain to be the worst.

### RESULTS
#### Systematic Literature Review
#### Study Selection

Figure 1 presents the Preferred Reporting Items for Systematic Review and Meta-analysis flow diagrams for the study selection process for SLRs limited to those with study duration of 4 weeks and those with study duration of 24 weeks.

#### Study Characteristics

The study characteristics of the included studies are presented in Table II. Nine RCTs (12 publications) with 4 weeks of follow-up were eligible for review, and relevant outcome data were extracted.[6,8–10,20–27] Five trials were open-label,[6,8,20,23–26] and 1 of the

included trials also published a post hoc subgroup analysis to assess the effect of TIP and TIS in children, adolescents, and adults[24] as well as the main analysis.[23]

Seven RCTs (9 publications) with 24 weeks of follow-up were eligible for review, and the relevant outcome data were extracted.[6,8,22–26,28,29] Four trials were open-label,[6,8,23–26] and 1 of the included trials also published a post hoc subgroup analysis to assess the effect of TIP and TIS in children, adolescents, and adults[24] as well as the main analysis.[23]

A risk-of-bias assessment conducted by using the tool recommended by the Cochrane Collaboration revealed that a high risk of bias was suspected due to the large number of studies with an open-label design (Table III). The risk of bias could not be fully assessed (in particular, allocation concealment and detection bias) because the full methodology was not detailed in every publication.

#### Comparators

For the trials with a study duration of 4 weeks, 6 (66.7%) of the 9 trials included TIS as a treatment comparator and 4 (44.4%) of the 9 trials included placebo as a treatment comparator. LIS was assessed in 3 trials (33.3%), aztreonam in 2 trials (22.2%), colistimethate sodium inhaler powder in 1 trial (11.1%), and colistimethate sodium inhaler solution in 1 trial (11.1%). For the trials with study duration of 24 weeks, all trials included TIS as the treatment comparator.

#### Patient Characteristics

Table IV presents the baseline characteristics (intervention, age, sex, body mass index [BMI], $FEV_1\%$ predicted, previous inhaled antibiotic use, and concomitant treatments) of these patients in the included trials. Due to the differences in inclusion criteria among the studies and the time period that these studies were conducted, there are notable differences in patient characteristics. The patients in the trial reported by Chuchalin et al[29] and Nasr et al[22] had a lower mean age compared with the other trials. Because age and $FEV_1\%$ predicted status are thought to have an inverse correlation, it might be expected that the patients in these trials could be earlier in their stage of chronic *P aeruginosa* infection than those in the other trials. The baseline $FEV_1\%$ predicted value reported by Nasr et al was much higher than that

Table III. Summary of risk bias assessment of identified randomized controlled trials.

| Author/Year | 1/Random Sequence Generation | 2/Allocation Concealment | 3/Blinding of Participants and Personnel | 4/Detection Bias, Patient-Reported Outcomes | 5/Detection Bias, Mortality | 6/Attrition Bias, Short-Term Outcomes | 7/Attrition Bias, Longer Term Outcomes | 8/Selective Reporting |
|---|---|---|---|---|---|---|---|---|
| Ramsey et al,[28] 1999 | √ | ? | √ | ? | ? | √ | √ | √ |
| Chuchalin et al,[29] | √ | ? | √ | ? | ? | √ | √ | √ |
| Hodson et al,[20] | √ | ? | × | × | × | √ | √ | √ |
| McCoy et al,[21] 2008 | √ | ? | × | √ | ? | √ | √ | √ |
| Nasr et al,[22] 2010 | √ | √ | √ | ? | √ | √ | √ | √ |
| Konstan et al,[23] 2011 Geller et al,[24] 2014 | √ | ? | × | × | × | √ | √ | √ |
| Schuster et al,[25] 2013 | √ | ? | × | × | × | √ | √ | √ |
| Assael et al,[26] 2013 | √ | ? | × | × | × | ? | ? | √ |
| MPEX-204 report[9] Geller et al,[27] 2011 | √ | ? | √ | ? | ? | √ | √ | √ |
| MPEX-207 report,[10] Flume et al,[30] 2016 | √ | √ | √ | ? | √ | √ | √ | √ |
| MPEX-209 report,[8] Elborn et al,[6] 2015 | √ | √ | × | × | × | √ | √ | √ |

Check mark indicates low risk; question mark indicates unclear risk; and cross mark indicates high risk.

Table IV. Baseline characteristics of patients. Values are given as mean (SD) unless otherwise indicated.

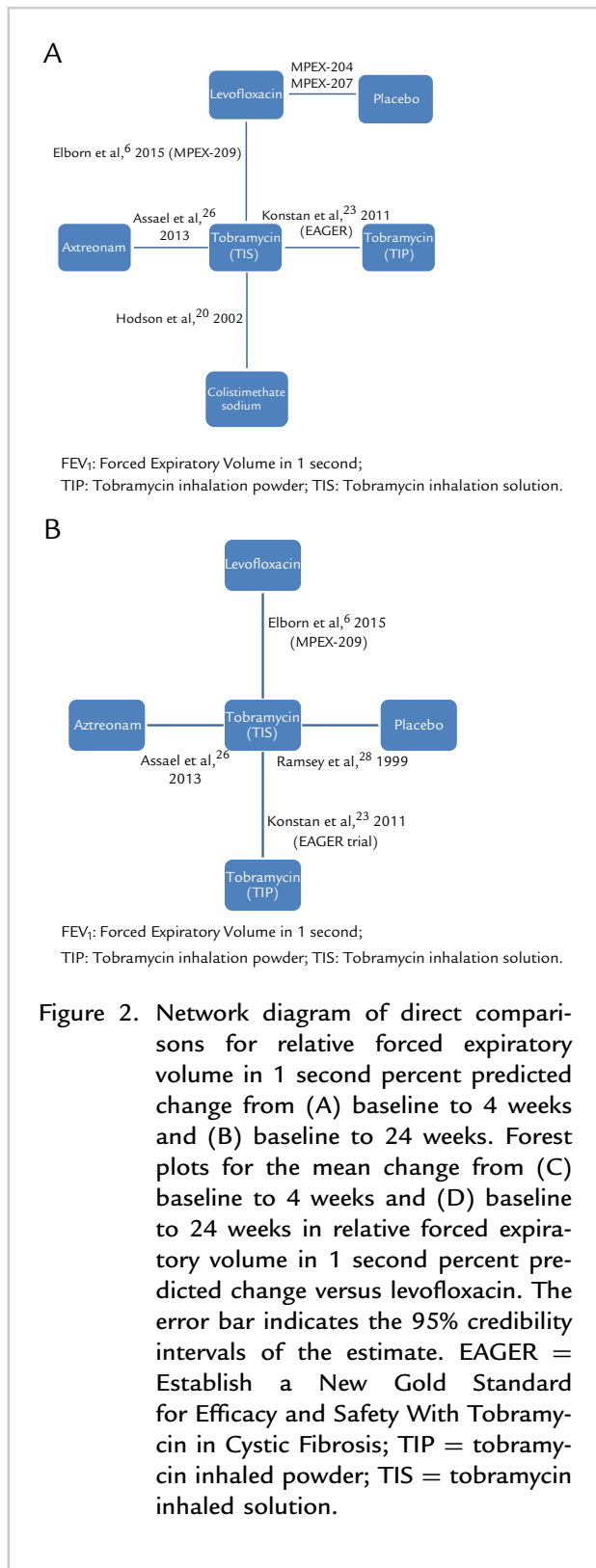| Study | Intervention | Age, y | Male/Total (%) | BMI, kg/m$^2$ | FEV$_1$% Predicted | Previous Antibiotic Use | Concomitant Treatment |
|---|---|---|---|---|---|---|---|
| Ramsey et al,[28] 1999 | Tobramycin nebulizer solution 300 mg BID | 20.8 (9.50) | 149/258 (58%) | NR | 49.9 (15.5) | NR | Dornase alfa: n = 198 (77%) |
| | Placebo | 20.6 (10.00) | 132/262 (50%) | NR | 51.2 (16.8) | NR | Dornase alfa: n = 204 (78%) |
| Chuchalin et al,[29] 2007 | Tobramycin nebulizer solution 300 mg BID | 14.8 (5.70) | 89/161 (55.3%) | 16.9 (2.8) | 60.7 (14.8) | NR | Dornase alfa: 88% |
| | Placebo | 14.7 (6.60) | 46/84 (54.8%) | 16.8 (2.9) | 63.6 (15) | NR | Dornase alfa: 88% |
| Hodson et al,[20] | Tobramycin nebulizer solution 300 mg BID | 21.3 (9.60) | 20/53 (37.7%) | NR | 55.4 (22.9) | Tobramycin use in 6 mo: n = 25 (47.1%) Colistin use in 6 mo: n = 45 (84.9%) Other in previous 6 mo: n = 48 (90.6%) | Other: n = 36 (67.9%) |
| | Colistimethate sodium nebulizer solution 80 mg BID | 20.1 (9.40) | 32/62 (51.6%) | NR | 59.4 (22.6) | Tobramycin use in 6 mo: n = 29 (46.7%) Colistin use in 6 mo: n = 51 (82.2%) Other in previous 6 mo: n = 50 (80.6%) | Other: n = 34 (45.2%) |
| McCoy et al,[21] 2008 | Aztreonam nebulizer solution 75 mg BID | 26.5 (NR) | 38/69 (55.1%) | 20.9 (3.3) | 56.3 (14.8) | No. of previous antibiotic courses in previous year: 5.46 | Azithromycin use: 69.6% Dornase alfa: 81.2% Hypertonic saline: 8.7% |
| | Aztreonam nebulizer solution 75 mg TID | 24.1 (NR) | 38/66 (57.6%) | 21 (4.5) | 55.4 (16.3) | No. of previous antibiotic courses in previous year: 5.26 | Azithromycin use: 74.2% Dornase alfa: 84.8% Hypertonic saline: 12.1% |
| | Aztreonam pooled | 25.3 (NR) | 76/135 (56.3%) | 20.9 (3.9) | 55.8 (15.5) | No. of previous antibiotic courses in previous year: 5.36 | Azithromycin use: 71.9% Dornase alfa: 83% Hypertonic saline: 10.4% |
| | Placebo | 27.9 (NR) | 45/76 (59.2%) | 21.7 (3) | 53.9 (15.3) | No. of previous antibiotic courses in previous year: 5.26 | Azithromycin use: 65.8% Dornase alfa: 89.5% Hypertonic saline: 11.8% |
| Nasr et al,[22] 2010 | Tobramycin nebulizer solution 300 mg BID | 11.81 (7.46) | 6/16 (37.5%) | NR | 95.73 (17.21) | NR | NR |
| | Placebo | 15.86 (7.25) | 6/16 (37.5%) | NR | 83.71 (21.07) | NR | NR |
| Konstan et al,[23] 2011 (General) Geller et al,[24] 2014 (aged ≥20 y) | General population Tobramycin inhaler powder 112 mg BID | 26 (11.4) | 171/308 (55.5%) | 20.7 (4) | 53 (14.2) | Tobramycin use: 82.1% Antipseudomonal antibiotic use (last use before first dose): ● 1 month: n = 78 (25.3%) ● >1–3 mo: n = 171 (55.5%) ● >3–6 mo: n = 33 (10.7%) ● >6 mo: n = 11 (3.6%) | NR |

(continued)

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Table IV.   (continued).

| Study | Intervention | Age, y | Male/Total (%) | BMI, kg/m² | FEV₁% Predicted | Previous Antibiotic Use | Concomitant Treatment |
|---|---|---|---|---|---|---|---|
| | Tobramycin nebulizer solution 300 mg BID | 25 (10.2) | 115/209 (55%) | 20.4 (3.5) | 53 (SD 15.9) | Tobramycin use: 82.3% Antipseudomonal antibiotic use (last use before first dose):<br>● 1 month: n = 46 (22%)<br>● >1–3 mo: n = 112 (53.6%)<br>● >3–6 mo: n = 24 (11.5%)<br>● >6 mo: n = 9 (4.3%) | NR |
| | Aged ≥20 y Tobramycin inhaler powder 112 mg BID | NR (NR) | 126/214 (58.9%) | NR | 50.7 (13.8) | Tobramycin use: n = 176 (82.2%) Antipseudomonal antibiotic use: n = 200 (93.5%) | NR |
| | Tobramycin nebulizer solution 300 mg BID | NR (NR) | 79/143 (55.2%) | NR (NR) | 52 (SD 15.7) | Tobramycin use: n = 113 (79%) Antipseudomonal antibiotic use: n = 128 (89.5%) | NR |
| Schuster et al,[25] 2013 | Colistimethate sodium inhaler powder 1,662,500 IU BID | 21.3 (9.72) | 103/183 (56.3%) | 18.67 (3.396) | N/A (SD N/A) | NR | NR |
| | Tobramycin nebulizer solution 300 mg BID | 20.9 (9.30) | 101/191 (52.9%) | 18.46 (3.584) | NA | NR | NR |
| Assael et al,[26] 2013 | Aztreonam nebulizer solution 75 mg TID | 25.8 (9.10) | 68/136 (50%) | 20.2 (3) | 52.3 (15.6) | Tobramycin use in previous year:<br>● <84 d: n = 21 (15.4%)<br>● ≥84 d: n = 115 (84.6%)<br>● Colistin use in previous year: n = 50 (36.8%) | Azithromycin use at baseline: n = 85 (62.5%)<br><br>Dornase alfa use at baseline: n = 92 (67.6%)<br>Hypertonic saline use at baseline: n = 44 (32.4%) |
| | Tobramycin nebulizer solution 300 mg BID | 25.1 (9.00) | 66/132 (50%) | 20.5 (2.8) | 52.2 (14.6) | Tobramycin use in previous year:<br>● <84 d: n = 19 (14.4%)<br>● ≥84 d: n = 113 (85.6%)<br>● Colistin use in previous year: n = 53 (40.2%) | Azithromycin use at baseline: n = 89 (67.4%)<br>Dornase alfa use at baseline: n = 91 (68.9%)<br>Hypertonic saline use at baseline: n = 46 (34.8%) |
| MPEX-204 report[9] Geller et al,[27] 2011 | Levofloxacin nebulizer solution 120 mg QD | 28 (6.90) | 20/38 (52.6%) | 21.2 (3.4) | 52.9 (17.68) | No. of previous antibiotic courses in previous year: 4.5 (1.6) | Azithromycin use: n = 29 (76.3%)<br>Dornase alfa use: n = 26 (68.4%)<br>Hypertonic saline use: n = 13 (34.2%)<br>Salbutamol use: n = 29 (76.3%) |

(continued)

Table IV.   (continued).

| Study | Intervention | Age, y | Male/Total (%) | BMI, kg/m$^2$ | FEV$_1$% Predicted | Previous Antibiotic Use | Concomitant Treatment |
|---|---|---|---|---|---|---|---|
| | Levofloxacin nebulizer solution 240 mg QD | 27.5 (9.10) | 21/37 (56.8%) | 20.9 (3.3) | 55.4 (14.41) | No. of previous antibiotic courses in previous year: 4.8 (1.7) | Azithromycin use: n = 26 (70.3%) Dornase alfa use: n = 32 (86.5%) Hypertonic saline use: n = 13 (35.1%) Salbutamol use: n = 25 (67.6%) |
| | Levofloxacin nebulizer solution 240 mg BID | 29.2 (10.00) | 25/39 (64.1%) | 21.8 (2.6) | 48.79 (15.154) | No. of previous antibiotic courses in previous year: 4.8 (1.5) | Azithromycin use: n = 32 (82.1%) Dornase alfa use: n = 29 (74.4%) Hypertonic saline use: n = 22 (56.4%) Salbutamol use: n = 23 (59%) |
| | Placebo | 30.1 (9.90) | 19/37 (51.4%) | 21 (3.4) | 52.38 (13.417) | No. of previous antibiotic courses in previous year: 5.4 (2.3) | Azithromycin use: n = 25 (67.6%) Dornase alfa use: n = 31 (83.8%) Hypertonic saline use: n = 22 (59.5%) Salbutamol use: n = 25 (67.6%) |
| MPEX-207 report[10] Flume et al,[30] 2016 | Levofloxacin nebulizer solution 240 mg BID | 29.4 (10.33) | 115/220 (52.3%) | 22.5 (3.96) | 56.53 (15.748) | No. of previous antibiotic courses in previous year: 5.9 (2.65) | NR |
| | Placebo | 28.8 (10.94) | 63/110 (57.3%) | 22.1 (3.79) | 56.32 (15.906) | No. of previous antibiotic courses in previous year: 6.0 (2.77) | NR |
| MPEX-209 report[8] Elborn et al,[6] 2015 | Levofloxacin nebulizer solution 240 mg BID | 28.1 (8.96) | 103/189 (54.5%) | 21.8 (3.57) | 54.78 (17.022) | No. of previous antibiotic courses in previous year: 6.0 (2.83) | NR |
| | Tobramycin nebulizer solution 300 mg BID | 28.8 (10.94) | 56/93 (60.2%) | 21.5 (3.30) | 53.2 (15.7) | No. of previous antibiotic courses in previous year: 6.0 (2.79) | NR |

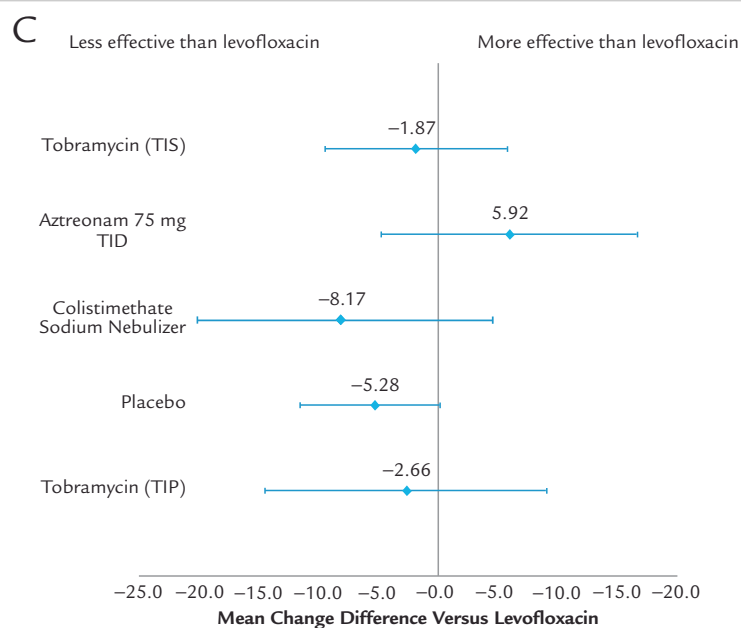BMI = body mass index; FEV$_1$ = forced expiratory volume in 1 second; NA = not available; NR = not reported

FEV$_1$: Forced Expiratory Volume in 1 second;
TIP: Tobramycin inhalation powder; TIS: Tobramycin inhalation solution.

Figure 2. Network diagram of direct comparisons for relative forced expiratory volume in 1 second percent predicted change from (A) baseline to 4 weeks and (B) baseline to 24 weeks. Forest plots for the mean change from (C) baseline to 4 weeks and (D) baseline to 24 weeks in relative forced expiratory volume in 1 second percent predicted change versus levofloxacin. The error bar indicates the 95% credibility intervals of the estimate. EAGER = Establish a New Gold Standard for Efficacy and Safety With Tobramycin in Cystic Fibrosis; TIP = tobramycin inhaled powder; TIS = tobramycin inhaled solution.

from other included trials. BMI at baseline was not reported in 3 trials[20,22,28] or in the adult population of the EAGER (Establish a New Gold Standard for Efficacy and Safety With Tobramycin in Cystic Fibrosis) trial.[23] The BMI values reported by Chuchalin et al were slightly lower than in other trials.

Concomitant medication use could not be compared among the trials because few data were reported. When reported, dornase alfa was the most commonly reported concomitant medication. Subjects in the MPEX-204, MPEX-207, and MPEX-209 trial had all used inhaled antimicrobials in the year before study participation.[8–10] Similarly, most of the patients in the EAGER trial[23] and in the trial reported by Assael et al[26] were previously exposed to inhaled tobramycin. The improvement in FEV$_1$% predicted from baseline to the end of the treatment cycle by tobramycin has been documented to peak in the first cycle of treatment, with the effect becoming attenuated over time with repeated treatment.[28] Thus, an attenuated effect on the improvement in FEV$_1$% predicted in treatment-experienced patients in these trials may be expected given that the maximal effect on FEV$_1$% predicted may have already occurred before starting the trial. Four trials did not report the previous antibiotics use rate.[22,25,28,29]
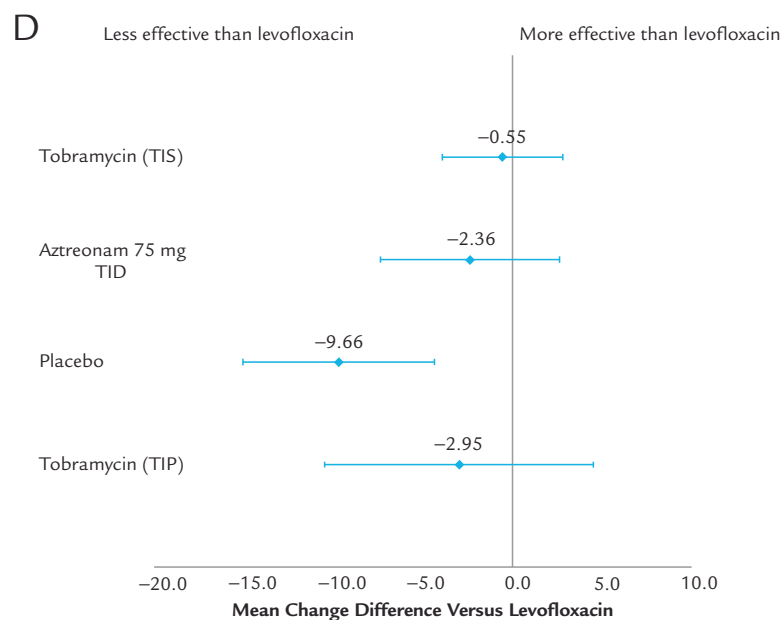
Given that age, BMI, concomitant medications, prior exposure to antipseudomonal antibiotics, and FEV$_1$% predicted all have prognostic value in CF, it is difficult to determine whether these study populations are comparable in terms of overall health and propensity to benefit from antipseudomonal treatments. These factors should be taken into consideration when making comparisons across studies.

NMA Results

For NMA using trials with 4 weeks of follow-up, both fixed effects and random effects models were performed; for all outcomes, a random effects model was chosen due to better fit in terms of deviance (DIC value). Due to the small number of trials with 24 weeks of follow-up and only 1 trial per comparison except for TIS and placebo comparison in the study withdrawal rate comparisons, only fixed effect models were used for all of the outcomes.
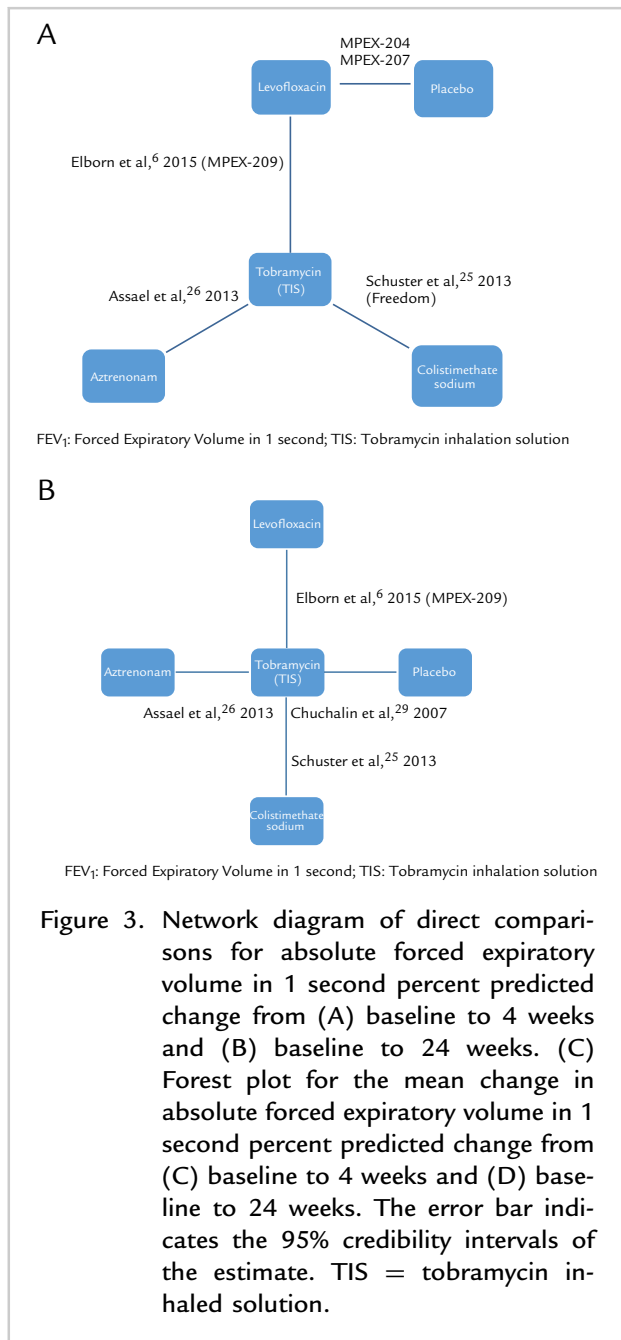
C

Less effective than levofloxacin | More effective than levofloxacin

Tobramycin (TIS) −1.87

Aztreonam 75 mg TID 5.92

Colistimethate Sodium Nebulizer −8.17

Placebo −5.28

Tobramycin (TIP) −2.66

−25.0 −20.0 −15.0 −10.0 −5.0 −0.0 −5.0 −10.0 −15.0 −20.0

**Mean Change Difference Versus Levofloxacin**

The error bar indicates the 95% CrI of the estimate. $FEV_1$: Forced Expiratory Volume in 1 second; TID: Three times a day; TIP: Tobramycin inhalation powder; TIS: Tobramycin inhalation solution.

D

Less effective than levofloxacin | More effective than levofloxacin

Tobramycin (TIS) −0.55

Aztreonam 75 mg TID −2.36

Placebo −9.66

Tobramycin (TIP) −2.95

−20.0 −15.0 −10.0 −5.0 0.0 5.0 10.0

**Mean Change Difference Versus Levofloxacin**

The error bar indicates the 95% CrI of the estimate. $FEV_1$: Forced Expiratory Volume in 1 second; TID: Three times a day; TIP: Tobramycin inhalation powder; TIS: Tobramycin inhalation solution.

Figure 2. Continued.

A

MPEX-204
MPEX-207

Levofloxacin — Placebo

Elborn et al,[6] 2015 (MPEX-209)

Tobramycin
(TIS)

Assael et al,[26] 2013

Schuster et al,[25] 2013
(Freedom)

Aztrenonam

Colistimethate
sodium

FEV$_1$: Forced Expiratory Volume in 1 second; TIS: Tobramycin inhalation solution

B

Levofloxacin

Elborn et al,[6] 2015 (MPEX-209)

Aztrenonam — Tobramycin
(TIS) — Placebo

Assael et al,[26] 2013    Chuchalin et al,[29] 2007

Schuster et al,[25] 2013

Colistimethate
sodium

FEV$_1$: Forced Expiratory Volume in 1 second; TIS: Tobramycin inhalation solution

Figure 3. Network diagram of direct comparisons for absolute forced expiratory volume in 1 second percent predicted change from (A) baseline to 4 weeks and (B) baseline to 24 weeks. (C) Forest plot for the mean change in absolute forced expiratory volume in 1 second percent predicted change from (C) baseline to 4 weeks and (D) baseline to 24 weeks. The error bar indicates the 95% credibility intervals of the estimate. TIS = tobramycin inhaled solution.

## Relative FEV$_1$% Predicted Change From Baseline to 4 Weeks and Baseline to 24 Weeks

The network diagram for the relative FEV$_1$% predicted change from baseline to 4 weeks and baseline to 24 weeks is shown in Figures 2A and 2B, respectively.

The difference in mean change from baseline in relative FEV$_1$% predicted at 4 weeks compared with LIS is given in Figure 2C. The mean change from baseline in relative FEV$_1$% predicted for LIS was –5.28 (95% CrI, –11.55 to 0.13) versus placebo, but the 95% CrI included zero. A similar trend was also observed compared with TIS, TIP, colistimethate sodium, and aztreonam. Aztreonam 75 mg TID had the highest probability of being the best treatment (83.8%), with a SUCRA value of 0.951, followed by LIS with a 9.7% probability of being the best treatment, with a SUCRA value of 0.682.

The difference in mean change from baseline in relative FEV$_1$% at 24 weeks compared with LIS is given in Figure 2D. The effect of LIS was significantly better than placebo, with a mean change of placebo versus LIS of –9.66 (95% CrI, –15.01 to –4.33). Other treatments—including TIS (–0.55 [95% CrI, –3.91 to 2.80]), TIP (–2.95 [95% CrI, –10.44 to 4.51]), and aztreonam (–2.36 [95% CrI, –7.32 to 2.63])—were not better compared with LIS, as their respective 95% CrIs all included zero. At 24 weeks, LIS had the highest probability of being the best treatment (51.3%), with a SUCRA value of 0.807, followed by TIS with a 23.6% probability of being the best treatment, with a SUCRA value of 0.741.

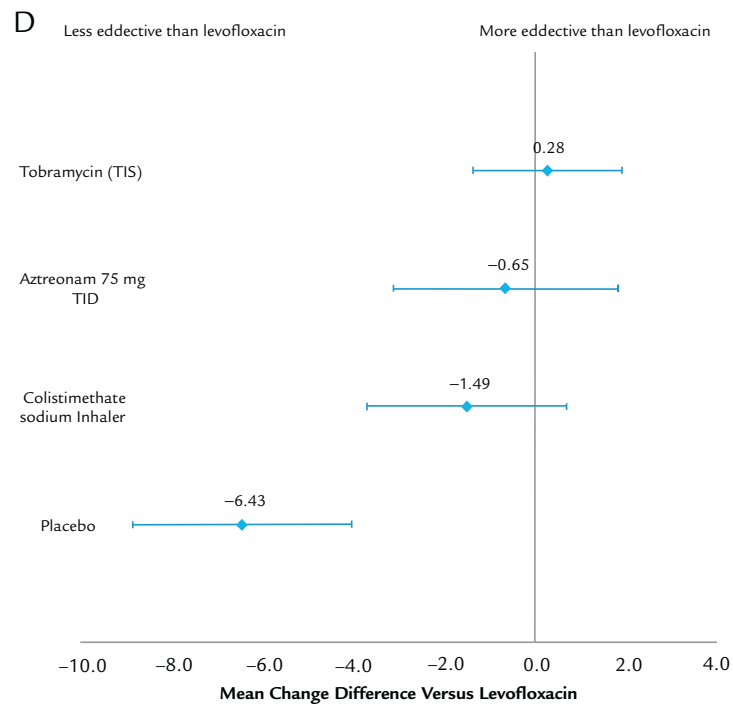## Absolute FEV$_1$% Predicted Change From Baseline to 4 Weeks and Baseline to 24 Weeks

The network diagram for the absolute FEV$_1$% predicted change from baseline to 4 weeks and to 24 weeks is shown in Figures 3A and 3B, respectively.

The difference in mean change from baseline in absolute FEV$_1$% predicted at 4 weeks compared with LIS is given in Figure 3C. The effect of LIS in mean change from baseline in absolute FEV$_1$% predicted was –2.68 (95% CrI, –7.49 to 1.76) versus placebo, but the 95% CrIs included zero. This trend was also observed when LIS was compared with TIS (–1.04 [95% CrI, –7.39 to 5.29], colistimethate sodium (–2.46 [95% CrI, –11.44 to 6.51]), and aztreonam (2.24 [95% CrI, –6.94 to 11.44]). Aztreonam 75 mg TID had the highest probability of being the best treatment (67.4%), with a SUCRA value of 0.841, followed by LIS with a 20.2% probability of being the best treatment, with a SUCRA value of 0.656.

The difference in mean change from baseline in absolute FEV$_1$% predicted at 24 weeks compared with LIS is given in Figure 3D. The effect of LIS was significantly better than placebo with the mean change of placebo versus LIS of –6.43 (95% CrI, –8.84 to –4.02). Aztreonam (–0.65 [95% CrI, –3.12 to
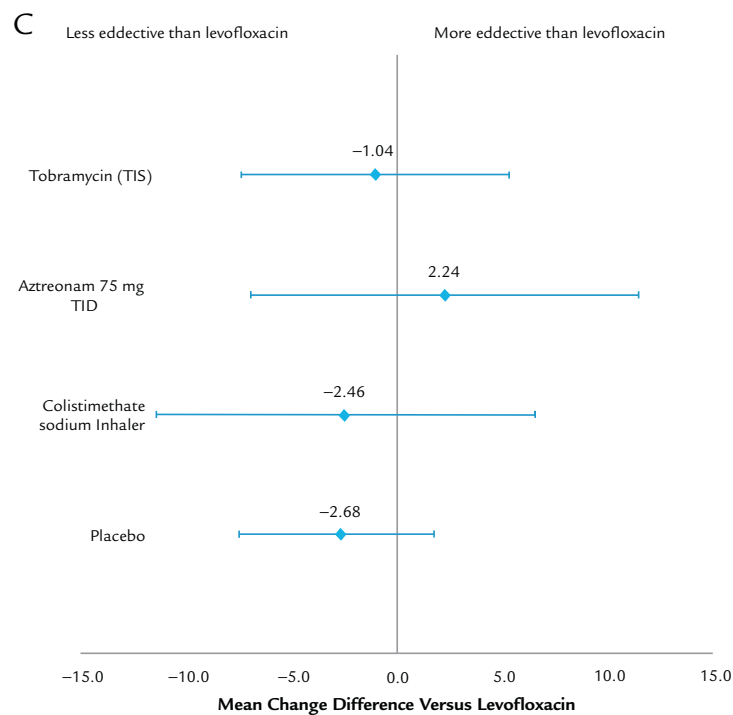
C

Less eddective than levofloxacin                    More eddective than levofloxacin

Tobramycin (TIS)                     −1.04

Aztreonam 75 mg
TID                                                  2.24

Colistimethate
sodium Inhaler               −2.46

Placebo                      −2.68

−15.0    −10.0    −5.0    0.0    5.0    10.0    15.0

**Mean Change Difference Versus Levofloxacin**

The error bar indicates the 95% Crl of the estimate. FEV$_1$: Forced Expiratory Volume in 1 second; TID: Three times a day; TIS: Tobramycin inhalation solution.

D

Less eddective than levofloxacin                    More eddective than levofloxacin

Tobramycin (TIS)                                     0.28

Aztreonam 75 mg
TID                                  −0.65

Colistimethate
sodium Inhaler                       −1.49

Placebo              −6.43

−10.0    −8.0    −6.0    −4.0    −2.0    0.0    2.0    4.0

**Mean Change Difference Versus Levofloxacin**

The error bar indicates the 95% Crl of the estimate. FEV$_1$: Forced Expiratory Volume in 1 second; TID: Three times a day; TIS: Tobramycin inhalation solution.

Figure 3.  Continued.

Table V. Estimates for mean change from baseline to 4 and 24 weeks in *Pseudomonas aeruginosa* sputum density versus levofloxacin nebulizer solution.

| Variable | Mean Change | SE | 95% CrI |
|---|---|---|---|
| **4 wk follow-up** | | | |
| Tobramycin (TIS) | –0.150 | 0.260 | –0.659 to 0.358 |
| Tobramycin (TIP) | –0.610 | 0.485 | –1.562 to 0.336 |
| Aztreonam 75 mg BID | –0.076 | 0.309 | –0.682 to 0.531 |
| Aztreonam 75 mg TID | –0.095 | 0.269 | –0.622 to 0.433 |
| Colistimethate sodium nebulizer | 0.111 | 0.400 | –0.672 to 0.894 |
| Placebo | 0.643 | 0.170 | 0.309 to 0.977 |
| **24 wk follow-up** | | | |
| Tobramycin (TIS) | –0.180 | 0.260 | –0.688 to 0.329 |
| Tobramycin (TIP) | –0.589 | 0.418 | –1.41 to 0.231 |
| Placebo | 0.221 | 0.297 | –0.36 to 0.802 |

CrI = credibility interval; TIP = tobramycin inhaled powder; TIS = tobramycin inhaled solution.

1.82]), colistimethate sodium (–1.49 [95% CrI, –3.69 to 0.70]), and TIS (0.28 [95% CrI, –1.36 to 1.92]) were all similar compared with LIS. TIS had the highest probability of being the best treatment (52.5%), with a SUCRA value of 0.865, followed by LIS with a 34.2% probability of being the best treatment, with a SUCRA value of 0.744.

### P aeruginosa Sputum Density Change From Baseline to 4 Weeks and Baseline to 24 Weeks

The differences in mean change from baseline in *P aeruginosa* sputum density compared with LIS at 4 and 24 weeks are shown in Table V. At 4 weeks, the effect of LIS was significantly better than placebo, with a mean change of placebo versus LIS of 0.64 $\log_{10}$ CFU/g sputum (95% CrI, 0.31–0.98). None of the antibiotics were noted to be better or worse than LIS. At 4 weeks, TIP had the highest probability of being the best treatment (74.3%), with a SUCRA value of 0.896, followed by aztreonam 75 mg BID with a 9.4% probability of being the best treatment, with a SUCRA value of 0.549.

At 24 weeks, the effect of LIS was similar to placebo with a mean change of placebo versus LIS of 0.22 $\log_{10}$ CFU/g sputum (95% CrI, –0.36 to 0.80). LIS seemed comparable to TIP (–0.59 [95% CrI, –1.41 to 0.23]) and TIS (–0.18 [95% CrI, –0.69 to 0.33]). Consistent with the 4 weeks' analysis, TIP had the

highest probability of being the best treatment (87%), with a SUCRA value of 0.935, followed by TIS with a 7.9% probability of being the best treatment, with a SUCRA value of 0.619.

### CFQ-R RSS Change From Baseline to 4 and Baseline to 24 Weeks

The change in CFQ-R RSS from baseline to 4 weeks was reported in 5 trials.[8–10,21,26] Mixed treatment comparisons with fixed effect model revealed that the effect of LIS (–1.07 [95% CrI, –4.00 to 1.87]), TIS (–3.11 [95% CrI, –6.65 to 0.42]), and aztreonam 75 mg BID (4.66 [95% CrI, –0.21 to 9.54]) was not different from placebo in reducing symptoms as measured by using the CFQ-R RSS. Only aztreonam 75 mg TID, having a mean change of 2.60 (95% CrI, –1.75–6.95), was likely to have a better improvement in CFQ-R RSS compared with LIS. The aztreonam 75 mg BID regimen had the highest probability of being the best treatment in improving symptoms (81.3%), with a SUCRA value of 0.947, followed by aztreonam 75 mg TID with a 17.0% probability of being the best treatment, with a SUCRA value of 0.753.

The change in CFQ-R RSS from baseline to 24 weeks was reported in only 1 trial comparing LIS with TIS.[8] In this study, although not statistically significant, a favorable change in the CFQ-R RSS score (mean [SE]) was observed in the LIS-treated

patients (2.85 [1.32]) compared with the TIS-treated patients (–0.07 [1.76]).

## Hospitalization

Hospitalization after 4 weeks of follow-up was reported in only 2 trials.[10,21] An indirect comparison was conducted instead of NMA due to the insufficient number of trials available. The use of aztreonam 75 mg BID (RR, 1.66 [95% CrI, 0.08–34.30]) and aztreonam 75 mg TID (RR, 0.96 [95% CrI, 0.05–18.06]) was associated with similar risk of hospitalization compared with LIS.

For trials with 24 weeks of follow-up, hospitalization was reported in 4 trials.[8,23,28,29] Patients treated with LIS had a statistically significantly lower probability of hospitalization than those receiving placebo (OR, 3.16 [95% CrI, 1.53–5.78]), TIP (OR, 2.25 [95% CrI, 1.01–4.34]), or TIS (OR, 1.92 [95% CrI, 1.01–3.30]). LIS was associated with the lowest risk of hospitalization with a 96.5% of probability of being the best treatment, with a SUCRA value of 0.984, followed by TIP with a 1.8% probability of being the best treatment, with a SUCRA value of 0.399.

## Additional Antibiotics Use

Additional antibiotics use, defined as the need for additional inhaled or systemic antipseudomonal antibiotics, was reported in 5 trials[8–10,21,26] at 4 weeks. Compared with LIS, the use of TIS was associated with a statistically significantly higher need for additional antibiotics (OR, 2.19 [95% CrI, 1.03–4.08]). A similar nonsignificant trend was also observed when LIS was compared with placebo (OR, 1.04 [95% CrI, 0.56–1.76]). Aztreonam use was associated with a similar probability of additional antibiotics use than LIS (OR, 0.72 [95% CrI, 0.20–1.83]). Aztreonam was associated with the lowest need for additional antibiotics and had a 73.3% probability of being the best treatment, with a SUCRA value of 0.859, followed by placebo with a 16.9% probability of being the best treatment, with a SUCRA value of 0.555.

Among the trials with a study duration of 24 weeks, additional antibiotics use was reported in 5 trials.[8,23,26,28,29] Compared with LIS, the use of placebo (OR, 2.86 [95% CrI, 1.49–5.03]) and TIP (OR, 2.57 [95% CrI, 1.28–4.65]) was associated with a statistically significant higher probability of additional antibiotics use. A similar nonsignificant trend was also observed when LIS was compared with TIS (OR, 1.63

[95% CrI, 0.93–2.70]). Aztreonam use was associated with a similar probability of additional antibiotics use compared with LIS (OR, 0.76 [95% CrI, 0.35–1.47]). Aztreonam was associated with the lowest need for additional antibiotics and had an 82% probability of being the best treatment, with a SUCRA value of 0.955, followed by LIS with an 18% probability of being the best treatment, with a SUCRA value of 0.782.

## Study Withdrawal Rate

Study withdrawal rates (categorized as study withdrawal due to any reason, lack of efficacy, or AEs) were summarized. The specific AEs leading to study withdrawal were not able to be assessed due to limited information provided in the selected studies.

Study withdrawal was reported in 3 trials with 4 weeks of follow-up.[9,10,20] A direct comparison was conducted instead of the NMA due to insufficient number of trials available. The RR for the occurrence of withdrawal for any reason in patients treated with placebo compared with LIS was 0.416 (95% CI, 0.111–1.557). Withdrawal rates due to lack of efficacy was not reported in any of the studies with 4 weeks' follow-up. As for withdrawal due to AEs, a direct comparison was conducted instead of the NMA due to insufficient number of trials available. The RR for the occurrence of withdrawal due to AEs in patients treated with LIS compared with placebo was 0.76 (95% CI, 0.18–3.2).

Rates of withdrawal for any reason were reported in all of the trials with 24 weeks of follow-up. However, study withdrawal rates varied substantially among the studies. NMA showed that, compared with LIS, colistimethate sodium (OR, 1.65 [95% CrI, 0.53–3.90]), TIP (OR, 1.58 [95% CrI, 0.56–3.47]), aztreonam (OR, 0.51 [95% CrI, 0.15–1.27]), and TIS (OR, 0.92 [95% CrI, 0.37–1.85]) were all associated with a similar risk for study withdrawal for any reason. Aztreonam was associated with the lowest risk of withdrawal for any reason with a 91.2% probability of being the best treatment, with a SUCRA value of 0.976, followed by LIS with a 6.1% probability of being the best treatment, with a SUCRA value of 0.519.

An NMA was not performed for rates of withdrawal due to lack of efficacy because only 1 study with 24 weeks of follow-up reported this outcome. The rates of withdrawal from the study for any AEs were reported in 5 trials. NMA showed that compared with LIS, risk of withdrawal due to AEs were

comparable with aztreonam (OR, 0.29 [95% CrI, 0.003–1.59]), TIS (OR, 0.40 [95% CrI, 0.01–1.72]), and TIP (OR, 0.72 [95% CrI, 0.01–3.26] as well as colistimethate sodium (OR, 4.10 [95% CrI, 0.05–21.91]). Placebo was associated with the lowest risk of withdrawal for AEs and had a 68.7% probability of being the best treatment, with a SUCRA value of 0.875, follow by aztreonam with a 27.1% probability of being the best treatment, with a SUCRA value of 0.79.

## DISCUSSION

LIS is a new formulation of levofloxacin recently approved in Europe for the treatment of chronic pulmonary infection due to P aeruginosa in adult patients with CF. The safety and efficacy of LIS were assessed in 2 Phase III RCTs. The studies compared LIS with placebo and with TIS in patients with CF aged ≥12 years.[8,10]

In a multinational, randomized (2:1), double-blind study comparing LIS with placebo in 330 patients aged ≥12 years with CF over a single cycle of treatment (28 days on/28 days off), LIS did not significantly reduce protocol-defined pulmonary exacerbations, which was the primary end point of the study. However, LIS was associated with significantly higher relative change in $FEV_1\%$ predicted from baseline to day 28 than placebo, with a least squares mean difference of 2.42 (95% CI, 0.53–4.30).[30]

In another Phase III study, LIS was compared with TIS in a randomized, open-label, parallel-group, non-inferiority study in 282 patients for 24 weeks.[6] In this study, the treatment cycle included 28 days of treatment with LIS or TIS daily followed by 28 days with inhaled antibiotics. The relative change in $FEV_1\%$ predicted from baseline to day 28 with LIS, which was the primary end point, was noninferior to TIS. Interestingly, in a categorical assessment of FEV1% predicted, it was observed that 70% of patients receiving LIS exhibited improvement in relative change in $FEV_1\%$ predicted from baseline to day 28 compared with only 53% of patients receiving TIS ($P = 0.03$).

In both studies, patients had to receive at least three 28-day courses (>84 days) of TIS over the past 12 months to be eligible for study enrollment. The mandate of prior inhaled antibiotic use might have selected a group of patients with CF who may be more

difficult to manage and more likely not to respond well to another course of therapy. The presence of Staphylococcus aureus was noted in >50% of patients in both studies. The presence of other pathogens may affect a patient's response to inhaled antibiotics. These observations are important to consider when interpreting the findings of this NMA.

A previous NMA conducted by Littlewood et al[3] did not include LIS and did not address any safety or tolerability aspects of inhaled antibiotics when treating chronic P aeruginosa lung infection in patients with CF. The investigators concluded that all inhaled antibiotics evaluated were comparable in terms of efficacy at 4 weeks as measured by change from baseline in $FEV_1\%$ predicted, P aeruginosa sputum density, and acute pulmonary exacerbations.

With the recent approval of LIS for the treatment of chronic P aeruginosa lung infection in adult patients with CF, the relative efficacy of all currently available inhaled antibiotics must be determined to successfully guide health care decision-making. The aims of the present review focused on examining the clinical evidence across a number of clinical end points to assess efficacy for the most widely used inhaled antibiotics for the management of chronic P aeruginosa lung infection in patients with CF in a systematic approach. We then compared the efficacy of the most widely used inhaled antibiotics for the management of chronic P aeruginosa lung infection by using a Bayesian mixed treatment comparison of RCTs. An examination of study withdrawal rates (including study withdrawals due to AEs) was performed.

Few RCTs of inhaled antibiotics meet the rigorous inclusion and exclusion criteria for review. Although 12 months of follow-up is recommended by regulatory agencies, the majority of these RCTs had only 4 to 8 weeks of follow-up. We performed the NMA on both short-term (4 weeks) and long-term (24 weeks) efficacy outcomes and anticipated that there would be significant heterogeneity across all trials.

The relative $FEV_1\%$ predicted change from baseline to 4 weeks seemed to be numerically highest with aztreonam. The relative $FEV_1\%$ predicted change from baseline to 4 weeks with LIS was numerically higher than with TIS, TIP, colistimethate sodium, and placebo, but all the 95% CrIs included zero. Similarly, the relative $FEV_1\%$ change from baseline to 24 weeks also seemed to be numerically higher for LIS compared with TIS, TIP, and aztreonam but not significantly better

than these comparators. At 24 weeks, LIS was found to be significantly better than placebo, which is consistent with the findings from the 2 Phase III studies.

Although $FEV_1\%$ is a well-recognized end point in assessing efficacy of inhaled antibiotics in patients with CF, other clinical outcomes (eg, changes in P aeruginosa sputum density, acute pulmonary exacerbation, hospitalization, additional antibiotics use) should also be considered when assessing the efficacy of these inhaled antibiotics.

The NMA for P aeruginosa density change from baseline to 4 weeks found that levofloxacin had significantly better P aeruginosa sputum density improvement than placebo (mean change vs levofloxacin, 0.64), but both tobramycin formulations (TIS and TIP) and aztreonam were found to be numerically more effective than levofloxacin at 4 weeks, although probabilities of inferiority of levofloxacin were <95%. The NMA for P aeruginosa density change from baseline to 24 weeks also found that both tobramycin formulations were numerically more effective than levofloxacin but were not significant because the 95% CrI included zero.

Acute pulmonary exacerbation is an important clinical outcome, but there is no standard definition for acute pulmonary exacerbation and no established guidelines on how this should be measured in clinical trials. As discussed earlier, one of the LIS Phase III clinical studies did not meet the primary end point of superiority in the time to pulmonary exacerbation compared with placebo.[30] Thus, for the purpose of this NMA, we adopted 2 proxies for CF acute pulmonary exacerbations: hospitalizations and additional antibiotic use.

For trials with 4 weeks of follow-up, an indirect comparison was conducted for hospitalization instead of NMA due to insufficient trials being available. Patients treated with aztreonam 75 mg BID were more likely to be hospitalized than patients treated with levofloxacin. However, this trend was not observed in patients treated with aztreonam 75 mg TID. In trials with 24 weeks of follow-up, hospitalization was reported in 4 trials with TIS and TIP, levofloxacin, and placebo. Patients treated with levofloxacin were significantly less likely to be hospitalized compared with placebo, TIP, and TIS. Because the definitions for hospitalization varied across studies, these findings should be interpreted with caution. There has been a trend of managing acute pulmonary exacerbations at home rather than at hospitals.

Additional antibiotics use was reported in 5 trials with 4 weeks of follow-up that were included in the NMA.[8–10,26,27] Compared with patients treated with levofloxacin, patients treated with TIS or who received placebo required additional antibiotics. These findings were comparable with the NMA conducted in trials with 24 weeks of follow-up.[6,23,26,28,29] The use of levofloxacin was associated with a numerically lower probability of additional antibiotics use than the use of TIS, TIP, and placebo. Similar to hospitalization, the definitions for additional antibiotics use varied between studies, and thus the results should be interpreted with caution.

Because not all studies reported AEs, we could not directly compare the safety profiles of these inhaled antibiotics. Although study withdrawal rates were examined, definitive conclusions about the relative safety profiles of these inhaled antibiotics could not be made. The study withdrawal rates due to any reason and due to any AEs were analyzed in the NMA by using trials with 24 weeks of follow-up. Compared with LIS, there was a trend of higher probabilities of study withdrawal for patients treated with colistimethate sodium, TIP, and placebo. A trend toward a lower probability of withdrawal was found for aztreonam and TIS compared with LIS.

Due to the limitations of the study design of each trial, the heterogeneity of these studies, and the variability of outcomes due to changes in clinical practice over time, the results of this NMA should be considered with caution. Additional evaluation and/or further studies may be warranted. An open-label study design is associated with risk of bias such as performance and detection bias for outcomes and study withdrawal. As such, the decision to withdraw from an open-label or unblinded study may be influenced by the physician or patient's knowledge of the treatment received. In addition, a patient's baseline characteristics such as prior antibiotic use and presence of other pathogens could influence the response to inhaled antibiotics. Because we excluded studies that involved patients aged <6 years, our findings cannot be extrapolated to patients in this age group.

Due to the limited number of studies available for inclusion, it was not possible to fully account for heterogeneity among the studies included in the NMA. Only fixed effect models were constructed for the NMA using trials with 24 weeks of follow-up.

Because we were unable to construct random models due to the small number of studies, the CrIs might not have represented the full extent of uncertainty around results. Additional research is therefore needed to determine the impact of other potential effect modifiers on outcomes and to assess their relative importance in influencing outcomes. The lack of significant evidence of this NMA does not imply that the inhaled antibiotics evaluated were not different in terms of efficacy. A difference in efficacy among these inhaled antibiotics may be present, but due to the limited data available for comparison, a significant difference may not have been observed. Thus, it is important to interpret our findings with caution and consider other clinical efficacy outcomes when selecting an inhaled antibiotic in treating pulmonary infection in patients with CF.

## CONCLUSIONS

Based on this SLR and NMA, the analyses for many of the outcomes evaluated did not provide significant evidence to indicate that the other inhaled antibiotics were either more or less effective than LIS. Although additional studies on each of these outcomes are needed, there is a trend in favor of LIS for the relative $FEV_1\%$ change from baseline at 24 weeks and for reducing the need of hospitalization. Because patients with CF with chronic *P aeruginosa* infections frequently require changes in treatment, the availability of LIS provides a useful option to preserve respiratory function over a longer period of time.

## ACKNOWLEDGMENTS

## CONFLICTS OF INTERESTS

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