iABC
inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis

Work Package 4

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Work Package 4 B
Status update on the iBEST-1 study

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iBEST-1 **i**ABC **B**ronchiectasis **E**fficacy **S**tudy with **T**IP (tobramycin inhalation powder)

Dose-finding Study to Assess the Efficacy, Safety and Tolerability of Tobramycin Inhalation Powder in Patients With Non-Cystic Fibrosis Bronchiectasis and Pulmonary P. Aeruginosa Infection

ClinicalTrials.gov Identifier: NCT02712983

iBEST-1 Study Status

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Key achievements (as of 1 June 2016):

- Study design revised in agreement with regulatory authorities:
  - EMA Scientific Advice (25 Jun 2015),
  - USA FDA type-C meeting (on 23 Jun 2015).
- Protocol finalized 24-Nov-2015
- 49 sites identified through the Trial Steering Committee
- Selection through public tender of the CRO (ICON Lab):
  - Contract executed 10-May 2016
  - Clinical trial kick-off meeting 31 May – 1 June 2016

Rationale for revising the iBEST-1 Study Design

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- In consultation with the EMA and US-FDA, the Trial Steering Committee has decided to test both treatment regimens: continuous versus cycling (28-days on/off) vs. placebo.
  - number of patients increased from 144 to 180, an increase in the number of visits, and increased treatment duration (from 84 days to 112 days of treatment).
  - The FDA has also requested additional evaluation of the QOL-B questionnaire.
- Inclusion of inflammatory biomarkers (sputum and serum), in line with IMI independent expert recommendations

iBEST-1 Study Overview

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Purpose and rationale	The purpose of this study is to support the selection of a safe and tolerable TIP dose, and regimen that exhibits effective bacterial reduction of P. aeruginosa in non-cystic fibrosis bronchiectasis (BE) patients.
Study treatment	• Tobramycin inhalation powder (TIP) drug-device combination product consisting of tobramycin dry powder for inhalation in capsules (TBM100 28 mg inhalation powder hard capsule) administered by the T-326 Inhaler. • Matching placebo capsules to TIP administered by the T-326 Inhaler.
Study design	• Blinded, randomized, dose- and regimen finding trial utilizing a 3 treatment cohort design
Population	180 male and female BE patients ≥18 years old
Duration	196 days (28 days screening + 112 days DB treatment + 56 days follow-up

iBEST-1 Sites identification and selection

8 countries with 49 sites

iABC Partner Sites			
Blasi	Francesco	Policlinico Ca' Grande Milano	Italy
Chalmers	James	Ninewells Hospital and Medical School	UK
Elborn	Stuart	Queens University Belfast	UK
Haworth	Charles	Papworth Hospital	UK
Hill	Adam	Royal Infirmary Edinburgh, Edinburgh	UK
Loebinger	Michael	Royal Brompton Hospital	UK
Polverino	Eva	Hospital Clinic i Provincial de Barcelona	Spain
Ringshausen	Felix	Medizinische Hochschule Hannover	Germany
Additional sites (with existing EcoMedics equipment)			
Dupont	Lieven	University Hospitals Leuven	Belgium
Knoop	Christiane	Hospital Erasme, Anderlecht	Belgium
Chiron	Raphael	Montpellier hospital	France
Schwarz	Carsten	Charité - Universitätsmedizin Berlin	Germany
Plant	Barry	Cork University Hospital	Ireland
Paggiaro	Pierluigi	University of Pisa	Italy
de Gracia Roldan	Javier	Hospital Vall D'Hebron	Spain
Wilkinson	Tom	University of Southampton	UK
Duckers	James	University Hospital Llandough, Cardiff	UK

- In addition, 32 sites identified through ECFS-CTN and EMBARC
- In total 37 sites will have LCI equipment (25 of them equipped through the iABC project)

iBEST-1 Study timelines

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Key Milestones	Planned	Actual	Traffic light[1]
Initiation of Public Tender		29 Sep 15	
Final Protocol		24 Nov 15	
Final Protocol Package		27 May 16	●
CRO start date	22 Apr 16	10 May 16	●
Ready to Initiate Site (RIS)	15 Sep 16		●
FPFV	22 Oct 16		●
LPFV	16 Oct 17		●
LPLV	03 Apr 18		●
DBL	18 May 18		●

Back-up slides

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Key Inclusion criteria

- Written informed consent must be obtained before any assessment is performed.
- Male and female patients of ≥18 years of age at screening (Visit 1).
- Proven diagnosis of non-CF BE as documented by computed tomography or high-resolution computed tomography
- 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 ≥ 30% predicted at screening (Visit 1).
- *P. aeruginosa*, must be documented in a respiratory sample at least 1 time within 12 months and also present in the expectorated sputum culture at Visit 1.

Key Exclusion criteria

- Patients with a history of cystic fibrosis.
- Patients with a primary diagnosis of bronchial asthma.
- Patients with a primary diagnosis of 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.
- Patients with active pulmonary tuberculosis.
- Patients currently receiving treatment for nontuberculous mycobacterial (NTM) pulmonary disease.
- Patients who are regularly receiving inhaled anti-pseudomonal antibiotic (during the study inhaled anti-pseudomonal antibiotics are not allowed other than the study drug).

Primary efficacy objective

- 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.

Selected secondary objectives

- 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 (lab, audiology, post-inahalational FEV1 changes)
- Change in *P. aeruginosa* colony forming units (CFU) 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).