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)

**BACKGROUND**

- Tobramycin inhalation powder (TIP) is approved worldwide for the management of *P. aeruginosa* infection in cystic fibrosis (CF) patients aged 6 years and above.
- TIP (28 days on/off treatment with 112 mg tobramycin via the T-326 inhaler twice-daily (BID)) achieves high antibiotic concentrations with minimal systemic exposure and has a well-established efficacy and safety profile in CF patients.
- TIP administered via the T-326 inhaler (Figure 1) is more convenient and has a faster administration time than tobramycin inhalation solution (300 mg/6 ml) via nebulisers.
- The present study (iABC Bronchiectasis Efficacy Study with TIP (iBEST-1)) is designed to support the selection of a well-tolerated 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 TIP in BE will be used to provide guidance on the dose selection and frequency of administration of TIP for the subsequent pivotal Phase III programme.

**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 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, audiologic and post-inhalational forced expiratory volume in 1 second [FEV1] 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 (QLI-B) score.

**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/jasmin (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 (Figures 2 and 3).
- The study is currently recruiting patients (NCT02712983).

**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.
- FEV1 <50% 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-tuberous 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).

**Rationale for testing continuous vs. cyclical dosing in bronchiectasis**

- Only long-term BE studies with continuous regimen[5,6] have shown reduction in exacerbations and improvements in patient reported outcomes (PROs).
- Trials using a cyclical regimen in BE have shown only limited evidence of no improvements in exacerbations and PROs[7–11].
- At the end of 28-days dosing, a rapid return of bacterial load to baseline values has been reported [12–14].
- CF patients treated with tobramycin become asymptomatic during the off-treatment in the cyclical regimen (and bacterial load returns to baseline values).
- Consequently, in clinical practice, CF patients are switched to a different inhaled antibiotic or are treated continuously with the same antibiotic[5,6].
- In terms of CF, no concerns related to toxicity or resistance of long-term dosing in BE were reported in the studies on gentamicin[2,3] 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**

- Amikacin/codexol amino-glycoside efficacy is driven by a concentration-dependent (maximum concentration (Cmax)-based) bactericidal effect coupled with a prolonged post-antibiotic effect[15,16].
- Studies on OD vs. BID vs. thrice daily parenteral dosing of amikacin/colistin for systemic infections indicate that OD dosing has equivalent efficacy to more frequent dosing, and is associated with less nephrotoxicity[17–19].
- OD inhaled tobramycin has shown to be effective and well tolerated in CF patients[20,21].

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

- iABC is a consortium within the IMI ND4BP (NEWDRUGS/AIDABUGS) collaboration platform, which aims to promote research and development of new antibiotics.
- The programme proposed by the iABC consortium (IMI AU 1117721) 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 (ECFTS-CTN), Combating Bacterial Resistance in European Laboratory Network (COMBACETE LAB-Net)

**REFERENCES**


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**Disclosure**

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