Inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis (iABC)

IMI 11th call: ND4BB Topic 7

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Outline

- Background
- Objectives
- iABC consortium & networks
- Work packages

Unmet clinical need

Cystic Fibrosis

- Long term infection with Gram-negative organisms, particularly *Pseudomonas aeruginosa* (PA)
- Resistance to current agents

Bronchiectasis

- No licensed therapy
- No evidenced based use of inhaled antibiotics
- Morbidity and mortality driven by PA

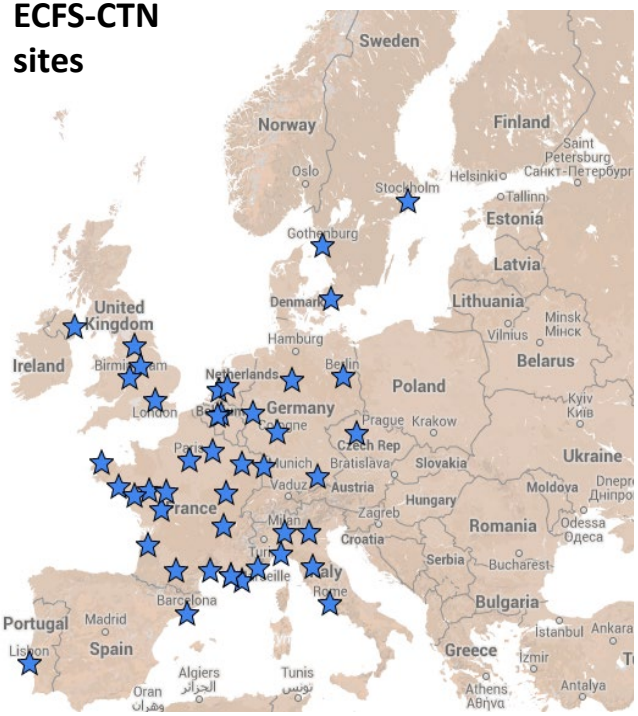
iABC Objectives

- To develop an inhaled formulation and dispersion device for BAL30072
- To determine the pharmacokinetics and safety of BAL30072 in CF and BE patients and to provide initial efficacy data
- To determine the therapeutic efficacy of TIP in BE patients
- To develop novel endpoints for clinical trials in CF and BE
- To build repositories of respiratory bacteria and sputum biobanks for future research
- To develop an EU-wide prospective BE registry

iABC consortium & networks

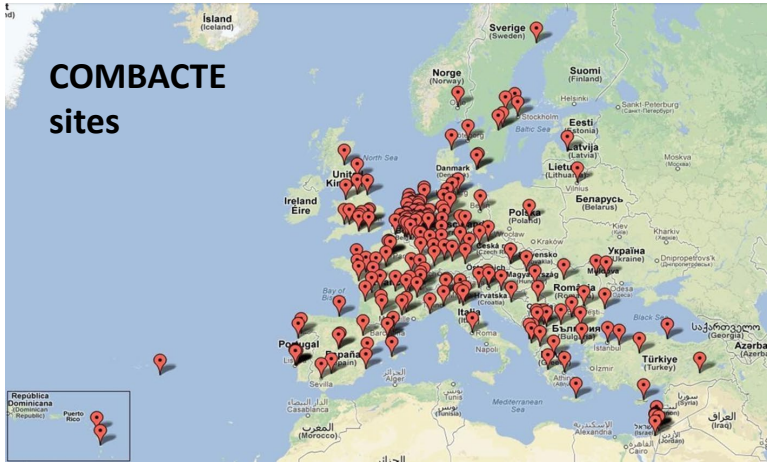
iABC Partners

ECFS-CTN sites

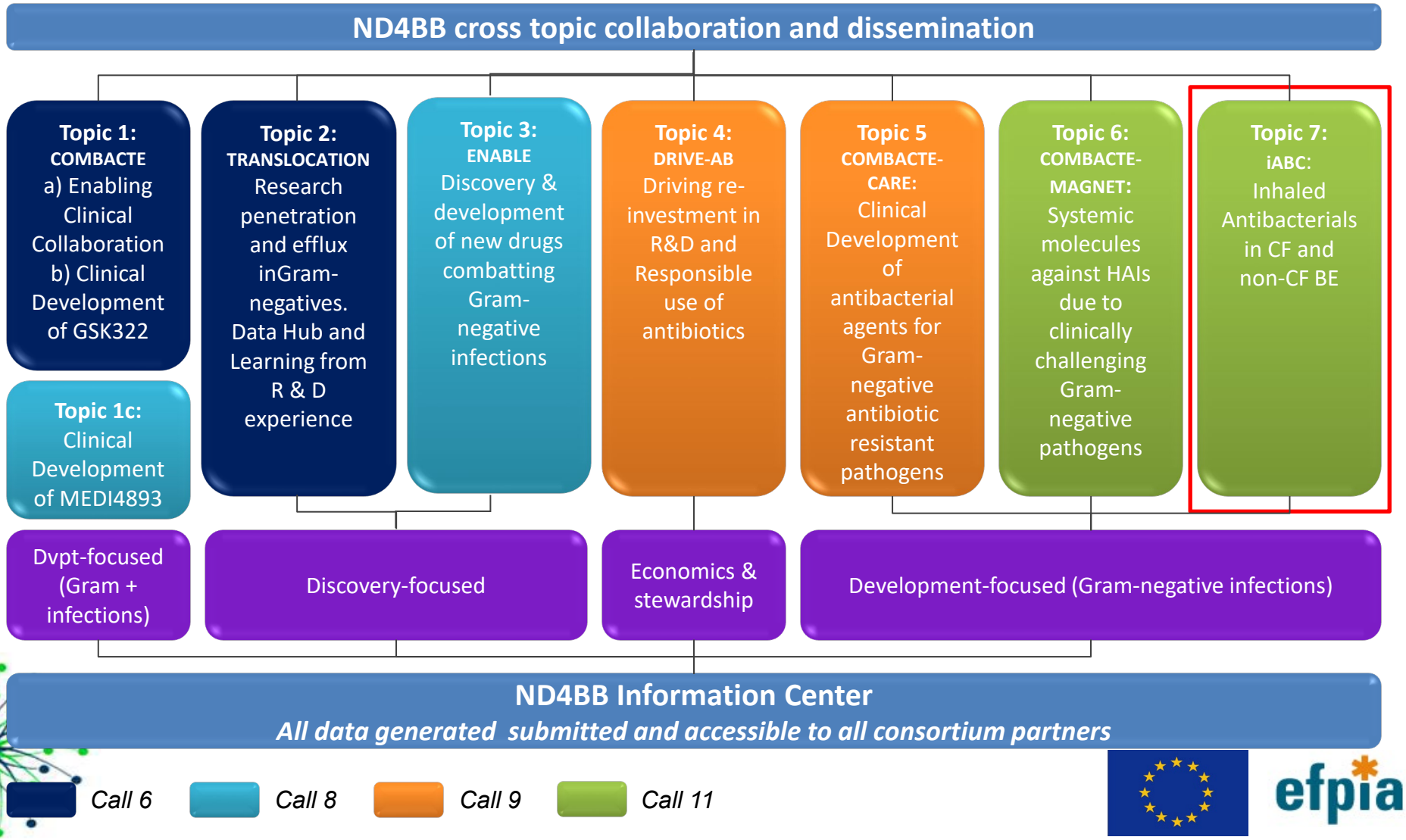


EMBARC sites

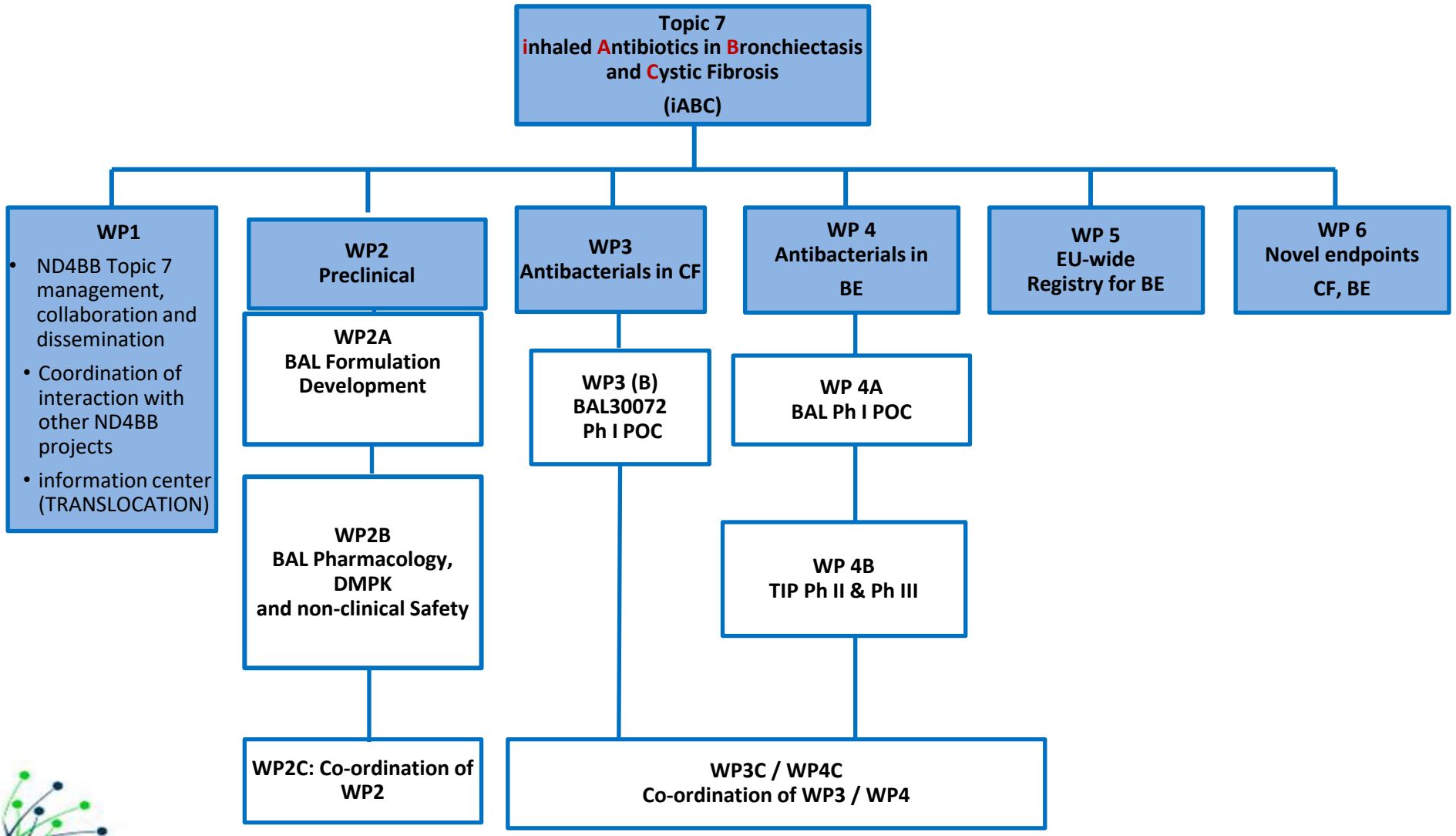
COMBACTE sites



Architecture of ND4BB



Structure of iABC work packages



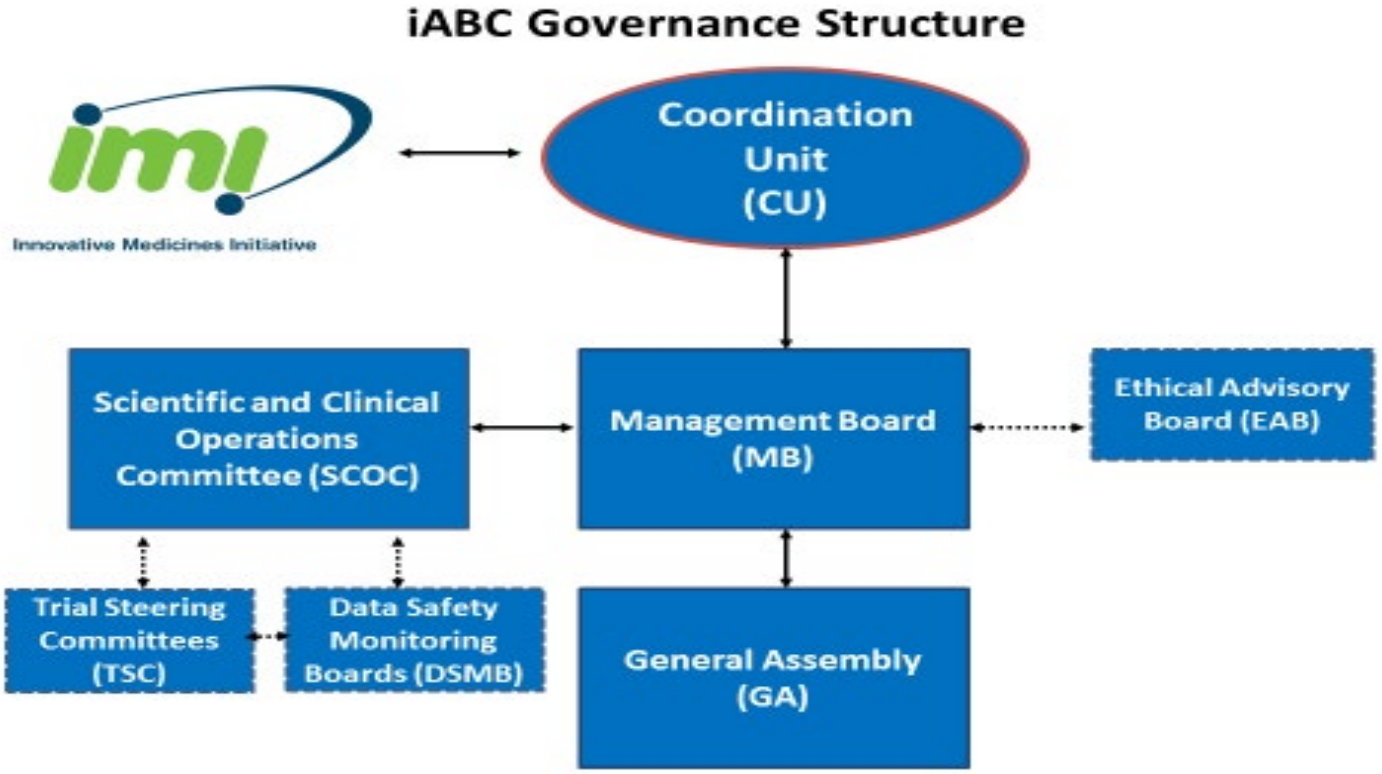
Integration of EFPIA and academic partners

- Each WP co-led by an EFPIA and academic partner
- WP1: Shared management structure and expertise
- WP2: Shared development of a new inhaled antibiotic
- WP3: Partnership between ECFS-CTN and Basilea
- WP4: Partnership between EMBARC, ECFS-CTN, COMBACTE, Novartis and Basilea
- WP5: Partnership between EMBARC and Novartis
- WP6: Cross work package development programme for public benefit

WP1: Project management and communication

- Objective-driven central project management
- Implementation of management structures
  - Project coordinator: Basilea
  - Managing Entity: QUB
- Set-up of governance structures including
  - Trial Steering Committees
  - Data Safety Monitoring Boards
  - Ethics Advisory Board (joint with other ND4BB projects)
- Monitoring and management of
  - Clinical trials
  - Data safety and ethical matters
  - Communication & dissemination

WP1: Project management and communication

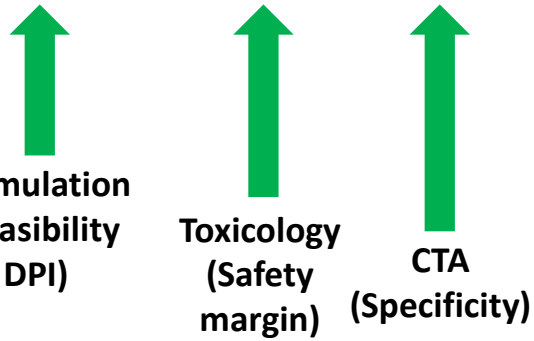


WP2: Pre-clinical development of BAL30072 as inhalation therapy

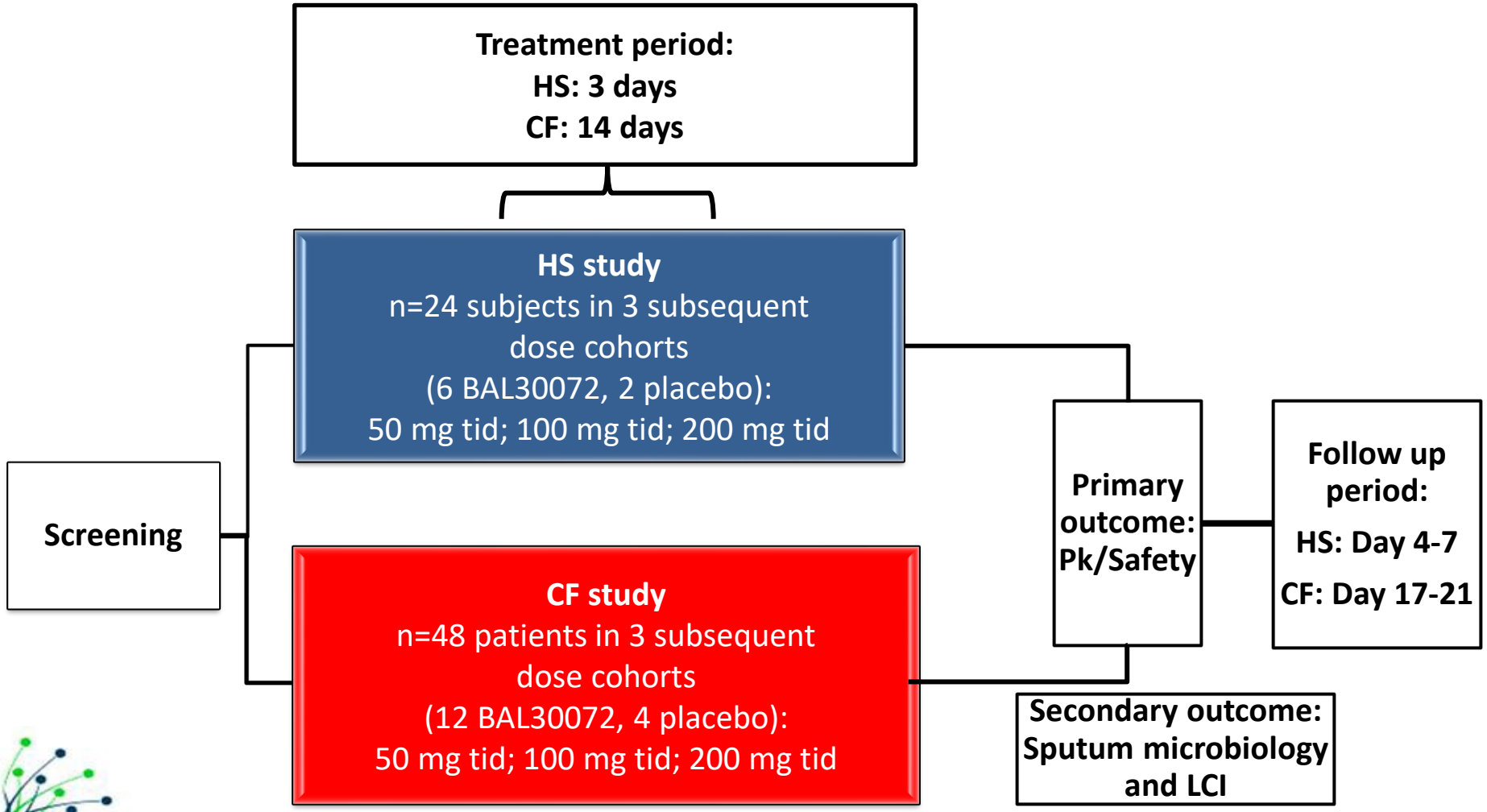
- Development of inhalation device for BAL30072
- *in vitro* antimicrobial activity of BAL30072 against respiratory isolates
  - Planktonic & biofilm susceptibility testing
  - WGS analysis of CF pathogens
  - Breakpoint development
- *in-vivo* activity of BAL30072 against CF pathogens
  - Mouse model of chronic lung infection
- Pre-clinical inhalation toxicology/toxicokinetics of inhaled BAL30072

WP2: Timelines and decision points

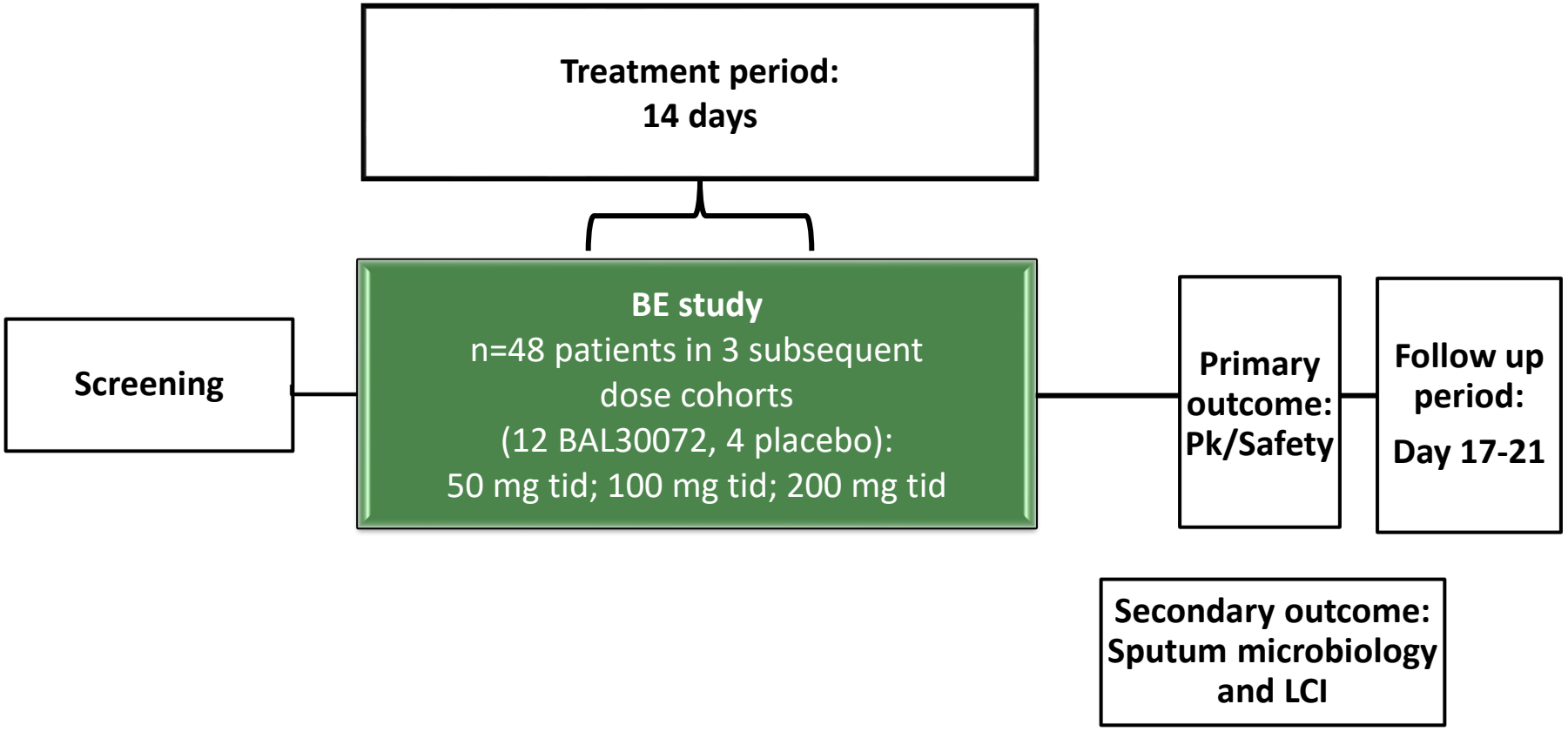
Task	Year 1 (2015)				Year 2 (2016)				Year 3 (2017)				Year 4 (2018)				Year 5 (2019)			
Quarter	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17	Q18	Q19	Q20
Month		3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
Feasibility DPI / Nebulizer		■	■	■																
Development nebulizer device		■	■	■	■	■														
Development of DPI					■	■	■	■	■											
In-vitro microbiology/ Biofilm models		■	■	■	■															
In-vivo efficacy		■	■	■	■	■	■	■	■											
Inhalation Toxicology (rat, dog)					■	■	■	■	■	■										
CTA manufacture										■	■									
Development ECOFFs and breakpoints		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■			
Management of WP2		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■			



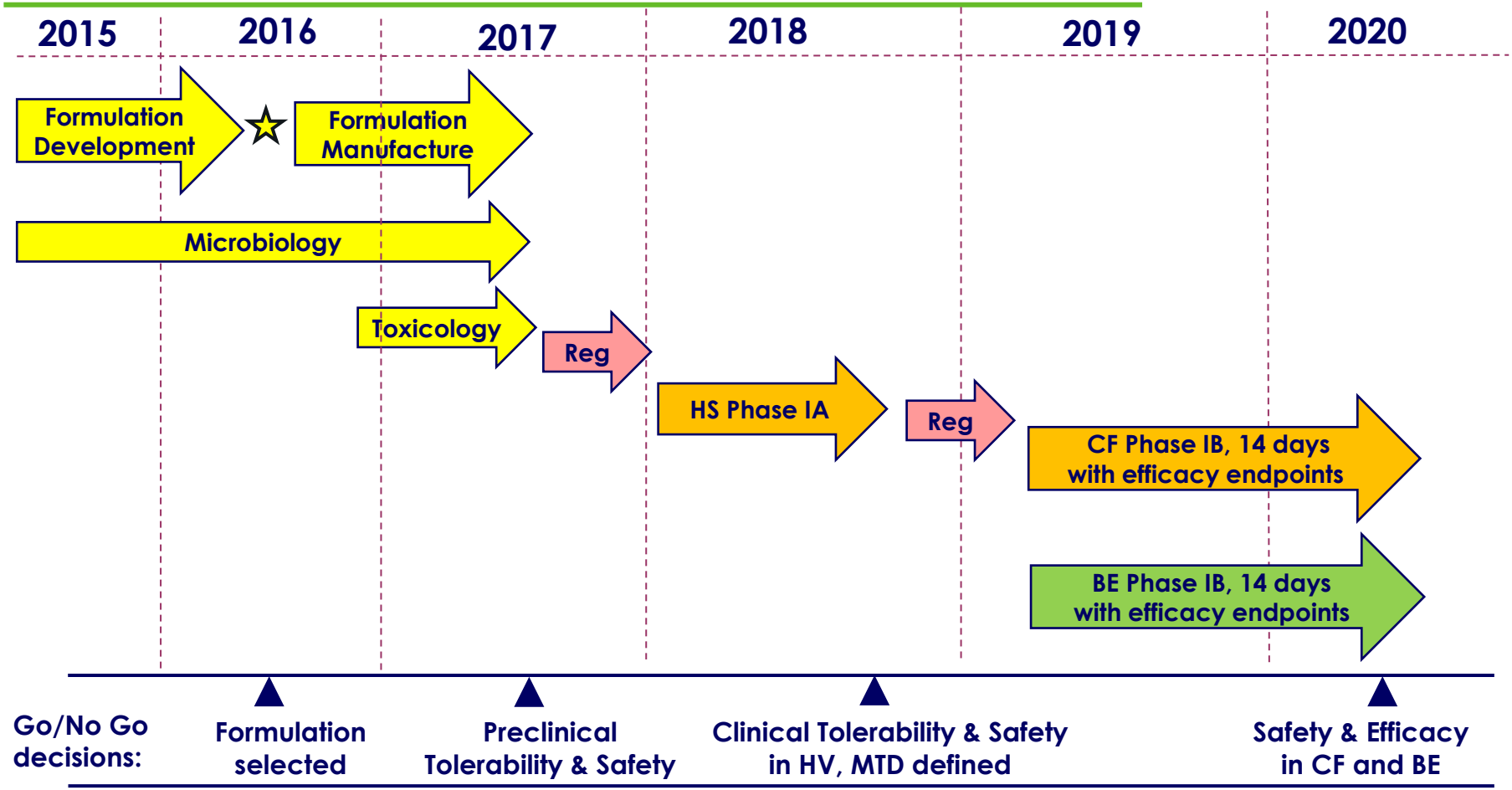
WP3: BAL30072 studies in HS & CF subjects



WP4A: BAL30072 study in BE subjects



BAL30072 programme:
Revised development plan allowing a manageable and achievable program within the 5 years IMI funding time frame



☆ Go/No Go decision for Dry Powder Inhaler vs Nebulizer

Reg: Regulatory; HS: Healthy Subject; CF: Cystic Fibrosis; BE: Bronchiectasis; MTD: Maximal Tolerated Dose

WP4B: Phase II TIP dose ranging study in BE

- **Study Design:** double-blind, parallel arm with multiple treatment arms, monthly visits
- **Study duration:** 1-4 weeks screening + 24 weeks treatment & follow-up
- **Sample size:** 180 patients (50 centers) randomized in 3 cohorts: 60 patients per cohort
- **Endpoints:** efficacy: bacterial load reduction, exacerbations (PE), PRO, change in sputum volume/colour, LCI, microbiome; safety and tolerability; PK
- **Recruitment:** approx. 12 months

Proposed design will be discussed with regulatory authorities (EMA, US FDA) – June 2015

WP4B: Dose selection and decision making

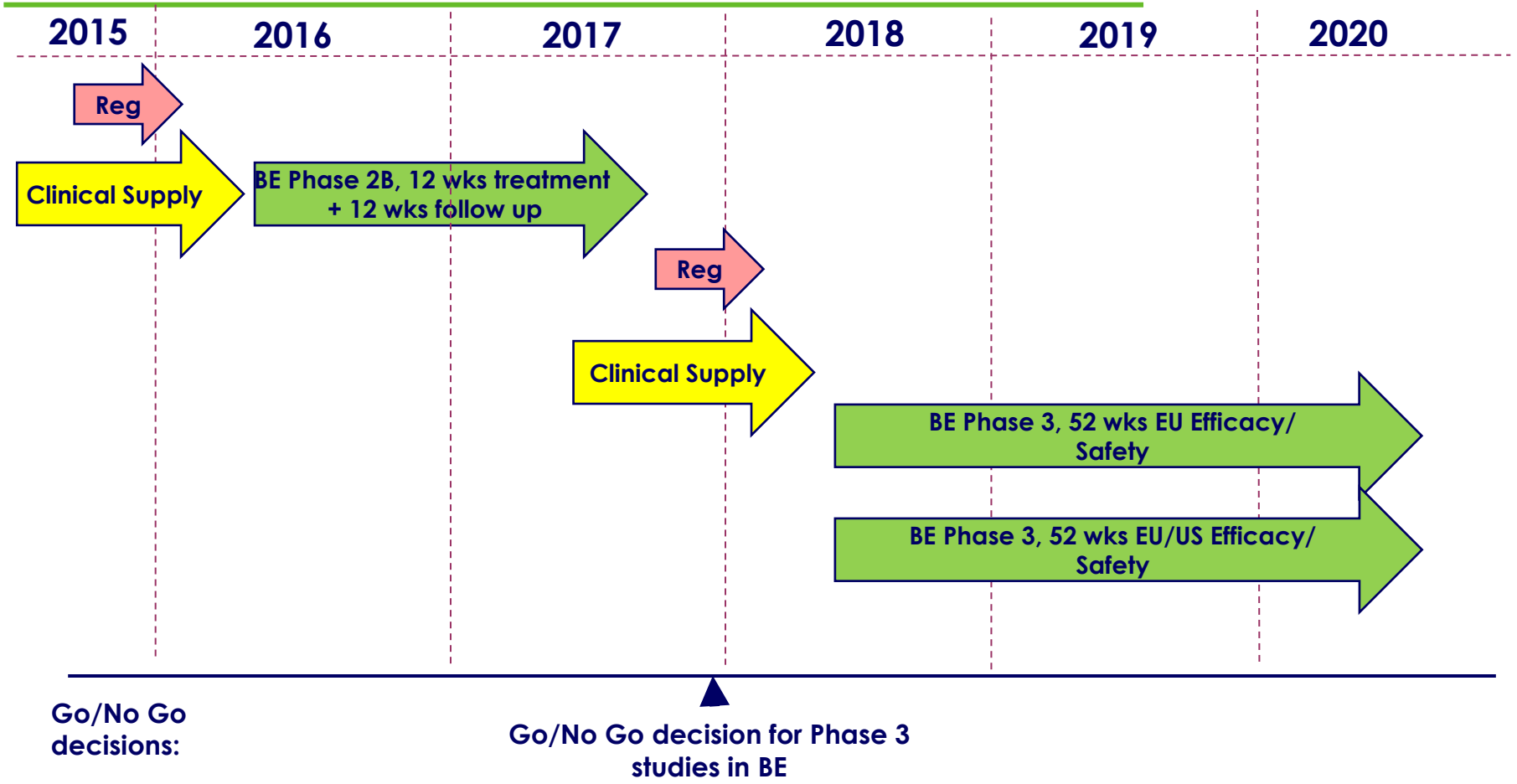
- Dose selection
  - Safe, well-tolerated dose that provides significant reduction in PA bacterial counts and shows a positive trend(s) in secondary and/or exploratory endpoints

- Phase III study design
  - Refined based on the phase II study data, BE registry (WP5 and US registry) and literature
  - Integrating regulatory advice (CHMP, US FDA)

WP4B: Phase III TIP efficacy study in BE

- **Study Design:** double-blind, parallel arm design, quarterly visits
- **Study duration:** 1-4 weeks screening + 52 weeks treatment
- **Sample size:** 250 patients 2 treatment arms
  - Two phase 3 studies planned: 1 EU (120 sites), 1 EU + US (80 EU + 40 US sites)
- **Primary endpoint** (subject to agreement with regulatory authorities): annualized mean rate of PE
- **Secondary endpoints:** safety and tolerability, lung function, clinical efficacy endpoints (exacerbations and PRO), microbiological endpoints (changes in CFU/g sputum and resistance) and novel endpoints (microbiome, LCI and CT)
- **Recruitment:** 12 months

Inhaled tobramycin programme: Development plan allowing a manageable and achievable program within the 5 years IMI funding time frame



Reg: Regulatory, BE: Bronchiectasis

WP5: Development of an EU BE registry

- To develop an EU-wide registry for BE
- Comprehensive data on the epidemiology, natural history and treatment of BE in Europe
- To achieve synergies with non-EU registry initiatives
- Generation of evidence-based recommendations on the management of patients with BE
- To make data from the EU BE registry accessible to the scientific community at large
- To ensure sustainability beyond the life of this project

Alignment of existing initiatives

EMBARC

The European Bronchiectasis Registry

BRONCH-UK
The National Bronchiectasis Network

ECFS PATIENT REGISTRY

LUNG FOUNDATION AUSTRALIA
"When you can't breathe... nothing else matters"™

BRONCHIECTASIS RESEARCH REGISTRY
A COPD FOUNDATION INITIATIVE

ERS EUROPEAN RESPIRATORY SOCIETY
every breath counts

S.I.Me.R.
SOCIETÀ ITALIANA di MEDICINA RESPIRATORIA

DZL
Deutsches Zentrum für Lungenforschung

WP6: Sputum microbiology

- Screening
  - Qualitative microbiology: presence of relevant organisms
  - COMBACTE LAB-Net laboratories
  - LAB-Net: quality assurance & training
- Clinical studies
  - Quantitative microbiology: bacterial load
  - Antimicrobial susceptibility testing
  - Central laboratories: QUB & Antwerp
- Repository of clinical isolates and clinical samples

WP6: Novel outcome measures for clinical trials

Exploratory endpoint	Regulatory endpoint	Clinical Trials	WP
Microbiome analysis Resistome analysis	Bacterial load (cfu/g sputum) Resistance development (MIC)	• TIP Phase II dose finding study: BE • BAL30072 Phase IB Pk/Safety studies: CF & BE • TIP Phase III efficacy /safety studies: BE	4B 3 & 4A 4B
Lung Clearance Index (LCI)	FEV_1	• TIP Phase II dose finding study: BE • BAL30072 Phase IB PK/Safety studies: CF & BE • TIP Phase III efficacy /safety studies: BE (in EU)	4B 3 & 4A 4B
Computed tomography (CT) scanning	FEV_1	• TIP Phase II dose finding study: BE • TIP Phase III efficacy /safety studies: BE	4B 4B

Key scientific gains from the iABC programme

- New antibiotic for use in CF and BE
- Post Phase III licensed antibiotic in BE
- Development of novel endpoints
- Integration of CF and BE centres
- Integration of microbiology labs across Europe
- EU BE registry

Watch out *Pseudomonas*… iABC are coming