Inhaled colistimethate sodium in patients with bronchiectasis and *Pseudomonas aeruginosa* infection: results of PROMIS-I and PROMIS-II, two randomised, double-blind, placebo-controlled phase 3 trials assessing safety and efficacy over 12 months

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Summary

Background Chronic lung infection with *Pseudomonas aeruginosa* is associated with increased exacerbations and mortality in people with bronchiectasis. The PROMIS-I and PROMIS-II trials investigated the efficacy and safety of 12-months of inhaled colistimethate sodium delivered via the I-neb.

Methods Two randomised, double-blind, placebo-controlled trials of twice per day colistimethate sodium versus placebo were conducted in patients with bronchiectasis with *P aeruginosa* and a history of at least two exacerbations requiring oral antibiotics or one requiring intravenous antibiotics in the previous year in hospitals in Argentina, Australia, Belgium, Canada, France, Germany, Greece, Israel, Italy, Netherlands, New Zealand, Poland, Portugal, Spain, Switzerland, the UK, and the USA. Randomisation was conducted through an interactive web response system and stratified by site and long term use of macrolides. Masking was achieved by providing colistimethate sodium and placebo in identical vials. After random assignment, study visits were scheduled for 1, 3, 6, 9, and 12 months (the end of the treatment period); and telephone calls were scheduled for 7 days after random assignment and 2 weeks after the end of treatment. The primary endpoint was the mean annual exacerbation rate. These trials are registered with EudraCT: number 2015–002743–33 (for PROMIS-I) and 2016–004558–13 (for PROMIS-II), and are now completed.

Findings 377 patients were randomly assigned in PROMIS-I (177 to colistimethate sodium and 200 to placebo; in the modified intention-to-treat population, 176 were in the colistimethate sodium group and 197 were in the placebo group) between June 6, 2017, and April 8, 2020. The annual exacerbation rate was 0·58 in the colistimethate sodium group versus 0·95 in the placebo group (rate ratio 0·61; 95% CI 0·46–0·82; p=0·0010). 287 patients were randomly assigned in PROMIS-II (152 were assigned to colistimethate sodium and 135 were assigned to placebo, in the modified intention-to-treat population), between Feb 12, 2018, and Oct 22, 2021. PROMIS-II was then prematurely terminated due to the effect of the COVID-19 pandemic. No significant difference was observed in the annual exacerbation rate between the colistimethate sodium and placebo groups (0·89 *vs* 0·89; rate ratio 1·00; 95% CI 0·75–1·35; p=0·98). No major safety issues were identified. The overall frequency of adverse events was 142 (81%) patients in the colistimethate sodium group versus 159 (81%) patients in the placebo group in PROMIS-I, and 123 (81%) patients versus 104 (77%) patients in PROMIS-II. There were no deaths related to study treatment.

Interpretation The data from PROMIS-I suggest a clinically important benefit of colistimethate sodium delivered via the I-neb adaptive aerosol delivery system in patients with bronchiectasis and *P aeruginosa* infection. These results were not replicated in PROMIS-II, which was affected by the COVID-19 pandemic and prematurely terminated.

Funding Zambon.

Introduction

Patients with bronchiectasis develop a chronic infection of the airways as a result of impaired mucociliary clearance and dysfunctional host immunity.[1] Increased bacterial load within the airway is associated with increased airway inflammation and an increased risk of exacerbation.[2] Preventing exacerbations is a key priority in the management of patients with bronchiectasis.[3]

Pseudomonas aeruginosa is the most common pathogen isolated from the airways of patients with bronchiectasis.[4,5] The identification of *P aeruginosa* in sputum is associated with greater airway inflammation, worse

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See Online for appendix

Research in context

Evidence before this study

Chronic *Pseudomonas aeruginosa* infections in patients with bronchiectasis are associated with increased exacerbation frequency and mortality. Inhaled antibiotics are widely used in clinical practice for the management of chronic *P aeruginosa* infections. We searched PubMed and Medline, from database inception to June 29, 2024, with no language restrictions, for randomised controlled trials on long-term use of inhaled antibiotics in adult patients with bronchiectasis and chronic respiratory infections. Search terms are listed in the appendix (p 43). We identified 165 studies, and after excluding studies that did not fit our criteria, we identified 19 randomised controlled trials of inhaled antibiotics in bronchiectasis. These studies found a 21% reduction in exacerbations and a 52% reduction in severe exacerbations with inhaled antibiotic treatment compared with placebo. High heterogeneity was observed between studies and most data were for inhaled fluoroquinolones.

Added value of this study

This study reports the results of two replicate, phase 3, double blind, randomised, placebo-controlled trials of colistimethate sodium delivered via the I-neb adaptive aerosol delivery device in patients with bronchiectasis—PROMIS-I and PROMIS-II. In PROMIS-I, a statistically significant reduction in the frequency of exacerbations, the primary outcome, was observed along with a significant reduction in severe exacerbations and a significant improvement in quality of life measured using the St Georges Respiratory Questionnaire. PROMIS-II was prematurely terminated due to the COVID-19 pandemic and after the positive results of PROMIS-I. No significant effect of colistimethate sodium was observed on exacerbation frequency or other endpoints in PROMIS-II. A post-hoc analysis identified that before the COVID-19 pandemic, the results of PROMIS-II were consistent with PROMIS-I, but no beneficial effect of treatment was observed during the COVID-19 pandemic period.

Implications of all the available evidence

The data from PROMIS-I and the pre-pandemic period of PROMIS-II show the efficacy of colistimethate sodium delivered via the I-neb system in patients with bronchiectasis and a *P aeruginosa* infection. Although the COVID-19 pandemic provides a highly plausible explanation for the inconsistent results in PROMIS-II, some other unknown and unmeasured factors might have contributed in part to the inconsistency observed between the two trials. The totality of the evidence provided by the PROMIS trials adds to the literature supporting international guideline recommendations to offer inhaled antibiotic treatment to patients with bronchiectasis, chronic *P aeruginosa* infection, and a history of frequent exacerbation.

symptoms and lung function, accelerated lung function decline, increased exacerbations of bronchiectasis, increased risk of hospitalisation, and increased mortality compared with patients not infected with *P aeruginosa*.[1] As a result of the worse outcomes associated with this infection, international guidelines recommend long-term antibiotic treatment for patients with chronic infection and frequent exacerbations.[3]

Inhaled antibiotics have major theoretical advantages over systemic antibiotics, delivering a high concentration of the antibiotic to the site of infection and therefore increasing efficacy and reducing the risk of antibiotic resistance.[6] Inhaled antibiotics have been the standard of care in cystic fibrosis for several decades but results in patients with bronchiectasis not caused by cystic fibrosis have been inconsistent.[7,8] A meta-analysis of 2596 patients enrolled in 16 trials found high heterogeneity in the treatment response between trials, but overall reported a significant reduction in exacerbations with inhaled antibiotics compared with no inhaled antibiotics, predominantly inhaled fluoroquinolones.[9]

Colistimethate sodium is the most widely used inhaled antibiotic for bronchiectasis in Europe.[10] A phase 2 trial of colistimethate sodium found a longer time to first exacerbation compared with placebo in a preplanned analysis of adherent patients.[6] There have been no previous large phase 3 trials of inhaled colistimethate sodium in patients with bronchiectasis. Here we report the results of two phase 3 trials of colistimethate sodium delivered via the I-neb adaptive aerosol delivery system in patients with bronchiectasis and chronic *P aeruginosa* infection.

Methods

Trial design and patients

These two phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel group interventional trials were performed in adult patients with bronchiectasis chronically infected with *P aeruginosa* in hospitals in in 12 countries in PROMIS-I (Australia, Belgium, Germany, Greece, Israel, Italy, Netherlands, New Zealand, Portugal, Spain, Switzerland, and the UK) and 12 countries in PROMIS-II (Argentina, Australia, Canada, France, Germany, Greece, Israel, Italy, New Zealand, Poland, Portugal, and the USA). Patients received inhaled colistimethate sodium (1 million IU; delivered dose, 0·3 million IU) or placebo via the I-neb device (Xellia Pharmaceuticals Aps, Copenhagen, Denmark) twice a day for up to 12 months. Eligible patients were 18 years or older with CT-confirmed bronchiectasis, a history of *P aeruginosa* respiratory infection, and a *P aeruginosa* positive sputum culture during the trial screening period. Participants also had to have had at least two pulmonary exacerbations requiring oral antibiotic treatment or one exacerbation requiring

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intravenous antibiotic treatment in the 12 months preceding the screening visit. Key exclusion criteria were bronchiectasis due to cystic fibrosis, current treatment for allergic bronchopulmonary aspergillosis or mycobacterial infection, a change in pulmonary treatment in the 30 days before the screening visit, or a change in treatment between the screening visit and random assignment. Treatment with long-term macrolides was allowed during the study. Complete eligibility criteria are provided in the appendix (pp 23–25). Treatment was administered using the I-neb adaptive aerosol delivery device, a vibrating mesh nebuliser device designed to adapt to changes in the patients' breathing pattern to optimise aerosol delivery to the airways.[11]

The trial was performed in accordance with the ethical principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Council for Harmonisation, and applicable regulatory requirements. Approval from independent ethics committees were obtained. All patients provided written informed consent. A data assessment committee reviewed masked data to ensure that the protocol defined pulmonary exacerbations were appropriately identified. The trials were prospectively registered under the EudraCT trial registration numbers 2015–002743–33 (for PROMIS-I) and 2016–004558–13 (for PROMIS-II).

Randomisation and masking

Patients who met the eligibility criteria during the screening period were randomly assigned 1:1 by an interactive web response system to receive colistimethate sodium or placebo by inhalation through the I-neb adaptive aerosol delivery system twice per day for up to 12 months. Randomisation was stratified by site and the stable use of macrolide antibiotics. Randomisation within each site and nested level of macrolide use was done using blocks of four to optimise the balance between colistimethate sodium and placebo at any stage of the enrolment. Adherence was recorded electronically by the I-neb. Masking was done by providing treatment and placebo in identical empty glass vials, to which the same saline diluent was added in exactly the same way as the active treatment by injecting the diluent through the rubber stopper. The glass vials were shrink wrapped with opaque white plastic.

Procedures

After randomisation, study visits were scheduled for 1, 3, 6, 9, and 12 months (the end of the treatment period); and telephone calls were scheduled for 7 days after randomisation and 2 weeks after the end of treatment.

A pulmonary exacerbation was defined as the concurrent presence of at least three of the following symptoms or signs for at least 24 h that resulted in antibiotic treatment: increased cough; increased sputum volume or consistency, or both; increased sputum purulence; new or increased haemoptysis; increased wheezing; increased dyspnoea; increased fatigue or malaise, or both; and episodes of fever. Severe exacerbations were those that led to treatment with intravenous antibiotics, hospitalisation, or were associated with episodes of radiologically confirmed pneumonia, or a combination. Further details of the recording of pulmonary exacerbations are outlined in the appendix (pp 26–27).

The St George's Respiratory Questionnaire and the Quality of Life Bronchiectasis questionnaire were administered at randomisation and at each subsequent study visit.[12,13] Further details on the quality of life tools are available in the appendix (pp 27–28). Sputum samples to measure *P aeruginosa* density (colony forming units [CFU] per mL of sputum) and colistimethate sodium minimum inhibitory concentration were collected at screening; randomisation; after 1, 6, and 12 months of treatment; and at the time of exacerbation.

Safety endpoints monitored from enrolment up to 2 weeks after the end of treatment included adverse events, clinical laboratory test results, vital signs, physical examination findings, 12-lead electrocardiograph measurements, spirometry, and treatment-related bronchospasm. During each patient contact, investigators were responsible for the detection of adverse events.

Endpoints and assessments

The primary efficacy endpoint was the annual pulmonary exacerbation rate. Key secondary efficacy endpoints, listed in hierarchical order of statistical analysis, were time to first exacerbation, quality of life (St George's Respiratory Questionnaire total score), change in *P aeruginosa* density, severe exacerbation rate, and time to first severe exacerbation. Further endpoints are listed in the appendix (pp 28–29).

Effect of the COVID-19 pandemic

As illustrated in the appendix (pp 33–34), the COVID-19 pandemic was announced by WHO on March 11, 2020, during the conduct of PROMIS-II, with PROMIS-I largely unaffected. The pandemic led to the implementation of protocol amendments in both studies to allow patients to continue with the trial with in-home assessments and trial drug provision. Modifications to the trial are reported in line with the CONSERVE 2021 statement.[14] Modifications to the trial were planned and implemented by the study sponsor in consultation with the regulatory authorities. Several visits were conducted remotely by phone (excluding screening and randomisation visits) to collect as much information as possible, in line with regulatory authority and ethics committee approvals. Exacerbation data and adverse event information were collected remotely, where necessary. However, some assessments such as physical examinations, blood sampling, and spirometry could not be performed remotely and were recorded as protocol deviations. A direct-to-patient supply of investigational medicinal product was also established where necessary to

minimise the patient's potential exposure to COVID-19 after investigators had confirmed that patients were safe to continue in the study. After consultation with the US Food and Drug Administration in October, 2021, PROMIS-II was prematurely terminated in March, 2022, as a consequence of recruitment difficulties related to the pandemic and because physicians did not belive it appropriate to randomise patients after the positive results of PROMIS-I.

Statistical analysis

The sample size was calculated considering the results from the previous phase 2 trial,[6] relevant literature, and the clinically meaningful benefit the treatment should provide. Annual exacerbation rates of 1·090 for placebo and 0·709 for colistimethate sodium were assumed, representing a 35% hypothesised treatment effect; with an assumed dispersion of 0·20 and a follow-up time of 1 year; a sample size per trial of 170 patients per group, which provided a power of 90%; and the 1-sided 0·025 α level. Allowing for a 20% dropout rate, the target sample size per trial was therefore initially 210 patients per treatment. A blind event rate review in PROMIS-I was conducted in January, 2020, which highlighted that the initial power calculation had assumed that patients who dropped out would not contribute data to the analysis. The blind event rate review used the observed overall exacerbation rate and the mean dropout time to establish that a sample of 188 patients per group (376 total, adjusted for dropout) would be sufficient to detect a 35% treatment effect (a magnitude chosen as being clinically meaningful) with 90% power.

Efficacy analyses were based on the modified intention-to-treat population, which comprised all patients who provided informed consent, were randomly assigned, and received at least one dose or a partial dose of the investigational medicinal product. Two-sided p values of less than 0·05 were considered statistically significant, and two-sided 95% CIs were presented where appropriate. To address multiplicity across endpoints, a hierarchical testing procedure was predefined to the key secondary endpoints with the following hierarchy: time to first exacerbation, quality of life (St George's Respiratory Questionnaire total score), change in *P aeruginosa* density, severe exacerbation rate, and time to first severe exacerbation. Further endpoints are listed in the appendix (pp 28–29).

The primary efficacy endpoint, the annual pulmonary exacerbation rate, was analysed using negative binomial modelling with terms for randomised treatment, country, and stable concomitant use of macrolides (the stratification factors) as fixed effects and log exposure time on treatment as the offset. To assess the potential effect of missing data on the results of the primary efficacy analysis, missing at random, copy reference, and tipping point sensitivity analyses using multiple imputation were performed.

The time to first pulmonary exacerbation event was analysed by Cox proportional hazards regression. The terms included were the same as those for the negative binomial model. Change from baseline in St George's Respiratory Questionnaire total score was analysed using a mixed model repeated measures analysis with terms for treatment, visit, treatment-by-visit interaction, use of stable concomitant therapy with oral macrolides, and country. *P aeruginosa* density, as established by change in $\log_{10}$ CFU/mL sputum from baseline to day 28 (visit 3), 6 months (visit 5), and 12 months (visit 7), was compared between treatment groups by mixed model repeated measures analysis with a log baseline value as the covariate. All safety variables were summarised overall and by treatment group using the safety population.

Because PROMIS-II was conducted predominantly during the COVID-19 pandemic, the effect of the pandemic on PROMIS-II outcomes was investigated in exploratory analyses. To assess the consistency of results between trials, a fixed effects meta-analysis of the phase 2 study, PROMIS-I, and the pre-pandemic data from PROMIS-II was performed. Both fixed and random effect meta-analyses were performed.[15] The fixed effects analysis was a standard inverse variance weighted combination of log scale estimated treatment effects across the three trials. The random effects analysis considered trial as a random effect and incorporated a between-trial variance component, if any, into the weighted combination of treatment effects. All post-hoc and exploratory analyses did not include adjustment for multiple testing. More information on the statistical analysis, including sensitivity analyses to account for missing data, are provided in the appendix (pp 29–32). SAS version 9.4 was used for all statistical analyses.

Role of the funding source

The sponsor developed the protocol with the lead investigator (CSH) and conducted the data analyses in accordance with a predefined analysis plan, and was involved in data collection, data interpretation, and editing of the report. The funder of the study had no role in writing of the report.

Results

PROMIS-I was conducted at 86 sites in 12 countries. 538 patients were screened, of whom 377 were randomly assigned between June 6, 2017, and April 8, 2020. The first patient was enrolled in June, 2017, and the last patient completed follow-up in April, 2021. 177 were assigned to colistimethate sodium and 200 were assigned to placebo. The study completion rate was 123 (69%) patients in the colistimethate sodium group and 129 (65%) patients in the placebo group. The mean investigational medicinal product adherence was 87·6% (SD 23·4) in the colistimethate sodium group and 87·1% (22·1) in the placebo group.

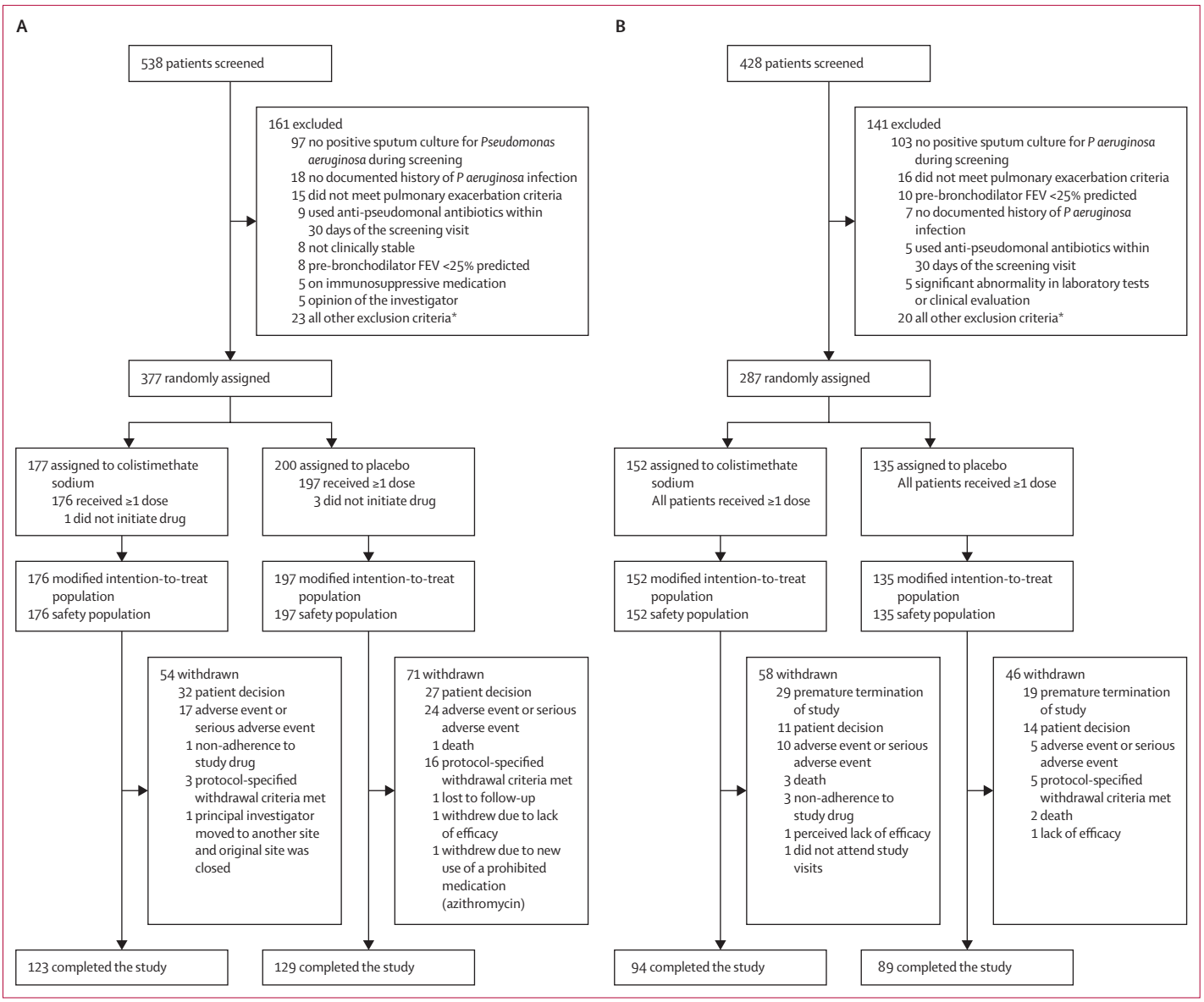

Figure: **Trial profile**
(A) PROMIS-I. (B) PROMIS-II. Patients could be excluded for more than one reason. *All other exclusion criteria for PROMIS-I include: 1 no informed consent, 3 no CT confirmation of bronchiectasis, 1 hypogammaglobulinaemia requiring treatment with immunoglobulin, 2 severe cardiovascular disease, 1 major surgery in the 3 months before screening, 1 allergic bronchopulmonary aspergillosis, 1 predominant lung condition being asthma, chronic obstructive pulmonary disease, or interstitial lung disease, 2 respiratory failure, 2 current active malignancy, 1 non-tuberculous mycobacterial infection, 2 intolerance of β2 agonists, 1 known or suspected allergy to colistimethate sodium, 1 new treatment with long-term macrolides, 3 significant abnormality in clinical evaluation or laboratory tests, and 1 participated in another investigational interventional trial within 30 days. All other exclusion criteria for PROMIS-II include: 3 no informed consent, 1 hypogammaglobulinaemia requiring treatment with immunoglobulin, 2 not clinically stable, 1 severe cardiovascular disease, 1 predominant lung condition being asthma, chronic obstructive lung disease, or interstitial lung disease, 2 respiratory failure, 3 on immunosuppressive medication, 2 current infection with *Mycobacterium tuberculosis*, 2 new treatment with longterm macrolides, and 3 opinion of the investigator.

PROMIS-II was conducted at 89 sites in 12 countries. 428 patients were screened, of whom 287 were randomly assigned between Feb 12, 2018, and Oct 22, 2021. The first patient was enrolled in January, 2018 and the last patient completed in March, 2022. 152 were assigned to colistimethate sodium and 135 were assigned to placebo. The study completion rate was 94 (62%) patients in the colistimethate sodium group and 89 (66%) patients in the placebo group. 29 (19%) in the colistimethate sodium group and 19 (14%) in the placebo group discontinued the study as a result of the premature termination of the study. Of the patients who did not reach the full 1-year follow-up, the median time on study was 189 days for the 58 patients in the colistimethate sodium group compared with 176 days for the 46 patients in the placebo group. The mean investigational medicinal product adherence was 89·9% (SD 20·9) in the colistimethate sodium group and 89·8% (20·6) in the placebo group. The CONSORT

	PROMIS-I		PROMIS-II	
	Colistimethate sodium (N=176)	Placebo (N=197)	Colistimethate sodium (N=152)	Placebo (N=135)
Age, years	64·2 (14·9)	64·2 (13·1)	59·9 (15·2)	59·6 (14·7)
Sex				
Female	123 (70%)	126 (64%)	104 (68%)	94 (70%)
Male	53 (30%)	71 (36%)	48 (32%)	41 (30%)
Ethnicity				
Hispanic or Latino	7 (4%)	7 (4%)	60 (39%)	55 (41%)
Not Hispanic or Latino	166 (94%)	187 (95%)	88 (58%)	77 (57%)
Not reported	3 (2%)	3 (2%)	4 (3%)	3 (2%)
Race				
Caucasian	167 (95%)	189 (96%)	146 (96%)	130 (96%)
Black	0	0	3 (2%)	3 (2%)
Northeast Asian	0	1 (1%)	0	0
Southeast Asian	5 (3%)	2 (1%)	2 (1%)	0
Mixed	0	1 (1%)	1 (1%)	1 (1%)
Other	4 (2%)	4 (2%)	0	1 (1%)
Baseline forced expiratory volume, % of the predicted value	62·4 (20·7)	64·5 (18·9)	57·9 (20·8)	58·7 (20·1)
Number of lobes affected				
1	14 (8%)	14 (7%)	18 (12%)	15 (11%)
2	47 (27%)	39 (20%)	35 (23%)	30 (22%)
3	30 (17%)	44 (22%)	28 (18%)	39 (29%)
>3	81 (46%)	95 (48%)	59 (39%)	39 (29%)
Not available	3 (2%)	5 (3%)	9 (6%)	11 (8%)
Missing	1 (1%)	0	3 (2%)	1 (1%)
Underlying cause of bronchiectasis				
Idiopathic or unknown	109 (62%)	124 (63%)	90 (59%)	90 (66%)
Infection	35 (20%)	52 (26%)	39 (26%)	29 (21%)
Fibrosis (traction bronchiectasis)	1 (1%)	0	1 (1%)	0
Inflammatory condition	2 (1%)	2 (1%)	5 (3%)	3 (2%)
Other	29 (16%)	19 (10%)	17 (11%)	14 (10%)
Not known	96 (55%)	111 (56%)	84 (55%)	81 (60%)
Common respiratory comorbidities				
Asthma	45 (26%)	35 (18%)	33 (22%)	27 (20%)
COPD	21 (12%)	17 (9%)	23 (15%)	22 (16%)
Macrolide use, N (%)	51 (29%)	70 (36%)	49 (32%)	48 (36%)
Never smoker, N (%)	124 (70%)	142 (72%)	108 (71%)	92 (68%)
Bronchiectasis history				
Exacerbations requiring oral antibiotics in 12 months before screening visit	2·3 (1·4)	2·3 (1·3)	1·9 (1·2)	1·9 (1·2)
Exacerbations requiring intraveneous antibiotics in 12 months before screening visit	0·5 (0·7)	0·4 (0·6)	0·5 (0·8)	0·5 (0·8)

Data are mean (SD) or n (%).

Table 1: **Demographics and clinical characteristics of the participants at baseline (modified intention-to-treat population)**

flowchart is shown in the figure. The demographic and clinical characteristics of the participants at baseline are summarised in table 1.

In PROMIS-I, there were 60 (34%) patients in the colistimethate sodium group with a total of 89 exacerbations. In the placebo group, 96 (48%) patients had a total of 163 exacerbations. The annual pulmonary exacerbation rate was 0·58 in the colistimethate sodium group and 0·95 in the placebo group. The rate ratio of exacerbations with colistimethate sodium relative to placebo was 0·61 (95% CI 0·46–0·82; p=0·0010). Sensitivity analyses accounting for patients with incomplete follow-up via multiple imputation supported the findings of the primary analysis (appendix pp 38–39).

In PROMIS-II there were 72 (47%) patients in the colistimethate sodium group with a total of 111 exacerbations. In the placebo group, 64 patients (47%) had a total of 98 exacerbations. The annual exacerbation rate was 0·89 in both groups. The rate ratio of colistimethate sodium relative to placebo was 1·00 (95% CI 0·75–1·35; p=0·98).

Statistically and clinically significant benefits were seen across multiple secondary endpoints in PROMIS-I. Time to first exacerbation was improved with colistimethate sodium compared with placebo (HR 0·590; 95% CI 0·432–0·806; p=0·00074). In PROMIS-I, statistically significant improvements with colistimethate sodium versus placebo were also observed for quality of life (St George's Respiratory Questionnaire total score), *P aeruginosa* density, annual rate of severe exacerbations, and time to first severe exacerbation. The secondary efficacy endpoints in PROMIS-I and PROMIS-II are presented in table 2. Additional secondary efficacy data are presented in the appendix (pp 40–42).

Because PROMIS-II did not reach significance on the primary endpoint, secondary efficacy endpoints are presented with effect estimates and 95% CIs without p values, as per the hierarchical analysis plan. Median time to first exacerbation was 53 days longer in the colistimethate sodium group compared with placebo (267 days *vs* 214 days; table 2). A greater reduction in *P aeruginosa* density was observed with colistimethate sodium compared with placebo (least squares mean treatment difference after 28 days, –1·60 $\log_{10}$/CFU per mL sputum; 95% CI –1·98 to –1·22) and over the full treatment period (–1·07 $\log_{10}$/CFU per mL sputum; –1·38 to –0·76).

The effect of the COVID-19 pandemic was investigated by evaluating the primary and secondary exacerbation endpoint data accruing before and after pandemic onset, delineated by the date on which WHO declared the pandemic (March 11, 2020). The appendix (pp 33–34) illustrates the number of patients randomly assigned and the exacerbation events occurring in both trials both before and after the pandemic onset. The primary efficacy and key secondary outcome data for the pre-pandemic and pandemic periods of PROMIS-II are shown in table 3. The pre-pandemic annual exacerbation rate ratio for colistimethate sodium versus placebo was 0·725 (95% CI 0·488–1·078) and the rate ratio was 1·403 (0·926–2·125) during the pandemic period. The annual exacerbation rate in the placebo group fell sharply by 50·8% after the start of the pandemic (from 1·263 pre-pandemic to 0·621 during the pandemic), with the

	PROMIS-I			PROMIS-II		
	Colistimethate sodium (n=176)	Placebo (n=197)	p value	Colistimethate sodium (N=152)	Placebo (N=135)	p value
Primary efficacy endpoint						
Annual exacerbation rate, least squares mean, negative binomial model	0·580	0·948	..	0·889	0·885	..
Annual rate ratio, least squares mean	..	0·612 (95% CI 0·457 to 0·820)	p=0·0010	..	1·004 (0·747 to 1·349)	p=0·98
Secondary efficacy endpoints, in order of protocol specified hierarchical testing						
Median time to first exacerbation, days	NR (95% CI 266·0 to NR)	208·0 (152·0 to 261·0)	..	267·0 (189·0 to 357·0)	214·0 (177·0 to 279·0)	..
Kaplan Meier, 25–75% percentile	122·0 to NR	67·0 to NR	..	73·0 to NR	83·0 to NR	..
Comparison of survival curves	..	..	p=0·00074	..	..	Not reported*
Hazard ratio for time to first exacerbation, Cox model	..	0·590 (95% CI 0·432 to 0·806)	..	..	0·928 (95% CI 0·671 to 1·284)	..
Change from baseline to 12 months or end of treatment in St George's Respiratory Questionnaire total score for quality of life between treatment groups, number of patients with data available	124	144	..	91	86	..
Change from baseline to 12 months or end of treatment in St George's Respiratory Questionnaire total score for quality of life between treatment groups, least squares mean, linear mixed model	..	−4·552 (95% CI −7·755 to −1·349)	p=0·0055	..	0·457 (95% CI −3·692 to 4·606)	Not reported*
Pseudomonas aeruginosa density, log_{10}/CFU/mL, change from baseline to day 28	101	148	..	87	98	..
P aeruginosa density, log_{10}/CFU/mL, change from baseline to day 28, least squares mean	−1·627 (95% CI −1·908 to −1·346)	−0·007 (95% CI −0·238 to 0·225)	..	−1·679 (95% CI −1·975 to −1·383)	−0·081 (−0·365 to 0·203)	..
Least squares mean difference in log_{10}/CFU/mL between the treatment groups from baseline to day 28	..	−1·620 (95% CI −1·987 to −1·254)	p<0·00001	..	−1·598 (95% CI −1·978 to −1·219)	Not reported*
Severe exacerbation annual rate ratio, least squares mean	..	0·409 (95% CI 0·227 to 0·738)	p=0·0030	..	1·334 (95% CI 0·689 to 2·585)	Not reported*
Time to first severe exacerbation, days, median	NR (NR to NR)	NR (NR to NR)	..	NR (NR to NR)	NR (NR to NR)	..
Time to first severe exacerbation, days, Kaplan Meier, 25–75% percentile	NR to NR	NR to NR	..	NR to NR	NR to NR	..
Comparison of survival curves	..	..	p=0·033	..	..	Not reported*
Patients with one or more instance of hospitalisation for exacerbation of all patients with at least one exacerbation	14/60 (23%)	25/96 (26%)	..	12/72 (17%)	10/64 (16%)	..
Relative risk ratio	..	0·627 (95% CI 0·337 to 1·167)	p=0·17	..	..	..
Annual rate ratio, least squares mean	..	..	..	..	1·009 (95% CI 0·516 to 2·343)	Not reported*

CFU=colony forming unit. NR=not reached. *Not reported due to statistical hierarchy.

Table 2: **Primary and key secondary endpoints for PROMIS-I and PROMIS-II in the intention-to-treat population**

corresponding rate in the colistimethate sodium group falling by only 5·4% after the start of the pandemic (from 0·916 pre-pandemic to 0·871 during the pandemic). Sensitivity analyses to assess the possible effect of patients with incomplete follow-up support the primary endpoint findings during the pre-pandemic and pandemic periods of the study. Median time to first exacerbation was numerically longer for colistimethate sodium in both the pre-pandemic and during pandemic periods. The median annual rate of hospitalisations for exacerbations in the pre-pandemic period was numerically lower with colistimethate sodium compared with placebo. A meta-analysis of the PROMIS trials indicated a consistency of results between PROMIS-I, the pre-pandemic period of PROMIS-II, and the phase 2 study[6] (appendix pp 35–36). In contrast, the appendix (p 37) shows that the pandemic data from PROMIS-II are inconsistent with the data from PROMIS-I, the pre-pandemic period of PROMIS-II, and the phase 2 study.[6]

In PROMIS-I, 142 patients (81%) in the colistimethate sodium group and 159 (81%) patients in the placebo group had at least one treatment emergent adverse event (TEAE), most of which were mild or moderate in severity (table 4). 45 serious TEAEs were reported in 31 (18%) patients in the colistimethate sodium group, compared with 67 serious TEAEs reported in 46 (23%) patients in the placebo group. Two patients (one in each group) died during the study period. The deaths were considered by the investigators to be unrelated to the study treatment. Bronchospasm was reported in five (3%) of 176 in the colistimethate sodium group and two (1%) of 197 in the placebo group.

In PROMIS-II, 123 (81%) patients in the colistimethate sodium group and 104 (77%) patients in the placebo group had at least one TEAE and most were mild or moderate in

	Colistimethate sodium	Placebo
Pre-COVID-19 period (before March 11, 2020)		
Number of patients with exacerbation data available	89	83
Annual exacerbation rate, least squares mean, negative binomial model	0·916	1·263
Exacerbation rate ratio	..	0·725 (95% CI 0·488 to 1·078)
Median time to first exacerbation, median number of days*	222·0 (95% CI 157·0 to 357·0)	189·0 (95% CI 139·0 to 246·0)
Median time to first exacerbation, days, Kaplan Meier, 25–75% percentile	75·0 to NR	84·0 to NR
Comparison of survival curves		
Number of patients with St George's Respiratory Questionnaire data available	85	76
St George's Respiratory Questionnaire least squares mean change from baseline in total score	−5·261 (95% CI −7·851 to −2·670)	−6·569 (95% CI −9·316 to −3·822)
Difference in least squares means	..	1·308 (95% CI −2·468 to 5·084)
Number of patients with *Pseudomonas aeruginosa* density data available	52	63
Overall *Pseudomonas aeruginosa* density, least squares mean change from baseline	−1·726 (95% CI −2·126 to −1·326)	0·038 (95% CI −0·322 to 0·397)
Difference in least squares means	..	−1·763 (95% CI −2·301 to −1·225)
Severe pulmonary exacerbations annual rate (least squares mean)†	0·208	0·195
Rate ratio of severe exacerbations	..	1·065 (95% CI 0·418 to 2·715)
Median time to first severe exacerbation, days	NR (95% CI NR to NR)	NR (95% CI NR to NR)
Median time to first severe exacerbation, days, Kaplan Meier, 25–75% percentile	NR to NR	NR to NR
Hospitalisations for pulmonary exacerbation annual rate, least squares mean	0·064	0·129
Rate ratio of hospitalisations for pulmonary exacerbations	0·494 (95% CI 0·143 to 1·707)	..
COVID-19 period (after March 11, 2020)		
Number of patients with annual exacerbation rate data available	127	109
Annual exacerbation rate, least squares mean, negative binomial model	0·871	0·621
Exacerbation rate ratio	..	1·403 (95% CI 0·926 to 2·125)
Number of patients with time to first exacerbation data available	102	81
Median time to first exacerbation, days*	363·0 (200·0 to NR)	230·0 (200·0 to NR)
Median time to first exacerbation, days, Kaplan Meier, 25–75% percentile	121·0 to NR	88·0 to NR
Number of patients with St George's Respiratory Questionnaire data available	121	105
St George's Respiratory Questionnaire least squares mean change from baseline in total score	−3·897 (95% CI −6·160 to −1·635)	−4·714 (95% CI −7·147 to −2·280)
Difference in least squares means	..	0·816 (95% CI −2·507 to 4·139)
Number of patients with *P aeruginosa* density data available	70	86
Overall *P aeruginosa* density, least squares mean change from baseline	−1·039 (95% CI −1·388 to −0·690)	−0·088 (95% CI −0·403 to 0·227)
Difference in least squares means	..	−0·951 (95% CI −1·421 to −0·481)
Severe pulmonary exacerbations annual rate, least squares mean†	0·010	0·005
Rate ratio	..	2·070 (95% CI 0·754 to 5·679)
Median time to first severe exacerbation, days	NR (95% CI NR to NR)	NR (95% CI NR to NR)
Median time to first severe exacerbation, days, Kaplan Meier, 25–75% percentile	NR to NR	NR to NR
Hospitalisations for pulmonary exacerbation annual rate, least squares mean	0·002	0·001
Rate ratio	..	2·063 (95% CI 0·618 to 6·886)

NR=not reached. *In the analysis of time to first pulmonary exacerbation before or during the COVID-19 pandemic, data from patients who were randomly assigned before pandemic onset and completed or discontinued the trial after pandemic onset are included in the pre-COVID-19 analysis and censored at the pandemic onset if patients did not have any exacerbation during this period and are included in the during-COVID-19 analysis starting from the date of the pandemic onset if patients did not have any exacerbation before pandemic onset. Data from patients included in the during-COVID-19 analysis who completed or discontinued the trial with no exacerbations were censored at the time of treatment completion or discontinuation. †The model used is number of severe pulmonary exacerbations during treatment period equals the treatment (colistimethate sodium or placebo) plus the use of stable concomitant therapy with oral macrolides, with the natural logarithm of time on treatment (in years) as an offset.

***Table 3*: Primary and key secondary endpoints in the pre-COVID-19 and COVID-19 periods of PROMIS-II in the modified intention-to-treat population**

severity (table 4). 36 serious TEAEs in 27 (18%) patients were reported in the colistimethate sodium group and 23 serious TEAEs in 17 (13%) patients were reported in the placebo group. Five (2%) patients died during this study (three [2%] patients in the colistimethate sodium group and two [1%] patients in the placebo group). None of the deaths were considered by the study investigators to be related to the study treatment. Bronchospasm was reported in seven (5%) of 152 patients in colistimethate sodium group and three (2%) of 135 patients in the placebo group.

	PROMIS-I			PROMIS-II		
	Colistimethate sodium (N=176)	Placebo (N=197)	Relative risk	Colistimethate sodium (N=152)	Placebo (N=135)	Relative risk
Any TEAE	142 (81%)	159 (81%)	1·000 (95% CI 0·797–1·253)	123 (81%)	104 (77%)	1·049 (95% CI 0·809–1·363)
Serious TEAEs	31 (18%)	46 (23%)	0·760 (95% CI 0·480–1·187)	27 (18%)	17 (13%)	1·391 (95% CI 0·773–2·568)
Study drug stopped due to TEAE	22 (13%)	30 (15%)	0·827 (95% CI 0·476–1·417)	16 (11%)	8 (6%)	1·708 (95% CI 0·772–4·054)
TEAEs possibly related to investigational medicinal product	36 (20%)	35 (18%)	1·151 (95% CI 0·725–1·828)	24 (16%)	10 (7%)	2·054 (95% CI 1·030–4·382)
TEAEs leading to death	1 (1%)	1 (1%)	1·119 (95% CI 0·117–10·751)	3 (2%)	2 (1%)	1·219 (95% CI 0·255–6·631)
TEAEs affecting ≤5% of any group						
Infective exacerbation of bronchiectasis	67 (38%)	110 (56%)	0·684 (95% CI 0·504–0·923)	69 (45%)	67 (50%)	0·914 (95% CI 0·654–1·279)
Cough	21 (12%)	19 (10%)	1·233 (95% CI 0·669–2·285)	11 (7%)	9 (7%)	1·072 (95% CI 0·458–2·566)
Dyspnoea	22 (13%)	16 (8%)	1·522 (95% CI 0·814–2·905)	7 (5%)	6 (4%)	1·021 (95% CI 0·360–2·967)
Haemoptysis	9 (5%)	19 (10%)	0·550 (95% CI 0·245–1·157)	9 (6%)	5 (4%)	1·514 (95% CI 0·553–4·549)
Sputum increase	13 (7%)	7 (4%)	1·995 (95% CI 0·846–5·062)	3 (2%)	2 (1%)	1·219 (95% CI 0·255–6·631)
Diarrhoea	12 (7%)	5 (3%)	2·501 (95% CI 0·974–7·27)	5 (3%)	6 (4%)	0·755 (95% CI 0·237–2·322)
Headache	4 (2%)	11 (6%)	0·448 (95% CI 0·139–1·231)	7 (5%%)	8 (6%%)	0·786 (95% CI 0·291–2·084)
COVID-19	0	0	1·119 (95% CI 0·029–43·653)	8 (5%)	4 (3%)	1·648 (95% CI 0·558–5·521)

Data are n (%). TEAE=treatment emergent adverse event.

Table 4: **Adverse events**

In PROMIS-I, three of 122 patients with data available in the colistimethate sodium group and two of 160 patients with data available in the placebo group had *P aeruginosa* isolates that were resistant to colistimethate sodium at the last available timepoint for each patient. In PROMIS-II, nine of 100 patients in the colistimethate sodium group and one of 108 patients with data available in the placebo group had *P aeruginosa* isolates that were resistant to colistimethate sodium at the last available timepoint for each patient.

Discussion

Two phase 3, randomised, double-blind, placebo-controlled trials evaluated the safety and efficacy of colistimethate sodium for the treatment of adult patients with bronchiectasis, chronic *P aeruginosa* infection, and a history of exacerbation. The results from the PROMIS-I trial, which was largely unaffected by the COVID-19 pandemic, showed a highly clinically relevant and statistically significant reduction in exacerbations of 39% and a reduction in severe exacerbations of 59%. A significant improvement in quality of life using the St Georges Respiratory Questionnaire was also observed. The findings of PROMIS-I were robust, including sensitivity analyses accounting for missing data and the early discontinuation of participants. The results of PROMIS-I were not replicated in PROMIS-II. In PROMIS-II, no statistically significant difference was observed between treatments in the frequency of exacerbations nor the key secondary endpoints. PROMIS-II was prematurely terminated due to difficulty with recruitment during the COVID-19 pandemic and because physicians did not believe it appropriate to randomise patients after the positive results of PROMIS-I.

The COVID-19 pandemic resulted in a once-in-a-generation disruption to the conduct of clinical trials and also resulted in a substantial change in circulating respiratory pathogens and the frequency of bronchiectasis exacerbations.[16–19] Crichton and colleagues[16] performed a prospective study of 173 patients with bronchiectasis in the UK and identified an increase in the proportion of patients with no exacerbations from 22·4% in 2018–19 to 52·3% in 2020–21. Åstrand and colleagues,[20] using a US health insurance claims database, showed a 43% reduction in bronchiectasis exacerbations during the pandemic period versus the pre-pandemic period. Similar occurrences have been observed with asthma and chronic obstructive pulmonary disease exacerbations.[21–23] Potential contributors to this effect include a substantial reduction in the circulation of viruses such as rhinovirus and influenza, which are commonly associated with exacerbations.[24] The effect of the COVID-19 pandemic therefore represents a biologically plausible explanation for the inconsistent results observed between PROMIS-I and PROMIS-II. Given the results of PROMIS-I, there was a less than 1 in 2000 chance of PROMIS-II not showing a statistically significant benefit of colistimethate sodium. Nevertheless, it is possible that some other unknown and unmeasured factors might have contributed to the inconsistency observed between the two trials. The target placebo exacerbation rate assumed for the power calculation was 1·09 per patient per year. We observed exacerbation rates in the placebo group of 0·95 and 0·89 in PROMIS-I and PROMIS-II, respectively, which were

slightly lower than expected, particularly in PROMIS-II, which was affected by the pandemic. Type 2 error refers to failing to reject the null hypothesis when it is false, also known as a false negative result. As noted above, the premature termination of PROMIS-II, the lower sample size, and particularly the effect of the pandemic would increase the likelihood of type 2 error.

Exacerbation reduction is a key clinical goal in the management of bronchiectasis.[25] Frequent exacerbations are associated with a poor quality of life, lung function decline, and increased mortality.[25] Bacterial load is related to inflammation, exacerbation risk, and symptoms; and reducing bacterial load reduces the risk of future exacerbations.[2,26,27] Airway clearance is the mainstay of therapy in bronchiectasis.[28] There are few additional therapies that are proven to reduce exacerbations in bronchiectasis and there are no therapies licensed by regulatory authorities in Australia, Europe, or the USA for this condition.[3]

There has been controversy over whether inhaled antibiotics are able to reduce symptoms to a clinically significant extent compared with placebo.[29,30] Previous trials of inhaled fluoroquinolones did not show clear improvements in symptoms, although subsequent analyses have suggested a benefit during on-treatment cycles for therapies given in an on and off cyclical method.[8,31,32] In PROMIS-I, a clinically relevant improvement in quality of life was observed, with the 4·6 point improvement being greater than the reported 4-point minimum clinically important difference.[33] A similar improvement in quality of life in the treatment group was observed in PROMIS-II, but the placebo group also improved during the study, which might reflect improved health status after a reduction in exacerbations during the pandemic period. Colistimethate sodium was administered continuously for 12 months rather than in a cyclical method and this might explain the consistent and sustained improvements in symptoms observed in both studies.

A key finding of this study was that colistimethate sodium had a very similar safety profile to placebo, and in particular bronchospasm was reported in 5% or less of patients in both PROMIS-I and PROMIS-II. Bronchospasm was reported in more than 10% of patients receiving other inhaled antibiotics and particularly increased with aminoglycosides.[9,34] Our data suggest that colistimethate sodium delivered through the I-neb is well tolerated and might carry a lesser risk of bronchospasm than other inhaled antibiotics. In-vitro resistance was also uncommon in this study, being reported in three patients in PROMIS-I and nine patients in PROMIS-II receiving colistimethate sodium, at the last available timepoint. This finding suggests a low risk of resistance induction with colistimethate sodium over the course of 12 months. Whether longer term treatment would be associated with greater resistance development is unknown, but it should be noted that the clinical significance of in-vitro resistance in the context of inhaled antibiotics is uncertain because it might not be associated with a loss of clinical efficacy.

In summary, PROMIS-I showed highly clinically relevant and statistically significant benefits in relation to the primary outcome of frequency of exacerbations and several key secondary endpoints. PROMIS-II did not replicate these results. PROMIS-II was conducted predominantly during the COVID-19 pandemic and was prematurely terminated. The current European Respiratory Society guidelines recommend the use of inhaled antibiotics for patients with *P aeruginosa* infection and frequent exacerbations.[3] The totality of the evidence from the PROMIS studies support these recommendations and suggest that continuous administration of colistimethate sodium via the I-neb is effective and well tolerated in patients with bronchiectasis, chronic *P aeruginosa* infection, and a history of exacerbations.

Contributors

Study conception and design: CSH, FP, PC, and JDC. Data collection and patient recruitment: CSH, MS, KW, AB, FB, KD, LCM, AEO, FCR, OS, RMT, and JDC. Data analysis: CSH, KJC, PC, and JDC. Writing of the manuscript: CSH, KJC, FP, PC, and JDC. Revising the manuscript for important content: all authors. All authors had access to the data; CSH, KJC, and JDC verified the data; and CSH and JDC were responsible for the decision to submit the manuscript for publication.

Declaration of interests

CSH reports consultancy or speakers fees from 30 Technology, AstraZeneca, CSL Behring, Chiesi, Infex, Insmed, Janssen, Lifearc, Meiji, Mylan, Pneumagen, Shionogi, Vertex, and Zambon. MS reports research grants from Glaxosmithkline, Trudell, and Tel Aviv League for Lung Disease; consulting fees or speaker fees for Astrazeneca, Boehringer Ingelheim, Dexcel, Kamada, Rafa, Synchrony Medical, Trumed, Vertex, Zambon, and Sanofi Insmed; and data safety monitoring board participation for Bonus Biotherapeutics and Boehringer Ingelheim. KW reports research grants from Insmed, Paratek, Red Hill Biopharma, AN2, Spero, and Renovion; consulting fees from Insmed, Paratek, Red Hill Biopharma, AN2, Renovion, Spero, Zambon, and Janssen; and data safety monitoring board participation for Janssen and Red Hill Biopharma. AB declares research funding from Zambon; and contributed to UptoDate. FB reports research funding from Astrazeneca, Glaxosmithkline, Chiesi, and Insmed; and consulting fees or speakers fees from Astrazeneca, Chiesi, Glaxosmithkline, Menarini, Grifols, Insmed, Novartis, Pfizer, Sanofi, Vertex, Viatris, and Zambon. KD reports payments for consultancy or lectures from Boehringer Ingelheim, GSK, Menarini, Novartis, Norma Hellas, Chiesi, Astrazeneca, and Zambon. LCM reports a leadership role with Lung Foundation Australia; research grants from Boehringer Ingelheim, Astrazeneca, Zambon, Insmed, and Glaxosmithkline; and consultancy or speaker fees from Boehringer Ingelheim, Astrazeneca, Zambon, Insmed, Sequirius, and Glaxosmithkline. AEO reports research grants from Zambon, Insmed, Boehringer Ingelheim, Armata, and the US COPD foundation; consultancy or speaker fees from Insmed, Boehringer Ingelheim, Zambon, and Electromed; participation in a data safety monitoring board for Paraxel; and fees from Academic CME, Vindico Medical Education, Answers in CME, Peer Review Institute, CE, and RMEI. FCR reports grant from the German Centre for Lung Research, German Centre for Infection Research, EU Innovative Medicines Initiative, Mukoviszidose Institute, Novartis, Insmed, Grifols, Bayer, and InfectoPharm; consulting fees or lecture fees from Parion, Grifols, Zambon, Insmed, Helmholtz-Zentrum fur Infektionsforschung, Astrazeneca, Insmed, and Grifols; participation in data safety monitoring board for Insmed, Grifols, Shionogi, and Boehringer Ingelheim; provided expert testimony to the Social Court Cologne; received support to attend meetings from German Kartagener Syndrome and Primary Ciliary Dyskinesia Patient Advocacy Group and Mukoviszidose; was a coordinator of the ERN-LUNG Bronchiectasis Core Network; was the chair of the German Bronchiectasis Registry PROGNOSIS; was a member of the SteerCo of the European Bronchiectasis Registry EMBARC and SteerCo of the European

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Data sharing

Study investigators have access to their own centre's data. Data sharing outside the study centre will require an internal investigator-initiated data sharing and transfer agreement between the qualified researcher and Zambon.

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