



Innovative Medicines Initiative

# Development of novel inhaled antibiotic regimens in patients with cystic fibrosis (CF) and patients with non-CF bronchiectasis (BE)

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# Warnings Renewed – Actions Required



The Lancet, **Antibiotic resistance: a final warning**  
Sept. 28th, 2013



On Sept 16, the US Centers for Disease Control and Prevention (CDC) released its report *Antibiotic Resistance Threats in the United States, 2013*—their first ever report on this subject. From the outset the tone is clear: in his foreword, Tom Frieden, director of the CDC, states that “antimicrobial resistance is one of our most serious health threats. Infections from resistant bacteria are now too common”. The stated aim of this report is to increase awareness of the threat resistance poses and to encourage immediate action to address this threat.

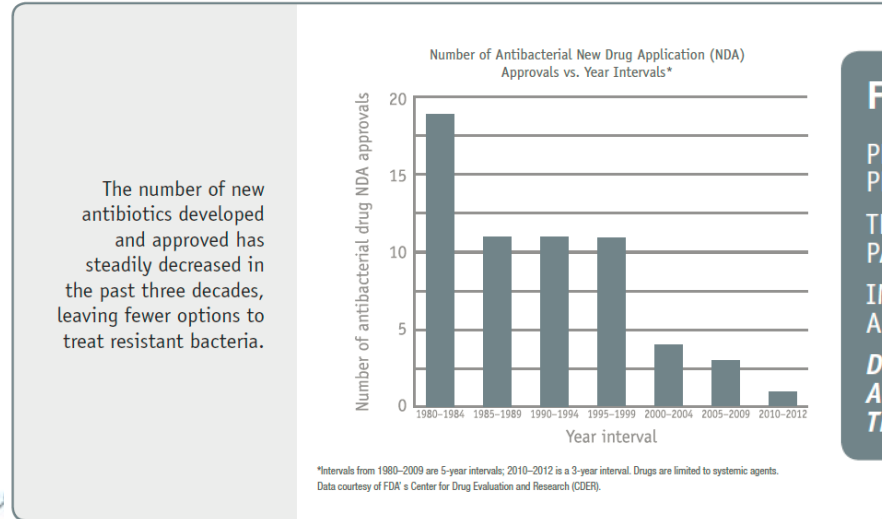
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INFEKTIONSSCHUTZGESETZ

## Bessere Hygiene-Standards

- ➔ [Hohe Infektionsraten und resistente Erreger](#)
- ➔ [Bisherige Maßnahmen des Bundes zur Verbesserung der Infektionshygiene und zur Verhütung und Bekämpfung resistenter Krankheitserreger](#)
- ➔ [Die Schwerpunkte des Gesetzes](#)
- ➔ [Die Neuregelungen im Einzelnen](#)
- ➔ [Weitere Neuregelungen](#)

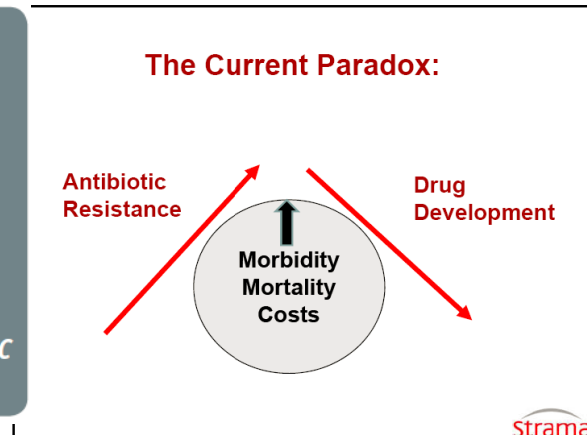
Mit dem „Gesetz zur Änderung des Infektionsschutzgesetzes und weiterer Gesetze“ hat die Bundesregierung gezielt verbesserte Voraussetzungen für die Verhütung und Bekämpfung von Krankenhausinfektionen und resistenten Krankheitserregern



The number of new antibiotics developed and approved has steadily decreased in the past three decades, leaving fewer options to treat resistant bacteria.

### FOUR CORE ACTIONS

- PREVENTING INFECTIONS, PREVENTING SPREAD.
- TRACKING RESISTANCE PATTERNS.
- IMPROVING USE OF ANTIBIOTICS.
- DEVELOPING NEW ANTIBIOTICS AND DIAGNOSTIC TESTS.**



CDC report on antibiotic resistance threat, 2013



# Need for public-private collaboration

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- Collaboration approach ensures best and diverse expertise from around the world is gathered and data and risks are shared, which will lead to higher chance of success in developing new inhaled antibiotics and in improving the use of antibiotics in patients with cystic fibrosis (CF) and non-CF bronchiectasis (BE).
- Basilea and Novartis have complementing expertise in development of inhaled antibiotics in CF and expertise in anti-infective drug development.
- Academic, SME, regulatory and other public partners are needed for their expertise with
  - Treating patients with CF, non-CF BE
  - Clinical endpoint research
  - Specific microbiology
  - Epidemiology
  - Data registries and data access solutions to optimally exploit the benefit of the data that will be generated
  - Regulatory Strategies and harmonization
  - Non-clinical studies with inhaled antibiotics
  - Development of extended release inhalation formulations

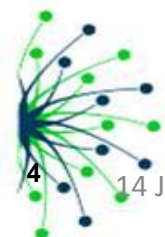


# ND4BB Vision

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The overall vision of ND4BB is to create an innovative collaborative Public-Private Partnership (PPP)-based approach that will encompass all aspects from the discovery of new antibiotics to Phase 2 and 3 clinical trials with the aim of reinvigorating antibiotic R&D.



# Objectives of the full project (1) – Cystic Fibrosis (CF)



To improve care in CF patients, there is an increasing need in gaining experience with inhaled antibiotic combination regimens, in particular in identifying combinations with additive or synergistic effects.

Novel inhaled antibiotics are needed for CF patients in view of new emerging and resistant pathogens. Especially resistant non-fermenters such as *P.aeruginosa* (Pa), *S. maltophilia* and *Burkholderia cepacia* increase the risk for rapid disease progression.

- Determine compound X with synergistic antibacterial effects against Pa and other difficult to treat Gram-negative bacteria when combined with tobramycin.
- Inhaled formulation and preclinical development of BAL30072 and compound X.
- Clinical PoC study to explore alternating monthly or simultaneous combination therapies of inhaled compound X and tobramycin dry powder (TIP) for long-term suppressive antimicrobial therapy
- Clinical development (ph1 and ph2 studies) of inhaled BAL30072 against respiratory infections with Gram-negative (including multidrug-resistant) pathogens in patients with CF.
- Explore novel endpoints such as lung clearance index and imaging.
- Build on LAB-net (COMBACTE) by defining and adding laboratories with a track record in the field of sputum microbiology and lung microbiomes.
- Build capability for storage of non-fermenter strain samples for future research.



# Objectives of the full project (2) – Non-CF Bronchiectasis

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In non-CF BE, infection with *P. aeruginosa* is linked with more rapid disease progression and a higher risk of morbidity and mortality. No inhaled antibiotics are approved for this indication and there is a high need for controlled studies with clinically relevant endpoints.

- Clinical development (ph2 and ph3 registration studies) of tobramycin powder for inhalation (TIP) against *Pseudomonas aeruginosa* (Pa) respiratory infections in patients with non-CF BE.
- Clinical development (ph1 study) of inhaled BAL30072 against respiratory infections with Gram-negative (including multidrug-resistant) pathogens in patients with non-CF BE
- Support alignment and coordination between current local or pan-European initiatives that have set up or are in the process of setting up registries for non-CF bronchiectasis with the goal to arrive at a EU-wide registry making important information on e.g., frequency of the disease, use of medication, microbiology, co-morbidities, prognosis etc. available.



# Pre-competitive nature

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- European-wide non-CF BE registry – contributes to general understanding of the disease and its therapies
  - Lab network with expertise in sputum microbiology – improves quality of diagnosis and tailored therapy
  - Storage capabilities for non-fermenter strains – enhance future research on these strains
  - Clinical endpoint research – makes future drug development easier and more clinically relevant in the areas of CF and non-CF BE
  - Data on resistance development and emerging pathogens – informs on new therapies and treatment regimens
  - All the above information and infrastructure will become available to the research community and general public.
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# Expected impact on the R&D process (1)

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- Studies of combinations of inhaled antibiotics will optimise the use of antibiotics in CF patients and might lead to additional benefits for CF patients due to synergistic effects. The studies will inform on resistance development and emerging pathogens in CF.
- Novel inhalation drug delivery technologies such as Dry Powder Inhalation (DPI) will reduce treatment burden for patients, improve adherence to medication and avoid health care associated infections through wet nebulisation.
- A novel antibiotic against difficult to treat Gram-negative bacteria especially non-fermenters including multi drug-resistant *P. aeruginosa* and *S. maltophilia*, *Burkholderia spp*, *Acinetobacter spp*, *Achromobacter xylosoxidans*, *Ralstonia spp*, and *Pandoraea spp* may become available for CF patients.
- Two new inhaled antibiotics may become available to patients with non-CF BE and are expected to reduce exacerbations, improve quality of life, reduce hospitalisations, and other burden to the healthcare system.





# Expected impact on the R&D process (2)

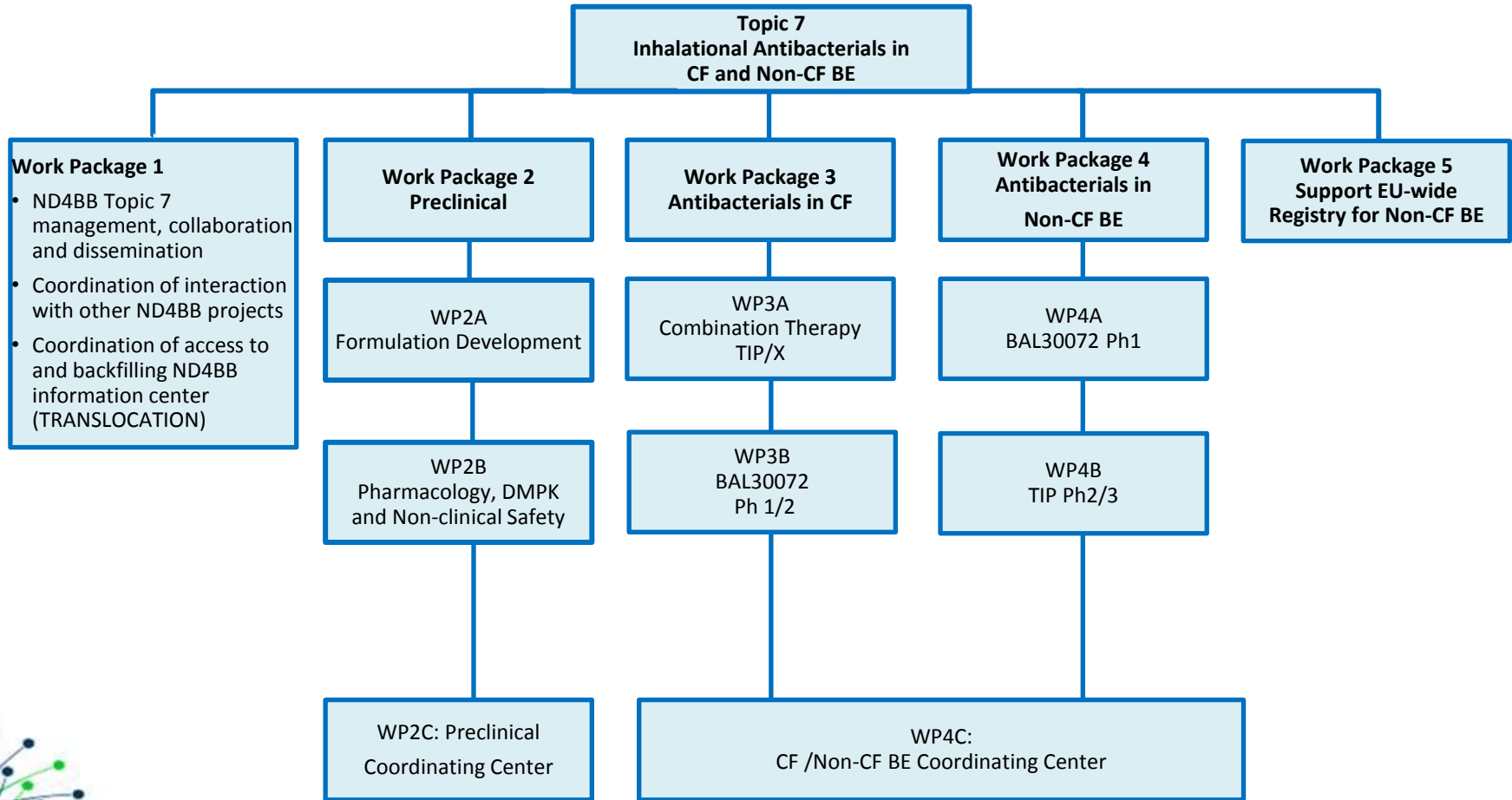
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- Clinical studies will generate data on clinically relevant endpoints in non-CF BE, such as frequency of exacerbations and the correlation with changes in bacterial load and will stimulate discussions with regulators to help define a regulatory path which will be of benefit to future development of new treatments.
- Characterisation of patient's microbiology will inform on clinical relevance of potentially pathogenic microorganisms (PPMs).
- Capability for storage of non-fermenter strain samples will be developed that will facilitate future research in the fields of CF and non-CF BE.
- A European wide registry gathering information on several aspects of the disease of non-CF BE that can be analysed to generate recommendations on the management and control of these patients.



# Suggested architecture of the project



# Expected contributions of the applicants

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- Proposal for and execution of a plan for the management of all aspects of the clinical studies, e.g. clinical sites selection/management, monitoring, collection and analysis for microbiology and PK, central evaluation of CT-scans.
  - Expertise in the design and conduct of CF and non-CF BE clinical studies incl. alternative study designs and endpoints (e.g. Imaging, LCI).
  - Laboratories with a track record in sputum microbiology.
  - Involvement with data-registries of non-CF BE.
  - Proposal for and execution of plans for microbiology and pharmacology studies to determine compound X.
  - Non-clinical data package BAL30072 and compound X.
  - Proposal for and execution of plans for inhalation formulation development of BAL30072.
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# Expected (in kind) contributions of EFPIA members



- Sponsorship of clinical studies including regulatory strategy and interactions with Health Authorities (HAs), safety reporting.
- Clinical supplies (Compound X, TIP, BAL30072)
- Support for coordinating activities, epidemiological, health outcomes and pharmacoeconomics support and advice.
- Expertise in inhalation formulation development of Compound X using PulmoSphere® dry powder particles and optimisation for delivery through an approved dry powder inhaler.
- Guidance on analysis of BAL30072 in biological fluids including practical assistance with analytics and data analysis when necessary.
- Expertise and guidance on drug substance characteristics of BAL30072 such as physicochemical properties and impurity as well as stability profile.
- Analytical methods to test and characterise drug substance and freeze-dried powder for solution to be used as a solution, which has the potential for use with air-jet nebulisers.
- Existing preclinical animal models for safety evaluation.



# What's in it for you?



- **Academia:**
  - Access to information, compounds, drug formulations and clinical protocols from Pharma companies active in CF and non-CF BE research
  - Actively contribute to the advancement of treatments for CF and non-CF BE patients
  - Access to funding for key research activities and capacity building
  - Network with key specialists and industry
  - Contribute to the first European non-CF BE registry
  - Contribute to develop European-wide standards for the management of non-CF BE patients
- **SMEs:**
  - Protocol, material and information exchange with industry and academia may lead to an expansion of future internal capacities (new contracts, new capabilities)
- **Patient Organizations:**
  - Active involvement in development of novel treatments
  - An open and scientifically driven collaboration will contribute to increase the transparency of all activities behind CF and non-CF BE research with a consequent increase in the awareness of and in the trust by patients' organizations.
- **Regulatory Agencies:**
  - Active and proactive interaction with both industry, academia and other consortium partners for the definition of best regulatory pathways and possible update/development of new disease guidelines
  - Discussion on clinically relevant endpoints for long-term studies with inhaled antibiotics
- **Payors:**
  - Determination of best way forward to overcome increasing health care costs due to non-availability of antibiotics or non-appropriate usage thereof.



# Key deliverables of the full project

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- Successful Phase 1 and Phase 2 (BAL30072) and successful Phase 2 and Phase 3 (TIP) clinical trials demonstrating the pharmacology, safety, and efficacy of new inhaled antibacterials against *Pseudomonas aeruginosa* and other clinically relevant Gram-negative pathogens in CF and/or non-CF BE.
- Successful clinical studies demonstrating best effective combination treatment regimen with TIP in CF patients infected with Pa and possibly other difficult to treat Gram-negative bacteria.
- Alignment and coordination between current local or pan- European initiatives that have set up or are in the process of setting up registries for non-CF BE with the goal to arrive at an EU-wide registry.
- An extension to the laboratory network established under COMBACTE (LAB-net) with sputum microbiology and lung microbiome expertise.
- Capability for storage of non-fermenter strains samples for future research.
- New insights into formulation technology and capabilities to enable the successful clinical development of novel inhaled antibacterials to improve clinical outcomes in difficult to treat lung infection in CF and non-CF BE patients.

New insights on novel endpoints such as lung clearance index and imaging.

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# Questions?

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- Contact the **IMI Executive Office**

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