Dose-finding study to assess the efficacy, safety and tolerability of tobramycin inhalation powder in patients with non-cystic fibrosis bronchiectasis and pulmonary *Pseudomonas aeruginosa* infection (iBEST-1)

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BACKGROUND

- Tobramycin inhalation powder (TIP) is approved worldwide for the management *P. aeruginosa* infection in cystic fibrosis (CF) patients aged ≥6 years[1]
- TIP (28 days on/off treatment with 112 mg tobramycin via the T-326 inhaler twice-daily [BID]) achieves high antibiotic concentration in airways with minimal systemic exposure and has a well-established efficacy and safety profile in CF patients[1]
- TIP administered via the T-326 inhaler (**Figure 1**) is more convenient and has a faster administration time than tobramycin inhalation solution (300 mg/5 mL) via nebulisers[2]
- The present study [**i**ABC **B**ronchiectasis **E**fficacy **S**tudy with **T**IP [**iBEST**]) is designed to support the selection of a well-tolerable dosing regimen for TIP that exhibits effective bacterial (*P. aeruginosa*) reduction in patients with non-CF bronchiectasis (BE)
- The Trial Steering Committee, in consultation with the European Medicines Agency (EMA) and the United States Food and Drug Administration (US-FDA), has decided to compare the treatment regimens of TIP (continuous and cyclical [28-days on/off]) vs. placebo
- Data from iBEST-1 study will be used to provide guidance on the dose selection and frequency of administration of TIP for the subsequent pivotal Phase III programme

Figure 1. Tobramycin inhalation powder administered with T-326 inhaler

Rationale for testing continuous vs. cyclical dosing in bronchiectasis

- Only long-term BE studies with continuous regimen[3,4] have shown reduction in exacerbations and improvements in patient reported outcomes (PROs)
- Trials using a cyclical regimen in BE have shown only limited effects or no improvements in exacerbation and PROs[5–7]
- At the end of 28-days dosing, a rapid return of bacterial load to baseline values has been reported
- CF patients frequently become symptomatic during the off-treatment in the cyclical regimen (and bacterial load revert to baseline values). Consequently, in clinical practice, CF patients are switched to a different inhaled antibiotic or are treated continuously with the same antibiotic[8,9]
- In terms of safety, no concerns related to toxicity or resistance of long-term dosing in BE were reported in the studies on gentamicin[3] or colistin[4]
- **Experts' opinion:** Clinical experience in BE suggests that continuous dosing of nebulised antibiotics is effective and well tolerated

Choice of the once-daily (OD) vs. BID dosing

- Aminoglycoside efficacy is driven by a concentration-dependent (maximum concentration [C_{max}]) bactericidal effect coupled with a prolonged post-antibiotic effect.[10-12] Studies on OD vs. BID vs. thrice daily parenteral dosing of aminoglycosides for systemic infections indicate that OD dosing has equivalent efficacy to more frequent dosing, and is associated with less nephrotoxicity[13]
- OD intravenous tobramycin has been shown to be effective and well tolerated in CF patients[14,15]

iBEST-1 is part of the iABC (inhaled Antibiotics for Bronchiectasis and Cystic Fibrosis) consortium

- iABC is a consortium within the IMI ND4BB (NEWDRUGS4BADBUGS) collaboration platform, which aims to promote research and development of new antibiotics
- The programme proposed by the iABC consortium (IMI JU 11th call Topic 7) aims to develop novel inhaled antibiotic regimens in CF and BE:
  - 18 academic partners in 7 countries
  - 3 pan-European networks: European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC), European Cystic Fibrosis Society Clinical Trials Network (ECFS-CTN), Combating Bacterial Resistance in Europe Laboratory Network (COMBACTE LAB-Net)
  - 2 industry members

STUDY OBJECTIVES

Primary objectives

- To evaluate the effect of different doses of TIP vs. placebo on change in *P. aeruginosa* bacterial load in sputum as assessed by the change in colony forming units (CFUs) from baseline to Day 29 of treatment
- To assess the safety and tolerability of 112-days of treatment with different doses and different regimens of TIP during the follow-up period (56 days) as compared to placebo

Secondary objectives include:

- Frequency of pulmonary exacerbations compared to placebo
- Use of anti-pseudomonal antibiotics compared to placebo
- Serum and sputum concentrations of tobramycin
- Safety profile of TIP (changes in laboratory, audiology and post-inhalational forced expiratory volume in 1 second [FEV_1] parameters)
- Change in *P. aeruginosa* CFUs in sputum from baseline to each post-baseline treatment visit and during the follow-up visits
- Respiratory Symptoms Scale Quality of Life Questionnaire for Bronchiectasis (QOL-B) scores

Exploratory objectives include:

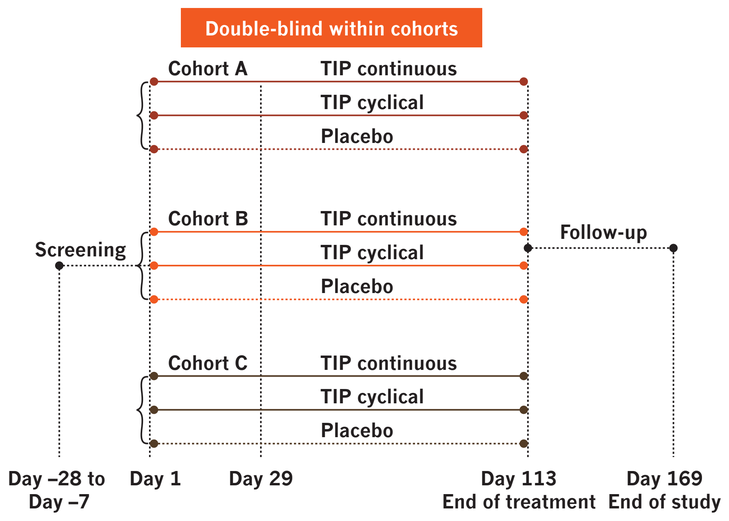
- Change in lung clearance index (Queen's University Belfast)
  - Training programme developed and delivered to sites
  - Central over reading service developed
- Chest computed tomography (CT) image analysis (EMC Rotterdam)
  - Protocols and website for chest CT standardisation developed
- Airways microbiome analysis (Queen's University Belfast)
- Inflammation biomarkers in sputum and serum/plasma (Queen's University Belfast)

METHODS

Study design

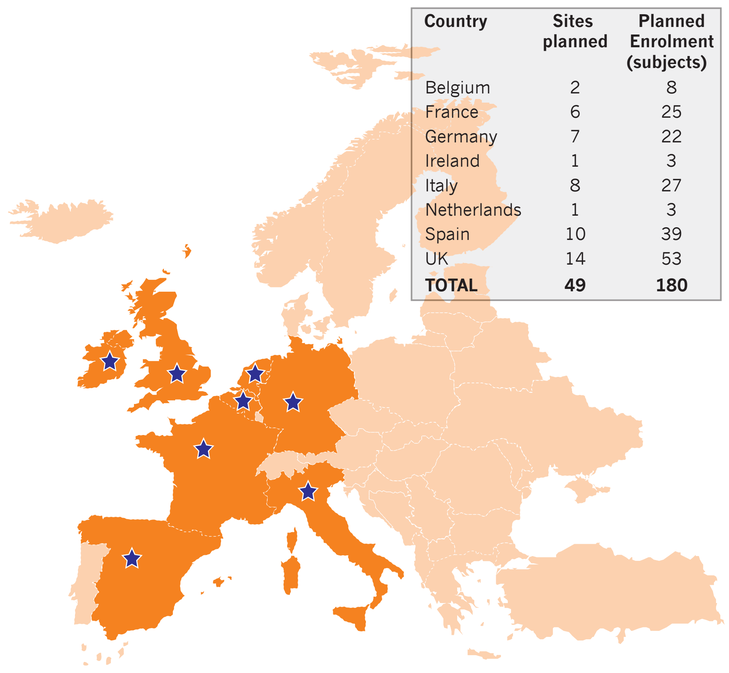
- This multicentre, double-blind, randomised, placebo-controlled study has been designed to assess three different daily doses of TIP in continuous and cyclical regimens (**Figure 2 and 3**)
  - The study is currently recruiting patients (NCT02712983)

Figure 2. Study design



TIP, tobramycin inhalation powder

Figure 3. iBEST-1 sites identification through EMBARC and ECFS-CTN (8 countries across 49 sites)



Country	Sites planned	Planned Enrolment (subjects)
Belgium	2	8
France	6	25
Germany	7	22
Ireland	1	3
Italy	8	27
Netherlands	1	3
Spain	10	39
UK	14	53
TOTAL	**49**	**180**

EMBARC, European Multicentre Bronchiectasis Audit and Research Collaboration; ECFS-CTN, European Cystic Fibrosis Society Clinical Trials Network

Key inclusion criteria

- Written informed consent must be obtained before any assessment is performed
- Male and female patients aged ≥18 years at screening (Visit 1)
- Proven diagnosis of non-CF BE as documented by chest CT
- At least 2 or more exacerbations treated with oral antibiotics OR 1 or more exacerbation requiring intravenous antibiotic treatment within 12 months prior to screening
- FEV_1 ≥30% predicted at screening (Visit 1)
- *P. aeruginosa* infection, which must be documented in a respiratory sample at least once within 12 months and also present in the expectorated sputum culture at Visit 1

Key exclusion criteria

- Patients with a history of CF or primary diagnosis of bronchial asthma or primary diagnosis of chronic obstructive pulmonary disease (COPD) associated with at least a 20 pack-year smoking history
- 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 patients' best interests
- History of hearing loss or chronic tinnitus deemed clinically significant by the investigator
- Patients with active pulmonary tuberculosis; patients currently receiving treatment for non-tuberculous mycobacterial pulmonary disease
- Patients regularly receiving inhaled anti-pseudomonal antibiotics (inhaled anti-pseudomonal antibiotics other than the study drug are not allowed during the study)

CONCLUSIONS

- This ongoing iBEST-1 study will test three different daily doses and compare continuous vs. cyclical treatment regimens
- The aim of the study is to generate data, allowing for selection of the optimal daily dose and regimen for Phase III studies involving patients with bronchiectasis and chronic *P. aeruginosa* infection
- The study will also inform about the utility of using novel endpoints in bronchiectasis and will contribute to biorepositories of respiratory isolates and sputum samples from patients with bronchiectasis

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Disclosure

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