Efficacy and safety of TOBI Podhaler in *Pseudomonas aeruginosa*-infected bronchiectasis patients: iBEST study

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Inhaled dry powder tobramycin (TOBI Podhaler) significantly reduced *Pseudomonas aeruginosa* sputum density and was well tolerated in patients with bronchiectasis https://bit.ly/3hsRQw9

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ABSTRACT The study aimed to determine the efficacy of a safe and well-tolerated dose and regimen of tobramycin inhalation powder (TIP) on *Pseudomonas aeruginosa* sputum density in patients with bronchiectasis.

This is a phase II, double-blind, randomised study in bronchiectasis patients aged ⩾18 years with chronic *P. aeruginosa* infection. Patients were randomised 1:1:1 to either cohort A: three capsules of TIP once daily (84 mg); cohort B: five capsules once daily (140 mg) or cohort C: four capsules twice daily (224 mg). Within each cohort, patients were further randomised 2:2:1 either to TIP continuously, TIP cyclically (alternating 28 days of TIP and placebo) or placebo for 16 weeks, respectively and were followed up for 8 weeks.

Overall, 107 patients were randomised to cohorts A (n=34), B (n=36) and C (n=37). All three TIP doses significantly reduced the *P. aeruginosa* sputum density from baseline to day 29 *versus* placebo in a dose-dependent manner ($p \leqslant 0.0001$, each). A smaller proportion of patients in the continuous-TIP (34.1%) and cyclical-TIP (35.7%) groups experienced pulmonary exacerbations *versus* placebo (47.6%) and also required fewer anti-pseudomonal antibiotics (38.6% on continuous TIP and 42.9% on cyclical TIP) *versus* placebo (57.1%) although not statistically significant. Pulmonary exacerbation of bronchiectasis was the most frequent (37.4%) adverse event. Overall, TIP was well tolerated, however, 23.4% of the patients discontinued the study drug due to adverse events.

Continuous- and cyclical-TIP regimens with all three doses were safe and effective in reducing the *P. aeruginosa* sputum density in patients with bronchiectasis and chronic *P. aeruginosa* infection.

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Introduction

Bronchiectasis (BE) is characterised by the presence of chronic and progressive inflammatory airway destruction that leads to repeated exacerbations [1]. In 2013, the prevalence of bronchiectasis in the USA and the UK was estimated to be 139 cases and 486–566 cases per 100,000 inhabitants, respectively [2, 3]. A higher prevalence of bronchiectasis is seen with increasing age and in women [4, 5]. Globally, bronchiectasis is thought to be the third most common chronic respiratory disease, after asthma and chronic obstructive pulmonary disease (COPD) [5].

Global mortality rates associated with bronchiectasis have been reported to be 10–30% at 5 years and up to 35% at 15 years [6]. Recently, a study in Germany has shown that bronchiectasis is associated with substantial mortality and financial burden [7]. *Pseudomonas aeruginosa* in the sputum of patients with bronchiectasis is a key driver of inflammation [8, 9]. Chronic *P. aeruginosa* infection is associated with frequent exacerbations, worsening of forced expiratory volume in 1 s (FEV_1), a three-fold increase in mortality, a seven-fold increase in risk of hospitalisation and worsening quality of life (QoL) [6, 10, 11].

In the recent European Respiratory Society (ERS) and British Thoracic Society (BTS) guidelines, long-term use of inhaled antibiotics, having localised airway delivery with minimal systemic exposure, are recommended for patients with bronchiectasis, chronic *P. aeruginosa* infection and frequent pulmonary exacerbations [4, 12]. A recent systematic review and meta-analysis involving 16 randomised clinical trials with over 2500 patients, demonstrated that inhaled antibiotics consistently reduce bacterial sputum density and achieve a small but statistically significant reduction (RR 0.81, 0.67 to 0.97; p=0.020) in the exacerbation frequency in patients with bronchiectasis [13].

Despite recommendations from ERS and BTS for use of oral/inhaled antibiotics, there is currently no inhaled antibiotic approved for the treatment of bronchiectasis. Most inhaled antibiotic trials have been conducted using an on/off strategy designed to minimise the emergence of antimicrobial resistance. There is lack of evidence comparing continuous *versus* intermittent inhaled antibiotic administration for bronchiectasis, and the European guidelines make no recommendation regarding the therapeutic regimen [14].

Tobramycin inhalation powder (TIP), TOBI Podhaler, has a proven efficacy and safety profile, and has been approved for the management of chronic *P. aeruginosa* pulmonary infection in patients with cystic fibrosis (CF). A potential benefit of the dry powder formulation is the reduced time burden compared with nebulised delivery, which may enhance treatment adherence [15, 16]. Several prospective studies with tobramycin solution for inhalation document its role in improving clinical bronchiectasis symptoms, reducing *P. aeruginosa* sputum density and improving QoL for bronchiectasis patients. However, data on adverse events (AEs) from these studies are not consistent and in the absence of more contemporary safety data, use of inhaled tobramycin in patients with bronchiectasis is limited [17–19].

This study aimed to determine the efficacy of a safe and well-tolerated dose and regimen of TIP on *P. aeruginosa* sputum density in patients with bronchiectasis. We tested the hypothesis that there is a dose-dependent effect of TIP on bacterial density and tolerability in patients with bronchiectasis.

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Patients and methods

Study design

This was a multicentre, phase II, randomised, double-blind, parallel-group, dose- and regimen-finding study that evaluated the efficacy, safety and tolerability of three different doses of TIP in patients with radiological evidence of bronchiectasis and chronic *P. aeruginosa* infection.

Participants were randomised in 1:1:1 ratio to one of three treatment cohorts in addition to the local standard of care: cohort A received three capsules of TIP once daily (84 mg); cohort B, five capsules once daily (140 mg); and cohort C, four capsules twice daily (224 mg). Each capsule was of 28 mg dosage strength and inhaled *via* the T-326 Inhaler. Within each cohort, patients were randomised in 2:2:1 ratio to receive either continuous TIP, or cyclical TIP/placebo (cycles of TIP for 28 days, alternating with placebo for 28 days) or placebo. Treatment duration of 16 weeks (112 days) was followed by an 8-week (56-day) follow-up. The study design has been previously published and presented in figure 1 [20]. Recruitment was closed after the acquisition of the product by another company when 107 out of 180 patients were recruited. This did not lead to any changes to the study protocol. However, the following previously planned analysis were not performed due to reduced sample size: a) subgroup analysis using age group, sex, bronchiectasis severity index (BSI) in patients with pulmonary exacerbations at screening; b) primary efficacy analysis after excluding patients who were not confirmed *P. aeruginosa* positive at baseline; c) primary efficacy analysis using multiple imputations where the respective treatment effect replaced missing values; and d) primary efficacy analysis using multiple imputations to account for patients who required treatment with anti-pseudomonal antibiotics for exacerbation post-baseline and up to and including day 29, by assuming the placebo treatment effect for those subjects requiring anti-pseudomonal treatment.

Due to the early recruitment halt and reduced sample size, the inferential analysis should be considered as exploratory and the results obtained should be interpreted with the caution.

Patients

Included in the study were patients (aged ⩾18 years) with a proven diagnosis (confirmed *via* chest computed tomography scan) of bronchiectasis and a history of ⩾2 exacerbations treated with oral antibiotics or ⩾1 exacerbation requiring parenteral antibiotic treatment as well as *P. aeruginosa* documented in a respiratory sample (expectorated sputum, deep-throat cough swab, oropharyngeal swab or bronchoalveolar lavage) at least once within the 12 months prior to screening. Patients with FEV_1 ⩾30% predicted and a positive *P. aeruginosa* sputum culture at screening were considered eligible. Patients with a history of cystic fibrosis, a primary diagnosis of smoking-associated COPD, a primary diagnosis of bronchial asthma and local or systemic hypersensitivity to aminoglycosides or inhaled antibiotics were not eligible. Pregnant and/or lactating women were also excluded. Other inclusion and exclusion criteria are detailed in the study design manuscript [20].

Ethical consideration

The study was conducted in accordance with the International Council for Harmonization Good Clinical Practice (GCP) regulations/guidelines and the ethical principles set forth in the Declaration of Helsinki. Either independent ethics committee or institutional review board approved the protocol. Written informed consent was obtained from all participants before the start of the study. An independent data monitoring committee regularly reviewed the safety data.

Outcomes

Efficacy endpoints

Primary endpoint

Change from baseline to Day 29 in *P. aeruginosa* density in sputum (log_{10} colony forming units (CFUs)) was evaluated to demonstrate the effect of different doses of TIP.

Selected secondary endpoints

Antimicrobial efficacy of TIP over the entire study duration; effect of different doses of TIP and different regimens on pulmonary exacerbation at the end of the treatment epoch (day 113) and over the study period; efficacy profile of different doses of TIP and different regimens as measured by anti-pseudomonal antibiotic usage during the treatment epoch (through day 113) and study period were evaluated.

Safety endpoints

Incidence rate and severity of adverse events and serious adverse events (SAEs) were assessed to evaluate the safety and tolerability profile of different TIP doses and treatment regimens over the treatment period

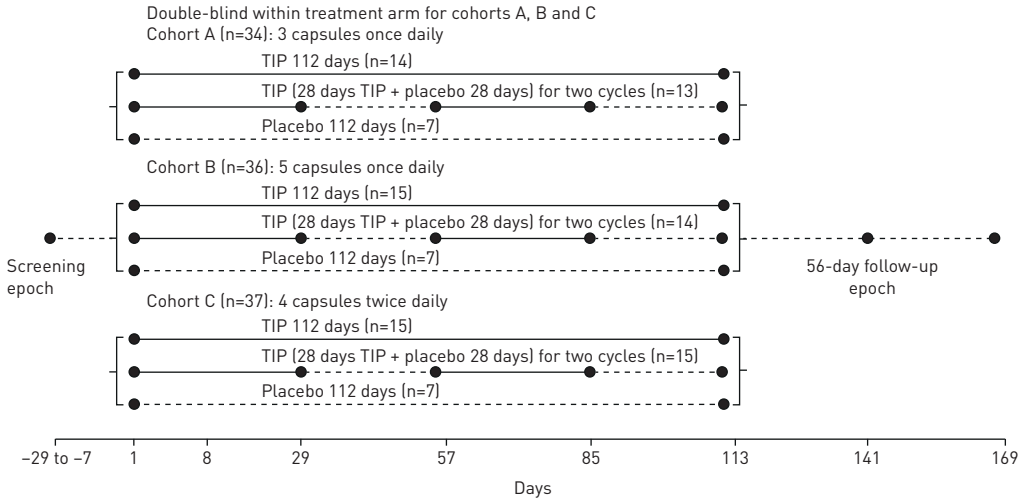

FIGURE 1 Study design (adapted from [20]). n: number of patients; TIP: tobramycin inhalation powder.

and study duration. Evaluation of clinical and laboratory parameters, post-inhalation events, measurement of bronchial hyperactivity and audiology testing were performed.

Selected exploratory endpoints

Treatment effect of TIP on the Respiratory Symptom Scale Quality of Life Questionnaire for Bronchiectasis (QoL-B RSS) was evaluated along with other scales of the QoL-B (*e.g.* physical functioning, vitality and health perceptions).

Statistical methods

Data were summarised and analysed by cohort/dose, treatment groups (including combined treatments) and/or pooled by continuous, cyclical and placebo, as appropriate. For the efficacy analyses, the placebo patients were pooled from the three cohorts.

Descriptive statistics (n, mean, SD, median, minimum and maximum) for patient demographics including age, weight, height, sex and other baseline characteristics were calculated for continuous data. Categorical data were summarised using "n" and percentages based on the number of non-missing values.

The primary efficacy endpoint was analysed using the analysis of covariance (ANCOVA) model using treatment and baseline macrolide use as fixed-effect factors, and baseline CFU (in $\log_{10}$ unit), as covariate. Step-wise Dunnett's procedure was used to control the family-wise type-I error rate at 5%.

Hazard ratios and 95% confidence intervals were provided for time to event variables using a Cox regression model. Relative risks and 95% confidence intervals were provided for count data using a generalised linear model. An *ad hoc* analysis of area under curve (AUC) for change from baseline in CFU (in $\log_{10}$ unit) were performed using an ANCOVA model using the same set of factors/covariates as included in primary analysis.

Data analysis was performed by ICON. Statistical analyses were performed using SAS Version 9.4. Further details of the statistical methods are provided in Supplementary methods.

Results

In total, 186 patients were screened from six countries (Belgium, France, Germany, Italy, Spain and the UK), 107 of whom were randomised (of 180 planned) to the three different treatment cohorts. 79 (42.5%) patients failed screening. Table 1 presents the patient demographics, disease characteristics and other baseline parameters.

The majority of patients were female (61.7%) except in the placebo group of Cohort A (42.9%). The mean±SD age across all treatment subgroups was 63.4±13.6 years except for cyclical TIP in cohort A (57.5±11.8 years) and placebo group in cohort C (71.3±10.4 years); 57.9% were aged ⩾65 years. The majority of patients were Caucasian (89.7%); in cohort C, all patients were Caucasians. These variations within the demographics between the treatment cohorts was expected for the given patient population size and also due to the enrollment from six different European countries (UK: 24.3%; Spain: 24.3%; Italy: 15.9%; Germany: 15.0%; France: 15.0%; and Belgium: 5.6%).

TABLE 1 Demographic characteristics of patients enrolled in the study

Characteristic	Cohort A: 3 capsules once daily			Cohort B: 5 capsules once daily			Cohort C: 4 capsules twice daily			Total
	TIP	TIP/PBO	PBO	TIP	TIP/PBO	PBO	TIP	TIP/PBO	PBO	
Patients n	14	13	7	15	14	7	15	15	7	107
Age										
<65 years	6 (42.9)	10 (76.9)	4 (57.1)	6 (40.0)	6 (42.9)	1 (14.3)	5 (33.3)	6 (40.0)	1 (14.3)	45 (42.1)
⩾65 years	8 (57.1)	3 (23.1)	3 (42.9)	9 (60.0)	8 (57.1)	6 (85.7)	10 (66.7)	9 (60.0)	6 (85.7)	62 (57.9)
Age years										
Mean±SD	63.4±12.7	57.5±11.8	61.3±7.5	64.3±17.9	62.4±16.7	69.1±13.2	66.1±12.2	60.8±13.0	71.3±10.4	63.4±13.7
Min–max	39–82	40–80	52–71	21–81	19–82	40–77	33–86	35–75	49–81	19–86
Sex										
Male	5 (35.7)	3 (23.1)	4 (57.1)	5 (33.3)	7 (50.0)	1 (14.3)	6 (40.0)	7 (46.7)	3 (42.9)	41 (38.3)
Female	9 (64.3)	10 (76.9)	3 (42.9)	10 (66.7)	7 (50.0)	6 (85.7)	9 (60.0)	8 (53.3)	4 (57.1)	66 (61.7)
Race										
Caucasian	12 (85.7)	11 (84.6)	7 (100.0)	13 (86.7)	11 (78.6)	5 (71.4)	15 (100.0)	15 (100.0)	7 (100.0)	96 (89.7)
Others	2 (14.3)	2 (15.4)	0	2 (13.3)	3 (21.4)	2 (28.6)	0	0	0	11 (10.3)
BMI kg·m^{-2}										
Mean±SD	24.6±4.0	25.1±4.3	24.5±4.9	24.0±4.3	25.7±3.6	22.9±5.4	24.5±4.5	24.5±4.1	26.4±5.6	24.7±4.2
Min–max	17.4–32.0	18.9–32.3	19.6–31.6	16.6–35.7	20.0–31.2	17.0–29.6	16.8–32.0	18.8–32.4	19.7–37.3	16.6–37.3
FEV_1 % predicted										
Mean±SD	58.9±25.6	64.0±16.5	64.3±25.5	62.4±26.3	58.7±22.4	54.7±16.6	60.8±21.1	53.9±17.4	59.5±11.4	59.7±20.8
Min–max	32.2–104.0	34.5–9 4.2	26.7–104.4	29.0–135.1	24.0–96.1	27.6–72.4	30.5–111.6	31.5–93.5	44.1–76.9	24.0–135.1
BSI										
Mean±SD	11.1±2.2	8.6±2.9	9.4±3.8	10.7±2.8	10.0±4.1	11.7±2.6	10.9±4.4	8.6±2.4	13.0±3.5	10.3±3.4
Min–max	8–15	5–14	6–16	4–14	5–19	8–15	6–19	4–14	9–19	4–19
Number of pulmonary exacerbations in the past 12 months										
⩽2	8 (57.1)	8 (61.5)	5 (71.4)	10 (66.7)	6 (42.9)	5 (71.4)	9 (60.0)	14 (93.3)	3 (42.9)	68 (63.6)
⩾3	6 (42.9)	5 (38.5)	2 (28.6)	5 (33.3)	8 (57.1)	2 (28.6)	6 (40.0)	1 (6.7)	4 (57.1)	39 (36.4)
Mean±SD	2.8±1.4	2.5±1.1	2.4±0.8	2.7±1.7	2.6±0.8	2.4±1.3	3.2±2.0	1.9±0.5	2.9±1.4	2.6±1.3
Min–max	1–6	1–5	2–4	1–8	1–4	1–5	1–8	1–3	1–5	1–8
***Pseudomonas aeruginosa* sputum density (log_{10} CFU) at baseline**										
Mean±SD	6.8±1.2	7.7±1.5	5.5±1.8	6.1±2.4	7.0±1.8	8.2±1.8	6.8±0.9	5.7±1.9	7.6±1.5	6.7±1.8
Min–max	4.8–8.9	4.8–10.2	2.0–7.2	2.0–9.0	3.9–10.1	6.1–10.9	4.9–8.3	2.0–9.2	5.7–9.7	2.0–10.9
Baseline tobramycin MIC										
>8 μg·mL^{-1}	2 (12.5)	0	0	0	1 (5.9)	0	0	1 (6.7)	0	4 (3.3)
⩽8 μg·mL^{-1}	14 (87.5)	16 (100.0)	7 (100.0)	14 (100.0)	16 (94.1)	9 (100.0)	20 (100.0)	14 (93.3)	9 (100.0)	119 (96.7)
Concomitant medications										
Macrolides	4 (28.6)	4 (30.8)	2 (28.6)	5 (33.3)	5 (35.7)	2 (28.6)	4 (26.7)	5 (33.3)	2 (28.6)	33 (30.8)
Bronchodilators[#]	14 (100.0)	10 (76.9)	6 (85.7)	13 (86.7)	11 (78.6)	4 (57.1)	14 (93.3)	12 (80.0)	5 (71.4)	89 (83.2)
Inhaled corticosteroids	1 (7.1)	2 (15.4)	0	2 (13.3)	2 (14.3)	1 (14.3)	2 (13.3)	3 (20.0)	0	13 (12.1)

Data are presented as n (%), unless otherwise stated. Age was calculated from date of informed consent and year of birth. Weight and height were taken from screening vital signs evaluations. Body mass index (BMI) was calculated based on raw data measurements. Percentage calculated based on number of female patients. TIP: tobramycin inhalation powder; PBO: placebo; Min: minimum; Max: maximum; FEV_1: forced expiratory volume in 1 s; BSI: bronchiectasis severity index; CFU: colony forming unit; MIC: minimum inhibitory concentration. [#]: includes both short- and long-acting bronchodilators.

From the ANCOVA model, it was shown that treatment effect ($p \leqslant 0.0001$) and baseline log_{10} CFU was statistically significant ($p=0.0003$), whereas macrolide use was not statically significant ($p=0.7742$). All three doses of TIP reduced the *P. aeruginosa* sputum density from baseline to day 29 significantly ($p \leqslant 0.0001$) when compared with placebo (figure 2). Antimicrobial efficacy of TIP *versus* placebo over the entire study duration showed the highest least square mean difference in cohort C. In addition, higher doses achieved higher reductions in *P. aeruginosa* sputum density (figure S1). These results were consistent with the changes in CFUs measured as AUC: a higher decrease (negative AUC) was observed in pooled continuous regimen (−242.8 log_{10} CFUs) than in the cyclical regimen (−194.7 log_{10} CFUs), indicating that continuous regimen has advantage over the cyclic regimen (table 2). Both results were statistically significant when compared with pooled placebo ($p<0.0001$ for both). Similarly, when comparing the three different daily doses, a higher decrease (negative AUC) was observed in cohort C (−185.8 log_{10} CFU) compared with cohort A (−122.9 log_{10} CFUs) or B (−145.8 log_{10} CFUs), indicating that twice daily dosing has advantages over once daily dosing (table 3). Statistical significance as compared to placebo was reported for all the cohorts (cohort A: $p=0.0004$; cohort B; and cohort C: $p<0.0001$).

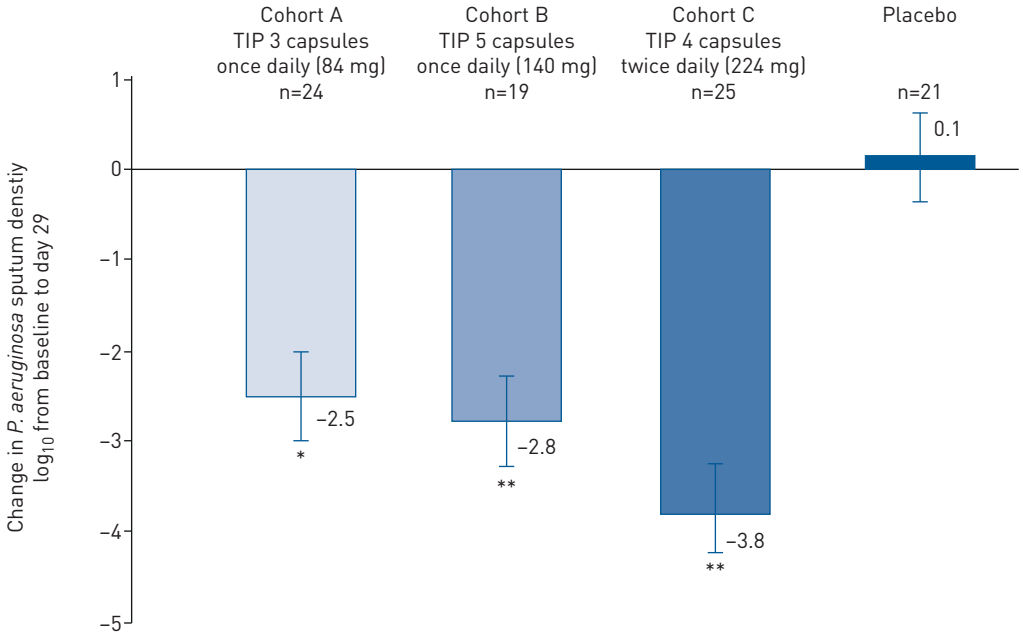

FIGURE 2 Change in *Pseudomonas aeruginosa* sputum density from baseline to day 29 for the treatment and placebo groups. CFU: colony-forming unit; n: number of patients; TIP: tobramycin inhalation powder. *: p=0.0001, **: p<0.0001, *versus* placebo. p-values for each treatment cohort are in comparison to the pooled placebo group.

During the treatment period, several patients had no *P. aeruginosa* detected in their sputum or deep throat cough samples. The proportion of patients with no *P. aeruginosa* detected at two consecutive post-baseline visits was similar in the continuous- and cyclical-TIP groups (23 (52.3%) patients and 21 (50.0%) patients, respectively). Of note, in the placebo group, only one (4.8%) patient had no *P. aeruginosa* detected during the course of the study. Moreover, at study completion about one-third of the patients in the active arms remained *P. aeruginosa*-free: continuous TIP 12 (38.7%) out of 31 and cyclical TIP 12 (36.4%) out of 33.

The majority of patients had a baseline isolate with a TIP minimum inhibitory concentration (MIC) of $\leqslant 8\ \mu g{\cdot}mL^{-1}$ (119 (96.7%) patients), indicating that this is a susceptible population. At the end of study, isolates from 11 patients showed four-fold or greater increase in the TIP MIC post-baseline with 10 of them in the active groups (table S1). Changes in susceptibility to the tested antibiotics were not relevant, with no particular trends in the emergence of resistance. No particular pattern was noted in the emergence of new bacterial and fungal pathogens observed in the pooled continuous- or cyclical-TIP groups, as they were irregularly found in different active groups.

There was a slightly smaller percentage of patients experiencing pulmonary exacerbation episodes (as defined per protocol) in the pooled continuous TIP group (15 (34.1%); RR: 0.81, 95% CI 0.39–1.68) and

TABLE 2 Area under the curve (log_{10} colony forming units) of change from baseline for different treatment cohorts during the treatment epoch

	Continuous TIP (n=44)	Cyclical TIP (n=42)	Pooled PBO (n=21)
Least square mean±SE	−230.0±27.87	−182.0±27.72	12.8±36.73
95% CI least square mean	−285.4–−174.7	−237.0–−126.9	−60.18–85.75
Least square mean difference±SE	−242.8±44.96	−194.7±44.91	
95% CI least square mean difference	−332.1–−153.5	−284.0–−105.5	
p-value	<0.0001	<0.0001	

Data calculated for number of evaluable patients (Continuous TIP: n=38; Cyclical TIP: n=37 and Pooled PBO: n=21). Least square mean differences and p-value are calculated against pooled PBO. TIP: tobramycin inhalation powder; PBO: placebo.

TABLE 3 Area under the curve (log_{10} colony forming units) of change from baseline for different treatment regimens during the treatment epoch

	Cohort A (n=27)	Cohort B (n=29)	Cohort C (n=30)	Pooled PBO (n=21)
Least square mean±SE	−111.2±23.58	−134.1±24.50	−174.0±22.53	11.7±25.43
95% CI least square mean	−158.03–−64.35	−182.74–−85.38	−218.79–−129.25	−38.77–62.25
Least square mean difference±SE	−122.9±33.63	−145.8±34.86	−185.8±33.33	
95% CI least square mean difference	−189.74–−56.13	−215.06–−76.54	−251.98–−119.54	
p-value	0.0004	<0.0001	<0.0001	

Data calculated for number of evaluable patients (Cohort A: n=25; Cohort B: n=22; Cohort C: n=28; Pooled PBO: n=21). Cohort A: TIP 3 capsules once daily (84 mg); Cohort B: TIP 5 capsules once daily (140 mg); Cohort C: TIP 4 capsules twice daily (224 mg). TIP: tobramycin inhalation powder; PBO: placebo.

pooled cyclical TIP group (15 (35.7%), RR: 0.96, 95% CI 0.49–1.91) when compared with placebo (10 (47.6%)). However, the results were not statistically significant (figure 3a).

Similarly, only 38.6% (n=17) and 42.9% (n=18) patients in the pooled continuous and cyclical groups, respectively, used anti-pseudomonal antibiotics during the study, compared with 57.1% (n=12) patients in the placebo group (figure 3b). The reduction in use of anti-pseudomonal antibiotics appears to be significant in the cohort C continuous TIP group (RR: 0.25, 95% CI 0.07–0.98). Of note, anti-pseudomonal antibiotics were used to treat either pulmonary exacerbations or certain respiratory events, which did not reach the protocol-defined criteria for pulmonary exacerbation.

Mean (95% CI) score for QoL-B by Respiratory domain is provided in (figure S2). No definite trend was noted across the entire study period in the scores of different QoL-B domains within the active treatment groups, except for the Respiratory Symptoms domain. In the TIP group in cohort B, least square mean difference *versus* placebo was noted to be 9.6 (95% CI: −3.81–22.94, repeated measure analysis), numerically exceeding the published minimum clinically important difference of 8 points [21]; however, with a large variability (as indicated by the large 95% confidence intervals). In the same cohort, mean change in scores from baseline until the end of study had similar trends, with improvements for role, emotional and social functioning along with health perceptions, without reaching significance.

Safety

Overall, the study drug was well tolerated with the majority of patients in each cohort achieving >90% compliance at each visit.

The most commonly reported adverse events by preferred term were infective exacerbation of bronchiectasis (37.4%), cough (18.7%) and dyspnoea (17.8%). The majority of infective exacerbations of bronchiectasis were mild or moderate in nature and only five (4.7%) patients experienced severe infective exacerbations of bronchiectasis. SAEs were observed in 20.6% (n=22) of the patients, with infective exacerbation of bronchiectasis being the most common (n=9; 8.4%) followed by haemoptysis and respiratory failure (n=3; 2.8% for each) (table S2). No death was reported in this study.

Overall, 92 (86.0%) patients experienced at least one treatment emergent adverse events (TEAE) regardless of study drug relationship, and the incidence was similar in both the active treatment (pooled continuous- and cyclical-TIP groups) and placebo groups. In total, 45 (42.1%) patients experienced TEAEs suspected to be study-drug related and the most frequent of these were cough (nine (8.4%) patients) and dyspnoea (nine (8.4%) patients). These adverse events were variable amongst cohorts. In 25 (23.4%) patients, TEAEs led to study-drug discontinuation and the numbers were higher in the active treatment groups compared with the placebo group. Highest discontinuations were observed in cohort C (14 (37.8%)) when compared with cohort A (five (14.7%) and cohort B (six (16.7%)). The most frequently reported TEAE, leading to study-drug discontinuation across all cohorts by preferred term, was infective exacerbation of bronchiectasis (five (4.7%)) (table 4).

With regard to specific adverse events of interest, based on the known aminoglycoside safety profile, five (4.7%) patients experienced ototoxicity (adverse events of special interest (AESI) and 12 (11.2%) patients experienced haemoptysis (one was during the screening epoch). Post-inhalation clinical events were higher in the five capsules once daily dosing cohort (cohort B; nine (25.0%)) followed by the three-capsules once daily dosing cohort (cohort A; seven (20.6%)) and subsequently the four capsules twice daily dosing cohort (cohort C; five (13.5%)). In addition, no signal of clinically significant bronchial hyperreactivity was observed.

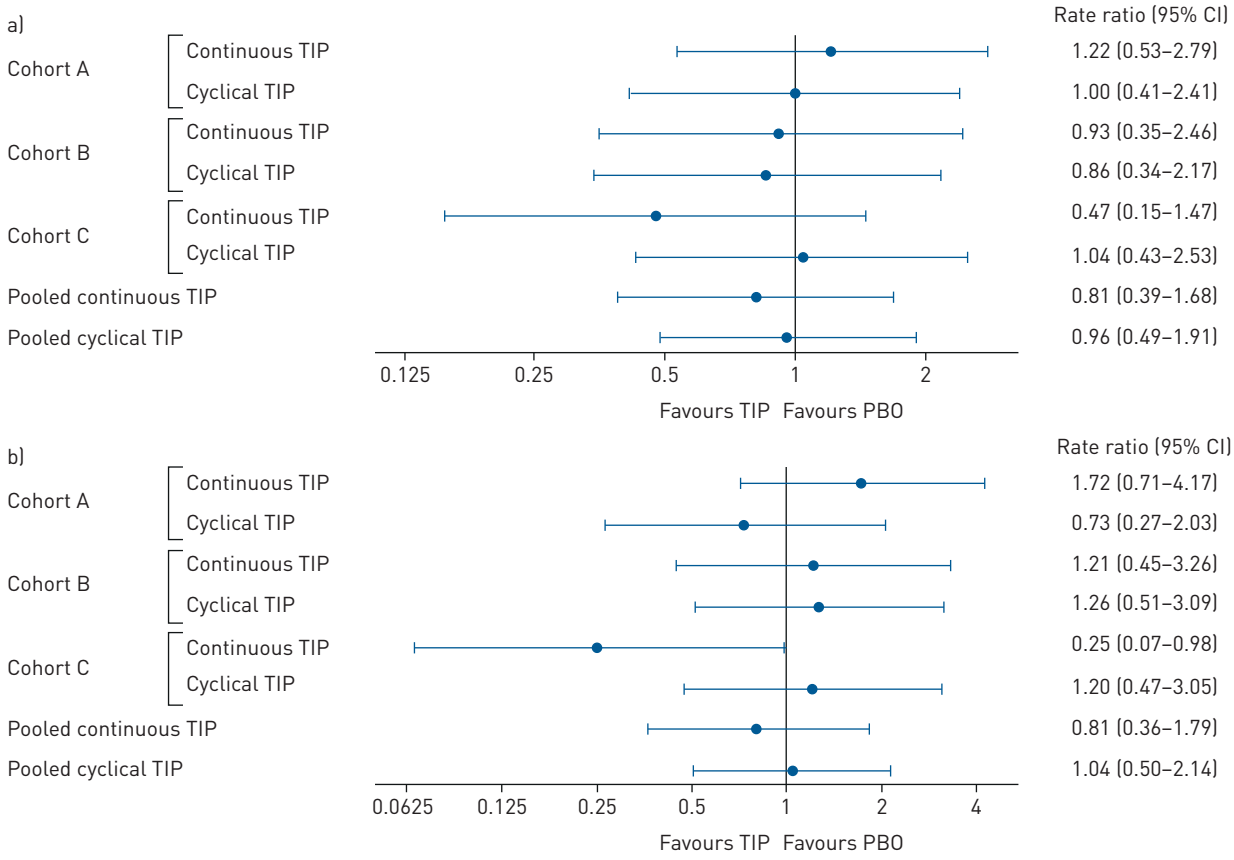

FIGURE 3 a) Forest plots showing the effect of different doses of TIP as compared to pooled PBO and different regimens on frequency of pulmonary exacerbation. b) Usage pattern of anti-pseudomonal antibiotics with different TIP doses as compared to pooled PBO and different treatment regimens. CI: confidence interval; PBO: placebo; TIP: tobramycin inhalation powder. Cohort A: TIP 3 capsules once daily (84 mg); Cohort B: TIP 5 capsules once daily (140 mg); Cohort C: TIP 4 capsules twice daily (224 mg).

In 12 patients, renal parameter changes were found to be clinically relevant, *i.e.* ⩾50% increase in serum creatinine and/or estimated glomerular filtration rate (eGFR) levels ⩽50 mL·min^{-1}·1.73 m^{-2}. Seven of the 12 patients had a plausible association between the renal event and study drug. Of these, six patients were treated with pooled continuous TIP (two were in cohort B and four were in cohort C), and one with cyclical TIP (cohort B).

Discussion

This is the first study to evaluate the safety and efficacy of different doses and dosing regimens of TIP in patients with bronchiectasis and pulmonary *P. aeruginosa* infection. The results demonstrated that all three doses of TIP (84 mg (three capsules) once daily, 140 mg (five capsules) once daily and 224 mg (four capsules) twice daily) significantly reduced the *P. aeruginosa* sputum density from baseline to day 29 compared with placebo. In addition, higher dose achieved higher reduction in *P. aeruginosa* sputum density. From the *ad hoc* AUC-based analysis, it was also seen that continuous regimens have advantage over cyclic regimens in reducing *P. aeruginosa* density.

This study demonstrated better reduction in *P. aeruginosa* sputum density compared with cystic fibrosis studies using TIP [22, 23]. In addition, the microbiology results are consistent with previous studies in patients with bronchiectasis, either with inhaled tobramycin solution [17] or inhaled dual-release ciprofloxacin [24]. Several earlier studies have documented the efficacy of inhaled tobramycin solution in reducing the *P. aeruginosa* sputum density and improving the clinical symptoms of bronchiectasis [17–19, 25, 26]. However, data from long-term studies are limited in numbers. This study provides valuable insights into the effectiveness of TIP in patients with bronchiectasis. Patients in the pooled TIP group maintained a high (⩾2.0) least square mean difference compared with the pooled placebo group at all visits, except for the follow-up visits: a pattern that is similar to previous studies with inhaled antibiotics [27–29]. Further, about half of the patients in the active groups had no *P. aeruginosa* detected at two consecutive post-baseline visits, with similar frequencies between the continuous- and cyclical-TIP groups

TABLE 4 TEAEs leading to study drug discontinuation by preferred term

	Patients n	Infective exacerbation of bronchiectasis	Glomerular filtration rate decreased	Blood creatinine increased	Dyspnoea	Percentage of patients with at least one TEAE
Cohort A: three capsules once daily (84 mg)						
Continuous TIP	14	2 (14.3)	0	0	0	3 (21.4)
Cyclical TIP	13	0	0	0	0	1 (7.7)
Placebo	7	0	0	0	0	1 (14.3)
Cohort B: five capsules once daily (140 mg)						
Continuous TIP	15	1 (6.7)	1 (6.7)	0	0	3 (20)
Cyclical TIP	14	0	1 (7.1)	1 (7.1)	1 (7.1)	3 (21.4)
Placebo	7	0	0	0	0	0
Cohort C: four capsules twice daily (224 mg)						
Continuous TIP	15	0	2 (13.3)	2 (13.3)	2 (13.3)	6 (40)
Cyclical TIP	15	2 (13.3)	0	0	0	7 (46.7)
Placebo	7	0	0	0	0	1 (14.3)
Total (n=107)	107	5 (4.7)	4 (3.7)	3 (2.8)	3 (2.8)	25 (23.4)

Data are presented as n (%), unless otherwise stated. TEAE: treatment-emergent adverse event; TIP: tobramycin inhalation powder.

(52.3% and 50%, respectively); while only one patient in the placebo group (4.8%) had no *P. aeruginosa* during the study. Moreover, at study completion, about one-third of the patients in the active arms was *P. aeruginosa*-free. Numerical differences were noted for frequency of pulmonary exacerbation episodes and use of anti-pseudomonal antibiotics favouring the TIP treatment groups. However, this study was not powered to demonstrate statistically meaningful differences for clinical outcomes. To do so, larger trials are warranted.

In this study, both continuous- and cyclical-TIP regimens showed effectiveness in reducing the *P. aeruginosa* sputum density (the LS mean difference was higher in the pooled continuous group compared with the cyclical group), the frequency of exacerbations and the use of anti-pseudomonal antibiotics. There was a higher decrease (negative AUC) in the pooled continuous regimen rather than the cyclical regimen. These results are consistent with previous observations suggesting that continuous antibiotic treatment controls the chronic bacterial infection and maintains treatment benefit [30]. A cyclical regimen was historically developed in CF patients with the aim to reduce the risk of the emergence of antibiotic resistance and to lower the cumulative exposure to antibiotics [31, 32]. It can be noted that in this study there was no particular trend towards an increase in TIP resistance in either treatment arm. Further, no clear trend was noted in general in the scores of different QoL-B domains with the active treatment groups.

A phase 2 study showed that BE patients experiencing improvement in their medical condition with inhaled tobramycin had a mean baseline bacterial load of 7.1 (1.4) $\log_{10}$ CFU·g^{-1} [17]. Treatment benefits in terms of QoL was observed in a 2-month study in bronchiectasis patients receiving nebulised gentamicin where the median baseline bacterial load was 8.0 (7.6–8.2) $\log_{10}$ CFU·g^{-1} [30]. Similar results were also noted with inhaled aztreonam where QoL was improved only in patients with high baseline bacterial load [33]. These results are in line with the present study where the mean±SD sputum density of *P. aeruginosa* was 6.4±1.8 $\log_{10}$ CFU.

The most frequently observed adverse events were infective exacerbation of bronchiectasis, cough and dyspnoea. SAEs observed were consistent with symptoms associated with pulmonary exacerbation and the population studied. While the efficacy outcomes tended to be better with higher TIP doses, there was a trend towards an increase in renal laboratory parameters (eGFR and blood creatinine) in this study. Of the 12 patients with plausible association between renal events and study drug, six had confounding factors. It was noted that most patients were poly-medicated and had pre-existing conditions (such as diabetes and hypertension). In addition, the exact timings of the renal events were difficult to ascertain as most of these were noted at the time of scheduled monthly clinic visits. Additionally, the advanced age of the study patients could be a predisposing factor. Previous trials with inhaled antibiotics in bronchiectasis patients did not report renal toxicity; however, they did not use the same stringent renal monitoring criteria as the iABC Bronchiectasis Efficacy Study with TIP (iBEST) study [17–25] and the events noted in this study are in line with the known safety profile of tobramycin. Cases of ototoxicity (mild tinnitus and deafness, moderate labyrinthitis,) noted in this study are consistent with a previous study [28]. Cases of tinnitus and deafness were mild, transient and did not lead to changes in the study medication administration. Also,

one case of tinnitus and the case of deafness were reported in patients receiving placebo. As per protocol, audiometry was to be performed for patients with hearing complaints, however this was not performed in these specific patients, therefore the results must be interpreted with caution. Post-inhalation clinical events were short in duration (⩽30 s) and did not demonstrate any dose-response pattern. TEAEs leading to study drug discontinuation were higher in active treatment cohorts with the most number of cases being in the highest dosage group (cohort C; four capsules twice daily.). Overall, TIP doses were well tolerated across all treatment groups and a compliance of ˃90% was noted. The observed type and rate of adverse respiratory effects with inhaled tobramycin is consistent with previously published studies [17, 19].

Limitations

The study was designed to demonstrate an antibacterial effect of different doses of inhaled tobramycin powder in comparison to placebo and hence was limited in terms of treatment duration and sample size. Enrolment in the trial was stopped before achieving the planned sample size after the acquisition of the product by another company. The study was not powered to demonstrate clinical outcomes such as reduction in exacerbations, use of antibiotics or hospitalisations; these endpoints would require much larger samples sizes and a longer treatment duration of at least 1 year [13, 34, 35]. The effect on *P. aeruginosa* density in all treated groups suggests that the study was over-powered for the primary outcome measure. Patients in this study had a high bacterial load at baseline, rendering them more likely to respond to TIP. The consistency of the effect on the reduction in *P. aeruginosa* CFUs across the treated groups increases confidence that this effect is a real effect of tobramycin dry powder inhalation.

Conclusion

Continuous and cyclical treatment with TIP was shown to be efficacious in reducing *P. aeruginosa* sputum density in patients with BE and chronic *P. aeruginosa* infection. All three doses of TIP reduced the *P. aeruginosa* sputum density significantly in a dose-dependent manner. Numerical differences favouring TIP were noted in terms of frequency of pulmonary exacerbation episodes and required use of anti-pseudomonal antibiotics. Overall, TIP was well tolerated with no new safety findings.

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