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Published in:
ERJ Open Research

DOI:
10.1183/23120541.00938-2023

Publication date:
2024

A phase 4 multicentre, 2×2 factorial randomised, double-blind, placebo-controlled trial to investigate the efficacy and safety of tobramycin inhalation solution for *Pseudomonas aeruginosa* eradication in bronchiectasis: ERASE

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Shareable abstract (@ERSpublications)
ERASE is investigating the efficacy and safety of inhaled tobramycin, alone or with oral ciprofloxacin, for eradicating *P. aeruginosa* in bronchiectasis. It is currently recruiting participants and results will provide randomised controlled trial evidence.

Cite this article as: Gao Y-H, Lu H-W, Zheng H-Z, *et al*. A phase 4 multicentre, 2×2 factorial randomised, double-blind, placebo-controlled trial to investigate the efficacy and safety of tobramycin inhalation solution for *Pseudomonas aeruginosa* eradication in bronchiectasis: ERASE. *ERJ Open Res* 2024; 10: 00938-2023 [DOI: 10.1183/23120541.00938-2023].

Received: 4 Dec 2023
Accepted: 5 Jan 2024

Abstract

Chronic *Pseudomonas aeruginosa* (PA) infection significantly contributes to morbidity and mortality in bronchiectasis patients. Initiating antibiotics early may lead to the eradication of PA. Here we outline the design of a trial (ERASE; NCT06093191) assessing the efficacy and safety of inhaled tobramycin, alone or with oral ciprofloxacin, in bronchiectasis patients with a new isolation of PA. This multicentre, 2×2 factorial randomised, double-blind, placebo-controlled, parallel-group trial includes a 2-week screening period, a 12-week treatment phase (with a combination of ciprofloxacin or a placebo at initial 2 weeks) and a 24-week follow-up. 364 adults with bronchiectasis and a new PA isolation will be randomly assigned to one of four groups: placebo (inhaled saline and ciprofloxacin placebo twice daily), ciprofloxacin alone (750 mg ciprofloxacin and inhaled saline twice daily), inhaled tobramycin alone (inhaled 300 mg tobramycin and ciprofloxacin placebo twice daily) or a combination of both drugs (inhaled 300 mg tobramycin and 750 mg ciprofloxacin twice daily).

The primary objective of this study is to assess the proportion of patients successfully eradicating PA in each group by the end of the study. Efficacy will be evaluated based on the eradication rate of PA at other time points (12, 24 and 36 weeks), the occurrence of exacerbations and hospitalisations, time to first pulmonary exacerbations, patient-reported outcomes, symptom measures, pulmonary function tests and the cost of hospitalisations.

To date no randomised trial has evaluated the benefit of different PA eradication strategies in bronchiectasis patients. The ERASE trial will therefore generate crucial data to inform future clinical guidelines.

Introduction

Non-cystic fibrosis (non-CF) bronchiectasis (henceforth referred to as bronchiectasis) is a chronic airway disease that is recognised to have global burden, with prevalence and incidence increasing worldwide [1–6]. The pathogenesis of bronchiectasis remains poorly understood, but chronic inflammation, infection, impaired mucociliary clearance and progressive structural lung damage are believed to play central roles in its development and progression [1, 7]. These factors contribute to recurrent exacerbations, impaired quality of life (QoL) and increased mortality.

Individuals with bronchiectasis are particularly susceptible to lung infections caused by *Pseudomonas aeruginosa* (PA). Studies have shown that PA is frequently isolated from sputum samples of bronchiectasis patients, affecting 20–50% of bronchiectasis patients in Europe, the USA and China [8–11]. The EMBARC registry reported a significant geographical variation in PA isolation, with patients from the majority of southern European countries having PA infection in >50% of cases, highlighting the need for better evidence to guide treatment [8]. Data from limited studies indicate that early initiation of antibiotics could potentially eradicate PA in bronchiectasis, but once chronic infection is established, eradicating PA becomes extremely challenging partly due to the formation of biofilm, bacterial adaptation to the microenvironment and development of antibiotic resistance [12–14].

The European Respiratory Society guideline for bronchiectasis recommends initiating inhaled antibiotic-based regimens promptly upon diagnosing PA infection to prevent progression to chronic infection [13]. However, these recommendations lack direct support from randomised controlled trials (RCTs) specific to bronchiectasis and are extrapolated from studies and clinical experience gained from treating people with CF. Several observational studies, however, have shown promising results with inhaled antibiotic therapy, suggesting eradication rates of 40–57% at 12 months, leading to reduced exacerbations and improved QoL [15–20]. The question of "When and how should PA be eradicated in patients with bronchiectasis" has been identified as a top research priority by the EMBARC consensus statement [21]. There is also uncertainty about whether inhaled antibiotics alone are sufficient to eradicate PA in bronchiectasis, considering the less severe nature of the disease compared to CF [19]. In other words, it remains unclear whether adding another antibiotic, such as oral ciprofloxacin, beyond inhaled antibiotics at the initial stage is necessary to enhance eradication. In addition, it is worth noting that patients with bronchiectasis are likely to be naive to inhaled antibiotics due to the previous unavailability of such treatments in the Chinese medical market. This creates a favourable condition for conducting an RCT in China, focusing on the eradication of PA using inhaled antibiotics.

To address these knowledge gaps, a multicentre, 2×2 factorial randomised, double-blind, placebo-controlled, parallel-group study is currently underway in individuals with bronchiectasis patients with a new isolation of PA. This study aims to investigate the efficacy and safety of tobramycin inhalation solution or ciprofloxacin alone and in combination in the successful eradication of PA in bronchiectasis. This paper outlines and discusses the methodology of the ERASE trial, the first randomised controlled trial

to evaluate the safety and efficacy of multiple eradication regimens *versus* no eradication in patients with bronchiectasis. It follows the Standard Protocol Items: Recommendations for Interventional Study (SPIRIT) guidance [22] (supplementary material).

Research methods

Study design

The ERASE study (NCT number: NCT06093191) is a multicentre, 2×2 factorial randomised, double-blind, placebo-controlled, parallel-group study to be conducted in ∼60 centres in China (the detailed study sites are listed in the supplementary material). The study will be divided into three periods: a 2-week screening period, a 12-week treatment period and a 24-week follow-up period (figure 1).

Using a factorial design, patients will be randomly assigned to one of the four treatment combinations: placebo (inhaled saline 5 mL twice daily for 12 weeks and oral ciprofloxacin placebo 750 mg twice daily for 2 weeks), oral ciprofloxacin alone (oral ciprofloxacin 750 mg twice daily for 2 weeks and inhaled saline 5 mL twice daily for 12 weeks), tobramycin inhalation solution alone (inhaled tobramycin 300 mg/5 mL twice daily for 12 weeks and oral ciprofloxacin placebo 750 mg twice daily for 2 weeks) and tobramycin inhalation solution (300 mg/5 mL twice daily for 12 weeks) in combination with oral ciprofloxacin (750 mg twice daily for 2 weeks). Both tobramycin and saline will be nebulised *via* a vibrating-mesh nebuliser (Air 360 mini+A; Feellife) provided by the Joincare Pharmaceutical Group industry, as described previously [23]. During the study period, bronchodilators can be used for maintenance therapy, except for 6–48 h before pulmonary function tests, depending on the type of inhalers used. The use of short-acting β_2-agonists (such as salbutamol) should be stopped for 6 h, long-acting β_2-agonists and inhaled corticosteroids (such as salmeterol and formoterol) should be stopped for 12 h, long-acting β_2-agonists (such as indacaterol) should be stopped for 24 h and long-acting muscarinic antagonists (such as tiotropium/glycopyrronium) should be stopped for 48 h before the tests. Detailed baseline clinical data to be collected can be found in the supplementary material. The first participant was randomised on 10 October 2023, and recruitment is anticipated to continue until March 2025, with the study expected to be completed before December 2025.

Blood, sputum and strains of PA will be collected and stored for future translational research.

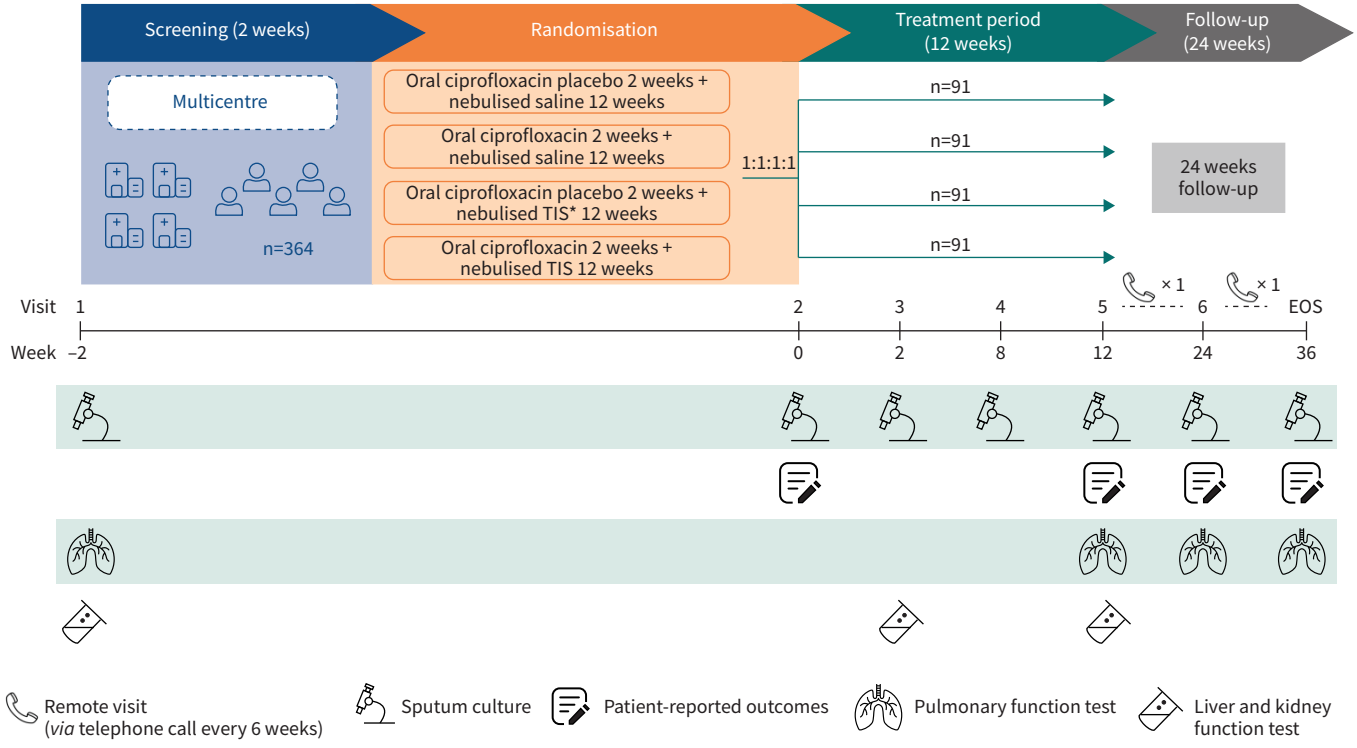

FIGURE 1 Study design. Usage and dosage of medications: ciprofloxacin 750 mg BD; ciprofloxacin placebo 750 mg BD; saline 5 mL BD; TIS 300 mg/5 mL BD. TIS: tobramycin inhalation solution.

Randomisation and masking

Eligible patients will be randomly assigned and screened within the −14- to 0-day period. Random assignment to one of the four treatment groups will be conducted using a predetermined computer-generated permuted block method. In addition, randomisation will be stratified based on whether patients were on macrolide antibiotic maintenance therapy. Maintenance therapy with oral macrolide will be allowed if the patients had been on stable treatment >3 months prior to randomisation. To facilitate randomisation, an electronic central randomisation system will be utilised.

Both investigators and participants will be blinded to the treatment assignment throughout the study. To maintain this blinding, placebos are used, which are made indistinguishable in appearance from the inhaled tobramycin solution and oral ciprofloxacin.

Data collection, monitoring and follow-up details

All collected data will be recorded by researchers who have undergone Good Clinical Practice training, using standardised data sheets. During enrolment, demographic and clinical data, spirometry and specimens (sputum, blood, and bacterial strains) will be collected. Demographic information include age, sex, height, weight, smoking history, family history, quantitative symptom measures (including cough, sputum volume, sputum colour, breathlessness, fatigue, cold and flu symptoms) [24], the number of exacerbations in previous year, the number of hospitalisations in the past 2 years, radiological severity, modified Medical Research Council dyspnoea scale (mMRC), medications and comorbidities, which are obtained from the patients and/or by reviewing the medical records.

Participants are required to return to the hospital for clinical follow-up at 2 weeks, 8 weeks, 12 weeks, 24 weeks and 36 weeks to conduct comprehensive assessments and collect specimens. An electrocardiogram and blood biochemical examination will be performed during the screening period and at the 2-week follow-up. In addition, two telephone visits by a clinical research coordinator in each centre will be conducted to monitor the disease progress between the 12-week and 36-week follow-up, including any occurrences of exacerbations and hospitalisations. Patients who discontinue the study medication prematurely and permanently will still be requested to attend future scheduled visits.

Exit criteria for participants include withdrawal of consent, experiencing severe study-related adverse events, intolerance to study medications, or any other clinical indication as determined by study site doctors, treating clinicians or the independent data monitoring committee (iDMC).

Sample size calculation

The study aims to enrol ∼364 adults with bronchiectasis, randomised in a 1:1:1:1 ratio to the four treatment groups. The sample size calculation takes into account a two-sided test with α set at 0.0245 and a test power of $1 - \beta$ at 0.90. Estimated eradication rates for the inhaled tobramycin plus oral ciprofloxacin and inhaled tobramycin alone groups are 50%, while for the inhaled saline plus oral ciprofloxacin and inhaled saline plus oral placebo groups, it is 25% [15–19]. Accounting for a 15% follow-up loss, the calculated sample size is 364 participants using PASS software, with 91 individuals in each group.

Objectives and end-points

The primary efficacy objective is to determine whether inhaled tobramycin, either alone or in combination with oral ciprofloxacin, increases the proportion of patients who successfully eradicate PA by the end of the study. Successful eradication is defined as a negative sputum culture for PA both at 24 weeks and 36 weeks after first drug administration (primary end-point).

Secondary objectives include assessing the eradication rate of PA at other time points (12, 24 and 36 weeks), determining the time to first pulmonary exacerbations, evaluating the occurrence of exacerbations and hospitalisations, measuring patient-reported outcomes and symptom measures, conducting pulmonary function tests, monitoring the emergence of other sputum pathogens by culture (*Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Burkholderia cepacia* complex, *Stenotrophomonas*, *Aspergillus*, *Candida* spp. infection and others) and evaluating the cost of hospitalisations and outpatient visits during the study period, along with safety during the treatment period (table 1).

Outcome assessments

The primary outcome is the eradication of PA from sputum samples, either spontaneous or induced, at both 24 and 36 weeks post-randomisation. Spontaneous sputum is the preferred sample for culture at these time points. However, if patients are unable to produce spontaneous sputum, induced sputum will be

TABLE 1 Primary and secondary efficacy, and safety end-points

Primary efficacy	Secondary efficacy	Safety
The proportion of patients who have negative sputum culture both at week 24 and week 36 after first drug administration	The proportion of patients who have negative sputum culture at week 12, week 24 and week 36 after first drug administration	Percentage of patients with treatment emergent AEs up to the end of the treatment (Week 12)
	Absolute change from baseline in QoL-B-RSS scores at week 12 and week 36 after first drug administration	Physical examination, vital signs, safety laboratory parameters, 12-lead ECG
	Absolute change from baseline in SGRQ total scores at week 12 and week 36 after first drug administration	Bacterial resistance up to the end of the study (Week 36)
	Absolute change from baseline in EQ-5D-5L scores at week 12 and week 36 after first drug administration	
	Absolute change from baseline in FEV_1 % predicted at week 12 and week 36 after first drug administration	
	Occurrence of exacerbations by week 12 and week 36 after first drug administration	
	Occurrence of hospitalisations by week 12 and week 36 after first drug administration	
	Emergence of other sputum microbiology (*Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Burkholderia cepacia* complex, *Stenotrophomonas*, *Aspergillus*, *Candida spp.* infection and others)	
	The cost of hospitalisations by week 12 and week 36 after first drug administration	

QoL-B-RSS: Quality of Life-Bronchiectasis-Respiratory Symptom Scale; SGRQ: St George's Respiratory Questionnaire; EQ-5D-5L: European Quality of Life Five Dimension Five Level Scale Questionnaire; FEV_1: forced expiratory volume in 1 s; AEs: adverse events.

obtained using 3% hypertonic saline before being sent for culture. Sputum cultures will be conducted in the microbiological laboratory of each participating centre using a standardised method. Training for this process was provided by the microbiological laboratory at Shanghai Pulmonary Hospital at the outset of the trial. This training included the development of a standardised process for bacterial culture from sputum and the production of an instructional video on sputum culture. In addition, any questions about sputum culture during the study period can be directed to the specialised microbiological staff at Shanghai Pulmonary Hospital. To ensure the quality of the sputum samples, each sample will be examined microscopically before being sent for culture. Samples with fewer than 10 squamous epithelial cells and >25 polymorphonuclear leukocytes per low power field will be considered suitable for sputum culture. Following these quality checks, the sputum samples will be cultured on blood agar, chocolate agar and MacConkey agar plates for 18–24 h. Suitable colonies will be chosen for pure culture, which are then utilised to identify the bacterial strains and carry out drug sensitivity testing [25].

Efficacy will be assessed using various measures, including disease worsening (time to first exacerbation, and rate of pulmonary exacerbation), patient-reported outcomes (*i.e.* Quality of Life–Bronchiectasis–Respiratory Symptom Scale (QoL-B-RSS), St. George's Respiratory Questionnaire (SGRQ) and EuroQol Five Dimensions Questionnaire (EQ-5D-5L)) and relative change from baseline in lung function (forced expiratory volume in 1 s (FEV_1), forced expiratory flow at 25–75% of forced vital capacity ($FEF_{25–75\%}$)).

Exacerbations will be defined as the worsening of three or more symptoms, including cough, sputum volume and/or consistency, sputum purulence, dyspnoea and/or exercise intolerance, fatigue and/or malaise, and haemoptysis, lasting for at least 48 h, which necessitated a change of treatment, specifically prescribed antibiotics for this study, following the 2017 international consensus definition of bronchiectasis exacerbations [26]. Additionally, sensitivity analyses will be performed for exacerbation episodes defined as worsening symptoms that required antibiotic treatment as judged by the investigators. Safety assessment will involve monitoring adverse events, conducting physical examinations, evaluating vital signs, abnormal laboratory findings, 12-lead electrocardiogram and bacterial resistance by culture.

Key inclusion and exclusion criteria

The study will enrol patients with confirmed bronchiectasis who are experiencing their first infection with PA or a new infection (having been PA-free for at least 2 years).

Eligible patients for the trial should have a confirmed diagnosis of bronchiectasis, as determined by computed tomography, and exhibit relevant clinical symptoms such as cough, sputum production and recurrent exacerbation. They should also meet one of the following criteria: 1) first-time isolation of PA; 2) PA isolation within 12 months before screening but have not received the eradication therapy; or 3) prior isolation of PA but became negative within the last 24 months (defined as having negative sputum culture results at least twice before starting antibiotic treatment). During the screening period, patients must remain clinically stable (no significant changes in respiratory symptoms and no upper respiratory tract infection or bronchiectasis exacerbations for 4 weeks) and have positive sputum PA culture.

Patients with confirmed CF will be excluded from the study. Other exclusions include patients who are resistant to tobramycin or ciprofloxacin based on sensitivity test *in vitro*, those with active allergic bronchopulmonary aspergillosis, active tuberculosis or active infection with non-tuberculous mycobacteria requiring regular anti-mycobacterial treatment, or those with a FEV_1 % predicted of <30%. The key inclusion and exclusion criteria are detailed in table 2, and a full list is available in the supplementary material.

Planned analyses and assessments

Standard approaches will be used to address missing data. Baseline characteristics, follow-up measurements (including week 36) and safety data will be described using the appropriate descriptive summary measures depending on the scale of measurement.

The primary analysis will follow a modified intention-to-treat basis. The modified intention-to-treat population will include randomised participants with data from at least one post-baseline efficacy assessment. A per-protocol analysis may also be conducted, involving a comparison of treatment groups with only those participants who completed the originally allocated treatment without protocol deviations.

Groups will be compared for the primary outcome (the proportion of patients who had negative sputum culture both at 24 weeks and 36 weeks after first drug administration) using a Z-test for normal approximation or logistic regression analysis. Regression models will adjust for baseline characteristics and other covariates. The factorial design allows for separate testing of the effects of inhaled tobramycin and oral ciprofloxacin on eradication rate and the detection of any interaction between them. These tests will be

TABLE 2 Key inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Male or female, aged 18 years and 80 years at screening	Patients who are allergic to or cannot tolerate the investigational drugs (tobramycin, ciprofloxacin)
Signed and dated written informed consent prior to admission to the study in accordance with local legislation	AST and/or ALT >2-fold ULN at end of screening period
Clinical history consistent with bronchiectasis (cough, chronic sputum production and/or recurrent respiratory infections) and investigator-confirmed diagnosis of bronchiectasis by CT scan	Serum creatinine >ULN at screening period
During the screening period, patients must have a positive *P. aeruginosa* culture in their sputum and must meet one of the following criteria: 1) they have never been isolated with *P. aeruginosa* from sputum or bronchoalveolar lavage fluid (BALF) before 2) they were isolated with *P. aeruginosa* from sputum or BALF for the first time within 12 months before screening 3) they had prior isolation of *P. aeruginosa* but not within the last 24 months (defined as having negative sputum culture results at least twice before starting antibiotic treatment)	Current diagnosis of allergic bronchopulmonary aspergillosis, hypogammaglobulinaemia, common variable immunodeficiency, mycobacterial infection (including pulmonary non-tuberculous mycobacterial disease) requiring treatment
During the screening period, patients must remain clinically stable (no significant changes in respiratory symptoms and no upper respiratory tract infection or bronchiectasis exacerbations for 4 weeks)	Patients with severe systemic diseases who are unstable or likely to experience progression, as judged by researchers, are not suitable candidates for participation in this clinical trial
During the screening period, *P. aeruginosa* is not resistant to tobramycin and ciprofloxacin based on the drug sensitivity test of sputum culture *in vitro*	Women of childbearing potential adhering to contraception requirements
Patient can tolerate nebulised inhalation therapy	Patients with FEV_1 % predicted <30%

CT: computed tomography; AST: aspartate transaminase; ALT: alanine aminotransferase; ULN: upper limit of normal; FEV_1: forced expiratory volume in 1 s.

implemented using three contrasts (representing inhaled tobramycin, oral ciprofloxacin and the interaction) in the models.

Groups will be compared for QoL-B-RSS and other continuous outcomes using analysis of covariance (ANCOVA), which will adjust for baseline characteristics and other covariates. A negative binomial regression model, with number of months in the study included as an offset, will be used to compare groups for the number of exacerbations, while Kaplan–Meier curves will be prepared to compare the groups for time to next exacerbation using the log-rank test.

Subgroup analyses will be conducted on the primary end-point based on the history of pulmonary exacerbations at baseline, the use of macrolides as a maintenance treatment at baseline and the different history of PA isolation.

All analyses will be two-sided and tested at an *a priori* significance level of p=0.05.

Discussion

Several bronchiectasis guidelines recommend inhaled antibiotic eradication therapy based on expert opinion for patients with initial or new isolation of PA [12, 13]. However, no prospective RCTs, including a control group (no eradication therapy), have been conducted to support this approach. Given the high prevalence and marked geographical variation of PA infection in bronchiectasis, as indicated by data from EMBARC and EMBARC-India [8, 27], and its association with frequent exacerbation, rapid lung function decline and reduced survival [28], there is an urgent need for an approved and optimised treatment approach based on RCTs to eradicate PA at an early stage. This clinical trial aims to determine the efficacy and safety of inhaled tobramycin solution, either alone or in combination with oral ciprofloxacin, for eradicating PA in patients with bronchiectasis who were initially or newly isolated with PA. The primary objective is to evaluate whether inhaled tobramycin, with or without oral ciprofloxacin, increases the proportion of patients who successfully eradicate PA.

The findings of the ERASE trial will be published in a peer-reviewed journal and presented at international conferences. They are expected to significantly influence international guidelines for PA eradication therapy in bronchiectasis, which will improve the prognosis of bronchiectasis patients. Key results will also be made accessible to the public through institutional websites after journal publication.

Strengths and limitations

The ERASE study's unique 2×2 factorial design allows for a comprehensive evaluation of inhaled tobramycin, both alone and in combination with oral ciprofloxacin, for the eradication of PA in bronchiectasis. This innovative approach enables assessments of the individual treatment and potential interactions between the two treatments, offering valuable insights for future clinical practices and trial designs, and even providing hypothesis-generating data for mechanistic understanding of how antibiotics work in combination. The study's follow-up period of 24 weeks, including two additional sputum cultures after 12 weeks of treatment, ensures a thorough assessment of PA eradication. Moreover, patient-reported outcomes and standardised instruments are used to measure symptoms, QoL and exacerbation frequency after eradication therapy, providing a holistic understanding of treatment efficacy. The multicentre nature of our study increases the generalisability of the future findings of our RCT. The study includes both patients with new PA and patients with recurrent PA following a period of PA negativity, which is consistent with how eradication therapy is used in practice and will allow subgroup analyses to determine which patients most benefit from eradication treatment. Finally, all patients participating in this study are expected to be naive to inhaled antibiotics due to the previous unavailability of such treatments in the Chinese medical market before the approval of tobramycin inhalation solution. This could provide an advantageous condition for conducting the PA eradication RCT in China.

However, the authors acknowledge that a longer follow-up period may be necessary to detect any potential long-lasting impact or recurrence of PA after completing eradication therapy. To address this limitation, an extended observational period of 2 years is planned as part of the ERASE study (ERASE-2), which will provide insights into the long-term effects of the treatment.

Conclusion

The ERASE trial addresses a critical knowledge gap in bronchiectasis management by evaluating the efficacy and safety of inhaled tobramycin, with or without oral ciprofloxacin, for PA eradication therapy. The study's results are expected to have a significant impact on clinical practices and patient outcomes in bronchiectasis.

Provenance: Submitted article, peer reviewed.

Acknowledgements: The authors would like to thank the trial patients, physicians and other participating personnel. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors.

The ERASE study group consists of 58 centres across China. Other principal investigators involved in the ERASE study are listed below.

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This study is registered at www.clinicaltrials.gov with identifier number NCT06093191. The individual participant data for this trial, including the data dictionaries, will not be shared until the final study report has been submitted to the funder and after publication. Subsequently, the data will be accessible for a minimum of 5 years following publication. Researchers who wish to access the data must submit a methodologically sound proposal to the ERASE steering committee. Proposals will be reviewed in compliance with our country's regulations on data sharing.

Author contributions: Conception and design: J-F. Xu and Y-H. Gao. Interpretation: J-F. Xu, J-M. Qu, J.D. Chalmers, Y-H. Gao, H-W. Lu, S.H. Chotirmall and H-Z. Zheng. Drafting the first version of the manuscript: J-F. Xu, Y-H. Gao, H-W. Lu and H-Z. Zheng. Review, editing and approval of the manuscript: all authors.

Conflict of interest: W-J. Guan reports consulting fees from Joincare Pharmaceutical Co. Ltd., lecture fees from Joincare Pharmaceutical Co. Ltd., support for travel to attend domestic meetings from Joincare Pharmaceutical

Co. Ltd., and is an associate editor of this journal. S.H. Chotirmall reports grants paid to his institution from the Singapore Ministry of Education, National Medical Research Council Singapore, consulting fees from CSL Behring, Pneumagen Ltd, Boehringer Ingelheim and Pneumagen Ltd, lecture fees from AstraZeneca and Chiesi, and participation in Data Safety and Monitoring Committees for Inovio Pharmaceuticals and Imam Abdulrahman Bin Faisal University. J.D. Chalmers reports grants from GSK, Boehringer Ingelheim, Genentech, Insmed, Grifols, Novartis, Gilead and AstraZeneca, consulting fees from AstraZeneca, Grifols, Genentech, GSK, Chiesi, Zambon, Trudell and Pfizer, and is an associate editor of this journal. J.F. Xu reports consulting fees from AstraZeneca and Boehringer Ingelheim. The remaining authors have nothing to disclose.

Support statement: This work will be supported by the National Natural Science Foundation of China (81925001, 82330070 and 82270047); Shanghai Pujiang programme (21PJD061); the Innovation Program of Shanghai Municipal Education Commission (202101070007-E00097); Program of Shanghai Municipal Science and Technology Commission (21DZ2201800); and Innovative research team of high-level local universities in Shanghai and Innovative team of Shanghai Pulmonary Hospital. The ERASE study will be funded by the Joincare Pharmaceutical Group industry. The authors did not receive payment related to the development of the manuscript. Funding information for this article has been deposited with the Crossref Funder Registry.

Ethics statement: The study will be carried out in compliance with relevant guidelines and regulations, including the Declaration of Helsinki, the ICH Harmonized Guideline for Good Clinical Practice, relevant Joincare Pharmaceutical Group Operating Procedures and other relevant regulations. Ethical approval will be secured in all participating centres before the study is conducted. The ethical approval number at the main ordinating site (Shanghai Pulmonary Hospital) is L23-286.

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