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Efficacy and safety of tobramycin inhalation powder in bronchiectasis patients with *P. aeruginosa* infection: Design of a dose-finding study (iBEST-1)

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A R T I C L E I N F O

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A B S T R A C T

In patients with bronchiectasis (BE), infection with *Pseudomonas aeruginosa* (*Pa*) results in disease progression, frequent pulmonary exacerbations and lung function decline. However, at present, no inhaled antibiotics have been approved for the treatment of these patients. Tobramycin inhalation powder (TIP), approved for treatment of *Pa* infection in cystic fibrosis, could be a promising candidate.

We aimed to assess effective and well-tolerated doses and regimens of TIP in BE patients with *Pa* infection.

In this phase II, double-blind, placebo-controlled, randomised study, three different daily doses of TIP are administered either as continuous or cyclical regimens. The study protocol comprises 7–28 days of screening, 112 days of double-blind treatment and 56 days of follow-up. The plan was to enrol 180 patients (aged ≥18 years) with BE, documented *Pa* infection and a history of exacerbations. The primary outcome is change in sputum *Pa* density from baseline. Key secondary outcomes include number of pulmonary exacerbations, use of antipseudomonal antibiotics, serum and sputum tobramycin concentrations, quality of life and safety. Exploratory endpoints include lung clearance index, sputum inflammatory markers and microbiome analysis.

As of October 2018, 107/180 patients were enrolled at 34 sites (six countries) following which recruitment was closed for administrative reasons unrelated to safety findings. Despite a reduced sample size from initially planned enrolment, the unique design may inform the benefit-risk profile of TIP in BE patients with chronic *Pa* infection. Moreover, several novel and exploratory endpoints (lung clearance index, inflammatory biomarkers, lung microbiome), will contribute to the advancement of research in this area.

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1. Introduction

Bronchiectasis (BE) is a chronic lung disease characterised by cycles of recurrent infections, pulmonary inflammation and irreversible dilatation of the airways as established on chest computed tomography (CT) [1,2]. BE is associated with significant morbidity, reduced quality of life (QoL), high treatment burden and increased mortality rates [2,3]. The prevalence of BE in the US has been estimated to be 139 cases/100 000 persons [4] and in the UK, it was estimated to be 566.1 in women and 485.5 in men/100 000 person-years in 2013 [1].

Chronic infection with *Pseudomonas aeruginosa* (*Pa*) has been associated with frequent exacerbations, worsening of forced expiratory volume in 1 s (FEV_1), a three-fold increase in mortality and a seven-fold increase in risk of hospitalisation [2,5]. Chronic productive cough is the most common symptom in patients with BE [2]. The persistence of *Pa* infection has been identified as a key determinant of BE severity [5].

The current strategies for the management of *Pa* in patients with BE are eradication of the pathogen from first isolation, treatment during acute exacerbations, and management of chronic infections [3]. Long-term antibiotic therapy may be required to reduce the sputum bacterial load and, consequently, the frequency and severity of exacerbations, resulting in improved QoL [3,5]. The recent European Respiratory Society (ERS) guidelines for BE recommend treatment with inhaled or oral antibiotic therapy for patients with three or more exacerbations per year with the aim of preventing exacerbations [3]. Inhaled antibiotics are preferred over oral for long-term therapy in cases of chronic *Pa* infection as they can offer several advantages including localised, high-concentration delivery into the airways with less systemic effects [6–9]. In patients with cystic fibrosis (CF), inhaled antibiotics have shown success in reducing exacerbations of respiratory infections and improving lung function [10].

Currently, no inhaled antibiotic is approved for the treatment of BE. Several studies have been conducted to evaluate the role of inhaled antibiotics in adults with BE, however, the results are less consistent than in CF and have not demonstrated sufficient efficacy for approval by any regulatory agency (Table 1) [11–22].

Tobramycin inhalation powder (TIP) is an inhaled antibiotic approved for the management of CF in patients with *Pa* infection [23]. TIP has shown efficacy and safety comparable to nebulised tobramycin solution with improved patient convenience, satisfaction and treatment adherence in placebo-controlled and comparative studies in CF [23].

Five prospective studies evaluating inhaled tobramycin solution in chronic *Pa* bronchial infection patients with stable BE have shown clinical improvement, reduction in bacterial density [11–14] and improved QoL [15]. The details of these studies are provided in Table 1. Of these, only two studies were with long-term treatment (6–12 months) [11,13]. The data from these studies reveal inconsistencies with regard to the effect on symptoms or QoL. In addition, adverse events (AEs), primarily therapy-induced airway obstruction, appear to be a potential limitation for the use of inhaled tobramycin in BE patients [24].

We describe the unique design of a phase II study aimed to explore different doses and treatment regimens of TIP that exhibit effective bacterial reduction of *Pa* in BE patients with a history of exacerbations. Moreover, several novel endpoints will be explored.

2. Methods/design

2.1. Study design

This is a phase II, randomised, blinded, parallel-group, multicentre study, with participation in six countries (Belgium, France, Germany, Italy, Spain and the UK) and involving 34 sites (clinicaltrials.gov identifier: NCT02712983). A total of 180 patients with BE were planned to be randomised 1:1:1 to one of three cohorts (corresponding to three dose-regimen levels): A, B and C (Fig. 1). Within each cohort, patients are randomised to receive either continuous TIP, or cyclical TIP/placebo (cycles of 28 days on- and 28 days off-drug [placebo]) or placebo in a 2:2:1 ratio. Of the planned 180 patients, 107 have been enrolled and the recruitment was closed for administrative reasons unrelated to safety on 02 October 2018.

The treatment period of the study is 112 days (six visits), followed by 56 days (two visits) of off-treatment follow-up after the last study drug dose. The screening visit (Visit 1) is conducted from Days 7–28, prior to the first study drug administration at randomisation (Visit 2). The total duration of the study is expected to be up to 196 days. After Visit 101 (Day 1), the patients will attend a visit after 7 days of treatment (Day 8, Visit 102), followed by a visit on Day 29 (Visit 103), and monthly thereafter (Day 57 [Visit 104] to Day 113, which is the end of treatment [EOT] visit [Visit 106]). Following the treatment period, patients will enter the 56-day follow-up period (no study medication, but baseline standard care according to the local guidelines) and attend two follow-up visits (Visits 201 and 202). Throughout the study, clinical, bacteriological and laboratory examinations are performed.

The study is being conducted in accordance with the International Conference of Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines, with the GCP guidelines applicable to all regions where the study is conducted and in accordance with the ethical principles set forth in the Declaration of Helsinki. The protocol was approved by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB). Written informed consent was obtained from all participants before inclusion in the study.

2.2. Intervention

TIP consists of capsules containing 28 mg tobramycin inhalation powder which is formulated using PulmoSphere™ technology for an improved intrapulmonary deposition efficiency. It is manufactured via an emulsion-based spray-drying process that yields uniform-sized, spherical hollow porous particles (pulmospheres). The drug is delivered via the breath-actuated T-326 inhaler, a portable, mechanical, capsule-based dry powder inhaler (DPI) (Fig. 2). The contents of the capsule, containing 28 mg TIP or placebo, are inhaled. Patients are allowed standard-of-care treatment throughout the study as defined according to local guidelines or practices. The treatment arms are provided in Table 2.

2.3. Planned inclusion/exclusion criteria

Men and women (aged ≥18 years) with a documented diagnosis of BE by chest CT are included in the study. Patients are required to have a FEV_1 ≥30% predicted, history of ≥2 exacerbations treated with oral antibiotics or ≥1 exacerbation requiring parenteral antibiotics in the past 12 months, and ≥1 positive sputum or throat culture for *Pa* within 12 months of screening and a positive sputum culture at the screening visit.

Patients with a history of CF, active or actively treated non-tuberculous mycobacterial infection or tuberculosis, a primary diagnosis of bronchial asthma or chronic obstructive pulmonary disease (COPD) associated with at least a 20 pack-year smoking history, or patients regularly receiving inhaled antipseudomonal antibiotics are excluded from the study. The other key exclusion criteria are provided in Table 3.

2.4. Randomisation and masking

At the randomisation visit (Visit 101), patients are randomised via interactive response technology (IRT) to one of nine treatment arms (three dose-regimen cohorts x three blind arms). Patients are first stratified by the use of macrolides, then randomised to a cohort in a 1:1:1 ratio; and within each cohort, patients are randomised further to one of three blind arms (continuous TIP, cyclic TIP, or placebo) in a

Table 1
Summary of evidence with inhaled antibiotics in chronic *Pa* bronchial infection patients with stable BE.

	Patients	Study design	Dose	Endpoints				
				CFU reduction (log_{10} decrease)	Eradication rate	Exacerbation rate	Hospitalisation	Other
Orriols et al. [11]	17	Randomised open-label, acute exacerbation treated with 14 days of IV antibiotics	Inhaled ceftazidime 1 gm b.i.d. and compounded tobramycin 100 mg b.i.d., 52-week treatment period Group A: inhaled antibiotics (n = 8); Group B: symptom based (n = 9)	Not reported	Transient	Not specified – not necessarily hospitalised	Group A: 0.6; Group B: 2.5 (p = 0.023)	Reduced LOS: Group A: 13.1 days; Group B: 57.9 days (p = 0.033)
Barker et al. [12]	74	Randomised, double-blind, placebo-controlled	TIS 300 mg b.i.d. (n = 37) 28-day (with 14-day follow-up) Placebo (n = 37)	−4.54 versus 0.02, $p < 0.01$	42% versus 0%	Not specified	5 versus 1, p = 0.20	Physician evaluation of improved condition: 62% versus 38% in favour of TIS (OR: 2.7)
Drobnic et al. [13]	30 NS[c]	Randomised, double-blind, placebo-controlled, crossover	Aerosolised tobramycin 300 mg b.i.d. 6-month continuous treatment period (1-month washout)	Decreased sputum *Pa* (p = 0.038)	Transient	0.9 versus 1.3, p = 0.330	0.15 versus 0.75, p = 0.038	Reduced LOS: 2.05 versus 12.65 days, p = 0.047
Bilton et al. [14]	53	Randomised, double-blind, active-comparator, parallel-design	TIS 300 mg b.i.d./oral CIP 750 mg b.i.d. (n = 26) 28-day treatment period Placebo/oral CIP 750 mg b.i.d. (n = 27)	3.25 versus 0.52, $p < 0.001$	34.6% versus 18.5%, not significant	Not specified	7.7% versus 14.8%	“cure”[a]: 50% versus 70.4% “failure of cure”[b]: 38.5% versus 18.5%
Scheinberg et al. [15]	41	Open-label	TIS 300 mg b.i.d. 14-day on/14-day off cycles over 12-week treatment period	Not reported	22.2%	Not specified	Not reported	Not reported
Murray, et al. [16]	65	Randomised-controlled	Nebulised gentamicin 80 mg b.i.d. (n = 27) 12 months (and 3 months follow-up) Saline (n = 30)	2.96 versus 7.67, $p < 0.0001$	30.8%	0 versus 1.5, $p < 0.0001$	Not reported	Not reported
Haworth et al. [17]	144	Randomised, placebo-controlled	Inhaled colistin 1 million IU nebulised (n = 73) 6 months or until first exacerbation Placebo (n = 71)	−1.6 versus −0.5, p = 0.008	Not reported	Not reported	Not reported	Not reported
De Soyza et al. [18] (RESPIRE 1)	416	Randomised, double-blind, placebo-controlled	CIP DPI 32.5 mg b.i.d. (n = 137) or placebo (n = 68) 14-day on/14-day off CIP DPI 32.5 mg b.i.d. (n = 141) or placebo (n = 70) 28-day on/28-day off over 48 weeks	Not reported	Not reported	0.6 versus 1.0, p = 0.0061 for the 14-day on/off regimen Not significant for the 28- day on/off regimen	Not reported	Time to first exacerbation reported for the 14 days regimen (p = 0.0005) but not for the 28 days regimen

(*continued on next page*)

Table 1 (*continued*)

	Patients	Study design	Dose	Endpoints				
				CFU reduction (log_{10} decrease)	Eradication rate	Exacerbation rate	Hospitalisation	Other
Aksamit et al. [19] (RESPIRE 2)	521	Randomised, double-blind placebo-controlled	CIP DPI 32.5 b.i.d. (n = 176) or placebo (n = 88) 14-day on/14-day off CIP DPI 32.5 b.i.d. (n = 171) or placebo (n = 86) 28-day on/28-day off over 48 weeks	Not reported	Not reported	14 days regimen: $p = 0.30$ 28 days regimen: $p = 0.0014$	Not reported	Time to first exacerbation: CIP DPI 14-day on/off: $p = 0.40$; CIP DPI 28-day on/off: $p = 0.0511$
Barker et al. [20] (AIR-BX1 and AIR-BX2)	AIR-BX1: 266 AIR-BX2: 274	Randomised, double-blind placebo-controlled	Two identical protocols (AIRBX1 and AIR-BX2) AZLI 75 mg t.i.d.: AIR-BX1 (n = 134) AIR-BX2 (n = 136) 2 cycles of 28-day (each cycle followed by 28-day off treatment), then open-label extension for a further 28 days	Decreases in CFU/g were larger for AZLI-treated patients than for placebo-treated patients at Week 4 and Week 12, increasing towards baseline values during off –treatment periods for both studies	Not reported	Not reported	Not reported	Time to first exacerbation: AIR-BX1 ($p = 0.33$); AIR-BX2 ($p = 0.35$) Difference between AZLI and placebo for adjusted mean change from baseline QOL-B-RSS was not significant at 4 weeks ($p = 0.68$) in AIR-BX1, but was significant ($p = 0.011$) in AIR-BX2
Serisier et al. [21] (ORBIT-2)	42	Randomised, double-blind placebo-controlled	Dual-release liposomal CIP for inhalation (150 mg) and free CIP (n = 20) 28-day on/28-day off in 3 cycles Placebo (n = 22)	4.2 (CIP dual release) versus −0.08 ($p = 0.002$)	Not reported	Not reported	Not reported	Time to first exacerbation: 134 (CIP dual release) versus 58 days; $p = 0.057$
Wilson et al. [22]	124	Randomised, double-blind placebo-controlled	CIP DPI 32.5 mg b.i.d. (n = 60) 28-day on/28-day off Placebo (n = 64)	−3.62 versus −0.27 ($p < 0.001$)	35% versus 8%, $p = 0.001$	36.7% versus 39.1%, $p = 0.605$	2 versus 5, $p = 0.338$	Not available

AZLI, aztreonam lysine for inhalation; BE, bronchiectasis; b.i.d., twice daily; CFU, colony forming unit; CIP, ciprofloxacin; DPI, dry powder for inhalation; LOS, length of stay; NS, not specified; o.d., once daily; OR, odds ratio; *Pa, Pseudomonas aeruginosa;* QOL-B-RSS, quality of life-bronchiectasis respiratory symptoms scores; SGRQ, St. George's Respiratory Questionnaire; t.i.d., three times daily.

[a] A cure was defined as a resolution or improvement of symptoms of acute exacerbation.

[b] Failure was defined as the persistence or worsening of symptoms of exacerbation, hospitalization, or the administration of additional antimicrobial therapy.

[c] The number of patients randomised in each group is not specified.

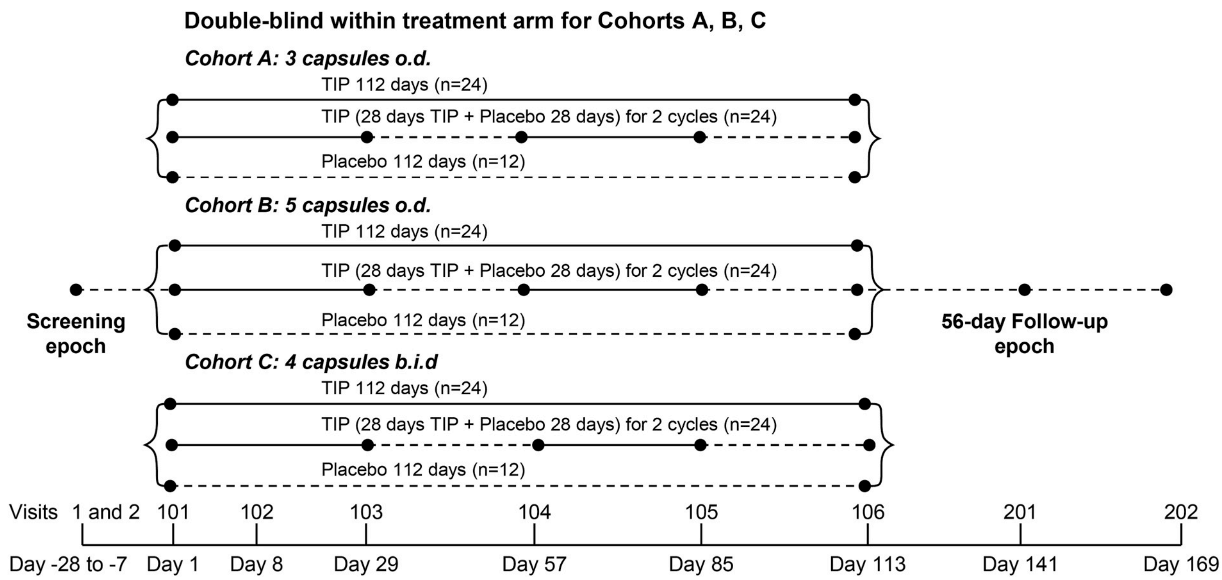

Fig. 1. Study design and treatment schedule. The number of patients in each arm represent the planned number of patients for this study. b.i.d., twice daily; o.d., once daily; TIP, tobramycin inhalation powder.

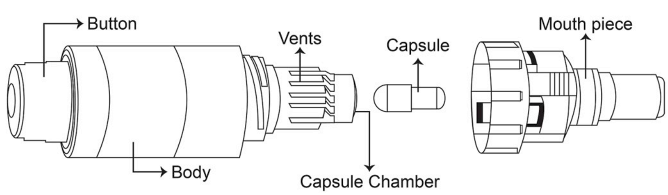

Fig. 2. Inhaler T-326 consisting of capsules containing tobramycin inhalation powder.

2:2:1 ratio. The double blinding is implemented within each cohort. The identity of the treatment is blinded from the time of randomisation until database lock.

2.5. Endpoints

2.5.1. Primary endpoints

The primary endpoint is the change in *Pa* bacterial load in sputum as assessed by the change in $\log_{10}$ colony forming units (CFUs) from baseline to Day 29 of treatment. Safety and tolerability during the treatment and follow-up period are the primary endpoints of the trial in respect to assessing the safety of this intervention.

2.5.2. Secondary endpoints

A number of secondary endpoints include frequency, rate, severity and time to first exacerbation, and antipseudomonal antibiotics used to treat pulmonary exacerbations (Table 4).

Table 3
Selected key exclusion criteria.

Any significant medical condition that is either recently diagnosed or was not stable during the last 3 months, other than pulmonary exacerbations, and that in the opinion of the investigator makes participation in the trial against the patient's best interests
Clinically significant (in the opinion of the investigator) hearing loss that interferes with the patient's daily activities
Chronic tinnitus
Patients with a past history of clinically significant hearing loss (in the opinion of the investigator) may be eligible only if their hearing threshold at screening audiometry is 25 dB or lower at frequencies of 0.5–4 kHz
Use of a hearing device is reflective of a clinically significant hearing loss, hence patients using hearing aids at screening are not eligible

2.5.3. Exploratory endpoints

Several exploratory endpoints (Table 4) are planned to complement the data collected in the primary and secondary endpoints. These include evaluation of changes in lung clearance index (LCI), serum and sputum inflammatory markers, marker composition of the airway microbiota, and sputum colour [25] and volume.

2.6. Assessments

Baseline assessments are performed either during screening or before the first dose of the study treatment on Visit 101 of the study. Each visit includes collection of a sputum sample, assessment of vital signs, treatment-emergent pathogens, pulmonary exacerbations, post-inhalation events, bronchial hyper responsiveness, AEs, serious AEs (SAEs), and physical assessment. The study visits are detailed in Table 5.

Table 2
Treatment regimens: Patients randomised to three cohorts, and within each cohort patients randomised to three treatment arms.

Cohort A (three capsules o.d.)	• three capsules of TIP o.d. for 112 days as a continuous treatment (total daily dose of 84 mg tobramycin), or • three capsules o.d. of TIP/placebo on cyclical treatment (cycles of 28 days on TIP and 28 days on placebo), or • three capsules of matched placebo
Cohort B (five capsules o.d.)	• five capsules of TIP o.d. for 112 days as a continuous treatment (total daily dose of 140 mg tobramycin), or • five capsules o.d. of TIP/placebo on treatment (cycles of 28 days on TIP and 28 days on placebo), or • five capsules of matched placebo
Cohort C (four capsules b.i.d.)	• four capsules of TIP b.i.d. in the morning and evening for 112 days as a continuous treatment (total daily dose of 224 mg tobramycin), or • four capsules b.i.d of TIP/placebo on treatment (cycles of 28 days on TIP and 28 days on placebo), or • four capsules of matched placebo

b.i.d., twice daily; o.d., once daily; TIP, tobramycin inhalation powder.

Table 4
Secondary and additional/exploratory endpoints.

Secondary endpoints
Changes in spirometry values such as FEV_1
Microbiology data pertaining to *Pa* bacterial load in sputum
Tobramycin concentration in serum and sputum
Pharmacokinetic concentrations of different doses of tobramycin compared to placebo
QoL-B score
Audiology findings
Time to first hospitalisation
Proportion of patients requiring hospitalisation
Duration of hospitalisation due to serious respiratory-related AEs
Additional/exploratory endpoints
Change in MIC of tobramycin for *Pa*
Rate and emergence of new bacterial pathogens from sputum
Proportion of patients with negative sputum cultures of *Pa*
Effect of comparing different active doses of TIP on the frequency, rate (by patient-months), and time to onset of pulmonary exacerbations over the entire study duration
Lung function at all post-baseline visits in terms of FEV_1, FVC and $FEF_{25\text{-}75}$ predicted
Impact of TIP on other scales of QOL-B, SGRQ, EQ-5D, PGIS and PGIC
Characteristics of post-inhalational events

AE, adverse event; EQ-5D, Euro-QoL 5 dimensions; $FEF_{25\text{-}75}$, forced expiratory flow at 25%–75% of vital capacity; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; MIC, minimum inhibitory concentration; *Pa, Pseudomonas aeruginosa;* PGIC, patient global impression of change; PGIS, patient global impression of symptoms; QOL-B, quality of life questionnaire-bronchiectasis; SGRQ, St. George's respiratory questionnaire; TIP, tobramycin inhalation powder.

Microbiological samples are obtained at each treatment visit, with sputum cultured for the presence of *Pa* and other typical respiratory pathogens including *Klebsiella spp.*, *Proteus spp.*, *Staphylococcus aureus, Stenotrophomonas maltophilia, Achromobacter xylosoxidans*, and *Aspergillus* species. Tobramycin minimum inhibitory concentration (MIC) values for *Pa* are determined before and after the treatment.

Pulmonary exacerbations and worsening of symptoms are defined in Table 6. For the above reported signs and symptoms, additional information is collected to document if the reported signs and symptoms last for more than 48 h, in line with the recently published consensus definition of pulmonary exacerbations for clinical research [26].

Chest CT scan images for all patients are sent to the central reader for advanced centralised image analysis to phenotype the structural lung abnormalities, and scored for the severity and extent of BE and other structural abnormalities. For each patient, the most recent chest CT is collected for centralised scoring by an independent Core Laboratory (LungAnalysis, ErasmusMC, the Netherlands) for the development of a dedicated BE scoring system to phenotype the structural lung changes.

Sputum or serum samples for pharmacokinetic analyses and patient-reported outcomes (PROs) are collected as detailed in Table 5.

3. Statistical analysis

Data are summarised by cohort/dose and/or by treatment arms (including combined treatments) as appropriate. For the efficacy analyses, the placebo patients are pooled from the three cohorts because placebo capsules are not expected to influence the efficacy assessments.

3.1. Study power and sample size

This study was powered to detect significance for the primary efficacy endpoint. A total of 180 subjects (n = 36/treatment group) should achieve 94% power to detect a reduction of 2.0 $\log_{10}$ CFU/g for each dose level versus placebo with a two-sided Bonferroni adjusted α-level of 0.0167 ($\alpha = 0.05/3$) by assuming the standard deviation is 2.0 $\log_{10}$ CFU/g and discontinuation rate is 20%. With the reduced sample size (N = 107, approximately 27 patients on an active dose and approximately 20 patients on pooled placebo), the power would be 81%.

3.2. Analysis of primary efficacy endpoints

The primary efficacy analysis on change in the bacterial load in sputum are performed using the analysis of covariance (ANCOVA) model based on non missing data. The pairwise comparisons between TIP doses (three capsules once daily [o.d.], five capsules o.d., and four capsules twice daily [b.i.d.]) versus pooled placebo are conducted using the step-wise Dunnet procedure to control the family-wise type-I error. Patients from the active treatment arms (continuous TIP and cyclical TIP/placebo) are pooled within each cohort, because they are receiving the same treatment during the first 28 days. The robustness of the results is further checked by various supportive and sensitivity analyses including the nonparametric Mann-Whitney-Wilcoxon test, analysis with missing imputation, and analysis using the per-protocol set etc.

3.3. Analysis of secondary efficacy endpoints

In general, the following six pairwise comparisons are performed for the secondary endpoints at the 5% significance level without multiplicity adjustment, wherever an inferential analysis is specified:

- TIP three capsules o.d. versus pooled placebo
- Cyclical TIP/placebo three capsules o.d. versus pooled placebo
- TIP five capsules o.d. versus pooled placebo
- Cyclical TIP/placebo five capsules o.d. versus pooled placebo
- TIP four capsules b.i.d. versus pooled placebo
- Cyclical TIP/placebo four capsules b.i.d. versus pooled placebo

Safety and tolerability as primary safety endpoints will be summarised descriptively.

4. Discussion

This is the first study designed to evaluate the potential doses and regimens of TIP that are well-tolerated over 28 weeks in patients with BE and pulmonary *Pa* infection. To date, clinical studies with inhaled antibiotics have demonstrated variability across patients and differences in the local standards of care and treatment regimens [27]. The current study is designed to provide insights into some of the long-term treatment outcomes in patients with BE.

This study includes patients with a chronic *Pa* infection who are more difficult to treat and have more frequent exacerbations than patients with other bacterial infections. In clinical practice, BE patients may only be seen when they have a pulmonary exacerbation, hence the number of historical microbiological cultures often depends on the number of exacerbations. Therefore, for this study, one historical *Pa* positive culture within the last 12 months and a confirmatory sample at screening was considered sufficient to document that a patient has chronic *Pa* infection.

In this study, three planned doses are assessed: 84 mg (three capsules) o.d., 140 mg (five capsules) o.d. and 112 mg (four capsules) b.i.d.. The doses were selected based on the previous pilot studies with inhaled tobramycin solution, which showed that BE patients may be less tolerant to inhaled therapy than CF patients [12,15]. The efficacy and safety of the 112 mg b.i.d. cyclical regimen has been established in previous studies in CF patients, and hence is used as a reference dose in this study [28,29]. The 84 mg tobramycin o.d. dose is expected to exceed the MIC based on a previous study [30] including highly resistant *Pa.* The 140 mg tobramycin o.d. dose will evaluate if superior safety and efficacy can be achieved compared to the four capsules b.i.d. dose. Tobramycin, an aminoglycoside, follows a concentration-dependent bactericidal effect, and therefore it is suited to o.d. dosing and may substantially enhance patient compliance. The cohort-based design,

Table 5
Summary schedule of study assessments.

Epoch		Screen	Treatment							Follow-up	
Visit number		1	2[a]	101[a]	102	103	104	105	106 or TD	201	202 or PSD
Day		−28 to −7	1	1	8	29	57	85	113	141	169
Randomisation and demographic data		X									
Collection of most recent available digital CT scan				X							
Serum specimen for safety laboratory assessment (standard: haematology, serum chemistry), inflammatory biomarkers[a,b] and urinalysis (standard)[a]		X		X	X	X	X	X	X	X	X
Pre-dose sputum specimens (two separate specimens) for central analysis (microbiology, microbiome and airway inflammation markers)[a,c] and sputum colour/volume				X	X	X	X	X	X	X	X
Serum specimen for PK tobramycin concentration[d]	0–1 h post-dose			X	X						
	1–2 h post-dose			X	X						
Audiology (only at selected sites)[a,e]			X			X	X	X	X	X[f]	X[f]
Spirometry[g]	Routine	X								X	X
	Pre-dose and 30 ± 15 min post-dose			X	X	X	X	X	X		
Multiple-breath nitrogen washout test for LCI (only at selected sites)[a]				X	X	X	X	X	X	X	X
QOL-B, EQ-5D, PGIS[h]			X		X	X	X	X	X	X	X
SGRQ[h]			X			X			X		X
PGIC[h]					X	X	X	X	X	X	X
AE/SAE recordings (including pulmonary exacerbations)		X	X	X	X	X	X	X	X	X	X
Record respiratory-related hospitalisations		X	X		X	X	X	X	X	X	X
Record post-inhalation events				X	X	X	X	X	X		

Visit 2 (baseline) and Visit 101 are performed on the same day (Day 1). Patients are required to complete specific 'baseline assessments (inclusion/exclusion criteria) prior to being randomised and moving into the treatment epoch (Visit 101).

AE, adverse event; CT, computed tomography; EQ-5D, Euro-QoL 5 dimensions; LCI, lung clearance index; PGIC, patient global impression of change; PGIS, patient global impression of symptoms; PK, pharmacokinetic; PRO, patient-reported outcome; PSD, premature subject/patient discontinuation; QOL-B, quality of life questionnaire-bronchiectasis; SAE, serious AE; SGRQ, St. George's respiratory questionnaire; TD, study treatment discontinuation; X, assessment to be recorded on clinical data base.

[a] To be performed prior to dosing.
[b] Inflammatory biomarkers not analysed at screening.
[c] Pre-dose sputum specimens (two separate specimens) will be collected from each patient for central analysis (one each for microbiology and microbiome/airways inflammation biomarkers).
[d] All subjects will have post-dose serum specimens collected during specified time windows.
[e] Audiological assessments will be conducted at selected study sites, at which auditory acuity will be measured at frequencies from 250 to 8000 Hz using a standard dual channel audiometer.
[f] If audiology is normal up to and including the end of the treatment epoch (Visit 106), audiological examination is not needed at Visits 201 and 202.
[g] Spirometric measurements will be conducted at approximately the same time of day to minimise the effects of diurnal variability in lung function.
[h] PROs to be completed for whom a validated version in a language well understood by the patient is available. Questionnaires should be completed before any other assessments and in the following order: 1. QOL-B, 2. SGRQ (when done as per the specified visits), 3. EQ-5D, 4. PGIC (when done as per the specified visits) and 5. PGIS.

Table 6
Definition of pulmonary exacerbation and worsening of symptoms.

Pulmonary exacerbation is defined as events for which it is clinically determined by the site investigator that antibiotic therapy is required, AND at least three criteria of the following six symptoms, signs or findings are present outside of normal variation:
1 Increased sputum volume, or change in viscosity/consistency or purulence for more than 24 h
2 Increased shortness of breath at rest or on exercise for more than 24 h
3 Increased cough for more than 24 h
4 Fever ≥38 °C within the last 24 h
5 Increased malaise/fatigue/lethargy for more than 24 h
6 A reduction in FEV_1 or FVC of at least 10% from screening
A worsening of symptoms that either does not meet the above symptom definition but is treated by the investigator with antibiotics, or that meets the symptom definition but is not treated with antibiotics, is not considered a pulmonary exacerbation for the study. The symptom definition of pulmonary exacerbation was decided before the recently published consensus [3,26].

FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

testing for three different daily doses will provide information about dose-related tolerability issues, as reduced tolerability was observed in previous studies with aztreonam [20].

The present study will evaluate both continuous and cyclical (28 days on/off) treatment regimens. Continuous antibiotic treatment may prevent return of bacterial load, reduce inflammation and prevent recurrence of symptoms [31]. An intermittent antibiotic regimen may result in prevention of antibiotic resistance, reduced treatment burden to patients and fewer side effects due to lower cumulative exposure than a continuous antibiotic regimen [31]. Studies with cyclical regimens of inhaled tobramycin in patients with CF have shown to improve pulmonary function and decrease the *Pa* density in sputum while reducing the emergence of resistance [32]. However, CF studies using a cyclical regimen have shown that, during the off-treatment period, bacterial load (CFU/g in sputum) reverts to near baseline values [28,29], and an increase in symptoms. Long-term studies in patients with BE with continuous therapies have shown improvements in exacerbations and PROs [16,17], whereas trials with cyclical regimens have either shown trends or no improvements in exacerbations and PROs [15,20,21]. Although the evidence is in support of a continuous therapy in BE, no direct comparisons between cyclical and continuous regimens have been performed to date [33]. The current study evaluates the trends between the two regimens in terms of exacerbations and PROs as a result of changes in bacterial load and patterns of resistance based on tobramycin MIC values.

The unique feature of the current study is that it enables the evaluation of novel exploratory endpoints in BE. The LCI is evaluated as an endpoint of lung disease severity and response to inhaled antibiotic therapy in patients with BE. The published evidence suggests that ventilation distribution as measured by LCI in BE is potentially more sensitive to changes in lung disease than FEV_1 [34]. Neutrophil elastase is thought to slow ciliary beat frequency, promote mucus production, impair clearance of apoptotic cells, and confer downstream effects on the activation of other proteases (e.g. matrix metalloproteases) [35]. A previously conducted study showed an association between inflammatory serum and airways biomarkers, bacterial load and exacerbations [36]; therefore, selected inflammatory biomarkers in sputum at baseline and over the study duration are planned to be assessed.

In addition, historical CT scans are being collected with the aim to establish a sensitive and reproducible BE-specific scoring system that can be used in clinical studies as a study endpoint, and to phenotype the heterogeneous group of BE patients. Imaging-related outcomes are becoming rapidly more important for the diagnosis and monitoring of a wide array of lung diseases [37]. CT-related outcome measures in CF have been well validated and shown to be predictive for exacerbations, QoL, survival, and are more sensitive than spirometry outcomes to monitor disease progression [38]. Furthermore, using CT, it was shown that there is a wide heterogeneity of structural lung abnormalities across patients. It is highly likely that substantial heterogeneity will be present in this BE cohort as well. Inclusion of chest CT to phenotype BE patients at baseline can be helpful to develop models to predict the individual response to therapies and contribute to developing personalised medicine [38,39].

The treatment duration is 112 days, followed by a 56-day follow-up period. The 112-day treatment period is selected because studies with a shorter duration with inhaled tobramycin have not shown significant improvement in clinical outcomes, indicating that a longer treatment duration is needed in BE [12,15].

This study is unique in its design with three treatment cohorts used to investigate three different TIP doses and regimens versus placebo in parallel. The study implements a within-cohort blinding approach. This allows assessment of the tolerability (defined as the rate of local AEs) of different doses and regimens of TIP. Previous studies in CF patients have shown that tolerability is associated with the amount of powder inhaled and its oropharyngeal deposition; hence, the tolerability of placebo is overall similar to that of TIP. A full blinding of the study would increase the treatment burden and would not allow the assessment of tolerability of the different daily doses.

5. Conclusion

Despite a reduced sample size from that initially planned in this study, its unique design is expected to provide information on the benefit-risk profile of TIP in BE patients with chronic *Pa* infection. Moreover, several novel and exploratory endpoints (LCI, inflammatory biomarkers, and lung microbiome) collected in this study, will contribute to the advancement of research in this area.

Data sharing statement

Elements of the information presented in the publication are available at clinicaltrials.gov (identifier: NCT02712983) and have been presented at Conferences: ERS 2018 (Abstract 11460). Results from this study, when available will be published in peer review journals.

Disclosures

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