Innovative Medicines Initiative

IMI-GB-DEC-2013-21 Annex 1

11th Call for Proposals 2013

Innovative Medicines Initiative

Version 2

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GENERAL PRINCIPLES

The Innovative Medicines Initiative Joint Undertaking (IMI JU) is a unique pan-European public-private partnership between the European Commission and EFPIA[1] driving collaboration between all relevant stakeholders including large and small biopharmaceutical and healthcare companies, regulators, academia, and patients.

The aim of IMI is to propose a coordinated approach to overcome identified research bottlenecks in the drug development process, in order to accelerate the development of safe and more effective medicines for patients, by fostering collaboration between all stakeholders such as industry, public authorities (including regulators), organisations of patients, academia and clinical centres, and enhancing Europe's competitiveness.

The revised IMI Scientific Research Agenda http://www.imi.europa.eu/content/research-agenda describes the research bottlenecks in the drug development process and identifies new and established research priorities correlated to at least one of the seven IMI Areas of Research Interest.

The IMI 11th Call 2013 for proposals includes topics covering the following key research priorities:

- Increasing Practicability of Biomarkers and Biobanks
- Coping with Regulatory and Legal Hurdles
- Neuro-Psychiatric Disorders/Brain Disease
- Infectious Diseases
- Inflammatory Diseases
- 'Beyond High Throughput Screening'- Pharmacological Interactions at the Molecular Level

[1] European Federation of Pharmaceutical Industries and Associations – www.efpia.eu

CALL TOPICS

The 11th Call topics are:

- Topic 1: Applied Public-Private Research Enabling Osteoarthritis Clinical Headway (APPROACH)
- Topic 2: European Platform For Proof of Concept for Prevention in Alzheimer's Disease (EPOC-AD)
- Topic 3: Blood-Based Biomarker Assays For Personalised Tumour Therapy: Value Of Latest Circulating Biomarkers
- Topic 4: Zoonoses Anticipation and Preparedness Initiative (ZAPI).
- Topic 5: Generation of Research Tools to Translate Genomic Discoveries into Drug Discovery Projects

Under the Theme New Drugs for Bad Bugs

- Topic 6: ND4BB Topic 6: Epidemiology Research and Development of Novel Systemic Antibacterial Molecules Against Healthcare-Associated Infections due to Gram-Negative Pathogens
  - Subtopic 6A: Epidemiology Research and Clinical Development of a Novel Bispecific IgG Antibody, Bis4αPA, for the Prevention of Serious Pseudomonas Aeruginosa Disease
  - Subtopic 6B: Clinical Development of a Novel Resistance-Breaking Beta-Lactam Antibiotic, AIC499, in Combination with a Beta-Lactamase Inhibitor (BLI) Against Severe Bacterial Infections due to Gram-Negative Pathogens
- Topic 7: ND4BB Topic 7: Development of Novel Inhaled Antibiotic Regimens in Patients with Cystic Fibrosis (CF) and Patients with Non-CF Bronchiectasis (BE)

And

- Topic 8: EcoRiskPrediction (ERP)

Applicant Consortia are invited to submit expressions of interest to one of the topics/subtopics.

The expressions of interest should address all aspects of the topic/subtopic to which the Applicant Consortia are applying.

The size of each consortium should be adapted to the scientific goals and the expected key deliverables.

While preparing their expressions of interest, Applicant Consortia should ensure that needs of patients are adequately addressed and, where appropriate, patient involvement is encouraged.

Further information can be found under the section 'Synopsis of Call and evaluation processes'.

Before submitting an expression of interest, the various Call Documents, such as *IMI JU Rules for submission, evaluation and selection of Expressions of Interest and Full Project Proposals, Rules for Participation*, the *IMI Intellectual Property Policy,* etc., shall be considered carefully. These documents are published on the IMI website www.imi.europa.eu at the time of the 11th Call 2013 launch.

Synergies and complementarities with other EU funded projects should be explored in order to avoid overlaps and duplications and to maximize European added value in health research.

DURATION OF THE PROJECTS

The indicative duration of the project is between 4 and 7 years.

Please note that the Council Regulation 73/2007 set up the IMI JU as a body responsible for implementing the 7th Framework Program for Research and Development for a period up to 31 December 2017. In accordance with the statutes of the IMI JU an ad hoc procedure will be set up to ensure appropriate management of the concerned Grant Agreement(s) after the termination of the IMI JU.

FUNDING OF THE PROJECTS

The indicative in kind contribution from the research-based companies that are members of the European Federation of Pharmaceutical Industries and Associations (EFPIA) will be EUR 201 045 105.

The financial contribution from the European Union (EU) to the IMI JU for the support of research activities will be a maximum of EUR 170 370 584.

Disclaimer: Given that the sum of amounts of indicative maximum IMI JU contribution for the individual topics indicated therein slightly exceeds the total available EU contribution, the final budget of the projects that will derive from this call may have to be adjusted, based on the proposed activities and independent experts' recommendations, so that the budget envelope is respected.

The Applicant Consortia shall keep in mind that the budget of each expression of interest is to be adapted to the scientific goals and the expected key deliverables of the project.

SYNOPSIS OF CALL AND EVALUATION PROCESS

The IMI JU supports research activities following open and competitive Calls for proposals, independent evaluation and the conclusion of Project and Grant Agreements.

The topics included in the 11th Call are associated with a group of pharmaceutical companies that are members of EFPIA (hereafter called the 'EFPIA Consortia') and which are committed to collaborate with public and private organisations eligible for funding by the IMI JU. The EFPIA members will provide 'in kind' contributions to support their activities within the research projects.

The IMI JU applies a two stage Call process. In the first stage, 'Applicant Consortia' (i.e. formed by academia, small and medium sized enterprises (SMEs), patient organisations, non EFPIA companies, etc.) are invited to submit, to the IMI JU, an expression of interest (EoI) in response to a Call topic/subtopic.

In preparing their EoIs, the Applicant Consortia should carefully read the *Guidance Notes for Submission and Preparation of Expression of Interest*[2] in addition to the specific Applicant Consortium expectations/requirements outlined within the description of the individual topic/subtopic.

The Applicant Consortium shall consider the research contribution that an EFPIA Consortium will make to a given project.

[2] published on the IMI website www.imi.europa.eu at the time of the 11th Call 2013 launch

Each EoI submitted will be reviewed by independent experts according to predefined evaluation criteria.

Each Applicant Consortium with the highest ranked EoI will be invited to develop a full project proposal (FPP) together with the EFPIA Consortium.

However in case of ND4BB Topic 6, the Applicant Consortium with the highest ranked EoI for each of the subtopics will be invited to jointly develop a full project proposal together with the EFPIA Consortium.

For each topic, the full project proposal will then be subject to a final review by independent experts according to predefined evaluation criteria.

Only a full project proposal that has been favourably reviewed in the evaluation process can be selected for funding. This project will then be invited by the IMI JU to conclude a Grant Agreement governing the relationship between the selected project consortium and the IMI JU.

For full details, applicants should refer to the *IMI JU Rules for submission, evaluation and selection of Expressions of Interest and Full Project Proposals*[3].

ELIGIBILITY TO PARTICIPATE IN PROJECTS AND TO RECEIVE FUNDING FROM THE IMI JU

Criteria of eligibility to participate in IMI projects and the criteria to receive funding from the IMI JU are specified under the *Rules for participation* in the IMI JU collaborative projects published on the IMI JU website www.imi.europa.eu.

The IMI JU financial contribution will be based on the reimbursement of the eligible costs. The following funding rates apply to the legal entities eligible for funding: For research and technological development activities, up to 75% of the eligible costs and for other activities (including management and training activities) up to 100% of the eligible costs charged to the project are eligible for funding. For the indirect costs (overheads), the

[3] published on the IMI JU website www.imi.europa.eu at the time of the launch of the 11th Call

legal entities eligible for funding may opt for one of the following indirect costs methods: the actual indirect costs; or the simplified method which is a modality of the actual indirect costs for organisations which do not aggregate their indirect costs at a detailed level, but can aggregate them at the level of the legal entity; or a flat rate of 20% of total eligible direct costs (excluding subcontracting costs and the costs of resources made available by third parties which are not used on the premises of the beneficiary).

For full details, Applicant Consortia are invited to refer to the *Rules for Participation* in the IMI JU collaborative projects (www.imi.europa.eu).

The research based companies that are members of EFPIA shall not be eligible to receive financial contributions from the IMI JU.

IMI INTELLECTUAL PROPERTY POLICY

The IMI Intellectual Property Policy (IMI IP policy, www.imi.europa.eu) has been developed to be aligned with the objectives of the IMI JU to ensure knowledge creation, together with the swift dissemination and exploitation of knowledge, and fair reward for innovation.

The IMI IP Policy sets out *inter alia* basic principles regarding ownership of Background and Foreground, access rights depending on the entity and the purpose, and dissemination.

In submitting an EoI, the Applicant Consortia fully understand the principles laid out in the IMI IP policy that will apply to all research projects conducted under the IMI JU.

The IP policy does not foresee all details and does not aim to answer to all possible practical situations participants may be faced with. Flexibility is provided for participants to establish the most appropriate agreements (e.g. the Project Agreement) serving each individual project's objectives, and considering the wider IMI objectives.

Applicant Consortia are invited to read carefully the *Guidance Note on the IMI IP Policy* (www.imi.europa.eu), whose purpose is to explore ways to handle related issues and pitfalls that participants may encounter during the preparation, negotiation and completion phases of the Grant Agreement and Project Agreement.

PROJECT AGREEMENT

The Project Agreement is a private agreement which the participants of an IMI project conclude amongst themselves to implement the provisions of the Grant Agreement and to regulate internal issues related to work organisation and objectives for each participant, consortium governance, IP, financial and other matters.

All participants of a selected IMI project are requested to start negotiation on the Project Agreement between them in parallel to the preparation of the full project proposal.

The Full Consortium shall ensure that the negotiation of the Project Agreement is completed no later than the finalisation of the full project Description of Work.

1. APPLIED PUBLIC-PRIVATE RESEARCH ENABLING OSTEOARTHRITIS CLINICAL HEADWAY (APPROACH)

BACKGROUND

Burden of disease: Osteoarthritis (OA) is the most common global arthritic disease and is becoming more prevalent as the population ages and obesity rates rise.

- OA is already one of the ten most disabling diseases in developed countries
- Between 2002 and 2007, OA moved from the twelfth to the sixth leading cause of years lost to disability or morbidity (WHO data), and between 1990 and 2010, OA moved from fifteenth to the eleventh leading cause of years lived with disability (YLDs) – Global Burden of Disease Study 2010.
- History of joint injury and manual labour increase risk, as do age, obesity and sedentary lifestyle
- Global estimates are that 9.6% of men and 18.0% of women over 60 have symptomatic OA
- 80% of those with OA will have limitations in movement and 25% cannot perform their major daily activities of life

Direct and indirect costs of OA for the EU are substantial; in the UK alone, total costs are estimated to be equivalent to 1% of the annual gross national product (GNP).

PROBLEM STATEMENT

Despite this large and growing disease burden, many pharmaceutical organizations have de-emphasised or abandoned OA drug development due to real and perceived hurdles. Ultimately, a number of highly visible and costly failures have highlighted the scale of the challenge and subsequently reduced the number of companies independently pursuing the development of disease modifying OA drugs (DMOAD).

Considering the scale of the problem and societal impact, there remains a major unmet need as current treatments are predominantly restricted to symptomatic relief or costly and invasive surgical intervention.

Multiple reasons have been identified as underlying causes of past DMOAD failures:

- Limited understanding of OA pathogenesis. Emerging data suggest OA is a heterogeneous disease with a variety of pathophysiologic drivers, some of which are amenable to pharmacologic intervention, and some of which are expected to be less so.

- Variable disease course. The majority of an unselected OA population do not progress radiographically or clinically in a given 2 year window; companies have not had the tools or knowledge base to prospectively identify patients at risk of progression who stand to benefit the most from effective therapies.
- Absence of personalised medicine mindset. Clinical development plans have frequently used a 'one size fits all' approach rather than matching mechanism of action to specific OA patient subpopulations.
- Reliance on relatively insensitive endpoints. X-ray-based joint space narrowing (the current standard endpoint to demonstrate disease modification) is insensitive, tends to be slowly evolving and does not allow visualization of the tissue most associated with the disease (cartilage).

NEED FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

The issues in OA drug development are large and complex, as described, and independent effort has led to slow clinical progress. These challenges can be best addressed by a Public-Private partnership of engaged, knowledgeable and complimentary industrial, academic, patient and governmental experts who can provide innovative and viable solutions.

We envision the proposed project will enhance the collective knowledge base around OA biomarkers and disease pathogenesis in the pre-competitive space and provide a setting for regulatory guidance, patient advocacy and healthcare agency interaction as well as build stronger collaborations among academic and industrial groups to enable effective therapeutic development.

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

Applicants have to take in consideration for the development of their Expression of Interest that there are already several initiatives on-going in the field, both in Europe and globally.

Synergies and complementarities should be considered, building from achievements, and incorporating when possible data and lessons learnt, while avoiding unnecessary overlapping and doubling of efforts.

Collaboration by design should be a cornerstone of the proposed strategy.

Some of these initiatives are listed below.

- Established IMI projects such as eTRIKS and EMIF for data handling curation, analysis platforms (however relevant resources to support the activity have to be considered)

- TreatOA – EU - FP7 funded initiative
    - Access to 28,000 patient cohort and control subjects
    - Largely genomics driven (Genome-Wide Association Study and functional genomics)
    - Limited set of biochemical markers included
- CHECK cohort – Dutch Arthritis Association funded
    - 10-year (~1000 participant) prospective hip and knee OA study with radiographic and biological samples
    - Many biochemical markers assessed
- Osteoarthritis Initiative (OAI) – NIH/Industry funded, publically accessible (http://oai.epi-ucsf.org/datarelease/StudyOverview.asp)
    - 6-year (~4800 participant) prospective study of knee OA patients, 'at risk' individuals and controls
    - Baseline and annual biological sample collection, demographics and imaging (radiograph and T2 MRI)
    - fNIH consortium substudy currently profiling 12 biochemical markers to assess rapid image-based progressors
- Multicentre Osteoarthritis Study (MOST) – NIH/NIA funded, publically accessible (http://most.ucsf.edu/studyoverview.asp)
    - MOST is a longitudinal, prospective, observational study of knee OA
    - MOST enrolled 3,026 study participants and has conducted five follow-up contacts at 15, 30, 60, 72, and 84 months
    - At each time point, clinical assessments were conducted and radiological data (x-ray and MRI) collected, as well as other measures and instruments, with the exception of the 72-month follow-up, which was a Telephone Interview only
    - The overall aims of MOST are to identify novel and modifiable biomechanical factors (including physical activity-related factors), bone and joint structural factors (including those assessed by MRI of the knee), and nutritional factors that affect the occurrence and progression of OA-related knee symptoms and radiographic knee OA.
- Nationalen Gesundheitsforschungsinitiative Arthrose (NGFA) Germany based OA cohorts
- Also, DOXY, KHOALA, Johnson county, etc.
- In addition the applicants should be aware of existing and emerging biobanking initiatives in Europe such as BBMRI-ERIC (www.bbmri.eu), BBMRI-LPC (www.bbmri-lpc.org) and Bioshare (www.bioshare.eu), among many others.

These existing and funded projects will enable smooth access to samples and data in the participating biobanks for most of the phenotypes listed. Also BBMRI.eu and BBMRI-LPC jointly catalog both population-based and clinical biobanks in Europe which information would potentially be very valuable for all the topics.

OVERALL OBJECTIVES

- Enable and implement comprehensive consolidation of existing data and high quality biomarker assessment to characterise OA patient subsets and support future regulatory qualification and endpoint validation
- Define the "right patient" to treat via stratification of patient subgroups – Link OA patient subsets to potential DMOAD targets based on phenotypic biomarkers, highlight specific disease drivers and progression criteria
- Assess next generation imaging techniques and human motion analysis to enable more efficient and reliable diagnosis and treatment
- Identify mechanistic targets and create a DMOAD development roadmap

EXPECTED KEY DELIVERABLES

- Consolidated existing complementary OA data sets (public and private)
- Characterised OA patient subsets with in-depth bioinformatics
- Identification of novel biomarkers
- Biochemical marker assay platform validation and development
- Validation of biochemical markers and next generation imaging and human motion analysis technologies in a cohort of OA patients
- User-friendly interface where data can be publically accessed and analysed
- Work with regulators to finalise guidance and initiate regulatory biomarker qualification process

EFPIA PARTICIPANTS

GlaxoSmithKline (coordinator), Merck KgaA (deputy coordinator), Servier

INDICATIVE DURATION OF THE PROJECT

The indicative duration of the project is 5 years.

INDICATIVE BUDGET OF THE PROJECT

The indicative EFPIA in-kind contribution will be up to EUR 7 500 000.
The indicative IMI JU contribution that will be made available to the applicant consortium will be a maximum of EUR 7 500 000.

Please note: Specific budget designations for each WP outlined below are for guidance purposes only and may be adjusted within the limits of the overall budget.

Examples of how EFPIA in-kind contribution can be designated
EFPIA partners may constitute expertise in the disease area, data and samples from existing clinical trials, sample handling, technology assessment, statistical analysis, data consolidation and logistics, among other areas.

- Expectation that consortium and work package co-leadership comes from EFPIA partners (4 WPs total)
- WP1 is largely analytical in nature therefore bioinformatic/statistical support from EFPIA partners is envisioned
- Additional options in WP2: assay platform expertise; WP3: sample management and associated costs, imaging expertise, sample testing expertise for biomarker validation, clinical OA study experience; WP4: regulatory and reimbursement expertise
- Direct funding is also an option in the form of reagents, kits, samples, equipment, etc.

APPLICANT CONSORTIUM

DESIRED EXPERTISE

Academic:

- Clinical centre expertise and access to OA patient and control cohorts
- Cutting-edge imaging and human motion analysis facilities and expertise
- Statistical and analytical expertise
- Proteomic/metabolomic discovery and technical expertise
- Mechanistic insights into the efficacy and safety aspects of DMOAD targets

Small and Medium Enterprises (SMEs):
Envisioned opportunity for SME involvement, where applicable, in the areas of:

- Proteomic/metabolomic discovery WP2

- Biomarker fit-for-purpose validation WP3a
- Biochemical marker testing WP3b
- Imaging technology and analysis systems WP3b
- Novel DMOAD compounds

Patient Advocacy Groups:
In addition to providing samples for assessment, a key component of patient involvement is envisioned through providing the patient perspective in WP4 and helping design the questionnaire to be utilised in WP3b. A good example is the currently planned initiative of the Arthritis Foundation in the US, undertaking an OA Research Initiative, including the development of a Pre-Competitive Consortium (PCCOA) whose mission is to advance the development of disease modifying therapies for the treatment of patients with OA.

Regulatory Agencies:
Envision a primary role for collaborative input and guidance from members of regulatory agencies (EMA and FDA) on WP4 to enable critical dialogue on project scope.

Healthcare Organizations:
Envision healthcare organization inclusion in WP4 with the intent of providing a better understanding of the economic burden of OA and comparison to current therapeutic strategies being utilised to help guide future approaches.

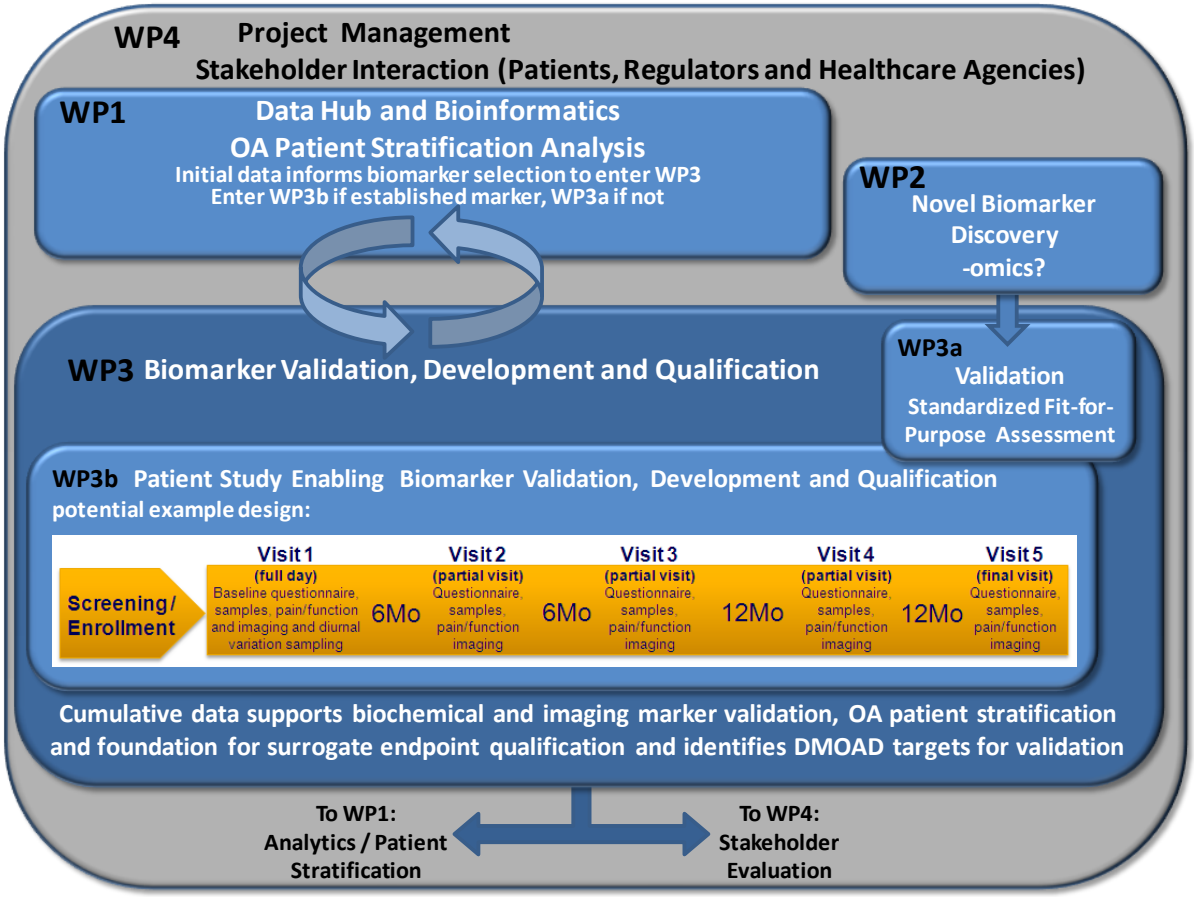
Measures of Success:

- It is envisioned that a successful proposal will outline a strategy to provide a more tenable pathway to select and clinically evaluate potential DMOADs:
    - Identify and characterise patient subsets and design framework for DMOAD development based on patient stratification
    - Increase in quality of preclinical DMOAD candidate data packages (link with translatable biomarkers and safety endpoints)
    - Increase in number of DMOAD clinical trials initiated (industry-wide)
    - Reduction of sample size and duration of Proof-of-Mechanism and Proof-of-Concept studies potentially leading to reduced clinical trial costs
    - Increase probability of success and reduction of failed studies
- Enable submission of biomarker qualification process(es) to health authorities in compliance with the regulations required (e.g. 510K rule and Pre-Market Approval):
    - Imaging

- Biochemical markers (based upon 'BIPED' criteria, listed in Additional Useful Information section)
- Genetic markers for prognosis

- Standardised data packages for comparison and use in regulatory environments
- Creation of cross industry and academic network of dedicated expertise
- Inclusion of representatives from patient advocacy, regulatory and health care groups as fundamental stakeholders to actively guide the efforts and help maintain focus

PROPOSED PROJECT ARCHITECTURE



WP1 – DATA HUB AND BIOINFORMATICS TO ENABLE OA PATIENT STRATIFICATION

Proposed Budget: €3.10 million (2.10 million EFPIA in-kind and 1 million IMI)

Bioinformatics approach for creation of dataspace using existing data (public and private) and subsequent data from WP3b

a. Assemble a scientific advisory board of internal and external experts to the project to guide decision-making

b. Define data packages to be used: biochemical, genetic and imaging

c. Consolidate and cross-check available datasets

d. Systems biology quantitative modelling of DMOAD targets

e. Review and compliance with ethics and privacy considerations

f. Create dataspace for investigations on available biomarker and validity for stage of disease/progression

g. Data compilation/analysis for identification of OA patient subsets: curate existing and IMI-derived data (WP3b) and perform analysis to identify and categorise patient subsets.

   Identify multivariate biomarkers (multi modal combinations) that may be utilised as criteria for inclusion (prognostic markers) and as clinical assessment criteria for running focused clinical trials

h. Selection of most suitable biomarkers for further development in WP3

   1. Existing biochemical markers of interest
      - Proposed: 10-20 total markers to progress into WP3
      - Possibility to Include genetic markers - potential to refine from ongoing TreatOA GWAS studies
      - Include potential markers of safety (BIPED-S) that have arisen from previous therapeutic efforts and known risk factors for OA patient population
      - Determination of where each marker fits into BIPED classification (listed below)
   2. Include imaging modalities (MRI [standard and specialised] /other novel approaches)
      - Proposed: 2 existing novel imaging modalities/analysis platforms maximum
        - One large joint modality (Next generation MRI: gagCEST, 7T, Sodium MRI, etc)
        - One small joint modality (possibly hand OA)
      - Comparison to x-ray in WP3b

EFPIA contribution

Existing data sets from clinical studies, biomarkers and bioinformatics/stats expertise

Note: Data collection and data management should be performed according to established data standards and/or collaboration with a data standards organisation (e.g. CDISC) to develop new data standards if no established data standards exist.

WP2- NOVEL OA BIOMARKER DISCOVERY/DEVELOPMENT

Proposed Budget: EUR 1 000 000 total (EUR 150 000 EFPIA in-kind and EUR 850 000 IMI)

Include proteomic/metabolomic opportunity to ID new markers

Potential for image and human motion analysis biomarker opportunity

Include safety endpoint-related new markers

EFPIA contribution

Novel proprietary biomarkers and data, assays and imaging modalities/expertise

WP3 - BIOMARKER VALIDATION AND QUALIFICATION:

Proposed Budget: EUR 9 850 000 total (EUR 4 500 000 EFPIA and EUR 5 350 000 IMI)

Standardised biomarker assay validation/qualification

This is primarily testing of marker assays to assess fitness-for-purpose and to understand and qualify performance characteristics.

Assay qualification would be a requirement for subsequent patient sample testing in work package 3b based on standardised assay criteria such as:

- Accuracy
- Precision
- Reproducibility
- Range of use (sensitivity and LLQ)
- Variability
- Practicality for widespread use (effectively means it should be simple, reproducible and low cost)
- Feasibility evaluation for widespread use (e.g. imaging sequences available on different equipment)
- Specificity (in depth understanding and applicability to disease progression)

Human sample collection for biomarker validation/qualification

OA patient (and healthy volunteer) sample collection to support standardised biomarker validation/qualification using criteria and markers selected from the analysis of existing cohorts. This will also include existing biobanks and samples from ongoing collections in different countries in the EU under the governance of the respective health ministries. For extension and further validation dedicated studies are envisaged.

The design would be to have clinical partners obtain samples/imaging data under controlled (consented) conditions with matched patient questionnaire, a suggested example for a longitudinal study is shown below:

- Demographics, disease criteria and co-medication, etc. info captured
- Biological samples for biochemical assessment (serum, plasma, urine and possibly synovial fluid), samples may be used for -omics component of WP2
- Radiographic (x-ray) imaging for grading and comparison with other imaging modalities
    - Novel imaging modalities for development should be run in parallel for subsequent analysis
        - One large joint modality (gagCEST, Sodium or 7T MRI)
        - One small joint modality (hand OA imaging)
- The samples should include ability to assess biomarker
    - In numerous matrices (primarily serum, plasma and urine, but possibly also a single synovial fluid sample for patients undergoing arthroplasty)
    - Includes multiple cohorts representing different 'stages' of disease
        - Non-surgical OA cohort (not currently planning joint replacement) - encompasses 'early' and 'established' OA (~750+ individuals)
        - Surgical OA cohort 'end stage' at arthroplasty (~100 individuals)
        - Possibly a 'post acute injury' cohort (~50 patients)
        - Healthy volunteer (~100 individuals) – no history of OA, age matched? Note: challenges with age and prevalence of undiagnosed OA
    - For variability
        - Within patient (diurnal and over a few weeks)
        - Between patients
    - Other parameters including volume controls for urine (creatinine) and synovial fluid (urea, etc)

Sample maintenance

The handling and storing of samples/data can be assigned to

- one/several of the EFPIA partners since most are set up for this (EFPIA in kind contribution), or
- an independent CRO to be subcontracted either by EFPIA partner or an IMI beneficiary. In case of subcontracting, the CRO shall be selected in compliance with IMI rules and any additional applicable rules and regulations.

Biomarker analytics and testing

- This needs to be done in a certified laboratory setting
- Results are included into WP1 analysis

Imaging analysis

To be carried out centrally (but images to be transferred to different central readers if we want to test different reading method) by imaging experts. Different reading methods to be tested. Results to be included in WP1.

EFPIA contribution

Proprietary biomarkers, sample handling and biomarker testing/bioanalytics and platform expertise, clinical studies coordination (setup and conduct) experience, data management, medical coding (baseline characteristics, comedication, comorbidities), regulatory experience

WP4 - PROJECT MANAGEMENT

Proposed Budget: €1 million total (0.75 million EFPIA and 0.25 million IMI)

This work package will address the strategy and implementation of the project management encouraging regular meetings and interaction between sub-groups and teams, to coordinate the efforts.

The intention is to have all the partners of the project (industry, academic, regulatory, patient groups and healthcare agencies) represented on a project steering committee to guide overall strategic vision and dissemination of data and information.

- Each work package will have 2 work package co-leaders (1 EFPIA/1 Academic) overseeing the project who will be responsible for ensuring the deliverables are addressed.
- Each work package will encompass different workloads throughout the duration of the project. Progress will be monitored through regular project meetings involving all participants.

EFPIA contribution

Project management and regulatory expertise

ADDITIONAL USEFUL INFORMATION

Definitions (from Hunter, et al. Curr Drug Targets 11(5):536-45. 2010)
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3261486/?report=classic

- **biological marker** (biomarker)— a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic agent.
- **surrogate marker or endpoint**—a biomarker that is intended to serve as a substitute for a clinically meaningful endpoint and is expected to predict the effect of a therapeutic intervention; and
- **clinical endpoint**—a clinically meaningful measure of how a patient feels, functions, or survives.

A **valid biomarker** is defined as "a biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results. The validity of a biomarker is closely linked to what we think we can do with it. This biomarker context drives not only how we define a biomarker but also the complexity of its qualification.

Types of OA biomarkers - BIPED system (from Bauer, et al. Ostoarthritis and Cartilage 14(8):723-27. 2006)

Table I. Summary of "BIPED" biomarker classification for OA

	Burden of disease	Investigative	Prognosis	Efficacy of intervention	Diagnostic	Safety
Definition	Biomarker associated with extent or severity of OA	Biomarker not yet meeting criteria for another category	Predicts onset or progression	Indicative or predictive of treatment efficacy	Differentiates diseased from non-diseased	
Type of biomarker	Variant only	Variant or invariant	Variant or invariant	Variant or invariant	Variant or invariant	Variant or invariant
Subjects	Must have OA	NA	With and/or without OA	With OA	With and/or without OA	With and/or without OA
Design	Cross-sectional, case–control	NA	Longitudinal	Controlled trial	Cross-sectional or case–control	
Outcomes	Extent or severity of OA	NA	New or worsening OA	New or ameliorated OA	OA vs no OA	
Analysis	Sensitivity, specificity, LR, AUC from ROC	NA	Risk or odds ratio with 95% CI	Risk or odds ratio with 95% CI among treated	Sensitivity, specificity, LR, AUC from ROC	
Criteria	Significant association between marker and extent or severity of OA	NA	Significant association between marker and onset or progression of OA	Significant association between marker and treatment effect	Significant association between marker and OA diagnosis	

In addition potential safety markers need to be considered, adding to BIPED-S as classification.

Validation is the process of assessing the biomarker and its measurement performance characteristics, and determining the range of conditions under which the biomarker will give reproducible and accurate data. The evidentiary process of proving a linkage between the biomarker and a clinical end point was termed 'evaluation' in preference to validation. More recently, evaluation has been replaced with qualification, which has become accepted terminology.

Qualification is the evidentiary process of linking a biomarker with biological processes and clinical end points. The biomarker literature occasionally uses "validation" and "qualification" or "evaluation" interchangeably. We have avoided this because the validation and qualification processes must be distinguished, and the term "validation" does not adequately describe the qualification process.

Reference documents

EU commission statement on personalised medicine:
COMMISSION STAFF WORKING DOCUMENT - SWD(2013) 436 final- Brussels, 25.10.2013
Use of '-omics' technologies in the development of personalised medicine,
http://ec.europa.eu/health/files/latest_news/2013-10_personalised_medicine_en.pdf

FDA document on PHC:
Paving the Way for Personalized Medicine - October 2013
http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PersonalizedMedicine/UCM372421.pdf

2. EUROPEAN PLATFORM TO FACILITATE PROOF OF CONCEPT FOR PREVENTION IN ALZHEIMER'S DISEASE (EPOC-AD)

BACKGROUND

The Alzheimer's disease (AD) epidemic is expected to quadruple by the year 2050, afflicting over 100 million people worldwide. The need to develop interventions for preventing Alzheimer's disease dementia has never been greater. Conventional drug development approaches for the treatment of Alzheimer's disease dementia have failed to produce success to date for a variety of reasons: the therapeutic targets may have been incorrect; the treatments may have been given too late in the disease process; phase 3 studies were undertaken before proof of concept was clearly demonstrated, and the utility of the clinical and biomarker endpoints that were incorporated in the trials were not understood as much as they might have been. Compounding these concerns, the current clinical trial process for developing proof of concept is inefficient. Pharmaceutical companies, often with similar agents and chasing similar targets, perform clinical trials independently, thereby utilizing precious patient and financial resources with huge redundancies of effort. Important lessons that could advance the field more rapidly - regarding study designs, subject enrichment, clinical efficacy, side effects, biomarker and clinical endpoints – are learned only too late after each company absorbs the impact of this information from their own clinical trials.

As inefficient as this process is for developing treatments for patients with Alzheimer's disease dementia, this clinical trial paradigm will likely be unworkable for developing agents to prevent Alzheimer's dementia in subjects with preclinical and pre-symptomatic AD. There is far less clinical trial experience at this stage of the disease with regard to appropriate targets, patient selection and endpoints. It is also likely that studying even greater numbers of subjects for a longer duration of time will be required at this stage of the disease.

Greater cooperation and collaboration between academia, government and industry could enhance the drug development process. A public-private partnership is proposed to promote more efficient clinical trial designs and execution of clinical trials aimed at preventing AD dementia. The plan would create a precompetitive space to enable collaboration for optimizing patient selection, clinical trials methodologies, and candidate

therapies, as well as conducting adaptive clinical trials that will produce the greatest likelihood of success.

The mission of EPOC-AD is therefore to advance this novel collaborative partnership and drive a more successful approach to drug development for preventing AD dementia. The goal is to enable rapid cycling of learning from registries and longitudinal cohorts into adaptive clinical trials that shorten timelines, improve efficiencies and permit more rapid dissemination of knowledge. A consortium of industrial, governmental and academic partners will be formed to advance this research program, the key features of which, will be: 1) a registry of individuals at risk ready to participate in clinical research, 2) a longitudinal observational cohort of individuals at risk that will provide deep insights into disease course and trajectory, and 3) a program of continuous adaptive trials to establish POC (Proof of Concept) testing of investigational compounds for the prevention of AD dementia. The interventions will be tested in individuals at-risk for developing AD dementia and will include both stand-alone and candidate treatment combinations. The clinical trials will adapt to emerging data by preferentially allocating subjects to those therapeutic approaches that appear most likely to be successful, allowing resources to be optimally allocated. The continuous learning cycle that will be created in this program will adaptively incorporate innovations and learning regarding endpoints and biomarkers that may emerge within, or external, to the project. The rapid recruitment of available subjects from the longitudinal observational cohort to the clinical trial component of the program, coupled with the adaptive nature of the clinical trials and utilization of a common control group, will reduce the time needed to evaluate individual treatment arms, while simultaneously allowing a greater number of compounds to be tested.

SPECIFIC AIMS

- Form the EPOC-AD registry through coordination with existing longitudinal cohorts and physician networks to identify subjects for the registry
- Maintain a longitudinal natural history cohort of a subset of subjects at risk in the EPOC-AD registry to maintain a "trial-ready cohort" with standardised run-in data (e.g. appropriate neuropsychological and biomarker observations) that will facilitate recruitment, conduct and analysis of the adaptive clinical trials
- Develop criteria and methods for selecting participants from the longitudinal natural history cohort for inclusion in AD prevention adaptive clinical trials based on subject demographic characteristics, clinical, genetic, biomarker, imaging and neuropsychological profiles

- Identify short/middle-term endpoints based on biomarkers specifically aimed at demonstrating efficacy (or at least target engagement) also considering mechanism of action (MOA) of the different therapeutics in POC trials.
- Establish an international collaborative group for advancing and conducting adaptive prevention trials for preclinical AD to early symptomatic AD
- Develop methods for the design and analysis of adaptive clinical trials for preventing AD that incorporate Bayesian statistical approaches (see http://www.fda.gov/downloads/Drugs/.../Guidances/ucm201790.pdf) for selecting treatments arms, dropping treatment arms and introducing new treatment arms, including drug combinations; A similar model (ISPY-2) has proven successful in the development of oncology therapies (Berry, Nat. Rev. Drug Discov, 2006; Barker et al., Clin. Pharmacol. Ther, 2009).

Indeed, proof-of-concept trials (POC) represent an important step in the clinical development pathway. They aim through a limited investment in early human trials to confirm that the preclinical models are supported by human data, that there is a viable dose range, that the treatment has predictable pharmacodynamic effects and that it demonstrates an important effect on a validated target. In an early Alzheimer trial, a POC trial would establish that the compound has an acceptable safety profile within the range of doses that have a pharmacodynamic effect on the planned target, and that viable doses move a relevant disease biomarker to a predicted level for clinical response. Importantly, while they are typically not powered for clinical efficacy, they may provide effect size estimates for cognitive benefits that can then be tested in larger confirmatory trials.

PROBLEM STATEMENT

Traditionally, new pharmacological treatments are developed and explored in a "silo" fashion. The long development process is conducted in a relatively isolated way by the company, investigator, or sponsor of the novel treatment. Limited information is released publicly and those developing potentially competing treatments have very limited communication or exchange of information. Precompetitive space has not been defined, developed, or prioritised. Valuable early findings that are of potential use to the field and those developing similar treatments are released very slowly and in a manner that limits an adaptive approach to be developed around new learning and insights. There is no framework for new treatments of a similar or different class to be tested head to head with other approaches on agreed to measures – either biological and/or clinical. Parallel group two-armed trials with long-term endpoint have remained the primary standard

even in early development and yet there are resource implications, risks and inefficiencies to this approach. In many cases, targets have not been fully validated before engaging in large scale trials; effective dose ranges are not fully ascertained in advance of such trials; and proof of concept is not established before moving forward into phase 3 development. These deficiencies are multiplied manifold in the case of AD prevention trials where clinical outcomes require large sample sizes, longer periods of observation and much greater financial investment.

Under the existing model for drug development, a single sponsor will run a conventional clinical trial with one dose, or regimen, of the investigational treatment compared to a placebo control. In Alzheimer's prevention, this single trial may take 10 years or longer to complete, involving thousands of subjects, with a half of all subjects being treated with placebo. Even with multiple companies running their own "silo" development programs over more than a decade of effort, no meaningful advances have been made. Each of these trials answers only one narrow question germane only to the treatment that was tried: How well does this one dose work in the research population compared to placebo?

The recent case of the failed gamma secretase inhibitor (GSI) development program underscores both the direct limitations of the silo approach, the lack of precompetitive space to exchange knowledge quickly and the risks of proceeding into phase 3 without addressing the decision tree points with a robust POC (Doody et al, N Engl J Med., 2013) in AD.

The problems with the current approach are obvious. Single trials are inefficient, expensive, lack synergy, and place half of all participants on no active treatment, leaving their illness progress unabated and placing a significant disease burden on the patient, their families, and the societies in which they live. Given the complexity of Alzheimer's disease, it is no surprise that this approach has failed and led to companies abandoning the area even as the worldwide burden is increasing dramatically.

NEED FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

Given that there has not been any new regulatory approved treatment for AD in the past decade, despite a multibillion dollar pharmaceutical investment, there is a groundswell of support building within industry, government, and academia to shift the paradigm. It has become obvious that only cooperation between academia, government and industry

might make the clinical development of AD prevention strategies possible. Studying prevention approaches in AD is challenging. Some of the scientific challenges include identifying subjects at risk, developing efficient study designs, constructing appropriate clinical endpoints, including relevant biomarkers and establishing methods for prevention.

A public-private collaborative approach will be required to enable efficient design and execution of clinical trials aimed at exploring how to prevent AD. A precompetitive space has to be established that enables collaborations in selecting best candidate therapies, and advancing clinical trials methodologies that enable adaptive approaches to optimize the investments that can be made, allowing the timely delivery of needed treatments to the patients.

It is proposed that the risks associated with proof of concept trials for the development of therapeutics for AD prevention are best addressed through a collective effort that minimizes the utilization of patient, health professionals and financial resources through duplicative efforts on the part of individual pharmaceutical companies. The shift in the treatment development paradigm of this proposal will focus on prevention of the disease, establishing a precompetitive space that enables collaborations in selecting best candidate therapies, establishing the most innovative public-private partnerships and advancing clinical trials methodologies that enable adaptive approaches to optimize the investments that can be made.

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

Applicants have to take in consideration for the development of their Expression of Interest that there are already several initiatives on-going in the field, both in Europe and globally.

Synergies and complementarities should be considered, building from achievements, and incorporating when possible data and lessons learnt, while avoiding unnecessary overlapping and doubling of efforts.

Collaboration by design should be a cornerstone of the proposed strategy.

Some of these initiatives are listed below.

- PHARMACOG, an IMI project developing biomarkers signatures to predict the efficacy of drug candidates in patients: http://www.alzheimer-europe.org/Research/PharmaCog
- EMIF, an IMI project integrating existing in-depth AD databases with large scale electronic health records. One of IMI-EMIF's goals is to establish and qualify early biomarkers of AD that might be beneficial in early intervention trials: (http://www.emif.eu/)
- AETIONOMY an IMI project aimed at developing a knowledge framework for 'druggable mechanisms' and a mechanism-based taxonomy of Alzheimer's and Parkinson's disease.
- The Joint Programming Initiative on Neurodegenerative Diseases: (http://www.neurodegenerationresearch.eu/)
- The Joint Programming Initiative A Healthy Diet for a Healthy Life (http://www.healthydietforhealthylife.eu/)
- Relevant FP7 activities and projects (e.g. PREDICT, PREDICTAD, EPOKS, EuroCoDe, projects generated from the research areas HEALTH.2012.1.2, HEALTH.2012.2.1, HEALTH.2013.0-1, HEALTH.2013.4.2-3, relevant ESFRI infrastructures, (http://ec.europa.eu/research/infrastructures/index_en.cfm?pg=esfri) e.g. ECRIN (http://www.ecrin.org/), BBMRI-LPC (http://www.bbmri-lpc.org/), BBMRI (http://bbmri.eu/), and BIOSHARE (www.bioshare.eu)).
- Relevant registries and projects on-going at National level.
- The New York Academy of Sciences 2ADAPT initiative; (http://www.nyas.org/Events/Detail.aspx?cid=a643a4ab-37b7-42f3-b0c9-c5e88909c9b4)
- The Global CEO Initiative on Alzheimer's Disease (CEOi): (http://www.ceoalzheimersinitiative.org/faqs)
- C-Path Coalition against Major Diseases (CAMD): http://c-path.org/programs/camd/
- The NIH/NIA Dominantly Inherited Alzheimer's Disease Network (DIAN): http://www.nia.nih.gov/alzheimers/clinical-trials/dominantly-inherited-alzheimer-network-trial-opportunity-prevent-dementia
- The Alzheimer's Disease Neuroimaging Initiative (ADNI): http://www.adni-info.org/
- The Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL): http://www.aibl.csiro.au/

- IMI knowledge management portfolio of projects: eTRIKS, DDMORE, Open PHACTS, EHR4CR (http://www.imi.europa.eu/content/ongoing-projects).

OVERALL OBJECTIVES

The key overall objective of the initiative is to create a novel clinical trial approach for prevention of AD that will allow the continuous testing of multiple different regimens, involving a shared and rotating placebo population to ensure that a greater percentage of participants receive investigational treatments. This approach will involve an adaptive trial design for comparisons across investigational options, permit disease modeling not possible under the current "lock step approach", and permit shared processes and centralized resources so that industry can put their resources towards innovation rather than trial execution. A similar model (ISPY-2) has proven successful in the development of oncology therapies (Barker et al., Clin. Pharmacol. Ther, 2009).

The overarching goal is more efficient and rapid learning using an iterative approach about which regimens are better for which patients (i.e., biologically important subtypes which also permits simultaneous assessment of biomarkers of disease subtype and/or progression). Directly comparing diverse treatments to a common placebo, and to each regimen, reduces the number of participants who must be treated with placebo and permits efficient determination of which investigational treatment arms should be explored for which patients and which arms should be abandoned and/or re-positioned for a different subgroup.

This will be a public-private initiative that de-risks the enterprise while increasing the synergy needed to ensure successful outcomes. It should be set up as an initiative built on the European strengths and resources but designed from the start as a highly collaborative enterprise that will become global. Because of the cooperative nature of the process involving public and multiple private partners (i.e., multiple pharmaceutical and biotech companies), many more treatments can be tested concurrently and tailored to specific subsets of patients. This approach can permit drug discovery within subsets rather than the current all or nothing approach. Additionally, combinations of treatment regimens can be explored within the same process, which may yield more effective treatment strategies and accelerate the trial timeline by many years.
The initiative will create a readiness registry of potential participants who will be sufficiently characterized in advance of the trial. This will both increase the efficiency of trial recruitment and increase the likelihood that the population will be able to optimally

answer the questions posed. Individuals at risk for developing Alzheimer's disease should be studied and characterized prior to entering a trial such that when individuals reach certain pre-specified criteria, they will be eligible for trials. These pre-qualified participants (based on the progression of their illness and/or biomarkers) will have a reduced likelihood of receiving placebo treatment and an increased chance of receiving treatment with multiple investigational agents alone or in combination.

Alzheimer's disease is heterogeneous, involving many different underlying conditions that contribute to varying rates of disease progression among patients and this will have to be taken in consideration.

This novel trial platform will enable sharing a common placebo arm, an expanded longitudinal natural history study with standardised information, identification and validation of a robust pool of biomarkers and qualification of biomarkers as new drugs are tested. Learning on biomarkers and compounds will be applied to the POC clinical trial process and will therefore benefit all contributing participants. Learning from external sources (including IMI EMIF, AIBL, ADNI and others) can be used to condition priorities of the proposed new activity.

Summary: Innovations and Efficiencies that should be provided via this initiative	
Innovations	**Efficiencies**
• Multiple treatment arms • Multiple patient subgroups • Adaptive randomization within subgroups • Moving arms in/out of the trial • Possible combination of arms for combined treatment • Disease modelling; the model is continually improved as the trial progresses	• 10-20% placebo rate instead of 50% • Increases sample size on better arms • Enables focusing on regimens within subsets • Economies of scale for all processes • Ability to compare arms/controls in single arena • Ability to explore many more treatments with this process than individual trials • Ability to combine regimens

EXPECTED KEY DELIVERABLES

- A strategy for developing the rationale for linking biomarkers, mechanisms of disease, read outs, primary outcome measures and treatment and patient selection. As both AD and its patients are heterogeneous, strategies will have to be developed to address the issue of patient selection/enrolment criteria. This might include genotyping for helping the stratification of the patients. There may be advantages to use populations with a specific genetic predisposition. The choice should be guided by the hypothesis that drives the trial. There should be a hypothesis driven decision making for selection of compounds/combination of compounds. The compounds should be used to learn more about the disease, providing guidance for the next step therapeutic intervention. A preferred goal is to evaluate both the effects of the drug on potential biomarkers and cognitive or clinical outcomes in the same intervention trial.
- The development of a registry of individuals at risk of developing AD dementia who are interested in clinical trial participation. This will involve particular emphasis on primary care physician networks and already started cohorts of at risk populations in Europe. The incorporation and leveraging by the project of the existing rich and complex data from observational and interventional studies on the temporal and causal relationships between potential biomarkers of preclinical AD states is going to be an asset.
- A longitudinal natural history study of at risk individuals that will qualify and validate biomarkers (genetic and imaging among others) and diagnostics that will be critical to AD prevention, and be the basis for the successful selection and stratification of individuals to be enrolled in the trials. This may include novel diagnostics and/or endpoints.
- An adaptive clinical trial which will enable more compounds to be tested with more uniform cognitive outcomes and biomarker readouts. That will in turn lead to the ability to select amongst those agents the ones most likely to succeed as treatment interventions and promote their most efficient development. This will include modelling and simulation with a mechanism that allows the system to adapt and evolve integrating seamlessly new knowledge as this is generated by the work. All key stakeholders have to be involved including regulators.
- The implementation of a clinical trial process and platform with continuous inclusion of investigational compounds and eventual recommendations as to whether to drop a treatment arm either for safety related concerns or futility or to advance it into a separate confirmatory clinical trial. This should include the

appropriate IP and legal framework. Multiple industrial and public partners should be able to enter their candidate therapies in the platform. That will in turn enable within and across class treatment comparisons so best candidates for large scale confirmatory trials can be identified.

- There could be scope for having several therapeutics that run in parallel, and all targeting the same disease hypothesis. Non-pharmaceutical/non-conventional approaches may also be tested.
- A Europe wide investigator network of Good Clinical Practice (GCP)-qualified investigational centres, with all necessary training, test materials, and instrumentation to conduct clinical studies of drugs and diagnostic devices and non-interventional trials in at risk individuals for AD and pre-dementia AD subjects.
- A strategy to insure harmonization and standardization. This can be particularly critical e.g. for imaging biomarkers. Existing standards have to be considered and/or collaboration with a data standards organization (e.g. CDISC) to develop new data standards, should no established data standards exist.
- A business plan for sustainability beyond the timeframe of the project.
- A public awareness campaign on Alzheimer's at national and international level.

EFPIA PARTICIPANTS

Janssen (coordinator), Eisai (deputy coordinator), Roche (deputy coordinator), AbbVie, AC-IMMUNE (EBE member), Amgen, Astellas, BIOGEN IDEC, Boehringer Ingelheim, Lundbeck, Pfizer and UCB.

INDICATIVE DURATION OF THE PROJECT

The indicative duration of the project is 5 years. A sustainability aspect should be built into the project architecture, facilitating continuation of the project beyond 5 years.

INDICATIVE BUDGET OF THE PROJECT

The indicative in kind contribution from the EFPIA companies is estimated to be EUR 28 193 000
The indicative IMI JU contribution is up to EUR 25 000 000.

Due to the complexities of running a global clinical trial designed to support regulatory submissions, it is common practice of both industry funded and FP7 projects to engage a

Contract Research Organization (CRO) to implement and monitor the clinical sites to ensure compliance. It is also worthwhile noting that while this is the preferred approach, in some instances it may be preferable for a SME/CRO in collaboration with the sponsoring company's internal operations groups to implement these clinical trials.

There are three possible scenarios for the inclusion/selection of the CRO:

1) The applicant consortium includes CRO expertise and capability.
2) If the applicant consortium does not include CRO capabilities, Applications should assume the requirement for subcontracting to a CRO in compliance with applicable rules and regulations. The Applicants should therefore consider that a percentage of the available funding for the project should be allocated to CRO activities to implement and monitor the clinical trials. The precise amount will be worked out at the Full Project Proposal stage. Direct financial contribution by the sponsoring EFPIA companies, if required, will supplement the CRO costs (up to 25%), incurred by public partners eligible for IMI funding ensuring that 100% of these costs will be reimbursed.
3) In the event that EFPIA are funding the CRO in its entirety as part of their contribution in kind, then the CRO will be appointed directly by the sponsoring EFPIA companies according to normal internal procurement practices. The EFPIA companies must be able to demonstrate 'value for money' to satisfy external auditors, otherwise this cannot be counted as contribution in kind.

APPROACH FOR ACCEPTING NON-EU EFPIA IN KIND CONTRIBUTION (SPECIAL CLAUSE 13B)

Ageing and its associated chronic diseases including dementia/AD is a major healthcare problem, also recognized by the EU that launched the European Innovation Partnership on Active and Healthy Ageing (http://ec.europa.eu/research/innovation-union/index_en.cfm?section=active-healthy-ageing) with the overall objective to increase the healthy lifespan of EU citizens by 2 years by 2020 and to connect and engage the main players within and outside EU institutions.

Although clearly a major societal challenge and a strong research base in Europe, efforts to develop new medicines addressing the societal challenge of AD are still limited in scope. Furthermore, most drug development efforts are of a global nature, and many are driven out of the U.S. The reduced investment in AD by the private sector is largely driven by the scientific challenges ranging from identifying subjects at risk, agreeing on appropriate clinical endpoints and biomarkers and establishing methods for prevention as well as the long durations (over up to 10 years) to run clinical prevention trials independently.

The current proposal provides the opportunity to remove these bottlenecks to investment. Therefore non-EU EFPIA in-kind contributions are accepted as part of the EFPIA in-kind contribution (see "Rules for Participation in the IMI JU research projects" http://www.imi.europa.eu/sites/default/files/uploads/documents/8th_Call/4_Annex%204.%20Call%206_Rules%20for%20Participation_2012%2005%2024.pdf).

The benefit to Europe of implementing Special Clause 13b

For the patient and society as a whole: The rapidly aging population is placing an unsustainable burden on healthcare systems in Europe and indeed across the globe and requires joint and urgent action to be taken if sustainable healthcare solutions are to be secured. Removing the bottlenecks currently preventing private investment in the field of AD and more specifically the prevention of AD will lead to increased recognition of patients at risk, better diagnosis, improved treatment options and management of the aging population. This will result in individuals having treatment options available to them to increase quality of life through improved physical activity as well as improved overall mental and social wellbeing. As a direct consequence of EPOC AD, fewer patients will be exposed to placebo trials over time. This will directly support the long-term sustainability and efficiency of health and social care systems as well as enhance the competitiveness of EU industry through an improved business environment providing the foundations for growth and expansion of new markets.

For public investigators and SMEs: Research into the prevention of AD is strong within the European Research community, however investment from the Pharmaceutical industry is currently low primarily due to the difficulties in the research and the heavy costs of individual clinical trials with limited success rate. The ability to utilize non-EU in kind contribution in the current project will allow EU investigators to foster international partnerships with drug developers currently operating in the US. This will lead to the combination of expertise in the diagnosis and management of AD prevention present in the public sector with the drug discovery expertise present in the private sector. This combined approach is required to remove the barriers to private investment much needed to develop preventative medicines in this field. It is also worth noting that all IMI JU funding will be directed to investigators and SMEs located in the EU, thus this initiative will bring significant funding to European investigators to support employment and growth.

For pharmaceutical and biotechnology companies developing new medicines: The opportunity to work with leading experts in the field, regulators, health technology

agencies and healthcare providers to gain consensus on the definition of the target population, agreement on clinical trial design and functional endpoints and assessment of value to the healthcare system. This initiative will provide the necessary framework to drive new investment in medicines development with a greater chance to select the best treatment options to be further invested in.

APPLICANT CONSORTIUM

The Applicant Consortium is expected to address all the research objectives and make key contributions on the defined deliverables in synergy with the EFPIA consortium.
The Applicant Consortium is expected to be multidisciplinary: to enable effective collaboration between key stakeholders (academia, hospitals, SMEs, patients and patient organizations, public health organizations, regulatory agencies, health technologies bodies) and to conduct innovative clinical trials with adaptive design. The consortium should cover the following critical fields of expertise: Neurodegeneration & AD disease knowledge (*epidemiology*), biomarker expertise (*biomarkers research and development, imaging*), CRO capabilities (see budget section) with adaptive design (*modelling and simulation, biostatistics, clinical research and clinical trial including design, operational, monitoring and GCP expertise, PK/PD relationship, data and knowledge management, regulatory, ethics, patients, and relationship with patients, effectiveness/health technology assessment*) and project management (*proven expertise and resources for managing major projects of this complexity and scale*).

Valuable assets will be

- Relevant existing datasets and existing clinical studies
- Clinical cohorts of at risk individuals and registries
- Access to primary care physician networks
- Compounds that can be brought into the POC trial
- Involvement of patient organizations and its ethical considerations

PROPOSED ARCHITECTURE OF THE FULL PROJECT PROPOSAL

The Applicant Consortium is expected to address all the research objectives and make key contribution to the defined deliverables in synergy with the EFPIA consortium.
The proposed architecture below is just an example; different innovative project designs are welcome, if properly justified, including different sizes for the registry, longitudinal study and randomized clinical trial or a different organization of the work packages.

The proposal should provide the first five year grant period research plan. The development of a registry of 24,000 subjects should be initiated immediately after the start of the project and accrue over 2 years. From this registry, it is estimated that there will be a prospective longitudinal cohort study of an estimated 6000 consenting subjects who will be followed for > 6 months and who will be offered the further opportunity following consent to be screened and randomized into a rolling adaptive randomized clinical trial (~1500 subjects). The first subject randomized into the interventional randomized clinical trial (RCT), having had their longitudinal course sampled in the longitudinal cohort study, should begin ideally within 1 year from project start with interventional trial results being evaluated thereafter throughout the 5 year funding period. Both the prospective longitudinal cohort and interventional studies may extend beyond the 5 year grant period via additional mechanisms, including a possible expansion into future Calls that should be considered while building the business case and will be further developed at the Full Project Proposal stage.

WORK PACKAGE 1: GOVERNANCE TO ADDRESS THE SCIENTIFIC CHALLENGES

A governance structure is needed to provide scientific oversight and guidance to the overall project which may include a steering committee and scientific advisory board; it is expected that members from both EFPIA and academia will serve on the steering committee and scientific advisory boards; together they will develop alignment on the:

- Definition of the relevant population and selection of subjects to be included in registries and longitudinal natural history study. The selection of subjects should consider the mechanism of action (MOA) of the drugs undergoing the trials. (for example drugs that may be working on amyloid metabolism, such as BACE, may require at risk individuals previous the deposit of amyloid and selected through a genetic profile, while those whose MOA is amyloid removal will need to be tested in subjects at risk defined through the positivity of amyloid markers.).
- Biomarkers and clinical endpoints to be included in natural history study and clinical trial process. The applicants should provide a strategy for how biomarkers will be chosen and how to link between hypotheses, drug mechanism of action, biomarker/clinical readouts, and patient characteristics.
- Rationale for selecting a compound/combination of compounds, including what is the information context to guide the selection. There should be a hypothesis driven decision making for the selection of compounds and the compounds should be used to learn on the disease guiding the next step.
- Design of adaptive clinical trial process (for example I-SPY2 like) feasible for Alzheimer's disease. The design should incorporate statistical methods (in

particular Bayesian approaches can be of particular value as indicated in the recent FDA draft guidelines http://www.fda.gov/downloads/Drugs/.../Guidances/ucm201790.pdf) to drop treatment arms and introduce new treatment arms, including drug combinations. The design should attempt to evaluate the effects of the drug on both biomarkers and clinical outcomes in the same interventional trial.

- Building of a qualified Clinical Trial network, including training.

EFPIA contribution:

- Epidemiological expertise with experience in setting up and maintaining patient registries and natural history methodology studies.
- Clinical expertise in AD trials.
- In house data and know-how on AD, including pre-clinical data and assets, and on-going longitudinal natural history/cohort studies
- Statistical expertise in adaptive trial methodology.

Expected Applicant consortium contribution:

All key expertise areas necessary to deliver on all scientific challenges, including:

- Expertise with regard to AD genetics, biomarkers, and neuropsychological and clinical assessments that may be useful for patient selection and study endpoints.
- Scientific rationale for selecting compounds and combinations to be tested.
- Innovative approaches to the adaptive clinical trial process.

WORK PACKAGE 2: ELABORATION OF EPOC-AD PROGRAMMATIC STRATEGY AND EPOC-AD TRIAL

EPOC-AD will envision an approach for the statistically, temporally, and financially efficient identification of promising treatments for the true prevention of AD, or for halting the progression of preclinical states into clinically apparent AD, that has as its foundation the following key features:

- The ability to incorporate and leverage the rich and complex pre-existing data, from both observational and interventional studies, on the temporal and causal relationships between dozens to over a hundred potential biomarkers of underlying preclinical and clinical AD states.
- The ability to capture and quantify the associations and likelihood of causal relationships between potential biomarkers and the progression of normal and preclinical AD states into clinically detectable AD.

- The ability to continually update knowledge regarding the relationships of biomarkers to each other and to the subsequent development of clinical AD, using data from both observational and interventional data, whether those data arise from external sources or from EPOC-AD as described below.
- The ability to simultaneously evaluate, in an on-going continuous clinical trial, the potential value of multiple pharmacologic therapies, and combinations of therapies, using early biomarkers to identify beneficial treatment effects as early as possible.
- The conduct of the pharmacological intervention part of EPOC-AD with the ability to rapidly identify promising therapies, or combinations of therapies, whose promise are sufficiently large -based both on substantial and internally consistent biomarker effects- to obviate the need to warrant separate evaluation in large scale standalone clinical trials.

EPOC-AD will use the following labels to clarify these cornerstones of the overall program: (1) use of pre-existing data; (2) identification of causal relationships; (3) continual updating; (4) simultaneous evaluation of drugs and combinations; and (5) the EPOC-AD trial. Each of these is described in more detail below.

Use of Pre-existing Data: Using a Bayesian framework (see http://www.fda.gov/downloads/Drugs/.../Guidances/ucm201790.pdf): the available pre-existing data will be incorporated as prior information in the development of a comprehensive Bayesian Network (BN) model (see below) to capture and leverage current knowledge regarding the distributions of biomarkers and their associations with the symptomology of AD.

Identification of Causal Relationships: A Bayesian Network (BN) will be used to capture, quantify, and represent the causal relationships between biomarkers and subclinical and clinical AD.

Continual Updating: As mentioned above, one feature of the BN model is the ability to continually update the model with new information, to improve its precision and the validity of predictions. EPOC-AD will use three categories of data types to update the model: (1) external observation data on biomarkers and manifestations of AD; (2) external interventional data from clinical trials that include data collection on biomarkers and manifestations of AD; and (3) internal interventional data from the IMI-EPOC-AD trial.

Simultaneous Evaluation of Drugs and Combinations: It is highly likely that effective treatments resulting in either the prevention of clinical AD or the substantial slowing or halting of progression will require combinations of pharmacological therapies. The efficient and coherent estimation of treatment effects associated with multiple drugs being evaluated simultaneously, and with combinations of those drugs, will be accomplished using Bayesian Hierarchical Modelling comprehensive representation of knowledge, regarding the observed and estimated treatment effects.

EPOC-AD TRIAL: EPOC-AD will conduct a continuous, global, multi-centre and multi-agent clinical trial designed to efficiently identify treatments, or combinations of treatments, with sufficient promise for the prevention or halting of progression of AD to warrant definitive confirmatory testing. A useful example for EPOC-AD is the successful ISPY2 trial in neoadjuvant breast cancer therapy (Barker et al., Clin. Pharmacol. Ther, 2009). Basically, the trial will serve as an efficient and rigorous screen or gateway prior to confirmatory standalone trials. It should be stressed that confirmatory trials will not be conducted under the auspices of EPOC-AD. Rather, if a compound is found to warrant further investment, it will go back to the company or a public institute – whichever is appropriate – for a confirmatory trial to be conducted with much higher probability of success thanks to the POC exploration conducted within EPOC-AD. In essence, EPOC-AD is the "learning" phase of treatment development and is conducted under the auspices of the public-private partnership established for this propose while the confirmatory studies required by regulatory agencies for treatment approval are conducted by the sponsors in the traditional way. Given the likely rarity of effective AD therapies, and the extraordinary time and costs associated with confirmatory evaluation of potential treatments, the pharmacological intervention part of EPOC-AD will only "graduate" (i.e. hand off the compounds back to the owner of the molecule) treatments demonstrating effects of multiple biomarkers in a pattern highly suggestive of true, disease modifying effect.

EFPIA contribution:

- Comparable to Work Package 1.
- Additional contributions of EFPIA companies might be integrated based on outcomes of WP1-2.

Expected Applicant consortium contribution:

- Comparable to Work Package 1.

WORK PACKAGE 3: EPOC-AD – OPERATIONAL WORKSTREAM

The aim of this work package is to ensure the proper functioning of the project in order to achieve the objectives, to complete the milestones on time and to deliver the deliverables. Specific cores or work groups will be required to take on these responsibilities as a joint venture between EFPIA and the other consortium partners. Such cores might be responsible for administration/project management, clinical operations, IT/ data management, biomarkers, imaging, regulatory interactions, pharmacovigilance, statistics, and publication:

- Put registries and longitudinal natural history studies in place.
- Execute the clinical trial process. The clinical trial design will undergo scientific advice from the EMA and/or FDA prior to study initiation.
- Ensure standardised data collection, including potential biomarkers, imaging, neuropsychological and functional instruments.
- Ensure timely regulatory filings and safety reporting for the clinical trial.
- Data basing, curation, harmonization, standardization and sharing are key activities that have to be addressed. Attention will also have to be given to relevant legal aspects. The project derived from this topic may decide to have a strong collaboration with other projects (e.g. the knowledge management platform created by eTRIKS) however relevant resources to support the activity have to be considered.

EFPIA contribution:

- Project management, Clinical operations, Data Management, Statistics, Pharmacovigilance, Regulatory interactions, CRO
- Direct financial contribution by the sponsoring EFPIA companies, if required, to supplement the clinical study costs (up to 25%), including CRO subcontracting if any, incurred by public partners eligible for IMI funding ensuring that 100% of these costs will be reimbursed.

Expected Applicant consortium contribution:

- Access to and coordination of on-going natural history studies and patient networks to develop the EPOC registry.
- Study instruments, biomarkers, imaging, data.
- CRO activities.

WORK PACKAGE 4: STRATEGIC CLINICAL TRIAL GUIDANCE AND ETHICS

The aim of this work package is to:

- Set-up a governance structure for oversight and guidance of the clinical trial, including a joint steering committee which will review recommendations on dropping treatment arms and introducing new compounds and treatment arms, including combinations thereof. This also opens the opportunity to identify subsets of patients as defined by biomarker signatures who might benefit from a particular treatment.
- Manage the ethical aspects of the project, including an ethical strategy and the establishment of an ethics advisory board.

It is envisaged that the consortium will engage external advisors to support the steering Committee. These external advisors would be chosen among key opinion leaders in the field and would provide additional, independent feedback and opinions on the progress of the trial. This work package, focusing primarily on the clinical trial, may include some or all of the same steering committee and advisors from workpackage 1 (governance to address scientific challenges).

EFPIA contribution:

Clinical expertise in AD, AD R&D and AD trials, Legal, Regulatory.

Expected Applicant consortium contribution:

All key expertise areas necessary for the implementation of the work package activities.

WORK PACKAGE 5: GOVERNANCE STRUCTURE AND PROJECT MANAGEMENT

The aim of this work package is to:

- Set-up governance structure for oversight and guidance at consortium and work package level.
- Ensure that the consortium's contractual duties are carried out. Support and strengthen the participants to comply with the EU regulations and their contractual and legal requirements. Abide by the "good practice" of resources management as presented in the Financial Guidelines. This can be regarded as the typical "triple constraint of time – cost – scope/quality" of project management
- An additional layer should be added on top of this project management in order to provide support to the coordinator and work package leads to help them cope with their leadership role next to their day to day activities (e.g. facilitate decision making, collaboration between academia and EFPIA partners, preparation of communication, good meeting practices, be pro-active)

EFPIA contribution:

- Project management

Expected Applicant consortium contribution:

- Project management.

WORK PACKAGE 6: - COMMUNICATION AND DISSEMINATION ACTIVITIES

The aim of this work package is to:

- Set up an effective communication infrastructure and tools and foster the integrative process both within the consortium (between work packages, team members, EFPIA and other participants) as well as outside the project to ensure alignment with all stakeholders and collaboration with other relevant projects and initiatives. This should include platform(s) for information sharing (e.g. sharepoint or similar for file-sharing, version control) as well as communication tools (e.g. templates, branding, teleconference, video conference, live filesharing etc).
- To develop and implement the communication and dissemination plan of the project

EFPIA contribution:

- Strategies on PPP collaborations; political engagement; legal and IP expertise; regulatory expertise.

Expected Applicant consortium contribution:

- Scientific and media communications expertise.
- Ethical expertise.
- Outreach to patients and other key stakeholders.
- Legal and IP expertise.

WORK PACKAGE 7: - BUSINESS MODEL

The aim of this work package is to:

- Work out how to enable the exploration of compounds within one clinical trial process, which might originate from competing pharma R&D organizations and or SMEs and public partners including intellectual property related questions and approach to regulatory challenges (multi-compound IND). Importantly, the business model needs to be sustainable beyond the initial IMI funding and take in consideration intellectual properties aspects among others.

EFPIA contribution:

- Business Development, Legal, Regulatory.

Expected Applicant consortium contribution:

- Expertise in setting up public-private partnerships

3. BLOOD-BASED BIOMARKER ASSAYS FOR PERSONALISED TUMOUR THERAPY: VALUE OF LATEST CIRCULATING BIOMARKERS

BACKGROUND

The goal of personalized medicine is to achieve better therapeutic effects (higher efficacy / less side effects) by identifying the right therapy for the individual patient. Cancer is a highly dynamic disease. A diagnostic evaluation at a single point in time is not sufficient to predict the best treatment in terms of personalized medicine. Access to predictive diagnostic assays is critical in this sense.

The identification of both predictive and prognostic biomarkers for solid tumours is hampered by the heterogeneity of the primary tumour, its molecular instability reflected by evolving genetic alterations and in many cases, the complete or partial inaccessibility of (repeated) biopsies to monitor disease progression and treatment response.

Recent progress in the molecular understanding of tumour pathogenesis and novel technologies to detect molecular changes at the single-cell-level offers a unique opportunity for a potential breakthrough in tumour biomarker research. Circulating Tumour Cells (CTCs), circulating free tumour DNA (ctDNA) and miRNAs as blood-based biomarkers may allow multiple "liquid biopsies" over time and therefore help to gain important knowledge about the molecular heterogeneity of the disease and make better treatment decisions earlier than tissue biopsies would allow.

Currently, the only system approved for enumeration of CTCs in the clinic is (CellSearch™, Veridex) which shows limitations since it does not allow the isolation of living cells from blood samples nor the analysis of other molecular characteristics of CTCs. Efforts to use CTCs as blood-based biomarkers are widespread. CTCs as blood-based biomarkers are considered to be a promising technology for therapeutic decision-making (Survey results, World CTC USA, Nov 12th-15th, www.ctc-summit.com/library; 190 clinical trials are ongoing: www.clinicaltrials.gov). Major obstacles are still the reproducibility and scarcity of CTCs in routinely analyzed patient's blood volumes. In the future, patients could benefit greatly from progress in the development of companion diagnostics based on a more detailed molecular analysis of CTCs and a thorough evaluation of ctDNA in minimal residual disease where the number of CTCs may be limited or CTCs are even undetectable. Therefore CTC and ctDNA approaches are considered to be complementary.

PROBLEM STATEMENT

"The tissue is the issue". At present, access to tumour tissue either by biopsy or resection is essential for adequate molecular characterization as a precondition for stratification approaches. Indeed all companion diagnostics approved for selection of suitable patients so far are based on tumour tissue. Access to tumour tissue presents serious limitations:

- Obtaining biopsies is an invasive and potentially painful procedure associated with serious risks e.g. bleeding,
- Monitoring during therapy is not feasible since tumour progression is associated with acquisition of novel mutations and the development of therapy resistance a typical event,
- Tumour biopsies may not be available and may not fully represent tumour heterogeneity.

In conclusion, it is desirable to have highly predictive and less invasive diagnostic systems e.g. blood-based. Recently many new technologies emerged (e.g. CellSearch™, DEPArray™, CellCollector™, IsoFlux™ and others) showing impressive sensitivity, suggesting, and partially demonstrating suitability. A comprehensive evaluation and head to head comparison of these technologies is missing and would allow assessment of their overall predictive value.

NEED FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

Establishment, evaluation and especially clinical validation of new methods in this area requires the cooperation of experts from different areas with complementary expertise:

- **Biotech companies** with their knowledge on new technologies;
- **Academia** with their knowledge on molecular disease mechanisms and access to clinical samples;
- **Diagnostic companies**, with well-established tissue based technologies and expertise in companion diagnostic development;
- **Pharmaceutical companies**, with their knowledge on new drugs development and companion diagnostics.

The comprehensive evaluation of several different technologies including them in clinical studies is a major effort not feasible by one or few institutions.

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

Synergies and complementarities with ongoing FP7 related activities should be explored in order to avoid overlaps and duplications and to maximize European added value in health research. In particular synergies should be sought with other IMI initiatives such as those already focusing on CTCs or ctDNA, including projects focusing on knowledge management e.g. eTRIKS, EMIF, DDMORE, Open PHACTS.

Albeit these related projects are more centred on the development of single technologies, we see a great chance in exploring synergies. Among these projects are:

- **MIRACLE** "**M**agnetic **I**solation and molecula**R** **A**nalysis of single **C**ircu**L**ating and disseminated tumour c**E**lls on chip" (http://www.miracle-fp7.eu/);
- **CTCTrap**, development of Therapeutic Apheresis (TA), as a way to isolate CTCs from larger volumes of peripheral blood in cancer patients (http://www.utwente.nl/tnw/ctctrap/):
- **CanDo** ("A CANcer Development mOnitor"), development of a device for CTC enumeration and analysis by integration of nanotechnology, biophotonics and surface-enhanced Raman scattering (SERS);
- **OncoTrack**, large scale deep sequencing program using clinically well-defined tissues (blood & biopsy samples) from patients with colon cancer in order to enable the direct comparison of the genome of the patients' tumour with that of its metastases. Analysis of the tumour methylome and transcriptome to provide a substantially complete description at the genetic level of the molecular changes accompanying development of the primary malignancy and subsequent metastatic events (http://www.oncotrack.eu/).
- **BBMRI-ERIC, BBMRI-LPC, Bioshare,** biobanking initiatives cataloguing both population-based and clinical biobanks in Europe which information would potentially be very valuable for the project (http://www.bbmri.eu; http://www.bbmri-lpc.org; http://www.bioshare.eu).

Bayer is leading OncoTrack and participates in CanDo, therefore advice on sample logistics and deep sequencing expertise can be available. Members of listed consortia are welcome to join the SAB of this project in order to ensure information exchange among these projects funded by the EU.

OVERALL OBJECTIVES

The aim of the project is the establishment, technical and clinical validation of methods for blood-based biomarkers enabling prediction i.e. *patient stratification/ predictive biomarkers*, monitoring of treatment response i.e. *surrogate biomarkers* and prognosis i.e. *prognostic biomarkers*.

Identification of new biomarkers per se using screening approaches (e.g. by proteomic methods) is **not** within the scope of this call.

With regard to the stratification approach the ultimate goal is the development of blood based companion diagnostics, ideally close to regulatory approval. The evaluated technologies should therefore have a certain degree of proven technical maturity.

Such assays have significant value for patients, physicians, and payers since they will prevent exposure of patients to drugs that are unlikely to be beneficial. Moreover robustly validated biomarker assays are extremely important for the pharmaceutical industry as they will help to reduce the very high attrition rate in clinical development, the key cost driver in drug development, by selection of well characterized patients with suitable preconditions for response.

EXPECTED KEY DELIVERABLES

- Establish criteria for evaluation of different CTC isolation technologies;
- Setting up a sample collection and developing storage protocols for selected CTC isolation technologies allowing shipment and bio banking for collection and analysis at different research sites;
- Comparison of methods for the molecular analysis of CTCs with respect to correlation with primary tumour material, clinical outcome, treatment response and ctDNA status of patients;
- Evaluation of different ctDNA analysis methodologies in terms of compatibility with sample collection and storage as well as reproducibility in clinical samples;
- Development of database and data analysis infrastructure for correlative studies of CTCs and ctDNA in clinical samples;
- Development of blood-based companion diagnostics ideally up to clinical approval.

EFPIA PARTICIPANTS

Bayer HealthCare (lead), Boehringer-Ingelheim, Eli Lilly, Menarini, Orion, Servier.

INDICATIVE DURATION OF THE PROJECT

The indicative duration of the project is 5 years.

INDICATIVE BUDGET OF THE PROJECT

The indicative EFPIA in-kind contribution is EUR 7 360 000.
The indicative IMI JU contribution is up to EUR 6 620 000.

In-kind contribution: Each participating company will fund their own participation and provide R&D resources such as staff, laboratory facilities, materials and clinical research, where applicable. FTEs will perform hands-on scientific work in the laboratories of the EFPIA partners and are involved in project management. Clinical samples collected by EFPIA partners will be provided to the consortium, if useful for its purposes. Furthermore, there is significant experience among EFPIA members with different technologies used for CTC isolation, molecular analysis. These protocols and expertise will be made available to the consortium.

APPLICANT CONSORTIUM

The academic/SME Applicant Consortium to be selected from Expressions of Interest (EoIs) should address all research objectives outlined in this call text to qualify. In particular, clinicians with expertise in the field and having access to clinical samples, academic research groups with a track record in the molecular analysis of CTCs or ctDNA and SMEs with established close-to-the-market technologies for CTC isolation and analysis would be of high value for the project. Additional required expertise includes bioinformatics, *in vivo* and *in vitro* models for CTCs.
Face-to-face meetings should be organised as soon as possible after the selection of the Applicant Consortium to team-up with the EFPIA partners.
The EFPIA Participants would highly welcome the involvement of regulatory authorities (EMA, FDA) early on in the project either as official partners or as member of the Advisory Board.

PROPOSED ARCHITECTURE OF THE FULL PROJECT PROPOSAL

Currently the most promising approaches within the field are the analyses of i) CTCs, ii) ctDNAs and iii) miRNAs (e.g. isolated from exosomes). Only CTCs offer the chance for isolation and subsequent functional testing. On the other hand, ctDNA and miRNA may be more likely to be detected and therefore suitable especially in early disease stages of

cancer or in minimal residual disease, where CTCs may only be present in low numbers. Within each technology platform, however, very different technologies/methods exist and should be investigated.

EFPIA CONTRIBUTION FOR EACH WORK PACKAGE COULD INCLUDE:

- Scientific expertise;
- Access to existing technologies and assay development;
- Logistic know-how and potentially the infrastructure;
- Bioinformatics and database infrastructure;
- Program management (all WP);
- Contribution to analytical data;
- Access to clinical samples;
- Training personnel.

PRE-EVALUATION PHASE (YEAR 1).

In a first step the most promising technologies should be selected based on available data either published or from partners. Criteria for evaluation of key parameters and user requirements need to be defined (e.g. what defines a circulating tumour cell?). Standardization is a key task for all technologies to be used. This phase could be organised in different Working Groups with tasks centred around:

- Definition of criteria for technology evaluation, based on clinical needs and utility, in collaboration with EFPIA, academic and SME partners
- Assessment of specific CTC isolation technologies (comparison of existing technologies and establishment of new protocols in existing clinical samples);
- Analytical technologies for single cell analysis or circulating nucleic acids (e.g. NGS, WGS, TAm-Seq, targeted-exome, dqPCR, BEAMing)
- Establishment of sample collection and transfer protocols
- Collection and storage of samples in a way that would allow repeated analysis or assessment of future technologies such as analysis of circulating proteins should be taken into account
- Assessment of multiplexing and miniaturization technologies that would allow parallel analysis of e.g. CTCs and ctDNA
- Establishment of bioinformatics and database infrastructure for the consortium; data collection and data management according to established data standards and/or collaboration with a data standards organization (e.g. CDISC)

- Evaluation of setting up a core laboratory for sample storage and analysis in order to standardise data acquisition

Milestones in this phase of the project, are required to move to the next phase and include agreements on indications, on technologies to be included in the Technical Evaluation Phase, on SOPs, and on establishment of logistics and infrastructure for the consortium.

TECHNICAL EVALUATION PHASE (YEAR 1-4).

The selected technologies should be applied using the standards and SOPs defined, preferentially head to head in the selected indications. Comparisons between isolated CTCs or circulating nucleic acids obtained with different technology platforms with primary tumour material will be done. An intense exchange between Work Package (WP) 1 and WP2 (see below) is planned to assess the applicability of the technologies used to more than just one tumour indication. The technologies should be then compared e.g. with regard to sensitivity, reproducibility, predictivity etc. Using *in vitro* (e.g. CTC cultivation) and animal studies (e.g. CTC-derived xenografts), the validity of these approaches to predict treatment response should be investigated.

WP1

Cross-comparison of different technologies selected during the pre-evaluation phase in a large indication with high unmet medical need and difficult access to (repeated) tumour biopsies. Study design for the Clinical validation phase including regulatory guidance.

WP2

Cross-comparison of different technologies selected during the pre-evaluation phase in a small indication with high unmet medical need and difficult access to (repeated) tumour biopsies. Study design for the Clinical validation phase including regulatory guidance.

WP3

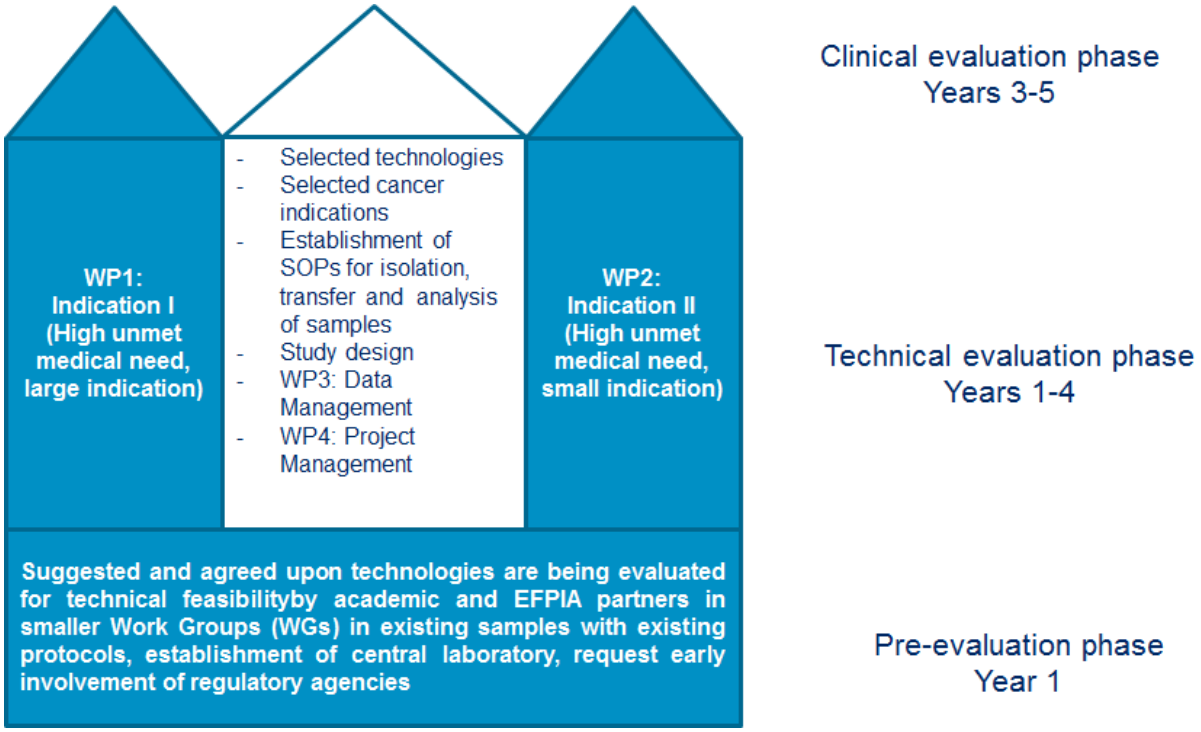
Data Management and Bioinformatics will be crucial for the success of the project as large amounts of data collected with different technologies need to be correlated. Data basing, curation, harmonization, standardization, and sharing are key activities that have to be addressed.

WP4

Project management, dissemination of project results (e.g. press releases, web page, meetings, interaction with patient advocacy groups) and organization of the consortium administration are within the responsibility of WP4 and will be supported by all consortium members. Importantly, legal and ethical issues have to be addressed in this WP.

CLINICAL VALIDATION PHASE (YEAR 3-5)

The technologies selected will be used to analyze blood-based biomarkers in retrospective samples (which can potentially be provided by EFPIA partners depending on the indications selected) from well-defined patients and in prospective clinical studies that may be conducted in the course of the project. Correlations between different parameters like CTC number, mutational status, chromosomal amplifications and cancer type, stage, grade, metastatic status will be investigated. A special focus will be put on longitudinal studies to enable an assessment of the predictive and prognostic value of CTCs and ctDNAs.



Schematic presentation of a possible consortium structure and timelines.

4. ZOONOSES ANTICIPATION AND PREPAREDNESS INITIATIVE (ZAPI)

BACKGROUND

Vector-borne viral or bacterial diseases (zoonotic and otherwise) are occurring at an increased frequency in EU and other countries in the world. There have been 25 documented emergent diseases that moved from wild or domestic animals to human populations in the last 20 years (EFSA Journal 2013;11(4):3129, The European Union Summary Report on Trends and Sources of Zoonoses, Zoonotic Agents and Food-borne Outbreaks in 2011). It is highly probable that zoonoses with rapid spread in one or several EU countries will continue or increase due to environmental and demographic changes. With the increase in movements of people and goods from both the southern and eastern continents, the EU has already been affected by many zoonoses over the past 20 years, for example West-Nile-Virus, Chikungunya or Influenza H5N1. The consequential economic and social impacts are reasonable precedents for those to come. Zoonoses clearly demonstrate that the health of people is related to the health of animals and the environment; zoonoses therefore require a 'one health' approach to research and measures in the human and veterinary field.

A review of the past decade confirms two categories of events. The first category occurs when 'known agents', such as West Nile Virus, leave well defined borders and enter a new vector environment, causing significant disease in animals as well as humans or the vector species spread to new areas allowing circulation of a pathogen, as is the case of the invasive mosquito species Aedes albopictus in Europe allowing circulation of dengue and chikungunya viruses. Other examples are when known agents undergo genetic changes, such as certain influenza A subtypes.

The second category involves completely unknown 'new agents', such as Severe Acute Respiratory Syndrome virus (SARS) in humans or Schmallenberg virus in animals, where the source of the disease must be determined through a challenging set of epidemiological and laboratory studies before a solution can be considered. A further distinction can be made between 'imported' pathogens and domestic pathogens (e.g. hantaviruses and arboviruses), which are ignored in many European countries however are equally important.

As it is difficult to predict zoonotic events, the rapid development of containment and control programs is critical for the well-being of domestic and wild animal as well as for human populations. To address the two categories of events, there are two fundamental

approaches to ensure readiness and to develop an adequate response in a rapid time frame:

1. Identification of, and agreement on, the agents most likely to move across borders and regions and pre-development of vaccines for those agents. An example of a pre-preparedness program is the rapid development and deployment of Bluetongue vaccines in the EU market in an 18-month period, based on industry's experience with vaccines previously developed to address the disease in the Mediterranean basin.
2. Establishment of technical platforms inherently designed for the rapid design of vaccines against (new) pathogens. A positive example of this approach is the development and registration of a West Nile vaccine based on an established and safe virus vector system for horses in less than 2 years' time in the United States.

In either case, no individual organization has either the expertise or the resources available to ensure full readiness for delivering efficient control tools against future outbreaks. Close collaboration among governmental regulatory agencies, academic groups, PPP funding agencies and industrial partners is a must for achieving such an ambitious objective.

It is therefore proposed to create, in close connection with existing epidemiological and surveillance networks, a programme that will identify the technologies allowing a rapid screening of protective immunogens/neutralizing antibodies, pre-validate up-scaled production of these targets, and establish fast track regulatory review process for delivering control tools in an integrated way. The objective of the programme is to deliver a strategically designed capacity for delivering efficient responses in face of the looming threat that could result in large economic and social losses.

PROBLEM STATEMENT

If we are to learn the lessons of the past, we must prepare ourselves to address both the predictable outbreaks (scenario 1 above) and the unpredictable ones (scenario 2). Many of the required tools listed below are overlapping and shared for defining the immunogens and corresponding antibodies, but the respective focus and disciplines are still unique.

- Characterizing the agent, proposing control solutions within 2 months
    - Identifying the protective immunogen(s) and corresponding neutralizing antibodies
    - Defining vaccines that are efficacious in all target species

- Defining vaccine/design manufacturing technology(ies) in such a way that it can provide both easy/simple QC release AND 'surge capacity' (true quality by design)
- Effecting the control measures in the field
- Designing vaccine manufacturing process(es) to enable instant surge capacity
- Defining in advance with regulatory authorities the conditions under which everyone can operate in a 'high fast track' mode.

NEED FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

No single industrial firm, academic centre, or governmental agency has the skills and the capacity to be able to plan ahead to meet the complex challenges associated with unexpected outbreaks. To meet one of these outbreaks effectively is challenging enough. To address more than one outbreak concurrently could be paralyzing without a closely coordinated and effective program tying together a network of actors with proven skills and capabilities. Hereafter is a list of basic requirements to meet such a need:

Technologies

- Design of expression constructs for prokaryote or eukaryote systems enabling very high expression levels (the general idea is to avoid the use of mammalian cell culture systems which are prone to supply bottlenecks for technical and logistical reasons in a context of surge capacity). Classical vaccine approaches could be considered if the proposals provide ways to very significantly accelerate the delivery of the commercial vaccines in the field.
- Universal antibody libraries combining immunoglobulin genes from multiple species (ensuring highest chance for finding high affinity neutralizing antibodies).
- High throughput screening technologies for neutralizing antibodies or antibody-like molecules.

Scientific knowledge

- Knowledge of reservoir species and of the kinetics of the immune response in natural and experimental infection plus elementary knowledge of the pathogenesis. In fact some diseases become worse after vaccination: such as: aleutian disease of the mink, dengue heterologous genotype infection or respiratory syncytial virus infection.

- Immunoprofiling/immunosignature technologies for defining protective immunogens.

- Immunodesign technologies for designing vaccine immunogens and corresponding antibodies (bioinformatics and immunostructural analyses).
- Comparative immunology approach for understanding common protective mechanisms / recognition of key protective immunogens between different target species.

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

Applicants have to take in consideration for the development of their Expression of Interest that there are already several initiatives on-going in the field, both in Europe and globally.

Synergies and complementarities should be considered, building from achievements, and incorporating when possible data and lessons learnt, while avoiding unnecessary overlapping and doubling of efforts.

Collaboration by design should be a cornerstone of the proposed strategy.

Examples of such EU projects are ENIVD, VBORNET, EDEN, EDENext, RiViGene, ARBOZOONET, EPIZONE, MEDVETNET, SILVER, EMPERIE, ANTIGONE, PREDEMICS, EVA, as well as similar networks on a national and international level. The project should also interact with relevant regulatory agencies, national veterinary and public health authorities and ECDC, WHO and OIE.

Synergies may also be sought with other IMI initiatives; in particular those already focusing on infectious diseases, diagnostics and vaccines: RAPP-ID, BioVacSafe, ADVANCE. In addition those on knowledge management should be considered e.g. eTRIKS, EMIF, DDMORE, Open PHACTS and others.

In addition the applicants should be aware of existing and emerging biobanking initiatives in Europe such as BBMRI-ERIC (www.bbmri.eu), BBMRI-LPC (www.bbmri-lpc.org) and Bioshare (www.bioshare.eu), among many others. These existing and funded projects will enable smooth access to samples and data in the participating biobanks for most of the phenotypes listed. Also BBMRI.eu and BBMRI-LPC jointly catalog both population-based and clinical biobanks in Europe which information would potentially be very valuable for all the topics.

OVERALL OBJECTIVES

The current practice, when a new animal or human pathogen occurs, is to adapt the virus on an existing cell line suitable for manufacturing cell line. This situation may not always exist and one could face more and more viruses which either are very difficult to adapt

on existing cell lines (with the risk of generating mutations deleterious for the immunogenicity) or do not grow on cell lines at all. As new outbreaks could spread over large territories in just a few months, the current programme is proposed to avoid this uncertain step in the development of the control tools.

The primary global objectives:

- To identify and collaborate with key players, associated with the critical technologies, who can effectively design vaccine/antibody products and develop manufacturing solutions and distribution infrastructure (such as labs, kits, vaccines, antibodies for serotherapy treatment, supply chain) within the required time frame of less than 6 months following the occurrence of a new zoonosis and identification of the new etiologic agent.
- To reach agreement with regulatory authorities on the definition of common guidelines that will allow the fast track implementation of new control products (vaccines and/or antibodies) both in human medicine and veterinary medicine.
- Deliver demonstration of rapid identification/confirmation of protective immunogens using combination of immunosignaturing and bioinformatics.
- Deliver demonstration of vaccine tools for selected families of pathogens (number (1, 2, 3) to be defined based on priorities).
- Deliver demonstration of examples for scale-up manufacturing technology(ies) associated with the delivery of vaccines, antibodies or antivirals.

EXPECTED IMPACT ON HUMAN HEALTH AND PUBLIC HEALTH

This proposal aims to reduce the impact of emerging pathogens on people in EU and in other countries around the world. The majority (more than 60%) of new infectious diseases in man originates in animals. In order to efficiently tackle zoonoses the 'one health' concept should be pursued. It is also less expensive to control new infectious diseases in animals compared to the high direct and indirect costs which are triggered once the disease spreads to people.

The focus of the project will be on examples of pathogens which occur first in animals before moving to man. The development of a fully new approach to address the challenges of short time delivery and large capacity in manufacturing will be beneficial both to veterinary and human vaccines, as the new methodology will be applicable to any new pathogen. This new 'development by design' will also have an important benefit for animal welfare by removing the need to use animals for performing batch QC releases.

Recent outbreak events due to new or re-merging pathogens indicate that only viruses, and more specifically arthro-borne viruses, have the potential for spreading over Europe

or other territories in a very short time period. This is the reason why the following targets are defined as models for ZAPI:

Targets for vaccines and antibodies

- Rift Valley Fever Virus
- Orthobunyavirus (Schmallenberg-like virus)

Target for antibodies

- MERS-CoV

However, it should be well understood that technologies and processes to be developed within the ZAPI project need to be also amenable to other types of pathogens (other families of viruses, bacteria, toxins, etc.)

EXPECTED KEY DELIVERABLES

Identification

- Kinetics of immune responses in key reservoir and target species
- Ultra-fast screening processes for identifying key protective immunogen(s) and corresponding neutralizing antibodies or antibody-like proteins

Fast implementation for control tools

- Validated vaccine manufacturing processes allowing necessary surge capacity and short / immediate, fully *in vitro*, QC batch release assays
- Manufacturing process enabling surge capacity and short QC release for neutralizing reagent (antibody or antibody-like)
- Interaction with regulatory authorities and key societal stakeholders to support definition of a process and key steps for fast track approval of the control tools in the context of a new zoonosis, both from political/societal perspective as well as regulatory perspective, in order to get full endorsement if the emergency outbreak situation occurs.

  This task is considered as one key deliverable and the corresponding work packages activities will encompass the whole duration of the project (5 years).

List of the 6 technical key deliverables:

- Control tool (either vaccine or antibody) to be a purified subunit
- Manufacturing technology(ies) to be based on bacterial system or a system allowing very high scale up with no need for extensive Capital Expenditure (Capex) investment (use of existing culture/fermentation equipment in the industry)
- Manufacturing/expression system to use a synthetic culture medium with no limiting ingredient supply for large scale up

- Manufacturing/expression system to be able to achieve high volumetric yields (in order to ease the downstream purification steps)
- QC release control tools to be exclusively based on in vitro techniques, able to provide analytical data in less than 24 hours
- Whole manufacturing process to ensure high robustness and consistent batch to batch quality

EFPIA PARTICIPANTS

Merial, a Sanofi company (coordinator), Animal Health Division of Sanofi, Boehringer Ingelheim Animal Health, Medimmune, a division of AstraZeneca

INDICATIVE DURATION OF THE PROJECT

The indicative duration of the project is 5 years.

INDICATIVE BUDGET OF THE PROJECT

The indicative EFPIA in-kind contribution is up to EUR 9 900 000
The IMI JU financial contribution will be a maximum of EUR 9 900 000

APPLICANT CONSORTIUM

The applicant consortium is expected to be a multi-disciplinary body consisting of academic research centres and institutes, small- and medium-sized enterprises (SMEs) and centres from national and/or supranational public and animal health bodies. The consortium should be in a position to provide an effective communication between the key stakeholders from academia, EFPIA, public and animal health bodies as well as regulatory authorities. It should be providing experience well established in the field of zoonoses research and diagnostics, immunology, microbiology, antibody library design, neutralization and immunoprofiling assay technologies, in silico immunogen design, interactive database development and operation, as well as for innovative expression systems able to support the objectives of the project.

PROPOSED ARCHITECTURE OF THE FULL PROJECT PROPOSAL

The Applicant Consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the EFPIA consortium.

The architecture below for the call is a proposal; different innovative project designs are welcome, if properly justified.

WP1

Definition and design of key protective immunogen(s) for the selected targets, for use in different expression systems and in multiple species. Design vaccines for large scale production and simple, fast, *in vitro* only, QC release tests.

WP 2.1. *in silico* design work for minimum protective immunogen for target model #1.

WP 2.2. *in silico* design work for minimum protective immunogen for target model #2.

WP 2.3. Workstream for combining public & private expertise for setting up the new disease challenge model in target species.

WP2

Basic knowledge of immunokinetics, pathogenesis and (eco)epidemiology is needed jointly with diagnostic efforts and immunogen development. For instance monitoring and modelling of rodent dynamics and/or climatic anomalies can be used to develop early warning systems for human epidemics. Definition and design of neutralizing antibodies / antibody-like molecules against the selected targets for use in different expression systems and in multiple species. Define and design reagents which will provide critical quality information for in vitro QC tests.

WP 2.1. Establish a multi-species, universal antibody library for future screening of optimal antibodies

WP 2.2. Identify the key neutralizing antibodies from infected animals or animals immunized with nucleic based vaccines; clone these antibodies and optimise sequences for *in vitro* expression

WP 2.3. Establish HTS *in vitro* neutralization assays

WP3

Design of a surge manufacturing process + associated QC release tools for protective immunogens, fully compliant with a pre-approved, fast track, regulatory registration process.

WP 3.1. Design manufacturing process (for subunits, or nucleic-based vaccines) ensuring highest yields, purity and minimum number of downstream steps.

WP 3.2. Validate the process steps on 2 selected targets.

WP4

Design of a surge manufacturing process + associated QC release tools for neutralizing reagents.

WP 4.1. Design manufacturing process (for soluble subunits) ensuring highest yields, purity, functionality of antibodies, and minimum number of downstream steps.
WP 4.2. Validate the process steps on at least 2 pre-defined target models.
WP 4.3. Validate the whole process through an emergency exercise test *(this can be optional depending upon final budget).*

WP5

Definition of coherent and effective connections with existing networks and organizations working as epidemiology and surveillance centres, in order to establish direct and open communication channels with industry for early warnings.
Define the process and key steps for fast track approval of the control tools, both from political / societal perspective and regulatory perspective in order to get full endorsement if the emergency outbreak situation occurs. This fast track approach process has to be defined and accepted by all stakeholders both in animal health and human health.
WP 5.1. Workstream for defining minimum requirements for a fast track approval and for immediate QC release of vaccine batches.
WP 5.2. Workstream for defining minimum requirements for a fast track approval and for immediate QC release of antibodies batches.
WP 5.3. Workstream for defining the rules for sharing all information on the pathogens and disease models to all industrial partners for setting up manufacturing consortia in the context of emergency.

WP6

Project management, coordination, communication and dissemination of results and achievements.

Note: Data collection and data management should be conducted according to established data standards and/or collaboration with a data standards organization (e.g. CDISC) to develop new data standards if no established data standards exist.

Expected inputs from Academia and SMEs

- Design a universal diagnostic tool and associated interactive databases for rapid identification of new pathogens.
- *In silico* design of candidate immunogens for expression as subunits or VLPs in recombinant systems.
- Design universal libraries for antibody molecules from multi-species origin.
- Design HTS techniques for neutralization assays.

- Provide basic knowledge for immunoprofiling assays.

Expected inputs from Industry / EFPIA members

- Perform comparative immunological studies in target species for validating design of protective immunogens.
- Implement HTS technologies for screening key antibody reagents out of the universal libraries.
- Lead WP for regulatory changes and IP discussions.
- Validate options for new QC release techniques.
- Validate new QC release techniques.
- Validate timelines for ZAPI approach.
- Validate industrial scale manufacturing options defined by ZAPI (test in actual industrial conditions).

Expected input from interaction with regulators (via consultation and/or advisory board)

- Contribute to the deliverables of WP5, along the objective to define an entirely new fast track approval process.
- Providing the current perspective for ensuring efficacy and quality of vaccines and therapeutic antibodies in a context of high emergency and of breakthrough technologies, for ensuring very short timelines in releasing life-saving products.

Management and Organization of the Project

Each work package should have a work package leader ensuring the deliverables are addressed. Overall project organization will be defined later within the full consortium.

Societal expectations and benefits

If successful, the program will deliver a general process which can accelerate very significantly the delivery of key control tools to people and animals when a new zoonotic outbreak occurs in EU and other developed countries. This process could also be used for providing control tools to developing countries if they face similar zoonotic outbreak issues.

5. GENERATION OF RESEARCH TOOLS TO ENABLE THE TRANSLATION OF GENOMIC DISCOVERIES INTO DRUG DISCOVERY PROJECTS

BACKGROUND

Genomic and epigenomic approaches, such as sequencing of cancers, epigenome analysis, exome sequencing of rare diseases, studies of disease-linked copy number variants and genome-wide association studies are revealing hundreds of proteins, pathways and protein families that are potential targets for therapeutic intervention. These discoveries hold significant promise because human genetic and epigenetic linkage to disease provides perhaps the strongest predictor of therapeutic relevance as compared with other basic research outputs. However, it is unclear which among these proteins and protein families might be both therapeutically relevant *and* amenable to selective modulation by small molecules. Thus the aim of this call is to accelerate the translation of potential targets "inspired" by genomics and epigenomics studies into drug discovery programmes by generating research tools to facilitate their understanding and then by evaluating them in novel assays derived from human disease tissue - with specific emphasis on inflammatory diseases that we know are amenable to treatment, but for which there are major unmet medical needs.

PROBLEM STATEMENT

Translation of genomic and epigenomic discoveries into drug discovery programmes is limited by several major issues. First commonly used laboratory cell lines and animal models often do not fully recapitulate human disease mechanisms. Second there is a lack of high quality research tools for functional characterization and testing of target hypotheses. Gene-based tools such si/shRNA, mouse knock-out or phenotyping approaches are typically insufficient and often misleading, and must be complemented by protein-based strategies and chemical tools.

Currently, research tools for each novel gene/protein are generated in an uncoordinated way, are often not readily available and their quality control is often inconsistent. Moreover, many potential target proteins are difficult to tackle in the current system; they lie outside the current focus of academic and industrial research (Edwards et al., Nature 470, 163, 2011; White et al., Cell 154, 452, 2013). In addition, even when research tools are available, they are rarely used to explore disease association in models

of human disease because getting access to the disease tissue and associated key opinion leaders is often difficult to achieve, expensive and time-consuming.

Taken together there is a need for an *integrated "gene-to-research tool" program* that produces a spectrum of publicly available protein-based tools for high value proteins in a cost effective way, and exploits these tools to uncover target-/disease links using physiologically relevant, high quality assays measuring disease-related phenotypes in human disease tissue. The called-for research tools include high quality purified protein, well-characterized antibodies, protein structural information, protein functional characterization, as well as an arsenal of biochemical, biophysical and cell-based assays that can be leveraged to develop well-characterized chemical probes. Physiologically relevant assays include cell-based assays using human disease cells and tissue, preferably obtained from patients. Emphasis should be placed on diseases involving inflammatory processes, e.g. osteoarthritis, atherosclerosis, inflammatory bowel disease and fibrosis.

NEED FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

This proposal tackles a problem of a scale and breadth that cannot be achieved rapidly within a single industrial or academic institution. A partnership to generate and exploit research tools, protein structures, and novel assays provides an opportunity to create knowledge in new areas of disease biology that otherwise may not be discovered in a timely manner. It also has the potential to leverage the resources and skills of a network of pre-clinical and clinical research scientists to drive understanding of biology and drug discovery, and tackles a problem of equally high interest for industry and academia.

A shared risk, shared investment in a pre-competitive space also allows the partnership to provide the wider community access to the generated reagents widely and quickly, thus amplifying its impact. Moreover, agreed-upon high standards of quality in the network ensure reproducibility of results, with concomitant increases in productivity and innovation obtained.

A partnership model also provides a forum to combine industry and academic expertise in the generation of "high value" tools - such as chemical probes, and to validate them for use in biological experiments. For example, the availability of protein reagents coupled with structural information forms the basis for fragment-based or activity-based chemical screening programmes as well as programmes that use structure-based optimization to

transform hits to leads. The "hit to lead" component of chemical probe development combines industry expertise in screening and medicinal chemistry with expertise in the target and its biological context, most commonly found in academia. In such a partnership model, these tools could also be used in a systematic way in cell-based assays derived from human tissue, which will involve clinical research scientists.

Finally, at a macro level, the shared risk aspect of the partnership would have the ability to break the academic and industry trend to "search under the lamp post", and to enter target space that is largely unexplored other than having genetic information. Providing tools to the global community is key to spur research in new fields of biology and generate a source of targets for proprietary projects in various therapeutic areas.

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

This proposed IMI project is expected to develop synergies and avoid duplication of effort with existing consortia. The details of these interactions will have to be defined at the Full Project proposal stage and agreed with the EFPIA partners. However, the application should include considerations how the interactions with ongoing consortia, such as the following ones, are envisaged and particularly which ones would add most value to the project.

1. The *European BLUEPRINT epigenome* project is a DNA-based analysis of the role of epigenomics in disease and development. Epigenetic marks are generated, read and erased by over 400 human proteins, most of which remain poorly characterized. BLUEPRINT exploits inhibitors of epigenetic targets in cell lines and human cells focused on Histone deacetylases (HDACs) and oncology. http://www.blueprint-epigenome.eu

   This IMI proposal, which will focus on other epigenetic protein families and with an emphasis on inflammation, should be both complementary and synergistic with BLUEPRINT.

2. Structural biology initiatives

   a. *Instruct*, as part of the European Strategy Forum for Research Infrastructures (ESFRI), is an infrastructure platform for structural biology in Europe. It provides access to cutting-edge technology, leading expertise

and training, and promotes new developments to refine the quality of structural biology research. http://www.structuralbiology.eu

This IMI proposal could benefit from the technology platform and methodologies provided by Instruct and contribute to demonstrating the impact of structural biology on drug discovery.

b. The *Structural Genomics Consortium* (SGC) focuses on a wide number of protein families and has developed techniques to promote rapid structure determination, and also has an epigenetics chemical probe program. http://www.thesgc.org

This IMI proposal has overlapping aims, and thus coordination with SGC would be important to avoid duplication of effort and to establish a technology-exchange partnership.

3. Chemical hit finding

a. The *European Lead Factory* (ELF), an on-going IMI project, focuses on identifying novel leads to pioneer drug targets. ELF has unparalleled access to industry chemical libraries and experience. http://www.imi.europa.eu/content/european-lead-factory.

b. *EU-OPENSCREEN*, as part of the European Strategy Forum for Research Infrastructures (ESFRI), is an emerging academic chemical biology initiative that intends to offer a wide range of assay technologies when it becomes operational as planned in 2015. http://www.eu-openscreen.de

This IMI proposal will be identifying new targets and will be developing assays, as well as determining their 3D structures. A partnership between this initiative and ELF and/or EU-OPENSCREEN could bring together world-class screening capabilities with structure-enabled hit to lead science – thus providing synergy and efficiency in the generation of chemical probes.

4. Other IMI projects

   a. *K4DD* focuses on elucidating the fundamental molecular mechanisms of drug – target interaction, with an eye to developing predictive tools. http://www.imi.europa.eu/content/k4dd

      By providing purified protein and 3D structural information, this project could expand the number of projects that K4DD could undertake and could provide complementary biophysical analyses of their interactions such as isothermal calorimetry. Similarly, insights made by K4DD scientists may increase the efficiency with which this project generates chemical probes.

   b. *STEMBANCC*, whose goal is to generate 1,500 iPS cell lines from 500 people, characterize them in terms of their genetic, protein, and metabolic profiles, and make them available to researchers. http://www.imi.europa.eu/content/stembancc

      This IMI proposal will generate small molecule inhibitors of proteins that regulate epigenetic signaling, many of which have been implicated in stem cell development. There is a strong chance that the chemical probes generated by this project will influence the development of stem cells, and perhaps even be used to increase the efficiency with which certain iPS cells are made.

   c. *BTCure* develops strategies to stratify patients with rheumatoid arthritis, and develop cell-based assays to test novel treatments. http://www.imi.europa.eu/content/btcure

      This IMI proposal intends to generate chemical probes for proteins that regulate epigenetic signaling and other protein implicated in inflammatory diseases and may identify new targets in rheumatoid arthritis.

   d. *OpenPHACTS* aims to develop an open access innovation platform, called Open Pharmacological Space. http://www.imi.europa.eu/content/open-phacts

OpenPHACTS could be a hub for the data generated by this IMI project, particularly to house the data from the use of the chemical probes in the various biological systems.

OVERALL OBJECTIVES

The objective of this call is to accelerate the translation of novel genomics- and epigenomics-inspired targets into drug discovery projects by establishing a programme that will (1) generate "enabling research tools" for proteins linked to disease, for their regulators and for other members of the relevant protein family, and (2) exploit these tools systematically in relevant models of human disease, based on access to human tissue, and in collaboration with top clinical research scientists, with an emphasis on inflammatory mechanisms.

The specific aims should be to generate research tools for proteins and protein families having members with genetic links to disease, with chemical probes as the highest priority. The scientific strategy should be to strike a balance between focus and flexibility, and between achievable and stretch objectives. Proteins selected from the families of epigenetic regulators (e.g. histone demethylases, bromodomains) should be selected initially because representatives from these families have already shown genetic links to diseases, and because an initial epigenetic focus provides significant synergy with other EU and IMI projects. Genetic variants of proteins in which function is altered might be included. At the same time, the project should look to the future and tackle challenging protein families and challenging structural targets – epigenetic protein complexes, ion channels & solute transporters should be prioritised. Other protein families should be considered and prioritised as the project proceeds and results emerge from genomic sequencing efforts. The stream of research tools emerging from this project should be used to explore the role(s) of the target in diseases such as oncology, cardiovascular, and especially inflammatory diseases, which should be the initial focus of this proposal.

Although the project should emphasize inflammatory mechanisms, immense additional value would be attained by making these research tools readily available to the community at large, in order to "discover the unexpected", leading to more drug discovery opportunities in the longer term. This may be especially the case for cancer, which shares many pathways with chronic inflammation.

EXPECTED KEY DELIVERABLES

- High quality research tools, the associated information and the resulting knowledge for "targets of the future"
- The reagents and knowledge to enable production of purified proteins and protein complexes
- Recombinant protein binders (antibodies/Fab's) to high-value proteins
- Biochemical or biophysical screening assays
- 3D crystal structures with and without ligands
- Chemical hits (fragment or small molecule)
- Cell-based assays to demonstrate "on target" efficacy of chemical probes
- Selective, potent and cell-active chemical probes for novel targets
- Information about the activities of chemical probes in phenotypic cell or tissue assays, with inflammation as the main emphasis – if possible, from patients who are genotyped.

Results and quality-controlled reagents will be made available to the scientific community for research purposes.

The project should be structured as a milestone-driven initiative. As a guideline based on the indicative budget and a rough estimation of resources required for the various deliverables, it is expected that over the course of the project ca. 100 novel protein structures, ca. 30 novel biochemical or cell-based assays, and ca. 15 chemical probes would be generated, and that these research tools would be explored in at least 100 different assays based on human tissue to be accessed in the wider scientific community. These estimates of the deliverables will be revisited at the Full Project Proposal stage. However the applicant should propose such milestones, and justify that they are achievable with the scientific plan proposed, and the available budget.

EFPIA PARTICIPANTS

Novartis (coordinator), Bayer, Janssen, Pfizer.

INDICATIVE DURATION OF THE PROJECT

The indicative duration of the project is 5 years.

INDICATIVE BUDGET OF THE PROJECT

The indicative contribution from the EFPIA companies is estimated at a total of EUR 21 600 000, of which EUR 14 800 000 is in kind and EUR 6 800 000 are in cash.
The indicative IMI JU contribution will be up to EUR 21 200 000.

APPLICANT CONSORTIUM

The Applicant Consortium (academic groups and SMEs) is expected to demonstrate:

- Expertise, leadership and a track record in protein science, including:
    - Expression, characterization and structure determination of soluble proteins, integral membrane proteins, and protein complexes in an integrated project at large scale, adopting a family-coverage approach to systematically map the knowledge space
    - Studies of human and therapeutically-relevant proteins
    - Production and characterization of high quality chemical probes in relevant biophysical, biochemical, and cellular/phenotypic assays
    - Quality control metrics established, and used in practice
    - Development of innovative technologies and approaches that have been widely adopted in academia and industry

The Applicant Consortium (academic groups and possibly SMEs) is also expected to demonstrate excellence and a track record in:

- Having an established network of recognised thought leaders in all relevant sectors, with a track record of success, as evidenced by collaborative publications
    - A global network that spans chemistry, biological assays, human biology, and clinical research
    - Proven track record of achieving high-value/high-impact outcomes catalysing research in pioneer target areas of drug discovery
    - History of collaboration with clinical researchers to achieve relevant results
    - Ability and history of leveraging additional funds with a variety of organizations, e.g., research programmes funded by patient groups
    - History of making research output widely available
    - Mechanism in place to efficiently and effectively disseminate chemical and biological research materials (e.g., chemical probes, protein constructs, antibodies)

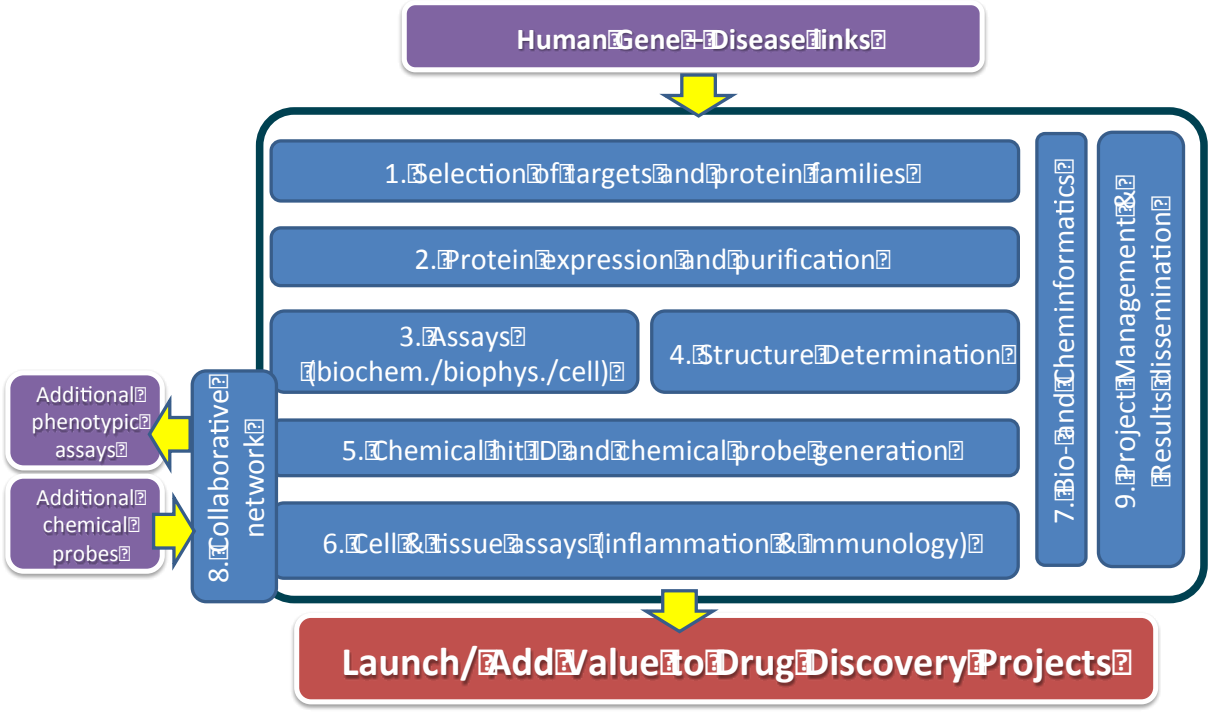
- Successfully collaborating in a network with industry
    - Demonstrated impact on launching or adding value to internal drug discovery projects in pharma
    - Demonstrated success in collaborations among networks of academics and SMEs – as evidenced through shared projects and co-authored publications
    - Demonstrated success in governing and managing large projects, including finance, intellectual property etc.
    - Demonstrated ability to consistently achieve milestones on time and within budget
    - Experience in managing varying interests of multiple stakeholders

PROPOSED ARCHITECTURE OF THE FULL PROJECT PROPOSAL

The Applicant Consortium is expected to address all the research objectives and make key contribution to the defined deliverables in synergy with the EFPIA consortium.

The architecture below for the call is a proposal; different innovative project designs are welcome, if properly justified.

It is suggested to structure the project in 9 work packages, as shown in the figure below.



WORK PACKAGE 1: SELECTION OF TARGETS AND HIGH PRIORITY PROTEIN FAMILIES.

Deliverable: Consortium-approved Target List

EFPIA contribution

- Each member provides a list of priority targets and target families, e.g., based on evaluation of gene –disease links (see Work package 7) and drug discovery experience.
- Define expectation of deliverables for the above (purified human protein and characterization, priority for structure generation and screening, fragment screening, chemical probe pipeline, functional assays)

Expected Applicant consortium contribution

- Generate list of priority targets and target families from large scale integrative genomic analysis and from publicly available data and other EU-based consortia, e.g. BLUEPRINT epigenome, Structural Genomics Consortium (see Work Package 7).
- Create joint prioritised Target List of human proteins and protein families
- In collaboration with EFPIA partners, create an action plan for each target or set of targets and target families, including which target/target family is prioritised by each EFPIA member

WORK PACKAGE 2: PROTEIN EXPRESSION AND PURIFICATION

Deliverable: Validated protein expression clones; protein purification protocols, recombinant antibodies; all to be made available.

EFPIA contribution

- cDNA clones for priority human protein targets
- Cell lines for expression
- Small molecule ligands to facilitate protein expression and/or purification
- Validated sh/siRNAs (or CRISPR reagents) for generation of knockdown cell lines for antibody validation

Expected Applicant consortium contribution

- Design of expression vectors

- Explore expression of human full-length proteins and protein domains in multiple systems (bacteria, eukaryote), likely including multiple expression strategies (e.g. constructs of different lengths, site-directed mutants, different tags)
- Protein expression for integral membrane proteins, relevant protein complexes in multiple systems (bacteria, eukaryote), likely including multiple expression strategies (e.g. constructs of different lengths, site-directed mutants)
- Purification of human proteins, human integral membrane proteins, human protein complexes
- Protein characterization (e.g. mass spectrometry to characterize novel high-priority protein complexes, to quantify tissue-specific expression and to assess relevant post-translational modifications)
- Recombinant binder production (e.g. Fabs, darpins, camelids etc) for high-priority proteins to facilitate assay development and protein characterization

WORK PACKAGE 3: BIOCHEMICAL, BIOPHYSICAL AND CELL-BASED ASSAYS.

Deliverable: Experimental conditions for 30 high quality biochemical and biophysical assays

EFPIA contribution

- Define assay parameters
- Contribute assays to the partnership
- Chemiproteomics technologies to characterize on-target activity in cells
- Validated sh/siRNAs (or CRISPR reagents) for generation of knockdown cell lines for validation of antibody and chemical probe specificity in cells

Expected Applicant consortium contribution

- Develop and implement new biochemical and/or biophysical assays to measure target inhibition/binding
- Develop and implement new assay formats to measure on-target inhibition in cells or tissues (such as chemical proteomics, fluorescent assays, etc)
- Implement novel biochemical and cell-based assays to quantify off-target effects of compounds in vitro and in cells or tissues
- Develop and implement assays demonstrating protein cellular or tissue localization using protein binders/antibodies and mass spectrometry

WORK PACKAGE 4: PROTEIN AND PROTEIN COMPLEX STRUCTURE DETERMINATION.

Deliverable: 100 protein structures deposited into the Protein Data Bank prior to publication in papers

EFPIA contribution

- Small molecule ligands to promote protein crystallization
- Access to synchrotron beamlines

Expected Applicant consortium contribution

- Infrastructure and expertise to carry out protein and protein-ligand crystallization and X-ray structure determination (to include challenging structures such as human integral membrane proteins, initially ion channels and solute transporters and protein complexes, such as those that regulate epigenetic signalling)
- Development of new, high-throughput methods to generate co-crystals of proteins and protein complexes
- Using mass spectrometry or other suitable technology, extend analysis from single high-priority proteins or domains to their protein complexes where the pharmacologically targeted proteins are viewed in the context of their functional multiprotein complex
- Develop mechanism to access X-ray free electron laser technology as potential "game-changer" for hard to achieve structures

WORK PACKAGE 5: CHEMICAL HIT IDENTIFICATION AND CHEMICAL PROBE GENERATION.

Deliverable: 15 well-characterized chemical probes, meeting stringent criteria for potency, selectivity, and with demonstrated on-target effects in cells

EFPIA contribution

- Computational chemistry to select and prioritise compounds for screening
- Design and access to fragment or other bespoke libraries
- HTS or focused screens to identify hits
- Expertise in triage and validation of screening hits
- Logistics, automation or infrastructure support of academic partners
- Design and access to fragment libraries
- Assays (eg selectivity screening panels) and structure determination to support probe development

- Design and synthesis of research chemical probes

Expected Applicant consortium contribution

- Mechanism to access chemical libraries from leading academic chemists and chemical biologists
- Small scale screening of fragment and EFPIA partner chemical libraries
- Secondary biochemical screens to validate and prioritise hits
- Protein-ligand structure determination to support probe development
- Establish quantitative chemical probe criteria
- Explore interactions with the European Lead Factory and/or EU-OPENSCREEN (see Possible Synergies, section 3.) for the identification of hits with high probability for chemical probe generation.

WORK PACKAGE 6: CELL AND TISSUE PHENOTYPIC ASSAYS LINKED TO INFLAMMATORY MECHANISMS OF DISEASES

Deliverable: Results from testing chemical probe(s) in >100 different cell-based assays, where possible derived from human primary cells and patient tissue.

EFPIA contribution

- Profile compounds in established biological assays

Expected Applicant consortium contribution

- Network of target and disease experts to profile each probe in inflammatory and other disease-relevant assays (e.g. cancer)
- Access to patient-derived human tissue, with track record of using patient-derived samples to advance drug discovery
- Ethics approval to engage in such collaborations
- Mechanism to characterize probes in other consortia with panels of cell-based assays (e.g. Sanger Institute, NCI panel, BTCure, STEMBANCC)
- Engage additional collaborators who are leading the field in functional cell assays and disease models for particular targets
- Mechanism to access additional relevant phenotypic assay panels in priority areas, e.g., inflammation, immunology, allergy

WORK PACKAGE 7: BIOINFORMATICS AND CHEM-INFORMATICS.

Deliverable: Develop mechanism to integrate all publicly available literature on selected targets

EFPIA contribution

- Review of gene – disease links to inform target selection (Work package 1)
- Chem-informatic analysis of hits from chemical probe generation campaigns

Expected Applicant consortium contribution

- Access to bioinformatics resource describing relationships between genetic variants in a given protein associated with selected disease indications (gene – disease links).
- Mining of this resource to prioritise target and/or indication selection for optimal contribution to overall objectives (see Work package 1).
- Annotation of proposed targets with enabling resources, for example existing structural information, knockouts, etc.
- For data of all Work Packages, define need and implement bio-/chem-informatics tools to extract, manage and integrate in-house generated data with those publicly available.
- Apply standards to facilitate integration of newly generated data with large repositories
- Electronic lab notebooks to facilitate data sharing among partnership

WORK PACKAGE 8: COLLABORATIVE NETWORK OUTSIDE OF CONSORTIUM

Deliverable: A functioning network of academic and clinical research collaborators, with a strategy to initiate collaborations, to define expected outcomes, to monitor progress toward objective and a mechanism, if necessary, to terminate unproductive collaborations. A strategic plan to involve disease foundations within the network.

EFPIA contribution

- Generate list of key opinion leaders for potential collaboration

Expected Applicant consortium contribution

- Identify list of key opinion leaders for potential collaboration
- Develop and implement mechanism to initiate, monitor and manage or terminate (if necessary) collaborations
- Identify robust mechanism to communicate results from IMI project

- Make results and research tools publically available in an efficient manner and according to pertinent standards (e.g., as being defined by OpenPHACTS)
- Implement plan to partner with disease foundations
- Implement a strategic plan to liaise with other IMI consortia, with timelines and metrics of success

WORK PACKAGE 9: PROJECT MANAGEMENT AND TRANSLATION OF RESULTS

Deliverable: A management structure that ensures that the project meets deliverables and that integrates input from academic and industry partners

The management plan must describe how progress against milestones will be monitored and actions to be taken if progress against milestones is not adequate. In addition, the plan must describe an IP and data sharing strategy that allows data and reagents to be made widely available without restriction to spur further research, but that respects the interests of the EFPIA members to innovate internally.
A joint steering committee will govern the project in all aspects, including scientific direction, resource allocation, progress monitoring, quality assurance for all research outputs, IP etc. The joint steering committee will also clearly articulate the research outputs to be made available publically, and any research outputs that might remain confidential to participating academic, SME and EFPIA consortium members.

EFPIA contribution

- Senior scientist to represent company on joint steering committee
- Experts in drug discovery to manage collaborations in specific scientific areas or on specific targets
- Contributions to collaborative scientific meetings, management of internal versus external activities
- Legal contributions to manage collaborative agreements

Expected Applicant consortium contribution

- An outstanding scientific and management plan is required to ensure success of the consortium, to identify new scientific opportunities, to identify and build strategic partnerships with other projects (e.g. patient groups, international consortia, other IMI projects)
- Senior scientists to manage projects to deliverables, to disseminate the project output and to engage in collaborations to maximize impact

- Exchange of scientists among academic and industry partners to ensure that all participants benefit maximally from the collaboration
- Manage finance, valuation of deliverables, IPR, communication etc.
- Disseminate results in the form of publications, standard data repositories, meeting presentations, and via the consortium's website.

TOPICS 6 AND 7: COMBATTING ANTIBIOTIC RESISTANCE: NEWDRUGS4BADBUGS (ND4BB)

BACKGROUND

Antimicrobial resistance (AMR) is a major global public health threat. Infections caused by resistant bacteria are increasing and are associated with increases in mortality, morbidity and length of hospitalisation.[4] In Europe, 25,000 deaths were reported in 2007 as a result of AMR, with two thirds of these deaths due to Gram-negative bacteria. This clinical burden is associated with soaring treatment and societal costs, with the cost of AMR being estimated at around € 1.5 billion per year in Europe (see European Centre for Disease Control [ECDC]/European Medicines agency [EMEA] joint technical report "The bacterial challenge: time to react," 2009). Despite the threat AMR poses to public health, the number of newly developed and approved antibiotics has steadily decreased over the past 3 decades (http://www.cdc.gov/drugresistance/threat-report-2013/).

The European Commission (EC) is committed to combatting AMR, as outlined in its recent communication to the European Parliament and Council entitled 'Action plan against the threats from antimicrobial resistance' (COM (2011) 48; (http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf) The EFPIA shares the views of the EC and recognises that although a number of activities have already been undertaken at the EU (including FP7 funded activities) and international levels, including the Trans-Atlantic Task Force on Antimicrobial Resistance, more concrete actions need to materialise to make meaningful change.

The Innovative Medicines Initiative (IMI) New Drugs for Bad Bugs (ND4BB) programme was launched in May 2012 in response to the challenge of rising AMR in Europe. The ND4BB programme's overall vision is to create an innovative, collaborative Public-Private Partnership (PPP)-based approach to drug development, from the discovery of new antibiotics to Phase 2 and 3 clinical trials, with the aim of reinvigorating antibiotic research and development.

[4] Cosgrove, SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. Clin Infect Dis. 2006; Jan 15; 42 Suppl 2:S82-9.

The ND4BB programme represents a core element of the "Action plan against the rising threats from Antimicrobial Resistance" adopted by the EC in answer to the Council Conclusions and European Parliament resolution to "establish an EU-wide plan to combat AMR." Action 6 of this action plan reads (http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf:

> *To promote, in a staged approach, unprecedented collaborative research and development efforts to bring new antibiotics to patients by:*
> *Launching rapidly with EFPIA, within the IMI-Joint Undertaking, a program for research on new antibiotics aimed at improving the efficiency of research and development of new antibiotics through unprecedented open sharing of knowledge.*

OVERALL OBJECTIVES OF ND4BB

The goal of the ND4BB research programme is to create an innovative and collaborative public-private partnership (PPP)-based approach that will positively impact all aspects of the development of drugs to combat AMR, from novel drug discovery through clinical development to the elaboration of new business models for antibiotic R&D and including the responsible use of antibiotics. The first two projects under the ND4BB programme, COMBACTE[5] and Translocation[6], originated in IMI's 6th Call for Proposals and started in January 2012. COMBACTE is creating a premier clinical investigator, site, and laboratory network for antimicrobial drug development with which to complete clinical trials of novel agents. These networks will be sustainable beyond the IMI project duration. The project is investigating scientific challenges associated with antibiotic penetration barriers and efflux mechanisms in Gram-negative bacteria. In addition, a data repository is being developed to provide a key information base for research projects focused on antibiotic resistance (ND4BB Information Centre). This data repository is also sustainable beyond the IMI project duration. All partners participating in projects under the ND4BB research programme will be expected to contribute data to the ND4BB Information Centre and collaborate to share data and experience as widely as possible amongst the antibiotic research community as a whole.

[5] http://www.imi.europa.eu/content/combacte

[6] http://www.imi.europa.eu/content/translocation

Three more projects from IMI's 8th and 9th Call for Proposals under the ND4BB research programme are in preparatory phases. One will support a collaborative drug discovery strategy among public and private partners to promote the generation of a pipeline of novel antibiotic candidates directed against Gram-negative pathogens. Another is an effort to address the misalignment of economic incentives in antibiotic research and development by developing options for new business models integrated with responsible use of antibiotics. Another project currently under development will support the clinical development of new drugs combatting antibiotic-resistant Gram-negative infections. Finally, IMI's 8th Call also included an addition to COMBACTE that will support the development of a novel monoclonal antibody (mAb) against *Staphylococcus aureus.*

The IMI's 11th Call proposes two new ND4BB Topics aimed at addressing the need to develop new drugs active against clinically challenging Gram-negative bacteria including *Pseudomonas aeruginosa*. The proposed research to be included in the 11th Call builds upon the significant epidemiology, clinical, and biomarker research infrastructure currently being developed under ND4BB. An effort to optimally utilise epidemiology data, both from within the ND4BB programme and from external sources, is included as part of ND4BB Topic 6 in this Call. ND4BB Topic 6 will also focus on the development of systemically administered novel molecules against health care-associated infections (HAIs) caused by Gram-negative pathogens including *Pseudomonas aeruginosa*. ND4BB Topic 7 is being proposed to support the development of novel inhaled antibacterial agents and novel treatment regimens to treat respiratory infections caused by *Pseudomonas aeruginosa* and other difficult-to-treat non-fermenters in patients with cystic fibrosis (CF) and patients with non-CF bronchiectasis (BE). Topic 7 also aims to support the establishment of a European-wide registry for non-CF bronchiectasis to attain further insight into the disease, as well as its microbiology and epidemiology.

PROBLEM STATEMENT

Pseudomonas aeruginosa and other clinically challenging Gram-negative bacteria are important contributors to morbidity, mortality, and cost. *P. aeruginosa* is a major nosocomial pathogen worldwide, responsible for substantial proportions of HAIs, especially hospital-associated pneumonia (HAP), ventilator-associated pneumonia (VAP), and bacteraemia. Other Gram-negative organisms are also important contributors to disease burden. Complicated urinary tract infections (cUTIs) and complicated intra-abdominal infections (cIAIs) caused by resistant Gram-negative bacteria such as extended-spectrum beta-lactamase (ESBL)-producing *E. coli* and *K. pneumoniae* as well

as drug-resistant *P. aeruginosa* are also on the rise. The treatment of patients with cUTIs and cIAIs due to multidrug resistant organisms is challenging for clinicians because of limited therapeutic options.

Pseudomonas aeruginosa is also the most frequently isolated pathogen in patients with cystic fibrosis (CF) and requires lifelong, suppressive inhaled antibiotic therapy. More recently it has also been demonstrated that patients with non-CF bronchiectasis (non-CF BE) who are infected with *P. aeruginosa* experience more rapid lung function decline and exacerbate more frequently leading to an increased risk for mortality, costly and frequent hospitalisations, and intensive care unit (ICU) admissions. No antibiotics are yet approved for non-CF BE. In addition to Pseudomonas infections, infections by other non-fermenters, including *Stenotrophomonas maltophilia, Burkholderia* spp., *Acinetobacter* spp., *Achromobacter* (or *Alcaligenes*) *xylosoxidans*, *Ralstonia* spp., and *Pandoraea* spp. are of high medical interest, although most are still rare. These pathogens are, however, noted with increasing frequency in patients with CF, and some of them, e.g., *Burkholderia* spp., can be associated with rapid deterioration of the respiratory function and poor outcome. To date no antibiotic for inhalation has been approved for the treatment of these difficult to treat pathogens.

Despite the recognised need for new antimicrobials to treat resistant infections, only two new classes of antibiotics have been brought to market in the last 30 years, and many drug developers have left the field. Key barriers to the development and delivery of effective antibiotics include the following:

- Discovery and development of novel antibacterial agents is scientifically challenging. For example, many traditional screening approaches have failed to unearth novel chemical starting points, and Gram-negative pathogens have many inherent barriers and mechanisms that prevent penetration of antibiotic agents.
- There are substantial regulatory challenges to the introduction of novel antibacterial agents.
- Antibiotics have a low return on investment relative to other medicines, making their development unattractive to drug developers, therefore limiting the future antibiotic pipeline.

The ND4BB programme aims to contribute to the development of an antibiotic pipeline by exploring new therapeutic opportunities such as monoclonal antibodies, novel resistance-breaking antibiotics, and combinations of antibiotics with different mechanisms of action.

A general challenge in many areas of drug development is a lack of mechanisms through which investigators, drug developers, and clinicians can share data and experiences from the development of both failed and successful drug candidates. This leads to duplication of effort and ultimately inefficiencies in the drug development process. A common element across ND4BB is the sharing of data and knowledge to increase the probability of success in the development of novel agents, thus accelerating the delivery of quality medicines to patients.

NEED FOR PUBLIC-PRIVATE PARTNERSHIP

The effort and skills needed to achieve significant advancements in the prevention of further AMR and in the clinical development of novel antibacterial agents is too great for a single entity; collaboration is therefore essential. Furthermore the diversity of expertise required to tackle the challenges faced requires contribution from a number of key stakeholders. For example, the lack of a robust pipeline illustrates the scientific challenges faced by the pharmaceutical industry; consequently, a framework for sharing knowledge and resources across distinct companies, small and medium-sized enterprises (SMEs), and academia is needed to increase the probability for success of antibiotic research and development, and to share risks in developing drugs for orphan diseases. Similarly, the academics and industry bring unique and complementary skills and strengths to drug discovery and development. For example, academics provide leadership in hypothesis-generating mechanistic and biomarker translational research, in addition to having intimate understanding of disease populations that would be critical to effective trial design; whereas industry brings novel molecules and the resources and infrastructure to support large synchronised drug development efforts. It is therefore essential that the antibiotic research community works together to ensure that societal needs for novel and effective antibiotics and treatment regimens are fulfilled for the foreseeable future.

PROPOSED EXTENSION TO THE ND4BB PROGRAMME ARCHITECTURE

In the current 11th Call for proposals, the ND4BB programme is expanded with the addition of Topics 6 and 7 (Figure 1):

- **Topic 6: Epidemiology research and development of novel systemic antibacterial molecules against healthcare-associated infections due to Gram-negative pathogens**

Total indicative budget for ND4BB Topic 6: EUR 91 607 905 EFPIA/ EUR 75 340 000 IMI JU

This topic is divided into two subtopics:

Subtopic 6A: Epidemiology research and clinical development of a novel bispecific IgG Antibody, BiS4αPa, for the prevention of serious *Pseudomonas aeruginosa* disease

Subtopic 6B: Clinical Development of a novel resistance-breaking beta-lactam antibiotic, AIC499, in combination with a beta-lactamase inhibitor (BLI) Against Severe Bacterial Infections due to Gram-negative Pathogens

- **Topic 7: Development of novel inhaled antibiotic regimens in patients with cystic fibrosis and patients with non-cystic fibrosis bronchiectasis**

  Total indicative budget for ND4BB Topic 7: EUR 31 000 000 EFPIA/EUR 27 000 000 IMI JU

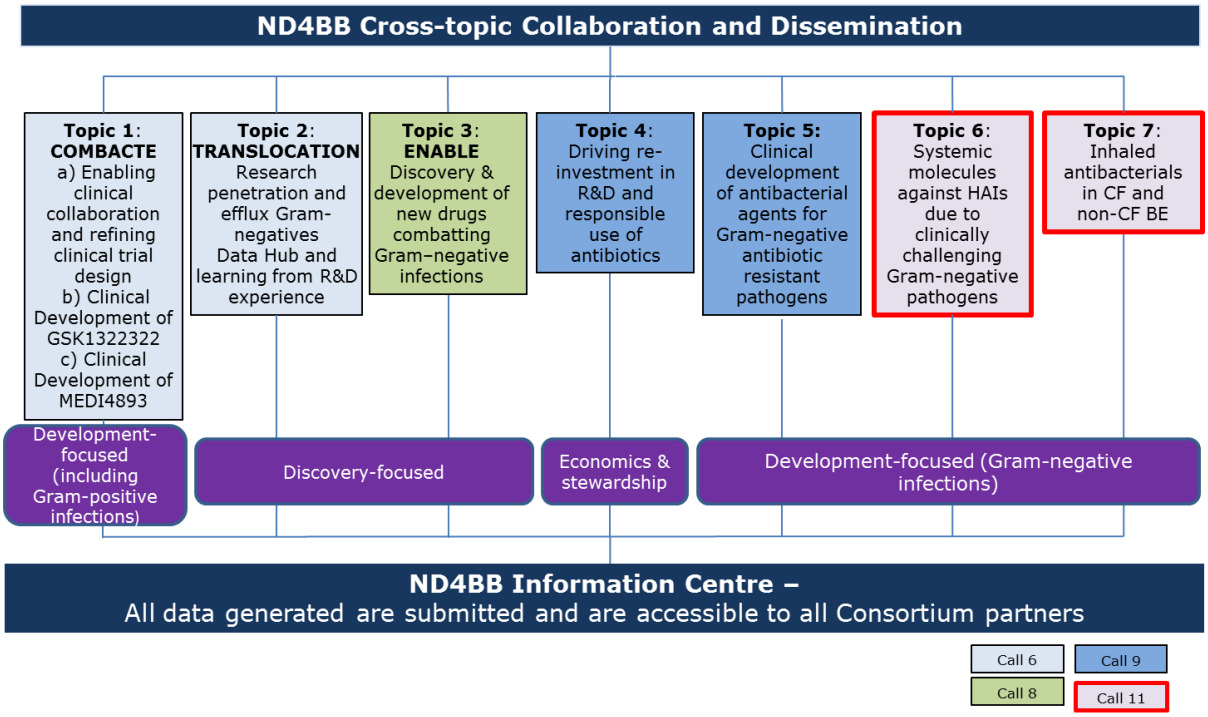


Figure 1 – Overall Architecture of the ND4BB Programme
BE = bronchiectasis; CF = cystic fibrosis; R&D = research and development

POINTS OF NOTE

- Current participants in other ND4BB projects that have either already started or are currently under development may apply to ND4BB Topic 6 or ND4BB Topic 7 of this Call.
- Applicants may apply to ND4BB Topic 6 and/or ND4BB Topic 7. For ND4BB Topic 6, applicants may apply to either one or both of the subtopics (6A or 6B).
- A separate expression of interest should be submitted for each subtopic/topic if a consortium applies to more than one subtopic/topic.
- For ND4BB Topic 6, the Applicant Consortium with the highest-ranked Expression of Interest for each of the two subtopics will be invited to merge and to jointly develop a full project proposal together with the EFPIA consortium in stage 2 of the evaluation process. Only one project will result from ND4BB Topic 6.
- Applicant Consortia are expected to propose options for novel study design addressing the objectives for each of the studies in both Topics to help clinical development of the proposed molecules. A discussion will take place between the EFPIA consortium and the successful Applicant Consortia with regard to the proposed study design of the planned studies.
- Funding for certain activities as described in some WPs will be allocated after milestone review in a stepwise manner. If, after milestone review, it is decided that additional expertise will be required, such as for the implementation of clinical studies, open and competitive Calls to select additional beneficiaries will be organised by the Consortium according to the Call process hereafter described.
- All Applicant Consortia are expected to provide plans and resources to support collaboration among projects funded under ND4BB. It is envisaged that this will be a shared activity across the projects generated by the current Call and existing ND4BB projects.
- All Consortia participating in projects conducted under the ND4BB programme will be expected to contribute data to the ND4BB Information Centre being developed in the Translocation project and to participate in cross-project team meetings as appropriate to ensure learnings, knowledge, and skill sets are maximised across the ND4BB teams.
- The projects resulting from ND4BB Topics 6 and 7 are expected to take advantage of the newly established CLIN-Net, LAB-net, and STAT-Net from the COMBACTE project where appropriate.
- The ND4BB programme may be expanded in future Calls (which would be launched under a successor programme to IMI, for which a Commission proposal

has been put forward in July 2013 and is under consideration by the EU legislator – see: http://ec.europa.eu/research/horizon2020/index_en.cfm?pg=h2020-documents) to include additional topics, including the clinical drug development of additional novel anti-infectives.

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

In addition to integration with other IMI projects under the ND4BB programme, complementarities and potential synergies with other initiatives on AMR should be taken into account, such as but not limited to:

- Joint Programming Initiative on AMR (http://www.jpiamr.eu/)
- EARS-net:http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/about_EARS-Net/Pages/about_network.aspx
- ESAC-NET:http://www.ecdc.europa.eu/en/activities/surveillance/ESAC-Net/Pages/index.aspx
- HAI-Net: ECDC Healthcare-associated Infections Surveillance Network http://www.ecdc.europa.eu/en/activities/surveillance/HAI/Pages/default.aspx
- National Institutes of Health (NIH)/Infectious Diseases Society of America (IDSA) initiative to set up a clinical research network on antimicrobial resistance ("Bad Bugs No Drugs – 10 by 20") to support the development of 10 new antibiotics by 2020. http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-12-019.html and http://cid.oxfordjournals.org/content/50/8/1081.full
- IMI RAPP-ID project dealing with the development of rapid point-of-care test platforms for infectious diseases (http://www.imi.europe.eu/content/rapp-id).
- Portfolio of FP7-funded projects in the area,
  e.g. AEROPATH, AntiPathoGN, DIVINOCELL and NABATIVI (see: http://ec.europa.eu/research/health/infectious-diseases/antimicrobial-drug-resistance/index_en.html). In addition, the EC recently announced the launch of 15 new research projects, some of which concern the development of new drugs, while another investigates stratified approaches for the treatment of cystic fibrosis patients (http://europa.eu/rapid/press-release_MEMO-13-996_en.htm).
- Complicated Intra-Abdominal Infections Observational European study (CIAO Study).

Expressions of interest should clearly outline the unique properties of the proposed plan of work and how potential interaction with these initiatives would be managed while avoiding the potential for duplication or overlap of activities.

THE OPEN CALL PROCESS FOR ADDITIONAL BENEFICIARIES TO PERFORM TASKS

- When open Calls from within the existing Consortium are required to engage additional beneficiaries (e.g., investigators, sites, laboratories, etc.), these will be handled by the Consortium with guidance from the IMI JU. The Consortium will propose procedures for implementing an open and competitive Call(s) in order to recruit investigators/sites for the conduct of clinical trials. The procedures will comply with the conditions established in the IMI model grant agreement and will be based on the following principles:

  The selection shall be based on openness, transparency, efficiency and equal treatment.

  Each open and competitive Call shall explicitly describe:

  - The activities to be carried out, the required capacities and the related dedicated budget;
  - The rules for participation (eligible entities);
  - The applicable evaluation, submission and selection procedures.

  Each open and competitive Call shall be subject to wide advertising and publication by the Consortium to ensure appropriate communication to any potential interested parties in Member States and associated countries. In order to achieve this, the Consortium shall publish the competitive call in at least one international journal and in three different national newspapers in three different Member States or Associated countries. It shall also be responsible for advertising the call widely using specific information support, particularly the IMI Internet site and Internet sites on the Seventh Framework Programme, the specialist press and brochures and through the national contact points set up by Member States and Associated countries. In addition, the publication and advertising of the Call shall conform to any instructions and guidance notes established by the IMI JU Executive Office. The Consortium shall inform the IMI JU Executive Office of the Call and its content at least 30 days prior to its expected date of publication.

  The competitive Call shall remain open for the submission of proposals by interested parties for a period of at least five weeks.

The proposals' evaluation shall be carried out by the Consortium:

- According to the criteria that governed the IMI JU's original evaluation and selection of the project. In case additional criteria are to be set up by the Consortium considering the specific features of the open and competitive Call, these shall receive prior approval by the IMI JU;
- With the assistance of at least two independent experts appointed by the Consortium on the basis of the criteria described in the 'IMI JU Rules for submission, evaluation and selection of Expressions of Interest and Full Project Proposals.' Experts shall be independent of any project's participant and any applicant to the open and competitive Call.

- The Consortium shall notify the IMI JU Executive Office of the proposed accession of a new beneficiary (ies) in accordance with Article II.35 of the IMI model grant agreement. At the same time, it will inform the IMI JU Executive Office of the means by which the competitive call was published and of the names and affiliation of the experts involved in the evaluation. The IMI JU Executive Office may object to the accession of any new beneficiary within 30 days of the receipt of the notification.
- Based on evaluation outcome, the Consortium will submit a report to IMI providing evidence that the principles of openness, transparency, efficiency, and equal treatment have been fulfilled. The costs incurred by the Consortium in relation to each open and competitive Call may be reimbursed or considered as in-kind contribution provided that the eligibility criteria laid down in the IMI grant agreement are fulfilled.

SPECIFIC APPROACH FOR ACCEPTING NON-EU CONTRIBUTION TO EFPIA IN-KIND CONTRIBUTION (SPECIAL CLAUSE 13B)

Given the current low level of drug development activity to combat antibiotic resistance, the fact that the majority of drug development activities are being conducted outside of the EU and the gravity of the health threat that antibiotic resistance offers, acceptance of non-EU EFPIA in-kind contributions as part of the EFPIA in-kind contribution has been agreed by the Founding Members under the following conditions:

For topics of interest to EU citizens that will benefit European academics and SMEs where there are few EFPIA research capacities in Europe while academic research is strong or substantially developed in Europe and, in particular, for research into rare diseases or

disease areas of high public interest where creation of a critical mass of research is needed:

> For these projects a global cap of 30% at programme level of the actual committed EFPIA in-kind contribution to research activities, with no limit per IMI collaborative research project, may apply when agreed at the time of the Call definition and confirmed at the time of the selection decision of full project proposals.

The benefit to Europe of implementing this Special Clause is:

- *For the patient and society as a whole*: Antibiotic resistance is an increasing threat to health across Europe and action is urgently required to support the development of new antibiotic agents. Without a joint and urgent action from public and private sectors, society will no longer have access to effective antibiotic agents to combat these resistant infections.
- *For public investigators and SMEs*: All IMI funding will be directed to investigators and SMEs located within the EU. Investigators will have a unique opportunity to gain funding to support the development of new and innovative approaches while at the same time gaining invaluable insight into the complexities of drug development as well as access to learning and experience from all partners involved in ND4BB. Academic partners will have the opportunity to build relationships with participating EFPIA companies and also those outside of ND4BB to strengthen their ability to identify partnering opportunities for further development of promising new drugs. It is anticipated that the opportunity to build a network of investigators through which academics and pharmaceutical and biotechnology companies can advance the pre-clinical and clinical development of new assets will attract future drug discovery efforts and future clinical trials to Europe. Investigators will also become part of the broader ND4BB research community through regular joint symposia and sharing of experiences through the ND4BB Information Centre.

  Having the opportunity for collaboration has already actively encouraged companies developing new antibiotic agents to focus on running clinical trials within the EU rather than outside of the EU where typically it is easier to recruit subjects with the appropriate resistant infections. This will bring revenue directly to hospitals, universities and SMEs through the ongoing studies as well as

establishing a network of European investigators with the expertise and resources required to participate in global trials.

- *For pharmaceutical and biotechnology companies developing antibiotic agents* : These companies will have the opportunity to work with leading experts in all fields required for successful drug discovery in order to tackle major challenges in drug discovery and development.

GENERAL PRINCIPLES FOR ALL STUDIES CONDUCTED UNDER ND4BB

STUDY MANAGEMENT

All clinical studies conducted in ND4BB will be conducted to Good Clinical Practice (GCP) standards to ensure that no process or data quality issues arise to jeopardize the outcome of the studies. In the case of the clinical trials, protocol compliance data quality and data integrity are essential to avoid the risk of a failed regulatory process. Noncompliance can severely jeopardise regulatory approval and pose ethical issues related to informed consent agreements with patients.

Due to the complexities of conducting a global clinical trial designed to support regulatory submissions, it is common practice of both industry-funded and FP7 projects that a clinical research organisation (CRO) is engaged to provide study management and to monitor the clinical sites to ensure compliance. While this may be the preferred approach, in some instances it may also be preferable for a SME/CRO in collaboration with the sponsoring company's internal operations groups to implement these clinical trials.

There are 3 possible scenarios for the inclusion of a CRO:

1) The applicant consortium includes the required level of study management and monitoring expertise and capability either internally or via a suitably capable partner CRO or similar organisation.

2) If the applicant consortium does not include the required level of study management and monitoring expertise and capability or if their proposed CRO is deemed during the EoI review to lack such capability and expertise, they should plan for an evaluation

process with agreement from IMI and the EFPIA partner to seek a suitably capable CRO to be subcontracted to fulfil the study management and monitoring requirement, in compliance with applicable rules and regulations. Direct financial contribution by the sponsoring EFPIA companies, if required, will supplement the CRO costs (up to 25%), incurred by public partners eligible for IMI funding ensuring that 100% of these costs will be reimbursed.

3) In the event that EFPIA are funding the costs incurred by a CRO in its entirety as part of their in kind contribution, then the CRO will be appointed directly by the sponsoring EFPIA companies according to normal internal procurement practices. The EFPIA companies must be able to demonstrate 'value for money' to satisfy external auditors, otherwise this cannot be counted as in kind contribution.

The criteria for the selection and identification of the CRO will be agreed upon between EFPIA and the selected consortium during the formation of the full project proposal and project negotiation phase in accordance with the applicable rules, with the intention of having the contract with the CRO in place as soon as the project agreements are completed. This CRO will be accountable for delivering the operation of the clinical trial, including monitoring of all investigational sites operating under Good Clinical Practice (GCP) standards. This CRO may be responsible for ensuring coordination across all clinical trial sites (i.e., those funded directly by the sponsoring EFPIA company as well as those engaging as part of the Applicant Consortium). This relationship will be governed through a specific Clinical Trial Agreement among the sites, Sponsor and CRO. Where CRO activities reside outside of the EU, this will be funded directly by the EFPIA Sponsor. In some clinical trials it may be possible that the EFPIA Sponsor may also recruit a CRO to manage non–EU based sites as part of a global study; in these situations an agreement between the EFPIA CRO and the consortium CRO will be established to ensure effective overall management of the trial. In all circumstances, only those hospital and healthcare institutions shown via site visits to be sufficiently compliant to be able to fulfil all aspects of the protocol to GCP standards will be permitted to recruit patients into the study.

MONITORING

Site Compliance

The EFPIA company that owns the asset will act as study trial Sponsor and as such will remain accountable for regulatory filings, pharmacovigilance, and all aspects of trial

conduct. If a CRO is used, it will be responsible for ensuring effective monitoring of all sites with respect to medical governance, data management, and GCP requirements.

Trial-related Decision Making

Standard decision-making processes will apply to progression of clinical trials and will be the responsibility of the Sponsor. As the sponsoring company is legally accountable for the safety of all patients on the trial all decisions regarding trial progression or termination due to emerging safety issues will remain the responsibility of the sponsoring company. In accordance with the requirements of the trial sponsor, the CRO will perform site inspections of investigator sites as needed to confirm the ability of the site to function up to GCP standards and to be capable of processing microbiology and serology specimens to laboratory certification requirements. Should a site fail to pass this inspection they would not be allowed to participate in the study, unless corrective measures can be taken by the site to address all critical insufficiencies.

Data Sharing in ND4BB

Data sharing is paramount to the success of ND4BB. The framework supporting this data sharing (i.e., the type of data to be shared and the access governing data sharing) will be established during the preparation of the full project proposal in line with IMI IP Policy and considering the overall approach agreed upon in the other ND4BB projects.

Clinical Trial Data

Disclosure of data from all ND4BB clinical trials supporting regulatory filings is subject to specific regulatory requirements with which EFPIA partners must comply. These regulations ensure that all data are presented and communicated in a responsible way by ensuring that efficacy data are presented with a balanced understanding/communication of the adverse event profile or other safety risks. Strict adherence to these regulations also ensures that data sharing activities will not be misrepresented as 'promotional activities,' as the conduct of such activities is prohibited prior to drug approval. While respecting these strict regulations, Sponsors of clinical trials conducted under ND4BB intend to disseminate results from trials conducted under the ND4BB programme as broadly as possible.

The goal of data sharing is to disseminate knowledge that is generally useful for others planning clinical trials. Examples of data sharing might include:

- Issues with specific inclusion criteria or endpoints

- Techniques for facilitating rapid enrolment of subjects at study sites
- Insights regarding pharmacodynamic markers/drivers of efficacy

Conversely, some data are very compound specific, and may have special handling and reporting requirements due to regulatory concerns. The most obvious such data are the safety and adverse event data for a particular product.

To address all of these concerns, ND4BB-related work will be shared in several ways. First, protocols and summary results from studies conducted under the ND4BB programme will be posted on internet registers, and clinical trial Sponsors will aim to publish results as journal manuscripts in searchable, peer-reviewed scientific literature, ensuring the accurate and balanced presentation of data. As such, for all clinical trials conducted under the ND4BB programme, Sponsors will ensure that:

- Protocols and informed consent documents clearly outline the intent to post a protocol summary on a publicly available protocol register and the clinical trial summary results on a publicly available results register, and to publish the results in searchable, peer-reviewed scientific literature.
- Primary publication of the study results, whether positive or negative, preferably as a journal manuscript (including primary and secondary efficacy endpoints and safety results and, when medically informative, exploratory analyses) will be mandatory. Publication of trial results will also be accompanied by public disclosure of the full study protocol (which may be redacted for proprietary content) on the Sponsor's Clinical Study Register.

In general, summary data from all clinical trials conducted under the ND4BB programme must be publicly posted within a reasonable period following study completion (typically considered the date of the last subject's last visit) or completion of the clinical study report. Once a clinical trial has been completed and the database locked for subsequent statistical analyses and reporting, data collected from study subjects at a specific investigator site can, at the Sponsor's discretion, be disclosed only to that specific investigator.

6. ND4BB TOPIC 6: EPIDEMIOLOGY RESEARCH AND DEVELOPMENT OF NOVEL SYSTEMIC ANTIBACTERIAL MOLECULES AGAINST HEALTHCARE-ASSOCIATED INFECTIONS DUE TO CLINICALLY CHALLENGING GRAM-NEGATIVE PATHOGENS

THE OVERALL OBJECTIVES OF TOPIC 6 ARE:

- To develop a coherent epidemiology strategy and organise pertinent expertise and available data sources in Europe and across ND4BB in support of public health and drug development priorities related to antimicrobials
- To describe the epidemiology of HAIs in Europe due to *Pseudomonas aeruginosa* and other Gram-negative pathogens to support the development of novel molecules and existing inhaled antibiotics against these infections.
- To estimate the frequency of serious *Pseudomonas aeruginosa* disease that would be averted by the development of successful interventions for its prevention or treatment and any resultant impact on the antimicrobial resistance of *P. aeruginosa.*
- To support the clinical development of BiS4αPa, a novel anti-pseudomonal monoclonal antibody for the prevention of serious disease caused by *P. aeruginosa*
- To describe the epidemiology of cUTIs (including pyelonephritis) caused by resistant Gram-negative pathogens, including *P. aeruginosa,* in Europe
- To support the clinical development of a novel resistance-breaking beta-lactam antibiotic, AIC499, in combination with a beta-lactamase-inhibitor (BLI) for the treatment of severe bacterial infections due to Gram-negative pathogens, including complicated intra-abdominal infections (cIAIs) and complicated urinary tract infections (cUTIs).
- To ensure coordination and alignment across all studies within Topic 6, a Topic 6 coordinating centre is being proposed (WP1), which will also ensure alignment with other Topics within the ND4BB programme.

THE STRUCTURE OF TOPIC 6 IS AS FOLLOWS:

Subtopic 6A:

WP1: ND4BB Topic 6 project management, collaboration oversight, and data dissemination

WP2: Development of capabilities in epidemiology

WP3: Epidemiology studies supporting development of anti-pseudomonal drugs

WP4: Clinical development of a novel bispecific IgG antibody, BiS4αPa, for the prevention of serious *Pseudomonas aeruginosa* disease

Subtopic 6B:

WP5: Epidemiology studies supporting development of drugs against Gram-negative organisms that cause cUTIs and cIAIs

WP6: Clinical development of a novel resistance-breaking beta-lactam antibiotic, AIC499, in combination with a beta-lactamase inhibitor to treat severe bacterial infections due to Gram-negative pathogens

THE OVERALL EXPECTED DELIVERABLES OF TOPIC 6 ARE:

- Europe-wide surveillance and epidemiological data relevant to the future use and development of novel products and treatment regimens.
- Successful Phase 1, Phase 2, and Phase 3 clinical trials demonstrating the pharmacology, safety, and efficacy of novel molecules against serious disease caused by *Pseudomonas aeruginosa* and other clinically relevant Gram-negative pathogens.

EFPIA PARTICIPANTS

AstraZeneca/MedImmune, AiCuris, GSK, Basilea, Sanofi, Novartis

INDICATIVE DURATION OF THE PROJECT

The indicative duration of this Topic will be 7 years; its duration may be less than 7 years depending on the study designs implemented. Current estimates for WP start dates and durations under Topic 6 are provided below.

INDICATIVE BUDGET OF THE PROJECT

The total indicative EFPIA in-kind contribution for ND4BB Topic 6 is up to EUR 91 607 905 The total IMI JU financial contribution for ND4BB Topic 6 will be a maximum of EUR 75 340 000.

- Subtopic 6A: WP1-WP3, WP4A-WP4D
  Total indicative budget: EUR 72 607 905 EFPIA / EUR 55 440 000 IMI JU
- Subtopic 6B: WP5, WP6A-WP6I
  Total indicative budget: EUR 19 000 000 EFPIA / EUR 19 900 000 IMI JU

PROPOSED PROJECT ARCHITECTURE

A summary diagram of the structure of Topic 6 as a part of the ND4BB programme is presented in Figure 2.

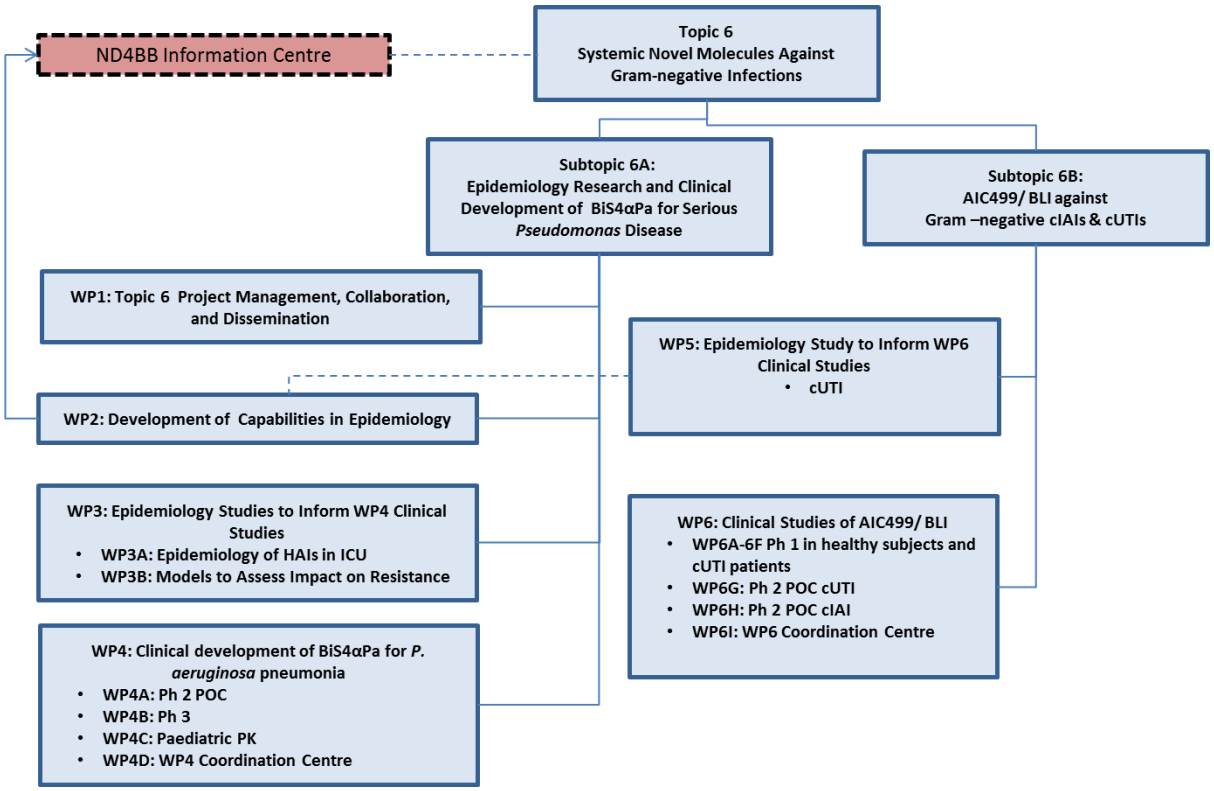


Figure 2 – Summary Diagram of ND4BB Topic 6

cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; HAI = healthcare-associated infection; ICU = intensive care unit; ND4BB = New Drugs for Bad Bugs; Ph = phase; PK = pharmacokinetics; POC = proof of concept; WP = work package

ALLOCATION OF FUNDING AND MILESTONE PROGRESSION DECISIONS FOR TOPIC 6

The success of drug discovery is uncertain; only a small percentage of those drug candidates entering clinical trials enter the marketplace.

Funding for the clinical studies described in WP4A, WP4B, and WP4C will therefore be allocated in a stepwise manner based on milestone review, including acceptance of milestone achievement by the EFPIA sponsor, the consortium and IMI. Results from the epidemiology study proposed in WP3A and any other epidemiologic data available at that point from within and outside ND4BB, the safety and PK data from the Phase 1 study that will be conducted in the United States of America by AstraZeneca/MedImmune, and guidance from regulatory agencies are all expected to impact plans for the conduct of WP4A, WP4B and WP4C studies.

The allocated funding for WP6, may be subject to changes on the basis of the results of the previous AiCuris single-dose escalation study as well as after regulatory input, expected for Q1-Q2 2015. Funding for the clinical studies described in WP6A-6F and WP6G-6H (Phase 2 Proof-of-Concept) will therefore be allocated in a stepwise manner based on milestones review, including acceptance of milestone achievement by the EFPIA sponsor and discussed within the Consortium and IMI.

In particular, the completion, review, and positive outcome of the multiple-dose escalation trial described in WP6A should be a prerequisite for the initiation of the study in renally impaired patients described in WP6F, while evaluation of the completed WP6B drug-drug interaction (DDI) study will be necessary for initiation of the subsequent DDI study described in WP6E. The studies described in WP6G-6H are planned to start only after the conclusion of WP5 as well as achievement of a positive outcome of WP6A, WP6B, WP6E and WP6F.

If required, open Calls as described in the overall introduction will be launched from within the Consortium to identify additional investigators and clinical sites to ensure the successful delivery of the clinical studies under WP4 and WP6. The budget for the additional partners to be recruited through an open Call will be taken from the overall budget agreed upon at the time of the Grant Agreement signature.

SUBTOPIC 6A: EPIDEMIOLOGY RESEARCH AND CLINICAL DEVELOPMENT OF A NOVEL BISPECIFIC IGG ANTIBODY, BIS4αPA, FOR THE PREVENTION OF SERIOUS *PSEUDOMONAS AERUGINOSA* DISEASE

THE OVERALL OBJECTIVES OF SUBTOPIC 6A ARE:

- To map sources of epidemiology data both within and outside the ND4BB programme and to define ways of optimal utilisation of available data to inform clinical study designs for this project as well as future efforts;
- To assess risk factors for and cost of healthcare-associated infections attributed to *P. aeruginosa* among intensive care unit (ICU) patients in Europe to identify the target population for the development of BiS4αPa for the prevention of serious disease caused by *P. aeruginosa*;
- To assess the potential impact of antimicrobial interventions on *P. aeruginosa*-attributed disease burden among ICU patients;
- To characterise clinically relevant strains of *P. aeruginosa* to determine the prevalence of expression of the BiS4αPa targets Psl and PcrV and to create a bank of organisms linked to patient-specific outcomes for future use;
- To assess the safety, efficacy, and pharmacokinetics (PK) of BiS4αPa and antidrug antibodies developed in response to BiS4αPa treatment in a Phase 2 proof-of-concept study in an enriched population;
- To demonstrate the efficacy of BiS4αPa against endpoints acceptable to the regulatory agencies, including European Medicines Agency (EMA) as well as its safety in a Phase 3 study conducted in the target population for launch;
- To assess the safety and PK of BiS4αPa in paediatric subjects.

THE OVERALL EXPECTED DELIVERABLES OF SUBTOPIC 6A ARE:

- Europe-wide surveillance and epidemiological data relevant to the future use and development of novel antibiotics
- Phase 2 and Phase 3 clinical studies demonstrating the pharmacology, safety, and efficacy of BiS4αPa against serious disease caused by *P. aeruginosa*

INDICATIVE BUDGET

The indicative EFPIA in-kind contribution is up to EUR 72 607 905.

The IMI JU financial contribution will be a maximum of 55 440 000
The total budget is to be divided along the following WPs:

Epidemiologic research

- WP1: ND4BB Topic 6 project management, collaboration oversight, and data dissemination
- WP2: Development of programme capabilities in epidemiology
- WP3: Epidemiology studies supporting the development of anti-pseudomonal drugs
    - WP3A: Analysis of a prospective epidemiologic study
    - WP3B: Mathematical modeling and analysis

WP4 Clinical development of a novel bispecific IgG1 antibody, BiS4αPa, for the prevention of serious *Pseudomonas aeruginosa* disease

- WP4A: Phase 2 study in patients at risk for *P. aeruginosa* ventilator associated pneumonia (VAP)
- WP4B: Phase 3 study in intensive care unit (ICU) patients at risk for *P. aeruginosa* pneumonia
- WP4C: Paediatric study
- WP4D: Clinical coordinating centre

The Applicant Consortium should apply with EoIs that address all WPs in Subtopic 6A. An application may include suggestions for biomarkers relevant to study endpoints. Approximately €3M is available for biomarker research for each of WP3A, WP4A, and WP4B and is included in the indicative budget figures provided above. Applications for biomarker research must align with the proposed endpoints for the studies, must not deter from the successful conduct of the programme, and should aim to inform the clinical development pathway for BiS4αPa.

OVERVIEW OF THE DEVELOPMENT OF BIS4αPA

The limitations of currently available antibiotics in treating drug-sensitive infections and the increasingly troublesome effects of infections caused by drug resistant organisms have led to the investigation of anti-bacterial strategies based on modern monoclonal antibody technologies. Monoclonal antibodies (mAbs) do not interact with the same bacterial targets as do antibiotics; therefore, they may complement antibiotics in the management of difficult-to-treat infections. In addition, mAbs have a relatively long half-life and, because they target bacterial (non-human) antigens, are anticipated to have an

acceptable safety profile. Monoclonal antibodies also would not be expected to contribute to antibiotic resistance or to the deleterious microbiome effects that can support the development of pseudomembranous colitis.

Monoclonal antibodies to both the Psl exopolysaccharide (DiGiandomenico A et al. J Exp Med 2012. 209:1273-87) and to the type 3 secretion system (T3SS) component PcrV (Warrener et al, Abstract F-1529 ICAAC 2012, San Francisco, CA) have recently been identified. These mAbs individually mediate potent serotype-independent protection in multiple *P. aeruginosa* infection models. PcrV is a component of the bacterium's T3SS and is responsible for the injection of multiple cytotoxic virulence factors into host cells. Importantly, studies of *P. aeruginosa* T3SS gene expression in clinical isolates reveal a correlation between exotoxin expression and transport and increased disease severity and poor clinical outcomes (El-Solh et al., 2012. Crit Care Med 40:1157-1163; El Solh et al., 2008. Am J Respir Crit Care Med 178:513-9; Roy-Burman et al., 2001. J Infect Dis 183:1767-74). Psl is an abundant serotype-independent exopolysaccharide implicated in initial colonization, establishment of persistent biofilm communities, and immune evasion (Jackson et al., 2004. J. Bacteriol. 186:4466-4475; Mishra et al., 2009. Cell Microbiol. 14:95-106).

Given the complementary roles that Psl and T3SS expression play in the establishment and persistence of *P. aeruginosa* infections (Mikkelsen et al., 2011. Environ. Microbiol. 13:1666-1681; Howell et al., 2013. MBio. 4:e00032-00013), it has been determined that a combination of the anti-Psl and anti-PcrV mAbs as a single drug candidate could enhance strain and disease coverage against *P. aeruginosa*. It was shown that combining anti-Psl and anti-PcrV mAb specificities into a single novel drug candidate, BiS4αPa, results in a mAb with activity in animal models that is superior to that of either monospecific mAb alone or to a mixture of parent progenitor mAbs (DiGiandomenico et al. Abstract B-1734 ICAAC 2012, San Francisco, CA).

BiS4αPa, a bivalent, bispecific IgG1 mAb, is being developed for the prevention of serious disease caused by *P. aeruginosa*. BiSα4Pa targets two important *P. aeruginosa* pathogenic components, Psl and PcrV. In the configuration shown in Figure 3, the anti-Psl binding unit is genetically inserted into the upper hinge region of the anti-PcrV mAb coding scaffold.

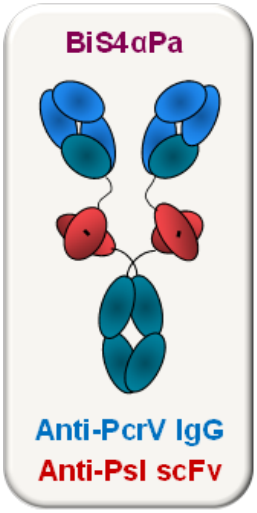


Figure 3 – Graphic Depiction of BiS4αPa

BiS4αPa provides 3 distinct mechanisms of action: the anti-PcrV component mediates potent inhibition of *P. aeruginosa* cytotoxicity, and the anti-Psl component mediates potent opsonophagocytic killing and also inhibits the attachment of *P. aeruginosa* to human epithelial cells. This multimechanistic approach enhances strain (>98%) and disease coverage, is expected to reduce the likelihood of immune escape, and permits the clinical development of a single multifunctional molecule.

BiS4αPa was first confirmed to mediate these potential protective activities *in vitro* at potency levels comparable or superior to those of the parent molecules. Interestingly, synergistic protective *in vivo* activity was observed when the anti-PcrV and anti-Psl activities were combined in either a mixture of parent antibodies or in the single molecule BiS4αPa configuration. However, the *in vivo* protective activity of BiS4αPa has been shown to be significantly superior to that of the antibody combination in multiple murine infection models with different strain types in both prophylactic and treatment modalities. The activity of BiS4αPa has been assessed in pneumonia (Figure 4), bacteraemia, and thermal injury *P. aeruginosa* murine infection models. In addition, BiS4αPa has been shown to be highly effective in a *P. aeruginosa* immunocompromised (neutropenic) pneumonia model and is capable of synergizing with multiple antibiotic classes (ICAAC 2013 and unpublished data). The pharmacokinetics, bioavailability, and stability of the BiS4αPa candidate molecule are comparable to that of a "normal" human IgG, and translational animal model and pharmacokinetics studies in mice and non-human primates indicate that the predicted effective human dose range for the prevention of *P. aeruginosa* pneumonia is readily achievable in the clinic.

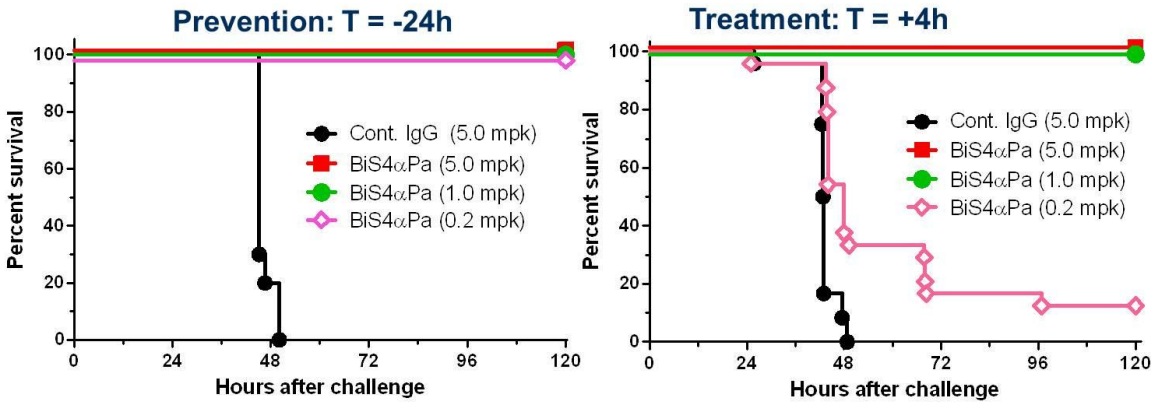


Figure 4 – Protection or treatment in the *P. aeruginosa* murine pneumonia model

BiS4αPa at the indicated dose was delivered 24 hours prior to or 4 hours post infection with a challenge dose of 5 times the 100% lethal dose of *P. aeruginosa* strain 6077.

mpk = milligrams per kilogram; IgG = immunoglobulin control; T = time of administration of antibody relative to challenge dose; h = hours

PROPOSED ARCHITECTURE FOR SUBTOPIC 6A

WP1: ND4BB TOPIC 6 PROJECT MANAGEMENT, COLLABORATION OVERSIGHT, AND DATA DISSEMINATION

The main purpose of this work package will be:

1) To ensure effective programme management across Topic 6, including annual scientific and financial reporting, project planning, and managing the process for open Calls;
2) To contribute to the overall scientific coordination of Topic 6, including programme governance, and to coordinate the support provided by the coordinating centres for WP4 (WP4D) and WP6 (WP6I).

A dedicated team will collaborate with members of other teams to ensure effective communication and collaboration among projects funded under the ND4BB programme. The activities of this team will include:

- Development of standard communication tools for all projects funded under the AMR research area/ND4BB programme; e.g., standard templates, externally facing website, etc.;
- A strategy for the dissemination of ND4BB-related communications to the broader scientific community that is coherent and aligned across all projects;

- Provision for ensuring that data from all projects are deposited into the ND4BB Information Centre in accordance with the ND4BB framework.

A similar work package is part of all projects launched under the ND4BB programme to ensure a close collaboration between all ND4BB projects.

Optimal alignment of the objectives of studies carried out in IMI projects with the needs and challenges encountered by patients is an important point on IMI's overall agenda. Therefore, this work package should also make sure to fully exploit options for interactions and collaboration with stakeholders.

EFPIA Partner Contribution:

EFPIA Partner Contributions include:

- Organizational support: Project/Alliance Management personnel, meeting facilities, communication expertise, and arrangements
- Provision of workshops/seminars/Q&A sessions
- Providing training and oversight to ensure clinical and laboratory sites remain "audit ready."

EPIDEMIOLOGIC RESEARCH

WP2: DEVELOPMENT OF CAPABILITIES IN EPIDEMIOLOGY

The overarching goal of WP2 is to develop a coherent epidemiology strategy and organise pertinent expertise and available data sources in Europe and across ND4BB in support of public health and drug development priorities related to antimicrobials. There are many efforts currently underway to describe different aspects of the epidemiology of serious bacterial infections within Europe, including initiatives being funded by the European Commission. Public health agencies (e.g., ECDC) conduct surveillance programmes designed to inform national or EU-wide public health decisions; these programmes are wide in geographic scope and remain feasible by collecting a limited amount of patient and pathogen information. Pharmaceutical companies conduct epidemiology studies to directly support subsequent clinical trials of proprietary products under development; as such, these studies tend to collect more detailed data, but do so within a limited geographic scope and with potential issues regarding external validity. This proposed work package will aim to create a mechanism for the public health and industry perspectives to collaborate and, consequently, to maximise the value of existing and future epidemiology efforts in Europe.

The proposed approach is two-pronged: (1) coordination and data sharing across ND4BB epidemiology studies in order to prevent duplication of activities and ensure efficient use of resources; and, (2) collaboration with external public stakeholders to enrich the collective scientific knowledge and to align research strategies designed to address and inform pressing and ever-evolving public health priorities related to antimicrobial agents.

A dedicated WP2 team will:

- Pursue coordination with regional and/or governmental public health authorities (e.g., ECDC) regarding epidemiology efforts.
- Identify and catalogue ongoing epidemiologic research studies or surveillance efforts that may be of use to inform research questions of interest to current and potential future ND4BB and public partners
- Establish a network of individuals from academia, public health agencies, research/health foundations, and industry who can collectively provide strategic direction and scientific input to current and future epidemiologic studies.
- Investigate approaches that would allow for the proposed epidemiology capabilities to become available to the scientific community at large
- Collaborate with all ND4BB projects that have work packages related to epidemiologic prospective or retrospective studies or analyses to create a framework for observational data sharing within the ND4BB programme in order to:
    - Receive, store, and analyse study data from these relevant ND4BB work packages; considerations will include legal, IP, ethics, and confidentiality issues.
    - Ensure that data from all projects are deposited in the ND4BB Information Centre in accordance to the ND4BB framework and made available to all ND4BB partners.
- Receive, store, and analyse study data from external data sources, where available; considerations will include legal, IP, ethics, and confidentiality issues.
- Ensure a robust dissemination plan, which would be aligned with the overall ND4BB dissemination strategy, targeting the scientific community and public stakeholders.
- Conduct bi-annual meetings among all public and EFPIA partners to facilitate collaboration and scientific exchange.
- Propose a model that will make this effort sustainable beyond the duration of the current project, including the elaboration of a plan that will allow for inclusion of future epidemiologic analyses from ND4BB projects and external sources.

EFPIA PARTNER CONTRIBUTION:

- Expertise in epidemiologic methods, infectious disease surveillance, drug development
- Organizational support: Project/Alliance Management personnel, meeting facilities, communication expertise and arrangements

WP3A: ANALYSIS OF DATA FROM A PROSPECTIVE COHORT STUDY OF HEALTHCARE-ASSOCIATED INFECTIONS (HAIS) ATTRIBUTED TO *P. AERUGINOSA* AMONG INTENSIVE CARE UNIT (ICU) PATIENTS IN EUROPE

Rationale

Healthcare-associated infections cause considerable morbidity and mortality among hospitalised patients. Pneumonia caused by P. *aeruginosa* occurring in patients admitted to ICUs is an especially important contributor to this burden and to healthcare costs. The epidemiology of Pseudomonas ICU pneumonia in Europe has not been fully described, in part due to variation in the case definitions for ICU pneumonia and surveillance systems utilised by Member States in Europe. Efforts to standardise assessments of disease measures in hospitals across different countries are hampered by temporal and geographic variation in disease risk.

The overarching goal of WP3A is to systematically assess the impact of host- and pathogen-related factors on the incidence of ICU pneumonia caused by *P. aeruginosa* and other organisms in Europe and to identify the patient subgroups that bear a disproportionate disease burden in order to optimise patient selection for clinical trials.

No new study subjects will be enrolled in WP3A; instead, the work package aims to analyse existing prospectively-collected patient data with linked specimens, which will be tested for biomarkers to address P. aeruginosa-specific objectives. The source of these data will include the prospective study in Topic 1 WP6A conducted in the project COMBACTE, that are specific to addressing the proposed objectives of Topic 6 WP3A (see below under 'population' and 'details summary' for further information on the study Topic 1 WP6). Additional data sources in similar patient and disease settings may be proposed by the Applicants and will be considered for inclusion, provided these data are deemed appropriate to support the objectives of WP3A, WP4A, and WP4B. Specific agreements should be reached with data owners to ensure the most adequate access and use considering existing confidentiality and IP obligations.

Objectives

The objectives of this proposed analysis are:

1) To estimate the incidence of ICU pneumonia, including ventilator-associated pneumonia (VAP), attributed to *P. aeruginosa*
2) To ascertain factors (e.g., patient demographics, co-morbidities, colonization status, biomarkers) independently associated with ICU pneumonia attributed to *P. aeruginosa*
3) To describe antimicrobial susceptibility patterns and the prevalence of antigen expression and virulence factor profiles among clinical *P. aeruginosa* isolates from ICU patients with serious disease, including pneumonia
4) To explore the association of host biomarkers (e.g., pre-existing antibodies against *P. aeruginosa* virulence factors) with ICU infections, disease severity, and outcomes
5) to describe incremental cost and resource utilisation attributed to *P. aeruginosa* among patients in the ICU
6) To compare participating study sites and sites participating in routine HAI surveillance (e.g., ECDC HAI-Net or other external data sources) to further inform external validity of results.

Population

This study aims to analyse the accessible data that are collected from patients enrolled into a prospective cohort study conducted as part of Topic 1 WP6A in COMBACTE. Eligible patients will be those admitted to participating ICUs and who, upon admission, do not show signs or symptoms of an acute bacterial infection and are expected to stay in the ICU for at least 2 days. Only patients with appropriate consent will be eligible for inclusion in this study.

Details Summary

WP3A will not engage in patient recruitment or specimen collection. Subject to agreement(s) with the data owner(s), data from patients enrolled into a prospective cohort study under COMBACTE Topic 1 WP6A (the "source study") will be analysed and patients' stored specimens tested to address WP3A objectives. The primary outcome for this analysis is ICU pneumonia, including ventilator-associated pneumonia (VAP), attributed to *P. aeruginosa* infection**.**

Briefly, the source study will be a prospective cohort study nested within routine prospective surveillance among ICU patients in 6-12 European countries. Routine

surveillance data (e.g., demographic, clinical, and outcome data) will be captured in participating ICUs from a minimum of 5,000 ICU patients over the period of 1 year ("surveillance population"). During that 1-year period, a subset of the surveillance population of approximately 2,000 ICU patients will be consented and enrolled into a prospective cohort study ("cohort population"). Cohort study subjects will provide demographic and clinical data, as well as specimens for biomarker and colonization testing, at enrollment. Active follow-up, including post-discharge surveillance, of up to 3 months will ensure identification of bacterial infections. Enrolled subjects will comprise the study population, and analyses of their data will address all study objectives. A comparison of the distribution of certain of these factors among the cohort and the surveillance population will inform the generalisability of inferences drawn from the study population; such comparison will be done using de-identified, surveillance data from the surveillance population.

Additional data sources in similar patient and disease settings may be proposed by the Applicants, provided these support the specific objectives of WP3A, WP4A, and WP4B.

Estimated Study Start: 1Q2015
Estimated Study Duration: 36 months
Interim Analysis: Anticipated 3Q2015
Estimated Study Close-out and Report Generation: 4Q2017

The ND4BB Topic 6 Consortium is expected to collaborate with the COMBACTE consortium, which will be conducting the source study, in order to gain access to patient study data and specimens for further analysis. Furthermore, the Applicant Consortium should demonstrate its ability to consult with public health agencies (e.g., the European Centre for Disease Prevention and Control [ECDC]) and to utilise existing data (e.g., other observational study data, ECDC data/reports) to inform WP3A analyses and objectives.

EFPIA Contribution:

- Study implementation-related expertise (infectious disease epidemiology and surveillance, translational research, clinical research, project management, data management, and biostatistics). Novel immunologic biomarker assays
- Direct financial contribution by the sponsoring EFPIA company to supplement the study costs (up to 25%) incurred by public partners ensuring that 100% of these costs will be reimbursed

WP3B: IMPACT OF DIFFERENT INTERVENTIONS ON *P. AERUGINOSA*-ATTRIBUTED DISEASE BURDEN AMONG PATIENTS IN THE ICU

Study Rationale

Patients receiving care in ICUs are at high risk for HAIs, which result in adverse patient outcomes and contribute to high healthcare costs. The emergence of antimicrobial-resistant pathogens in this setting further complicates care and impacts ICU patients' prognoses.

The approach to the prevention of HAIs caused by *P. aeruginosa* in the ICU that is proposed in WP4 is novel not only in that it focuses on prevention but also because of the inherent limited spectrum of mAbs. The use of BiS4αPa is a pathogen-specific approach. There is a paucity of conceptual frameworks and supportive data that attempt to estimate the impact of interventions, pathogen-specific interventions in particular, on the development of antimicrobial resistance based on both patient- and contextual-level factors.

A better understanding of the inter-relationships between pathogen, patient, and environment may allow for public health and clinical decisions to arrive at the most impactful single or combination interventions.

STUDY OBJECTIVES

The objectives of the proposed study are:

1) To develop mathematical model(s) to describe healthcare-associated pneumonia in the ICU setting including those that:
    a. Estimate the burden of disease attributed to *P. aeruginosa* and the development of antimicrobial resistance by *P. aeruginosa* among ICU patients.
    b. Estimate the impact of different interventions, e.g., BiS4αPa, on the burden of disease attributed to *P. aeruginosa* and on the development of antimicrobial resistance by *P. aeruginosa* among ICU patients.

Study Preparation: 1Q 2015-4Q2015
Estimated Start: 1Q2016
Estimated Study Duration: 36 months
Study Close-out and Report Generation: 4Q2018

Study Details Summary

This study will attempt to develop new and/or refine existing theoretical constructs to describe the epidemiology of healthcare-associated pneumonia among ICU patients in Europe. It is expected that the impact of P. aeruginosa-specific interventions will be examined in the context of other pathogen-attributable ICU HAI interventions (e.g., *S. aureus* interventions) and of other pathogen-specific and broad-spectrum interventions. It is important to take into account antimicrobial use, since use patterns may define environmental pressure on the pathogen which, in turn, can contribute to the development of resistance. A wide variety of data sources should be utilised to inform model assumptions and inputs, including the medical literature, HAI surveillance data, and results from ND4BB clinical and observational studies. Close collaboration among academic, government, and EFPIA expertise and data is encouraged and would be instrumental for the successful conduct of WP4.

EFPIA Contribution:

- Expertise in infectious disease epidemiology and biostatistics
- Direct financial contribution by the sponsoring EFPIA company to supplement the study costs (up to 25%) incurred by public partners ensuring that 100% of these costs will be reimbursed

WP4: CLINICAL DEVELOPMENT OF A NOVEL BISPECIFIC ANTIBODY, BIS4αPA, FOR THE PREVENTION OF SERIOUS *PSEUDOMONAS AERUGINOSA* DISEASE

Clinical trial designs for the studies described in WP4 will go through input from EMA/FDA prior to their initiation.

WP4A: PHASE 2 PROOF-OF-CONCEPT TRIAL OF BIS4αPA SAFETY, EFFICACY, PHARMACOKINETICS, PHARMACODYNAMICS, AND ANTIDRUG ANTIBODIES

For this Phase 2 study of the prevention of serious disease caused by *P. aeruginosa*, approximately 492 subjects will be enrolled at approximately 120 sites within Europe and countries that are eligible for IMI JU funding. Sample size and study specifics will be informed by on-going analyses of available epidemiology data (e.g., Topic 6A WP3, etc.) and results from a Phase 1 safety and a PK study.

Study Objectives

The objectives of the proposed study are:

1) To evaluate the effect of BiS4αPa on the incidence of *P. aeruginosa* pneumonia in mechanically ventilated patients

2) To evaluate the safety and tolerability of BiS4αPa administered to mechanically ventilated ICU patients
3) To evaluate the PK of BiS4αPa in serum and endothelial lining fluid (ELF) in mechanically ventilated patients
4) To determine serum antidrug antibody (ADA) responses to BiS4αPa
5) To compare measures of *P aeruginosa* disease severity in patients with *P. aeruginosa* pneumonia by study arm
6) To evaluate biomarkers associated with *P. aeruginosa* disease severity and outcome
7) To evaluate the impact of BiS4αPa on healthcare resource utilization in mechanically ventilated patients at risk for *P. aeruginosa* pneumonia for pharmacoeconomic analysis

Study Population

The proposed study population consists of subjects in the ICU who are predicted to be at increased risk of developing serious disease caused by *P. aeruginosa*. The study population at high risk has yet to be defined, but it is likely to include subjects who have been mechanically ventilated for a given number of days and might include only subjects in whom *P. aeruginosa* has been identified in respiratory secretions. Applicants are expected to propose a population at ≥ 20% risk of developing *P. aeruginosa* pneumonia while in the ICU.

Study Design

The proposed study is a Phase 2, randomised, placebo-controlled, double-blind, dose-ranging design, with a superiority endpoint.

Key efficacy endpoint: Reduction in the incidence of *P. aeruginosa* ventilator-associated pneumonia (VAP)

Key safety endpoints: Adverse events and serious adverse events

Estimated Start: January 2015

Estimated Study Duration: 40 months

Study Preparation: 1Q2015

Site Recruitment: 2Q2016-3Q2017

Study Close-out and Report Generation: 2Q2018

EFPIA Contribution:

- Study implementation-related expertise (clinical and clinical operations, regulatory support, translational science, pharmacokinetic analysis, health outcomes and

pharmacoeconomics data analysis, project management, data management, biostatistics, pharmacovigilance).

- Novel immunologic biomarker assays
- Investigational products
- Direct financial contribution by the sponsoring EFPIA company to supplement the study costs (up to 25%) incurred by public partners ensuring that 100% of these costs will be reimbursed.

WP4B: PHASE 3 TRIAL OF BIS4αPA EFFICACY AND SAFETY

For this Phase 3 study of the prevention of serious disease caused by *P. aeruginosa,* approximately 980 subjects will be enrolled at approximately 200 sites, with approximately 50% of the sites located within Europe and eligible for IMI JU funding, and approximately 50% of the sites located outside of Europe with 100% funding supplied directly by AstraZeneca/MedImmune. Sample size and study specifics will be updated based on data from the Phase 2 study as well as epidemiologic data available from the WP3 study and regulatory guidance.

Study Objectives

The objectives of the proposed study are:

1) To evaluate the effect of BiS4αPa on the incidence of serious disease caused by *P. aeruginosa* in patients in the ICU
2) To evaluate the safety of BiS4αPa administered to patients in the ICU at high risk of serious disease caused by *P. aeruginosa*
3) To evaluate the PK of BiS4αPa in a large population
4) To determine serum antidrug antibody (ADA) responses to BiS4αPa in a large population
5) To compare measures of *P. aeruginosa* disease severity in patients with *P. aeruginosa* pneumonia by study arm
6) To evaluate biomarkers associated with *P. aeruginosa* disease severity and outcome
7) To evaluate the impact of BiS4αPa on healthcare resource utilisation in mechanically ventilated patients at risk for *P. aeruginosa* pneumonia for pharmacoeconomic analysis

Study Population

The proposed study population consists of subjects admitted to the ICU who are at high risk of developing serious disease caused by *P. aeruginosa*. The population at high risk

will be defined based on data from the Phase 2 study (WP4A) as well as data from the epidemiology study (WP3) and regulatory guidance.

Study Design

The proposed study is a pivotal, randomized, placebo-controlled, double-blind design, with a superiority endpoint.

Key efficacy endpoint: Reduction in the incidence of serious disease caused by *P. aeruginosa*

Key safety endpoints: Serious adverse events and adverse events

Estimated Start: 2Q 2017
Estimated Study Duration: 37 months
Study Preparation: 2Q 2017
Site Recruitment: 2Q2018-3Q2019
Study Close-out and Report Generation: 2Q2020

EFPIA Contribution:

- Study implementation-related expertise (clinical and clinical operations, regulatory support, translational science, pharmacokinetic analysis, health outcomes and pharmacoeconomics data analysis, project management, data management, biostatistics, pharmacovigilance).
- Novel immunologic biomarker assays
- Investigational products
- Fifty percent of study enrolment to occur outside EU; 100% of the relevant costs to be covered by the Sponsor
- Direct financial contribution by the sponsoring EFPIA company to supplement the study costs (up to 25%), including CRO subcontracting if any, incurred by public partners ensuring that 100% of these costs will be reimbursed.

WP4C: PHASE 1 TRIAL TO ASSESS THE SAFETY AND PK OF BIS4αPA IN PAEDIATRIC SUBJECTS AT HIGH RISK FOR DISEASE CAUSED BY *P. AERUGINOSA*

An estimated 40 subjects will be enrolled at approximately 6 sites within Europe that are eligible for IMI JU funding. Sample size and study specifics will be updated based on

results of on data from studies in adults as well as to the agreed upon EU Paediatric Investigation Plan (PIP).[7]

Study Objectives

The objectives of the proposed study are:

1) To evaluate the safety and tolerability of BiS4αPa administered to neonates, infants, and children at risk for serious disease caused by *P. aeruginosa*
2) To evaluate the PK of BiS4αPa in serum in neonates, infants, and children at risk for serious disease caused by *P. aeruginosa*
3) To determine serum antidrug antibody (ADA) responses to BiS4αPa in a paediatric population

Study Population

The proposed study population consists of paediatric patients at high risk for serious pseudomonal disease from multiple age groups.

Study Design

The proposed study is a Phase 1, open-label, single-dose study.
Key safety endpoints: Serious adverse events and adverse events

Estimated Start: 2Q2017
Estimated Study Duration: 43 months
Study Preparation: 2Q2017
Site Recruitment: 2Q2018-2Q2020
Study Close-out and Report Generation: 1Q2021

EFPIA contribution:

- Study implementation-related expertise (clinical and clinical operations, regulatory support, translational science, pharmacokinetic analysis, project management, data management, biostatistics, pharmacovigilance).
- Investigational products

[7] EU Paediatric Regulation:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000023.jsp&mid=WC0b01ac05800240cd

- Direct financial contribution by the sponsoring EFPIA company to supplement the study costs (up to 25%) incurred by public partners ensuring that 100% of these costs will be reimbursed.

WP4D: WP4 COORDINATING CENTRE

The overall purpose of WP4D is:

1) To establish a coordinating centre to provide programme management, project coordination, and strategic alignment across all clinical studies within the proposed BiS4αPa clinical development program and with the WP1
2) To contribute to the overall scientific coordination of Topic 6, including programme management and governance;
3) To ensure adequate training and qualifications of investigators within the Consortium conducting WP4A-4C.
4) To arrange meetings, including at least one face-to-face training prior to initiation of the project, with additional meetings as appropriate during the course of the work including investigator meetings prior to the opening of each clinical trial
5) To ensure coordination of clinical trial operations and management, including data management, as appropriate
6) To develop a system of mentoring and coordination within the Consortium to facilitate information-sharing, and training among the Consortium investigators

EFPIA Partner Contribution:

- Organizational support: Project/Alliance Management personnel, meeting facilities, communication expertise and arrangements
- Provision of workshops/seminars/Q&A sessions
- Providing training and oversight to Consortium laboratories (with emphasis on those serving as central laboratories) to ensure compliance with Good Laboratory Practice standards
- Providing training and oversight to ensure clinical and laboratory sites remain "audit ready."
- Sharing of learning from clinical networks and the conduct of clinical trials in emerging economies
- Information/expertise in clinical trial design, epidemiologic methods, infectious disease surveillance, regulatory requirements, quality assurance monitoring, clinical microbiology requirements and data quality standards.

SUBTOPIC 6B: CLINICAL DEVELOPMENT OF A NOVEL RESISTANCE-BREAKING BETA-LACTAM ANTIBIOTIC, AIC499, IN COMBINATION WITH A BETA-LACTAMASE INHIBITOR (BLI) AGAINST SEVERE BACTERIAL INFECTIONS DUE TO GRAM-NEGATIVE PATHOGENS

THE OVERALL OBJECTIVES OF SUBTOPIC 6B ARE:

- To provide recent information about the clinical management and outcomes of patients with cUTI (including pyelonephritis) in Europe with known or suspected increased resistance rates in clinically-relevant Gram-negative pathogens, including *P. aeruginosa*
- To investigate the safety, tolerability and PK after multiple increasing doses of AIC499
- To explore the microbiological efficacy of AIC499 and clavulanic acid or a novel beta-lactamase inhibitor (BLI) after multiple dosing in patients with cUTI
- To determine the influence of AIC499 on the PK and safety of the BLI and vice versa
- To evaluate the mass balance of AIC499
- To identify AIC499 metabolites in plasma and excreta (urine, faeces) and the routes of elimination of AIC499 in humans
- To investigate the pro-arrhythmic risk by looking at the effects of AIC499 (alone or in combination with BLI) on the QT/QTcF interval
- To investigate the influence of AIC499 (alone or in combination with BLI) on the PK of other drugs and/or vice versa
- To investigate the effect of renal impairment on the PK of AIC499 (alone or in combination with BLI)
- To assess the safety, tolerability, efficacy and pharmacokinetics/ pharmacodynamics of AIC499/BLI in cUTI patients
- To investigate the safety, tolerability, efficacy and pharmacokinetics/ pharmacodynamics of AIC499/BLI combined with metronidazole in cIAI patients
- To assess the efficacy of AIC499/BLI in cases caused by multidrug resistant Gram-negative pathogens in cUTI and cIAI

THE OVERALL EXPECTED DELIVERABLES OF SUBTOPIC 6B ARE:

- Retrospective observational study to assess the clinical management and outcomes of hospitalised patients with cUTI in the EU
- To assess the safety, tolerability, PK, and efficacy of AIC499 (and BLI) in a Phase 1 trial and in two Phase 2 proof-of-concept trials

INDICATIVE BUDGET

The indicative EFPIA in-kind contribution is up to EUR 19 000 000
The IMI JU financial contribution will be a maximum of EUR 19 900 000

The total budget is to be divided along the following WPs:

- WP5: Epidemiological study on cUTI
- WP6A: Multiple dose escalation study
- WP6B: Drug-drug interaction study AIC499 with BLI
- WP6C: Mass balance/metabolite identification study
- WP6D: TQT prolongation study
- WP6E: Drug-drug interaction study AIC499/BLI with other drugs
- WP6F: Renal impairment study
- WP6G: Phase 2 PoC trial in cUTI
- WP6H: Phase 2 PoC trial in cIAI
- WP6I: WP6B coordinating centre

OVERVIEW OF THE DEVELOPMENT OF AIC499/BLI

The European Centre for Disease Prevention and Control (ECDC) antimicrobial resistance surveillance reported for 2011 a general increase of antimicrobial resistance in the European Gram-negative pathogens under surveillance (*Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*). Over the last few years, resistance rates for 3rd-generation cephalosporins steadily increased for invasive *E. coli* and *K. pneumoniae* isolates, primarily as a result of the rapid dissemination of extended-spectrum beta-lactamases (ESBLs) in hospitals. The fact that these resistance determinants can now also be identified in the community is worrisome.

ECDC also reported that in both pathogens multidrug resistance (combined resistance to 3rd-generation cephalosporins, fluoroquinolones, and aminoglycosides) significantly increased over the last years in one third of the European countries participating in the

studies. For some patients, only a few therapeutic options, e.g. carbapenems, remain available to treat life-threatening infections. This situation becomes worsened by the fact that carbapemem resistance in *K. pneumoniae* is rising. The prevalence of resistance to carbapenems in *Enterobacteriaceae* in Europe is still generally low for most countries; however, the situation is different for some of them such as Greece and Italy, where resistance in *K. pneumoniae* is increasing due to the spread of carbapenemases such as IMP-, VIM- and KPC-beta-lactamases, indicating their potential threat. Furthermore, outbreaks with carbapenemase-positive isolates (KPC, VIM, IMP and OXA-48) of *Enterobacteriaceae* and *P. aeruginosa* have been reported worldwide. Infections caused by NDM-1 metallo-beta-lactamase producers are relatively rare; however, these isolates are highly multiresistant and fatal infections have occurred.

Apart from acquisition of carbapenemase genes, *P. aeruginosa* has an intrinsic ability to develop carbapenem resistance. Three quarters of European countries report resistance prevalence rates higher than 10% in invasive isolates, and numbers in the USA are comparable. Combined resistance is the dominant threat imposed by invasive *P. aeruginosa*; 4.6% of European invasive *P. aeruginosa* isolates were shown to be resistant to five compounds or compound classes tested. The recovery of *P. aeruginosa* isolates susceptible only to polymyxins from critically ill patients has left colistin as the only treatment choice for these patients and there is great concern that clinicians are practically left with no treatment options for patients infected by these bacteria.
The urgent need for novel resistance-breaking compounds for the treatment of Gram-negative bacterial infections is evident.

The selection of AIC499 as a candidate compound was the culmination of a few years of work to identify potent leads with specific better stability in front of beta-lactamases. Preclinical microbiological studies by AiCuris have demonstrated that AIC499 exhibits broad antibacterial activity against Gram-negative pathogens, including clinically relevant non-fermenters such as *P. aeruginosa* and *Acinetobacter spp.* Alone or in combination with several approved or novel BLIs, AIC499 is active against multidrug resistant isolates producing beta-lactamases that include Ambler class A beta-lactamases (ESBL and KPC-enzymes), class B metallo-enzymes, class C enzymes (AmpCs) and some class D enzymes (such as OXA-48). Therefore, pathogens producing beta-lactamases that are already commonly detected in clinical isolates or seen as potential future threats would be targeted.

In Subtopic 6B, the clinical safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of AIC499 alone or in combination with BLI will be investigated in Phase 1 and Phase 2 clinical trials to develop a safe and highly effective antibiotic for patients also addressing multi-resistant pathogens.

PROGRAM OVERVIEW

The preclinical program for intravenous administration of AIC499 is currently ongoing and AiCuris is planning to enter Phase 1 in 2014; therefore, a first time in human (FTIH), single-dose escalation trial with AIC499 is planned to be conducted by AiCuris prior to the start of Subtopic 6B. In addition, since further studies will be needed if a non-approved BLI is selected by AiCuris, these studies, e.g., a multiple-dose study, will not be part of Topic 6B; relevant data will be provided and shared by AiCuris and/or its potential affiliate (under discussion) to the applicant consortium as it becomes available.

PROPOSED ARCHITECTURE FOR SUBTOPIC 6B:

WP5: RETROSPECTIVE OBSERVATIONAL STUDY TO ASSESS THE CLINICAL MANAGEMENT AND OUTCOMES OF HOSPITALISED PATIENTS WITH COMPLICATED URINARY TRACT INFECTIONS (cUTI)

The objective of WP5 is to conduct a retrospective observational study to understand the clinical management and outcomes of patients with complicated urinary tract infections (cUTIs), particularly in regions of high prevalence of antibiotic resistance.

Study Rationale

Current data on the clinical management patterns and outcomes of hospitalised patients with cUTIs caused by multidrug-resistant Gram-negative pathogens in areas of emerging and endemic antibiotic resistance are limited. The aim of this research is to understand the management cUTIs in countries in Europe (e.g., Greece, Turkey, Italy, Spain, and Balkan nations) where there is a higher prevalence of resistant Gram-negative pathogens. This study will identify patients with associated risk factors for treatment failure. Additionally, the relationship between treatment failure and specific clinical outcomes in patients with cUTIs and the prevalence of resistant organisms will be investigated.

Specific knowledge of the management of patients with cUTIs across the selected geographies will help in the design of future studies of new antibacterial agents targeting

multidrug resistant Gram-negative pathogens responsible for cUTI and similar infections, and could expand the historical information needed by EU regulatory agencies to evaluate the efficiency of new therapies in the registration process. All available data will be used. There is a potential to compare participating study sites and sites participating in routine HAI surveillance (e.g., ECDC HAI-Net) to further inform external validity of results.

Study Objectives

The objectives of the proposed study are:

1) To characterize the distribution of demographic factors of the hospitalised cUTI patient population in relation to co-morbidities and MDR-related risk factors
2) To assess antibiotic resistance patterns and identification of the proportions of cUTI patients with unmet medical need in the selected geographical areas
3) To assess clinical outcomes (duration of hospital stay, morbidity, and mortality)
4) To ascertain the frequency of treatment failures due to general risks (tolerability-related, secondary infections, emergent morbidity) and treatment failures related to documented antibiotic resistance
5) To describe clinical management, including time to initiation of antimicrobial therapy, time to culture result, and the specifics of the antimicrobial and other therapeutic interventions utilised in these patients
6) To describe cost and resource utilization for use in cost-benefit analysis

Study Population

Diagnosis of patients with cUTI will be determined by review of charts and electronic records (where appropriate) by the investigator, based on previously agreed upon CD-9 codes or similar methodologies.

Study Design

The proposed study is a retrospective, observational, multinational, multicentre cohort study of hospitalised patients with a diagnosis of cUTI within 2-years prior to study start. The study will be performed over an estimated 6- to 12-month period in approximately 700 patients from at least 6 countries with a higher prevalence of resistant Gram-negative pathogens (e.g., Greece, Turkey, Italy, Spain, and selected Balkan nations, e.g., Bulgaria, Croatia, Serbia, and Romania). The number of sites per country will depend on the availability of hospital networks within the countries in which the study will be conducted, but is expected to range from 5 to 10 per country.

Estimated Start: Q2-Q3 2015
Estimated Study Duration: 6 to 12 months

Applicant Consortia are expected to suggest an approach on how to conduct this study based on the outline provided above and within the indicative budget.

Applicant Consortia need to be aware of any complementary and potentially duplicative planned and ongoing research, as well as to take advantage of the existing networks, including those created in the ND4BB programme. It is also expected that Applicant Consortia will identify how this may be most usefully integrated from an operational, data management, scientific, and clinical perspective.

EFPIA Contribution:

- Study implementation-related expertise (infectious disease epidemiology and surveillance, clinical research, project management, data management, and biostatistics).

WP 6A: MULTIPLE DOSE ESCALATION TRIAL IN HEALTHY YOUNG SUBJECTS WITH AIC499 AND IN cUTI PATIENTS WITH AIC499 AND CLAVULANIC ACID OR ANOTHER BLI TO INVESTIGATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS (PK), AND PHARMACODYNAMICS / MICROBIOLOGICAL EFFICACY OF AIC499.

Study Objectives

The objectives of the proposed study are:

Part A

1) To assess the safety and tolerability of multiple doses of AIC499 administered intravenously to healthy subjects, with the purpose of characterising the dose-dependent adverse event profile, and to determine a maximum tolerated dose (MTD)
2) To assess the PK of AIC499 after multiple IV administrations at two dose levels

Part B

3) To assess the microbiological efficacy of AIC499 and CLAV or novel BLI in cUTI patients
4) To assess the safety and tolerability of multiple doses of AIC499 and CLAV or novel BLI administered intravenously to cUTI patients
5) To assess the PK of AIC499 and CLAV or novel BLI

Study Population

Healthy volunteers in Part A and patients with cUTI (without pyelonephritis) in Part B. An estimated 24 healthy subjects (Part A) and 20 patients with cUTI (Part B) will be recruited for this study.

Study Design

Part A of the study will be conducted in a single-centre, double-blind, randomised, placebo-controlled design. Multiple doses of AIC499 or placebo will be administered intravenously to subjects in two groups / dose levels. The doses will be defined with consideration of the results from the first-time-in-human study. Within each of the two groups, 12 healthy subjects will receive multiple IV doses for a minimum of 5 and a maximum of 14 days, with 8 subjects receiving AIC499 and 4 subjects receiving placebo. Dosing of subjects in Group 1 will be conducted prior to dosing of subjects in Group 2. The safety and PK results of Group 1 will be evaluated in a blinded manner by a Risk-Benefit-Committee prior to the start of dosing in Group 2.

Part B will be conducted after blinded review of data from Group 2 in Part A and will be conducted in a single-centre, open-label design. AIC499 and CLAV or novel BLI will be administered to 20 patients with cUTI for a minimum of 5 and maximum of 14 days; the dose will be defined based on the results of the first-in-time-in-human trial and Part A of this study.
Key safety endpoint: Adverse events and serious adverse events
Key efficacy endpoint (Part B only): Clinical and microbiological endpoints

Study Preparation: 1Q2015Estimated Start: 2Q2015
Site Recruitment: 2Q2015-4Q2015
Estimated Study Duration: 8 months
Study Close-out and Report Generation: 4Q2015-2Q2016

At the onset of this study only safety, tolerability, and PK data after single dosing will be available from the first-time-in-human study. Sample size and trial specifics will be updated after the results of GLP toxicology studies and the first-time-in-human single dose escalation study as well as scientific advice from regulatory agencies are available.

EFPIA Contribution:

- All study implementation-related expertise (infectious disease epidemiology and surveillance, clinical, project management, data management, and biostatistics).

- Investigational products

WP6B: DRUG-DRUG INTERACTION TRIAL IN HEALTHY YOUNG SUBJECTS TO INVESTIGATE THE POTENTIAL INTERACTION BETWEEN AIC499 AND BLI IN TERMS OF PK AND SAFETY (INCLUDING LUNG PENETRATION STUDIES)

Study Objectives

The objectives of the proposed study are:

1) To investigate the effect of AIC499 at steady-state on the PK of the BLI at steady-state and vice versa
2) To investigate the safety and tolerability of the combination of AIC499 and BLI
3) The penetration of drugs into the lung may also be evaluated in this study

Study Population

Healthy volunteers

Study Design

This study will be conducted in a randomised, single-centre, and open-label design. Sixteen healthy subjects will receive AIC499 alone (treatment 1) until steady-state in one period, the BLI alone (treatment 2) until steady-state in another period and the combination of AIC499 and BLI (treatment 3) for 1 week in a third period. The sequence/order of treatments will be assigned to each subject due to a randomisation plan.
Key endpoints: Safety and tolerability, PK, and, optionally, lung penetration by investigational products

Study Preparation: 2Q2015-3Q2015
Estimated Start: 2Q/3Q 2015
Site Recruitment: 3Q2015-4Q2015
Estimated Study Duration: 3 months
Study Close-out and Report Generation: 1Q2016-2Q2016

An estimated 16 healthy subjects will be recruited for this study. Sample size and trial specifics will be updated after the results of pre-clinical DDI potential and further clinical data as well as scientific advice from regulatory agencies are available.

Prerequisites for this study are the data derived from the multiple dose study of AIC499

from Part A of WP6A and externally provided multiple dose study data for the BLI. Of note, the multiple dose study for the BLI will not be part of Topic 6B; information will be provided by AiCuris and/ or its potential affiliate (under discussion). Whether or not data from this study are a prerequisite for Part B of WP6A depends on the preclinical drug-drug interaction (DDI) potential of AIC499 and the BLI as well as on the safety margins generated from multiple dose studies for AIC499 and the BLI.

EFPIA contribution:

- All study implementation-related expertise (infectious disease epidemiology and surveillance, clinical, project management, data management, and biostatistics).
- Investigational products

WP6C: MASS BALANCE / METABOLITE IDENTIFICATION TRIAL IN HEALTHY SUBJECTS

The purpose of this PK study is to determine whether the whole amount of drug that enters the human body will also be completely excreted, which metabolites are formed in humans, and to what extent. Information on mass balance of AIC499, the human metabolites, and the routes of elimination are important for the further development programme. Prerequisites for this study are the multidose study data of AIC499 from Part A of WP6A

Study Objectives

The objectives of the proposed study are:

1) To evaluate the mass balance of AIC499, to identify AIC499 metabolites in plasma and excreta (urine, faeces) and to identify the routes of elimination of AIC499 in humans
2) To obtain additional information on the safety and tolerability of AIC499

Study Population

Eight healthy volunteers

Study Design

This study will be conducted in a single-centre and open-label design.

Eight subjects will receive therapeutic IV doses of AIC499 until steady-state is achieved. The last dose will be spiked with a single IV micro-dose of ^{14}C-labelled AIC499. Accelerator mass spectrometry (AMS) will be used in this trial as an extremely sensitive

method for quantifying isotopes that can detect very small amounts of ^{14}C (only 1000 atoms are required for a valid measurement). Because the technique is so sensitive, it is possible to administer a relatively small dose of ^{14}C, and then accurately measure the amount of ^{14}C in biological samples.
Key endpoints: Safety and tolerability, PK, mass balance, metabolites

Study Preparation: 1Q2016
Estimated Start: First Subject In (FSI) 2Q2016
Site Recruitment: 2Q2016-1Q2017
Estimated Study Duration: 3 months
Study Close-out and Report Generation: 1Q2017

The study is planned to be conducted by a single CRO/clinical site. Sample size and trial specifics will be updated after the results of preclinical mass balance and metabolite identification and further clinical data as well as scientific advice from regulatory agencies are available.

EFPIA contribution:

- All study implementation-related expertise (infectious disease epidemiology and surveillance, clinical, project management, data management, and biostatistics).
- Investigational products

WP6D: TQT TRIAL WITH AIC499 IN HEALTHY SUBJECTS

This trial is proposed to investigate the potential of AIC499 (alone or in combination with BLI) to cause QT/QTc prolongation and to obtain guidance for cardiac safety monitoring in studies enrolling to larger patient populations. Although QT is an imperfect biomarker for pro-arrhythmic risk, there is a qualitative relationship between QT prolongation and risk for Torsades de Pointes.

Prerequisites for the conduct of this study are multiple-dose study data of AIC499 from Part A of WP6A and preclinical cardiological safety data. Of note, the relevant data for BLI will be provided by AiCuris and/ or its potential affiliate (under discussion).

Study Objectives

The objectives of the proposed study are:

1) To define the effects of AIC499 (alone or in combination with BLI) in healthy subjects on the QT/QTcF interval

2) To assess the PK of single doses of AIC499 (alone or in combination with BLI) and to examine the correlation between AIC499 (alone or in combination with BLI) plasma concentration and its effects, if any, on the QT/QTcF interval
3) To evaluate additional electrocardiographic effects of AIC499 (alone or in combination with BLI)
4) To show the QT/QTcF interval assay sensitivity by assessing the effects of moxifloxacin (positive control) on the QT/QTcF interval
5) To further investigate the safety and tolerability of AIC499 (alone or in combination with BLI)

Study Population

An estimated 40 healthy subjects will be recruited for this study.

Study Design

This study will be conducted in a single centre, Phase I, randomized, placebo-and positive-controlled cross-over design. It is double-blind with regard to AIC499 (alone or in combination with BLI) and placebo and it is open-label for moxifloxacin.

Forty healthy subjects will be included in this study. During the conduct of the study each subject will receive a single dose of AIC499 as a therapeutic and supra-therapeutic IV dose, moxifloxacin as a positive control (tablet), and IV placebo treatment according to a 4-fold cross-over randomization schedule. To test the effect of BLI, 2 additional cross-over arms will be added for all subjects with a therapeutic and a supra-therapeutic IV dose of BLI.
Key endpoints: Safety and tolerability, PK
Study Preparation: 2Q2017
Estimated Start: FSI 3Q2017
Site Recruitment: 3Q2017-4Q2017
Estimated Study Duration: 4 months
Study Close-out and Report Generation: 1Q2018

Sample size and trial specifics will be updated after the results from preclinical cardiological safety data and ECG results from human studies as well as scientific advice from regulatory agencies are available.

EFPIA Contribution:

- All study implementation-related expertise (infectious disease epidemiology and surveillance, clinical, project management, data management, and biostatistics).
- Investigational products

WP6E: DRUG-DRUG INTERACTION TRIAL IN HEALTHY YOUNG SUBJECTS TO INVESTIGATE THE POTENTIAL INTERACTION BETWEEN AIC499/BLI AND OTHER DRUGS

This study will be conducted to obtain information on a potential PK interaction between AIC499/BLI and another drug(s), e.g., typical concomitant medications (e.g. metronidazole or antibiotics targeting Gram-positive pathogens), or drugs used to investigate the drug-drug interaction potential mechanistically. The drug(s) to be tested will be determined with the input of the experts from the applying and selected Consortia.

Study Objectives

The objectives of the proposed study are:

1) To investigate the effect of AIC499/BLI on the PK of another drug(s) and vice versa
2) To investigate the safety and tolerability of AIC499/BLI and the other drug(s)

Study Population

An estimated 16 healthy subjects will be recruited for this study.

Study Design

This study will be conducted in a randomised, single-centre and open-label design. Sixteen healthy subjects will receive AIC499/BLI alone (treatment 1) in one period, the other drug alone (treatment 2) in another period and the combination of AIC499/BLI and the other drug (treatment 3) in a third period. The sequence/order of treatments will be assigned to each subject according to a randomisation plan.
Key endpoints: Safety and tolerability, PK

Study Preparation: 1Q2016
Estimated Start: FSI Q2 2016
Site Recruitment: 2Q2016

Estimated Study Duration: 3 months
Study Close-out and Report Generation: 3Q2016-4Q2016

Sample size and trial specifics will be updated after the results of clinical data as well as scientific advice from regulatory agencies are available.

EFPIA Contribution:

- All study implementation-related expertise (infectious disease epidemiology and surveillance, clinical, project management, data management, and biostatistics).
- Investigational products

WP6F: RENAL IMPAIRMENT TRIAL TO INVESTIGATE THE INFLUENCE OF RENAL IMPAIRMENT ON THE PK OF AIC499

This study will be conducted to obtain information on the influence of renal impairment on the PK of AIC499 (alone or in combination with BLI). The study should be conducted prior to the cUTI Proof-of-Concept trial, since these patients may have bacteraemia and renal parenchymal damage. Since renal impairment can influence the plasma concentrations of drugs, its influence on the PK of AIC499 (alone or in combination with BLI) should be examined at this drug development stage.

Prerequisites for this study are multiple-dose study data of AIC499 from Part A of WP6A and of the BLI, when included in this trial. Of note, the relevant data for BLI will be provided by AiCuris and/ or its potential affiliate (under discussion).

Study Objectives

The objectives of the proposed study are:

1) To investigate the effect of moderate and severe renal impairment on the PK of multiple iv doses of AIC499 (alone or in combination with BLI)
2) To investigate the safety and tolerability of AIC499 (alone or in combination with BLI)

Study Population

Twenty-four healthy volunteers (Group 1), moderately renally impaired patients (Group 2), and severely renally impaired patients (Group 3)

Study Design

This is an open-label, single-centre, non-randomized trial with multiple IV administrations of AIC499 (alone or in combination with BLI) in each of the participating subjects.
Twenty-four healthy or renally impaired subjects will be assigned to 1 of 3 groups (8 subjects per group; group definition provided above) according to the estimated glomerular filtration rate (eGFR) based on the Modification of Diet Renal Disease (MDRD) equation.
Key endpoints: Safety and tolerability, PK

Study Preparation: 1Q2016
Estimated Start: FSI 2Q2016
Site Recruitment: 2Q2016-4Q2016
Estimated Study Duration: 7 months
Study Close-out and Report Generation: 1Q2017-2Q2017

Sample size and trial specifics will be updated after the results of clinical data as well as scientific advice from regulatory agencies are available.

EFPIA Contribution:

- All study implementation-related expertise (infectious disease epidemiology and surveillance, clinical, project management, data management, and biostatistics).
- Investigational products

WP6G: PHASE 2 PROOF OF CONCEPT TRIAL FOR THE TREATMENT OF GRAM-NEGATIVE PATHOGENS IN HOSPITALISED PATIENTS WITH COMPLICATED URINARY TRACT INFECTIONS (CUTI)

The indication cUTI is of high medical importance, since it is the most common type of hospital-treated infections and up to 15% of hospital-acquired blood stream infections arise from UTIs. It is mostly produced by Gram-negative organisms that may present multidrug resistance and hence be difficult to treat. Moreover, the positive outcome of this study would facilitate future studies focused in other diseases with higher mortality and lower prevalence.

Prerequisites for this study are the conclusion of WP5 as well as achievement of a positive outcome of WP6A, WP6B, WP6E and WP6F.

Study Objectives

The objectives of the proposed study are:

1) To investigate the safety, tolerability, efficacy and pharmacokinetics/ pharmacodynamics of AIC499/BLI in patients with cUTI.
2) To assess the efficacy of AIC499/BLI in cUTI cases caused by multidrug resistant Gram-negative pathogens
3) To evaluate if the patients are intestinally colonized by a drug resistant Gram-negative pathogens

Study Population

The proposed study population consists of 210 hospitalised adults (18-90 years) with known or suspected Gram-negative cUTI, with approximately 30% of cases presenting with pyelonephritis.

Study Design

The proposed study is a Phase 2, multi-centre, randomised, double-blind, active-controlled trial.
Key endpoints: Clinical and microbiological efficacy, safety and tolerability, pharmacokinetics/pharmacodynamics

Estimated Start: 1Q2017
Estimated Study Duration: 18-24 months
Study Preparation: 4Q2016
Site Recruitment: 2Q2017-3Q2018
Study Close-out and Report Generation: 3Q2018-4Q2018

Sites with high rates of multidrug resistant Gram-negative pathogens should be targeted and an estimated sample size of 210 patients should be recruited for this study. Sample size and study specifics will be updated using the results of the studies described in WP5 and WP6A-6F, as well as scientific advice from regulatory agencies.

EFPIA Contribution:

- All study implementation-related expertise (infectious disease epidemiology and surveillance, clinical, project management, data management, and biostatistics).
- Investigational products

- Direct financial contribution by the sponsoring EFPIA company to supplement the study costs (up to 25%), including CRO subcontracting if any, incurred by public partners ensuring that 100% of these costs will be reimbursed.

WP6H: PHASE 2 PROOF-OF-CONCEPT TRIAL FOR THE TREATMENT OF GRAM-NEGATIVE PATHOGENS IN HOSPITALISED PATIENTS WITH COMPLICATED INTRA-ABDOMINAL INFECTIONS (CIAI)

Complicated intra-abdominal infections are frequently associated with poor prognoses and high morbidity and mortality rates. Despite advances in diagnosis, surgery, and antimicrobial therapy, mortality rates associated with cIAI remain exceedingly high. In the last decade, the emergence of multidrug resistant Gram-negative bacteria has become a pressing issue in the treatment of intra-abdominal infections as they are frequently related to the most severe cases.

Prerequisites for this study are the conclusion of WP4A as well as achievement of a positive outcome of WP6A, WP6B, WP6E and WP6F and at least interim results from WP6G.

Study Objectives

The objectives of the proposed study are:

1) To investigate the safety, tolerability, efficacy and PK/pharmacodynamics of AIC499/BLI in patients with cIAI
2) To assess the efficacy of AIC499/BLI in cases of cIAI caused by multidrug resistant Gram-negative pathogens

Study Population

The proposed study population consists of 225 hospitalised adults with known or suspected Gram-negative cIAI.

Study Design

The proposed study is a Phase 2, multicentre, randomised, double-blind, active-controlled trial. Since a percentage of cases of cIAI are caused by anaerobic bacteria and AIC499 does not show sufficient coverage of these pathogens, metronidazole is planned to be part of the therapy with AIC499/BLI.
Key endpoints: Clinical and microbiological efficacy, safety and tolerability, PK/pharmacodynamics

Estimated Start: 1Q2018
Estimated Study Duration: 18-24 months
Study Preparation: 4Q2017
Site Recruitment: 2Q2018-3Q2019
Study Close-out and Report Generation: 3Q2019-4Q2019

Sites with high rates of multidrug resistant Gram-negative pathogens will be targeted. Sample size and study specifics will be updated using the results of studies described in WP5 and WP6A-F, as well as scientific advice from regulatory agencies.

EFPIA Contribution:

- All study implementation-related expertise (infectious disease epidemiology and surveillance, clinical, project management, data management, and biostatistics).
- Investigational products
- Direct financial contribution by the sponsoring EFPIA company to supplement the study costs (up to 25%), including CRO subcontracting if any, incurred by public partners ensuring that 100% of these costs will be reimbursed

WP6I: WP6 CLINICAL COORDINATING CENTRE

The overall purpose of WP6I is:

1) To establish a coordinating centre to provide program management, project coordination, and strategic alignment across all studies within the proposed within the proposed AIC499/BLI clinical development program and with the WP1;
2) To contribute to the overall scientific coordination of Topic 6, including programme management and governance;
3) To ensure adequate training and qualifications of investigators within the Consortium conducting WP6.
4) To arrange meetings, including at least one face-to-face training prior to initiation of the project, with additional meetings as appropriate during the course of the work including investigator meetings prior to the opening of each clinical trial
5) To ensure coordination of clinical trial operations and management, including data management, as appropriate
6) To develop a system of mentoring and coordination within the consortium to facilitate information-sharing, and training among the Consortium investigators

EFPIA Partner Contribution:

- Organizational support: Project/Alliance Management personnel, meeting facilities, communication expertise and arrangements;
- Provision of workshops/seminars/Q&A sessions.
- Providing training and oversight to Consortium laboratories (with emphasis on those serving as central laboratories) to ensure compliance with Good Laboratory Practice standards
- Providing training and oversight to ensure clinical and laboratory sites remain "audit ready."
- Sharing of learning from clinical networks and the conduct of clinical trials in emerging economies
- Information/expertise in clinical trial design, epidemiologic methods, infectious disease surveillance, regulatory requirements, quality assurance monitoring, clinical microbiology requirements and data quality standards.

Applicant Consortium

(to be selected on the basis of the submitted EoI)

Applicant consortia are expected to propose options for novel study design addressing the objectives for each of the studies to help clinical development of the proposed molecules. The expectation is that the applicants will build upon the stated key objectives to help develop full study protocols, including leading the development of robust clinical and biomarker endpoints.

Overall, the successful Applicant Consortium for Subtopic 6A must document in the EoI the capability for leadership in the epidemiology of serious bacterial infections in Europe (WP2), conducting epidemiology studies/analyses in the ICU populations (WP3), and clinical studies in ICU (WP4A, WP4B), including among paediatric subjects (WP4C).

For Subtopic 6B, the successful Applicant Consortium must document in the EoI the capability for conducting epidemiology analyses in the cUTI populations (WP5), and in Phase 1 and Phase 2 studies in healthy subjects and those with cUTIs and/or cIAIs.
Applicants should be able to fulfil within the indicated time frame the patient recruitment and study personnel resourcing requirements of all studies described under Subtopic 6A and 6B.
Participating sites must conduct studies in accordance with the ethical principles in the Declaration of Helsinki, and consistent with ICH GCP and the applicable local regulations.
Other requirements of successful Applicants include:

- Expertise in infectious disease epidemiologic surveillance and observational study design and conduct
- Demonstrated interactions with public health agencies relating to epidemiologic data and inferences
- Expertise in providing clinical project management, including cross-functional collaborations, budget/timeline management, and regular status reporting
- Expertise in establishing and complying with standards for data extraction, data recording, database architecture, data analysis, and data privacy principles
- Ability to provide bacterial isolates and associated microbiological and epidemiologic data to a central regional laboratory
- Experience in supplying on-site training to ensure compliance with clinical study protocols
- Expertise in statistics and preclinical PK/PD modeling approaches
- Data from existing clinical studies to contribute to the ND4BB Information Centre
- Expertise in GCP and local and global regulations as they pertain to clinical trial design

Laboratory Requirements

Minimum local and central regional microbiology laboratory requirements include:

- Expertise in performing microbiologic testing, including standardised Gram stain and *in vitro* MIC (minimum inhibitory concentration) testing (according to CLSI guidelines)
- Ability to perform microbiology testing on a variety of patient samples, e.g., nasopharyngeal, skin, deep surgical, blood, respiratory including sputum, endotracheal aspirate, bronchoalveolar lavage, or protected brush
- Documentation of appropriate quality control/quality assurance programme
- Laboratory accreditation by a country-specific agency

Minimum local and central regional serology laboratory requirements include:

- Ability to perform standardised serologic assessments of antibacterial antibody responses on samples from clinical subjects. The lab should provide evidence of expertise in developing or adopting and, subsequently, validating new serologic assays, and in providing the assays to clinical and/or epidemiology surveillance research under Good Laboratory Practice (GLP) conditions.
- Ability to perform enzyme-linked immunosorbent assays (ELISAs) using rabbit red blood cells under GLP conditions as recommend by the Medicines and Healthcare Products Regulatory Agency (MHRA) or other comparable regional guidance for

laboratories testing samples from clinical studies.

- Documentation of appropriate quality control/quality assurance programme
- Laboratory accreditation by a country-specific agency

Requirements Specific to Subtopic 6A, WP2-WP4

- Epidemiologic surveillance experts to inform study protocols and to determine the relevant pathogens, antimicrobial agents, clinical correlates, and analyses.
- Expertise in bacterial, especially *P. aeruginosa* virulence factors and in developing and performing relevant serologic assays on samples from clinical subjects, preferably under GLP conditions[8]
- Proposals for novel diagnostics/biomarkers to be utilised in clinical trial designs. Relevant diagnostics should be close to validation and with sufficient turnaround time (< 60 minutes) to identify subjects for enrollment and/or biomarkers which can be incorporated into the trial design with little or no impact on the collection of study data required for regulatory submissions.
- Expertise in mathematical modeling to measure impact of interventions on resistance patterns.

Requirements Specific to Subtopic 6A, WP4A and WP4B

- Expertise in current standard of care for patients requiring ICU care especially those at risk for *P. aeruginosa* disease
- Clinical study experience with antibacterial or mAb treatments, preferably with the capability of administering infusions to maintain double-blinding of studies and with the ability to follow patients upon discharge, and the ability to track recurrences or new disease onset requiring outpatient or inpatient management.
- Expertise in immunointervention or prophylaxis for infectious diseases, particularly in the intensive care unit populations.
- 24-hour availability of an unblinded pharmacist/third party for preparation and dispensing of IV infusions and trained blinded staff to administer IV infusions.
- Investigators with research and clinical backgrounds in intensive care and pulmonology, or with an established track record of conducting research in pneumonia, ventilator-associated pneumonia, or infections in the ICU. Investigators are expected to provide summary data on the number of ICU

[8] Special consideration will be given to laboratories capable of providing serologic testing support to other member sites

infections at their site; in particular, the number of pneumonia infections in the ICU, ideally by etiologic agent. Sites should have a patient load capable of supporting enrollment of 10-20 study subjects per site over a 12-month period.

- Investigators with experience in obtaining informed consent in patients requiring mechanical ventilation and/or sedation.
- Investigators with track record of performing research involving risk factors for ICU infections and/or pneumonia.
- Applicants are expected to propose ICU patient population(s) that have an increased risk (25% or higher) for developing ICU pneumonia due to *P. aeruginosa*.

Requirements Specific to Subtopic 6A, WP4C

- Investigators with research and clinical backgrounds in paediatrics with an established track record of conducting Phase 1-2 safety and PK studies in paediatric patients; in particular paediatric patients considered at risk for *P. aeruginosa*. Investigators are expected to provide site-specific summary data on the number of *P aeruginosa* pneumonia and other serious infections within the paediatric population. Sites should have a patient load capable of supporting the enrollment of 6 study subjects per site over a 24-month period.
- Investigators with experience in obtaining informed consent and assent in paediatric patients.
- Applicants are expected to propose paediatric population(s) that would be considered at risk for *P. aeruginosa* disease.

Requirements Specific to Subtopic 6B, WP6A-6F

The Applicant Consortium should ensure that the EoI describes the availability of the following facilities:

- Standardised measurements of ECG, vital signs, safety lab and regular questioning regarding occurrence of AEs must be possible.
- Centrifuge and -20°C freezer available to process PK- and other samples immediately.
- The Applicant consortium should include one or more CRO/clinical sites with large experience in the conduct of early phase 1 trials, including conduct of drug-drug interaction (DDI), AMS, TQT, and/or renal impairment phase 1 trials.
- Large healthy volunteer and patient database to find subjects who stay on the ward the time proposed in the study designs.
- Moreover, the following special requirements will be taken into account

- WP6A:
    - Expertise in current standard of care for patients with cUTI
    - One-lead ECG for safety monitoring over a certain time should be available.
- WP6C: Applicant should have experience with the conduct of accelerator mass spectrometry (AMS) studies, since this method is very sensitive and mistakes in the conduct could lead to failure of the study.

Requirements Specific to Subtopic 6B, WP6G and WP6H

The Applicant Consortium should ensure that the EoI describes the ability to recruit and retain the targeted patient population in addition to describing recent clinical experience conducting randomized comparator-controlled antibacterial studies. Moreover, the following criteria should be fulfilled:

- Each hospital and healthcare institution engaging in ND4BB clinical studies should have the expertise and facilities (including quality clinical microbiology labs and expertise) to address all aspects of the outlined protocols.
- Expertise in current standard of care for patients with cUTI and cIAI.
- Clinical study experience with antibacterial treatments
- Demonstrated ability to recruit patients with the target characteristics (cUTIs and cIAI). Centres should have a reasonable likelihood of enrolling patients with infections caused by multidrug resistant Gram-negative pathogens based on previous experience. To ensure that recruitment goals for the trial can be met, the potential clinical research sites must demonstrate capacity to recruit and provide follow-up care in the proposed clinical trial. Preferentially the site should have no other clinical studies that may compete for the target patient groups. Qualified sites that do have potentially competitive studies should be assessed to determine if they have sufficient patients and appropriately qualified and trained staff to participate in multiple studies.

7. ND4BB TOPIC 7: DEVELOPMENT OF NOVEL INHALED ANTIBIOTIC REGIMENS IN PATIENTS WITH CYSTIC FIBROSIS (CF) AND PATIENTS WITH NON-CF BRONCHIECTASIS (BE)

BACKGROUND

Antimicrobial resistance (AMR) is a major global public health threat which is continuing to worsen. Infections caused by resistant and newly emerging bacteria are increasing and are associated with increases in mortality, morbidity, length of hospitalisation, and frequency of re-hospitalisations. Despite the recognition of this problem since many years the number of new antibiotics developed and approved is continuing to decrease leaving fewer treatment options.

Pseudomonas aeruginosa (Pa) is the most frequently isolated pathogen in patients with cystic fibrosis (CF) and requires lifelong, suppressive inhaled antibiotic therapy. More recently it has also been demonstrated that patients with non-CF Bronchiectasis (BE) who are infected with Pa experience more rapid lung function decline and exacerbate more frequently leading to an increased risk for mortality, costly and frequent hospitalisations, and intensive care unit (ICU) admissions. In addition to Pa infections, infections with other non-fermenters, including *Stenotrophomonas maltophilia, Burkholderia* spp., *Acinetobacter* spp., *Achromobacter* (or *Alcaligenes*) *xylosoxidans*, *Ralstonia* spp., and *Pandoraea* spp. are of high medical interest, although most of them are still rare. These pathogens are however noted with increasing frequency in patients with CF and some of them e.g. *Burkholderia* spp., can be associated with rapid deterioration of the respiratory function and poor outcome. To date no antibiotic has been approved to treat these lung infections of non-CF BE patients and no inhaled antibiotic has been approved to treat other bacteria than Pa in CF patients.

The development of novel therapies or combinations of antibiotics with different mechanisms of action and synergistic effects is warranted to address this significant unmet medical need.

Topic 7 is being proposed to support the development of novel inhaled antibacterials and novel treatment regimens in patients with CF. In addition, Topic 7 is proposed to support the development of inhaled antibacterials for patients with non-CF BE. The proposed research included in the current Call 11 builds upon the significant epidemiology, clinical, and biomarker research infrastructure currently being developed under ND4BB.

BENEFITS OF A COLLABORATIVE APPROACH

The paradox of further increasing antibiotic resistance and decreasing development of antimicrobials is still existent although it has been recognised since many years. Reversion of the paradox has to be accelerated through concrete actions and collaboration. A collaboration approach will ensure that the best and diverse expertise around the world is gathered and data and risks are shared which will lead to a higher chance of success in developing new antibiotics and in improving the use of antibiotics. In particular, for ND4BB Topic 7, private partners bring in programme-specific knowledge and general knowledge in antibiotic drug development; Basilea and Novartis will join forces by complementing their expertise in the development of inhaled antibiotics in CF and expertise in anti-infective development; academic and SME partners are needed for their expertise with CF, non-CF BE, specific microbiology and epidemiology expertise; clinical expert input is needed for clinical endpoint research; experience with data registries and data access solutions is needed to optimally exploit the benefit of the data that will be generated. A collaborative effort for topic 7 would lead to the following benefits:

- 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.
- The 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. For product development in non-CF BE patients the regulatory requirements related to study designs and endpoints are not well defined. Considerations around development of new compounds in this indication will stimulate discussions with

regulators and help define a regulatory path which will be of benefit to future development of new treatments as well.

- Characterisation of patient's microbiology will further inform on the relevance of potentially pathogenic microorganisms (PPMs) (for example *Proteus* and *Klebsiella*) in non-CF BE.
- 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 patients.
- Exploration of possible collaboration with other private and public enterprises including the European Cystic Fibrosis Clinical Trials Network (https://www.ecfs.eu/ctn) is key to add specific expertise in microbiology, formulation development, preclinical pharmacology, and CF study design and execution.
- Collaboration will allow risk sharing for the development of antibiotics for the treatment of an orphan disease (CF) and difficult indication.
- The development effort presented in ND4BB Topic 7 will benefit from and add to the research infrastructure of the ND4BB programme.

OVERALL OBJECTIVES

The overall objectives of ND4BB Topic 7 are, in no particular order of priority:

1. To 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 for example frequency of the disease, use of medication, microbiology, co-morbidities, prognosis etc. available.
2. To build on the laboratory network established under the ND4BB project COMBACTE (LAB-net) by defining and adding laboratories with a track record in the field of sputum microbiology and lung microbiomes.
3. To determine a currently available antibiotic 'compound X' which when used in combination with tobramycin, has the most pronounced synergistic antibacterial effects against *Pseudomonas aeruginosa* (Pa) and other difficult to treat Gram-negative bacteria in *in vitro* microbiology studies and in animal models, or when used alone should demonstrate similar antibacterial effects against Pa as for inhaled tobramycin, in *in-vitro* microbiology studies and in animal models.

Compound X represents any antibiotic currently available either as oral or iv formulation with demonstrated activity against Pa and possibly other Gram-negative bacteria that will have some synergistic effects with tobramycin. Several generic antibiotics that meet these criteria will be tested in formulation and pharmacology studies in the preclinical WP2. Candidate antibiotics might include but are not restricted to tetracylines (e.g., doxycycline) and fluoroquinolones. Novel antibiotic compounds may also be considered.

4. To study the formulation of antibiotic agents (BAL30072 and compound X) and of antibiotic combinations (compound X with tobramycin) in a preclinical setting to support the clinical development of inhaled therapy in patients with CF and non-CF BE reducing treatment burden and enhancing adherence to medication.
5. To establish the pharmacology, drug metabolism and pharmacokinetics (DMPK) and non-clinical safety of compound X determined in 3.
6. To establish the pharmacology, DMPK and non-clinical safety of a novel inhaled antibiotic agent, BAL30072.
7. To explore alternating monthly or simultaneous combination therapies of inhaled compound X and tobramycin dry powder (TIP) for long-term suppressive antimicrobial therapy in patients with CF (after the achievement of objectives 3,4 and 5), including exploration of novel endpoints such as lung clearance index or imaging.
8. To support the clinical development of inhaled BAL30072 against respiratory infections with Gram-negative (including multidrug-resistant) pathogens in patients with CF (after achievement of objective 4 and 6).
9. To support the clinical development of tobramycin powder for inhalation (TIP) against *Pseudomonas aeruginosa* (Pa) respiratory infections in patients with non-CF BE.
10. To support the clinical development of inhaled BAL30072 against respiratory infections with Gram-negative (including multidrug-resistant) pathogens in patients with non-CF BE (after achievement of objective 4 and 6).
11. To explore novel endpoints such as lung clearance index and imaging.

SUGGESTED KEY DELIVERABLES

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

EFPIA PARTICIPANTS

Novartis, Basilea

INDICATIVE DURATION OF THE PROJECT

The indicative duration of the project will be 5 years.

INDICATIVE BUDGET OF THE PROJECT

The indicative EFPIA in-kind contribution is up to EUR 31 000 000
The IMI JU financial contribution will be a maximum of EUR 27 000 000

Milestones related to the expected results over time will be defined for a staggered budget release to optimally manage risk of investment.

INFORMATION ON COMPOUNDS TO BE STUDIED IN TOPIC 7

BAL30072

BAL30072 is a sulfated monocyclic beta lactam (a monosulfactam). The compound is currently in Phase 1 of the clinical development for intravenous use. BAL30072 is currently being developed for the systemic treatment of severe and difficult to treat infections. Three Phase 1 studies with intravenous BAL30072 (single and multiple

ascending dose studies) have been completed. Further clinical development of intravenous BAL30072 foresees Phase 2 studies in various infections including complicated urinary tract infections (cUTI). Intravenous BAL30072 will also be tested alone and in combination with carbapenems, a combination which may exhibit synergistic antibacterial effects. This development programme for the intravenous formulation of BAL30072 (but not for the inhaled formulation proposed here) is funded by the US Biomedical Advanced Research and Development Authority (BARDA). BARDA funding, which is contingent upon milestones, is restricted to the development of BAL30072 for intravenous use, and includes microbiological, preclinical, clinical, manufacturing and associated regulatory activities. Due to the different drug administration route and the completely different target population, the development of BAL30072 for inhalation is an independent Basilea program, and is not related to the development of BAL30072 for intravenous use. BARDA funding does not include activities associated with the development of an inhaled formulation of BAL30072.

BAL30072 exhibits potent bactericidal activity against a broad spectrum of Gram-negative pathogens, including Enterobacteriaceae and non-fermentative bacteria such as Pa, *Acinetobacter* spp., *Burkholderia* spp., and *Stenotrophomonas maltophilia, Achromobacter xylosoxidans*, *Ralstonia* spp. and *Pandoraea* spp. which are becoming more frequent in patients with CF and are associated with poor outcomes. BAL30072 retains activity against multidrug-resistant (MDR) strains of the target species, including isolates resistant to all or virtually all other commercially available antibiotics, such as KPC producing *K. pneumoniae*, NDM-1 producing Gram negative bacteria, and carbapenem-hydrolyzing class D beta lactamase (CHDL) producing *A. baumannii*.
BAL30072 contains an iron chelating dihydropyridone substituent that has a probable role in promoting its uptake into Gram-negative bacteria via siderophore receptors (Page 2010). Like other beta lactams, the primary cellular targets for BAL30072 are penicillin-binding proteins (PBPs). The PBP binding affinity of BAL30072 is distinguished from other monocyclic beta lactams, and is complementary to that of the carbapenems (Dantier 2008).

BAL30072 has high affinity for *E. coli* PBP 3, and also exhibits significant inhibition of PBP 1a and 1b. This pattern of inhibition has been observed for other Enterobacteriaceae and for *P. aeruginosa* (Richalet 2010). BAL30072 has slight affinity for PBP 2, the principal target of carbapenem antibiotics. PBPs from *Acinetobacter* spp. are less well defined than other species, but BAL30072 has a binding profile similar to that of meropenem.

BAL30072 is stable in the presence of a range of clinically important beta lactamases, including ESBLs and carbapenemases (Page 2010), and as such is active against a

diverse array of carbapenemase producing, multi-drug resistant Enterobacteriaceae and non-fermentative species.

Overall, BAL30072 has excellent in vitro and in vivo bactericidal activity against a broad range of MDR Gram-negative pathogens including isolates with resistance against meropenem or colistin which are clinically relevant in CF and in non-CF BE. BAL30072 can therefore be considered as a promising new compound for the long term treatment of difficult to treat infections in CF and non-CF BE.

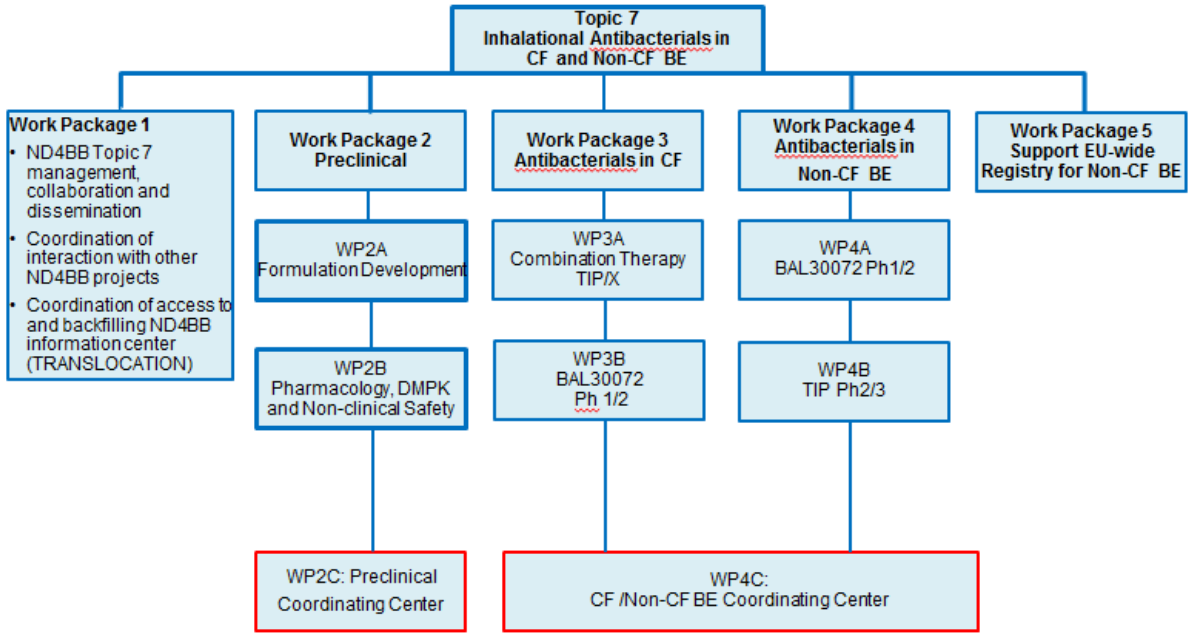
Tobramycin Powder for inhalation (TIP)

TOBI Podhaler or TIP is an inhaled dry powder formulation of the antibiotic tobramycin. It is used for the management of Pa lung infection in cystic fibrosis patients aged six years and older. TIP delivers tobramycin using a portable, pocket-sized inhaler and reduces administration time by approximately 70% relative to nebulised tobramycin. It is approved in over 55 countries including the EU and US.

Compound X

There are a number of antibiotics available in oral or intravenous form with demonstrated activity against *Pseudomonas aeruginosa*, and potentially other Gram-negative bacteria. One desirable outcome of this Topic 7 project would be the identification of a novel or existing antibiotic ("compound X") which when in an appropriate formulation and administered via the inhalation route may exhibit synergistic antibacterial activity together with inhaled tobramycin. It may be beneficial to combine inhaled antibiotics (either simultaneously or in alternating cycles) in order to reduce emergence of resistant strains, and to improve bacterial load reduction ultimately leading to better outcomes in CF patients. . Compound X represents any antibiotic currently available either as oral or iv formulation with demonstrated activity against Pa and possibly other Gram-negative bacteria that will have some synergistic effects with tobramycin. Several generic antibiotics that meet these criteria will be tested in formulation and pharmacology studies in the preclinical WP2. Candidate antibiotics might include but are not restricted to tetracylines (e.g., doxycycline) and fluoroquinolones. Novel antibiotic compounds may also be considered. The expectation is that a discussion will take place in the full consortium involving outside expert advice to select the most appropriate compound X to be tested both in the preclinical WP2 and in the clinical WP3A. Compound X will be formulated as an inhaled compound using PulmoSphere™ technology.

PROPOSED PROJECT ARCHITECTURE OF TOPIC 7



WP1: ND4BB PROJECT MANAGEMENT, COLLABORATION AND DISSEMINATION

The main purpose of this work package will be to conduct administrative tasks of the project, including annual scientific and financial reporting, project planning, managing the process for Open Calls, facilitating collaboration between Topic 7 investigators as well as cross-project interactions with other ND4BB consortia, and ensuring coherent dissemination of ND4BB results to the broader scientific community. This work package will also be responsible to ensure that information and learnings generated in this project will be deposited in the overall ND4BB Information Centre put in place by the ND4BB project TRANSLOCATION. **A similar work package is part of all projects launched under the ND4BB programme to ensure a close collaboration between all ND4BB projects.**

Optimal alignment of the objectives of studies carried out in IMI projects with the needs and challenges patients face is an important point on IMI's overall agenda. Therefore, this work package should make sure to fully exploit options for interactions and collaboration with patients.

Timelines:

Estimated start: Q1 2015

Estimated duration: 5 years

Budget for WP1:

The budget covering activities under this WP is covered by the budget estimations listed under WP2 to WP4. Applicant consortia are invited to plan accordingly.

WP2: PRECLINICAL DEVELOPMENT

WP2 covers the formulation development and the pharmacology, DMPK, and non-clinical safety assessment of inhaled BAL30072 and compound X. Several antibiotics will be tested as compound X for formulation and pharmacology studies, but only one compound X will be chosen for testing in clinical studies (WP3+4) based on the results that will be obtained from the efforts in WP2.

WP2A: FORMULATION DEVELOPMENT

Rationale:

BAL30072 is currently available as lyophilised powder to be reconstituted for intravenous administration. A formulation of BAL30072 for inhalation through an air-jet nebuliser has to be developed, and the feasibility for the development of a dry powder formulation needs to be investigated.

Compound X will be formulated similar to TIP as dry powder for inhalation using the PulmoSphere Technology and will be delivered through an approved dry powder inhaler.

Objectives:

- Develop a formulation of BAL30072 which can be applied through an air-jet nebuliser. Nebulised BAL30072 will be used in the pre-clinical and clinical studies of Topic 7.
- Test the feasibility of the development of dry powder of BAL30072 for dry powder inhalation (DPI).
- Selection of an adequate nebuliser device for the administration of nebulised BAL30072.
- Formulating candidates for compound X using PulmoSphere technology and delivery through an approved dry powder inhaler.

EFPIA consortium contribution:

The EFPIA partners will share expertise and guidance on drug substance characteristics of BAL30072 such as physicochemical properties and impurity as well as stability profile and will provide analytical methods to test and characterise the drug substance and freeze-dried powder for solution to be used as a solution, which has the potential for use with air-jet nebulisers. The EPFIA partners will also provide expertise in formulation development of Compound X using PulmoSpheres dry powder particles and optimisation for delivery through an approved dry powder inhaler.

Note: IP rights for PulmoSphere Technology and compound X in PulmoSpheres will remain with Novartis Pharma AG in accordance with the IMI policy and will therefore require agreement by the whole consortium.

Applicant consortium contribution:

The applicant consortium is invited to propose plans for the development of an extended inhalation formulation and for further characterisation of a nebulised inhalation solution (analytical methodology for droplet size determination), and for the selection or development of a suitable device for the drug administration. The applicant consortium should also contribute the necessary expertise to perform feasibility studies for the development of a single or multidose dry powder inhaler (e.g. specific salt and polymorph screening, and particle engineering for drug substance).

Timelines WP2A:

Estimated start: Q1 2015
Estimated duration: 1 year

WP2B: PHARMACOLOGY, DMPK AND NON-CLINICAL SAFETY

Rationale:

The pre-clinical studies shall provide standard data on the pharmacology, the toxicity, and the efficacy of inhaled BAL30072 and inhaled compound X.

Objectives:

- Assess DMPK of inhaled BAL30072 and candidates for compound X and the combination of candidates for compound X with TIP in test animals.
- Assess the safety of inhaled BAL30072 and compound X in test animals.
- Test the activity of BAL30072 against relevant pathogens in the presence of lung surfactant from test animals and from sputum of patients with CF.

- Test the *in-vivo* efficacy of BAL30072 and suitable comparator antibiotics in optimised models, using inhaled administration routes.
- Perform *in-vitro* microbiology studies to test for synergies of candidate for compound X in combination with tobramycin against Gram-negative bacteria to determine the best combination for treating patients with cystic fibrosis.
- Preclinical safety testing.

Preclinical safety studies will be conducted with the inhalation formulations developed under Work Package 2A. It is suggested that preclinical safety studies should include:

- An inhalation dose-range finding study in rats
- A 4-week inhalation toxicity study in rats
- An inhalation dose-range finding study in dogs
- A 4-week inhalation toxicity study in dogs

All *in vivo* toxicological studies will be substantiated by appropriate toxicokinetic monitoring and the 4-week inhalation studies will be performed under Good Laboratory Practice (GLP).

The pharmacokinetics of BAL30072 will be determined in study animals (mouse, rats, dogs) after parenteral drug administration and drug administration by inhalation.
The pharmacokinetics of compound X and/or its combination with tobramycin will be determined in study animals (mouse, rats, dogs) after drug administration by inhalation.

The microbiological studies may include:

- The determination of the *in-vitro* activity of BAL30072 and the combination of compound X with tobramycin against recent isolates of relevant pathogens, collected from lung infections, in the presence of lung surfactant from test animals and in sputum of patients with CF. The target pathogens include Pa especially multiple antibiotic-resistant Pa (MARPA), *Stenotrophomonas maltophilia*, *Burkholderia* spp., *Acinetobacter* spp., *Achromobacter* (or *Alcaligenes*) spp., *Ralstonia* spp., and *Pandorea* spp., as well *Haemophilus influenzae*.
- The investigation of the suitability of existing models of acute and chronic infection as well as colonisation of the lower respiratory tract in mice or rats.
- The optimisation of infection models using recent isolates of relevant pathogens collected from lung infections (in particular *Pa*, *Burkholderia* spp., and *Acinetobacter* spp.).
- The *in-vivo* efficacy testing of candidates for compound X combined with tobramycin in the optimised models, using inhaled administration routes.
- The *in-vivo* efficacy testing of BAL30072 and suitable comparator antibiotics in the optimised models, using inhaled administration routes.

- The confirmation of the *in-vivo* efficacy of formulated BAL30072 and selected combinations.

EFPIA consortium contribution:

The EFPIA contribution will include the facilitation of connection between ongoing studies running in the IMI project TRANSLOCATION regarding design and implementation of suitable rodent infection models. Regulatory input with regard to acceptability of proposed non-clinical safety studies with the inhalation formulation for both liquid and PulmoSphere formulations will be provided. Guidance on analysis of BAL30072 in biological fluids including practical assistance with analytics and data analysis when necessary. Guidance will also be given on combinations. Existing preclinical animal models for safety evaluation can be available for use by the project. Batches of compound X to be used in combination with TIP will be available from EFPIA partners.

Applicant consortium contribution:

The applicant consortium is invited to propose plans and options to address the objectives listed above. Expertise is required in conducting DMPK and inhalation preclinical safety studies.

The potential antibiotics for combinations with TIP will be chosen after discussion within the full consortium facilitated via the WP2 and WP 4 coordinating centers. This discussion will include outside expert advice to select the most appropriate compound X to be tested in the clinical WP3A. That discussion might also include pros and cons of a fixed-dose combination versus more flexible approaches.

Note: IP rights for the PulmoSphere formulation of compound X will remain with Novartis Pharma AG in accordance with the IMI IP policy and will therefore require agreement by the whole consortium.

Timelines WP2B:

Estimated start: Q1 2016
Estimated duration: 4 years (based on estimates for preclinical safety studies of 6 months, microbiology *in-vitro* studies of 1 year, microbiology *in-vivo* studies of 3 years)

WP2C: COORDINATING CENTER

The coordinating center for WP2 (pre-clinical development) will provide project management, coordination, and strategic alignment within Work Packages 2A and 2B,

and work in close interaction with the WP3/4 coordinating center, and with WP1 of ND4BB Topic 7.

Timelines WP2C:

Estimated start: Q1 2015
Estimated duration: 5 years

Indicative budget for complete WP2 (A-C):

Indicative Budget for WP 2: Total EUR 6 200 000 (EFPIA EUR 3 300 000; IMI JU EUR 2 900 000)

WP3: ANTIBACTERIALS IN CF (CLINICAL STUDIES)

Overall objectives for the entire WP3 are:

Endpoints for inhaled antibiotics studied include change in the number of organisms (CFU) and also changes in the composition of the microbial flora –e.g. emergence of other potentially pathogenic micro-organisms. The quality of the microbiological analysis is therefore crucial. Previously some studies have used a central laboratory for convenience and in order to standardise the methods used. However delays in processing sputum consequent on long distances between the clinical center and the analytic laboratory, may affect the results. This is specifically problematic for some pathogens other than Pa, which may not survive delays before the sputum is cultured. In order to reduce the time before culture it may be worth considering the option of using a network of laboratories in clinical or academic centers with a track record of excellence in the field of sputum microbiology. These labs could work using the same Standard Operating Procedures. Quality and reproducibility could be checked by sending out quality assurance samples and comparing the results between the different participating laboratories. This approach may also reduce costs. Therefore, one objective of WP3 is to define laboratories with a track record in the field of sputum microbiology and lung microbiomes and to add these laboratories to the Europe-wide laboratory network that is currently put in place by COMBACTE (LAB-net).

Another objective of the entire WP3 is to build capability for storage of non-fermenter strain samples for future research. This strain library will particularly be useful for future projects in CF including projects funded by IMI. Access to this strain library should be provided to consortium members and other qualified research groups. Applicants are invited to suggest a model for access and sustainability of this effort.

WP3A: ALTERNATING OR SIMULTANEOUS COMBINATION THERAPIES (TIP/ COMPOUND X): POC CLINICAL STUDY

Rationale:

Cyclical therapy of inhaled tobramycin for the treatment of chronic *Pseudomonas aeruginosa* (Pa) infections in cystic fibrosis (CF) patients has been established in phase 3 trials. The concept of cyclical therapy allowing for off-treatment periods has been established since the mid '90s, with the aim to reduce emergence of potentially resistant strains. After over a decade of use of inhaled tobramycin, including the recently approved tobramycin dry powder (TIP), inhaled tobramycin remains an effective therapeutic option to manage chronically infected CF patients. Recognising the need for a better antibiotic coverage, the European Consensus Group (Döring 2012) has recommended for CF patients with unstable disease, the administration of a second inhaled antibiotic in the off month cycle or administering continuously inhaled antibiotics. It may be beneficial to combine inhaled antibiotics (either simultaneously or in alternating cycles) in order to reduce emergence of resistant strains, while improving the bacterial load reduction due to potential synergistic effects. The clinical evidence of such combinations is limited to date (ongoing AZLI CAT study, NCT01641822). Pre-clinical data are suggestive of a synergistic effect of the colistin/tobramycin combination (Hermann 2010). The management of chronic *P. aeruginosa* lung infections in CF patients consists of using one inhaled antibiotic at a time. The reason is that, until recently, only nebulised antibiotics were available which add a considerable treatment burden on the patients and their families. With DPIs delivering high loads of antibiotics quickly and easily (TIP; colistimethate sodium dry powder for inhalation), patients may be able to use more than one antibiotic simultaneously for additional clinical outcome benefit.

Objectives for WP3A:

The proposed programme will explore the use of two inhaled antibiotics (inhaled tobramycin and inhaled compound X) with different modes of action in an alternating regimen or simultaneously administered, assessing the impact on lung function, time to exacerbation, and microbiology (bacterial load, MIC). Novel endpoints such as LCI and imaging may be explored. Microbiomes and biofilms may be analysed in substudies. Activities under WP3A include conducting a Phase 1 clinical PK and safety study and a PoC Phase 2 clinical safety, tolerability and efficacy trial.

Applicants are welcome to propose novel exploratory endpoints, e.g. imaging, LCI (lung clearance index) and to propose innovative approaches to the analysis of the microbiome and biofilms.

Suggested study designs:

- Phase 1 clinical PK and safety study: healthy subjects (3x8 subjects; 7 days)
- PoC (Proof of Concept) Phase 2 clinical safety, tolerability and efficacy trial
    a. Objectives
        i. Provide clinical and microbiological outcome data to describe the safety, tolerability and efficacy of TIP cyclically alternating or simultaneous application with compound X
        ii. Efficacy measurements to include change in relative and absolute FEV1 % predicted, bacterial load reduction, time to exacerbation and/or rate of exacerbations
        iii. Evaluate short term impact on resistance development of Pa as measured by change in MIC
    b. Study Design, Population, Setting
        i. Interventional prospective, outpatient CF with Pa colonisation
        ii. Minimum 56 day study for a single treatment cycle in phase II

EFPIA consortium contribution:

Clinical supplies for Compound X and TIP; Sponsorship of clinical studies: All activities regarding sponsor responsibilities including regulatory strategy and interactions with Health Authorities and safety reporting; Expertise in design of CF study.

Expected Applicant consortium contribution:

The applicant consortium is welcome to propose alternative study designs and endpoints for discussion within the full consortium, and is invited to propose and execute a plan for the management of all aspects of the clinical study; Clinical sites for study conduct; Expertise in design of CF study; Collection and analysis of samples for microbiology and PK (includes potential sub-studies regarding analysis of microbiome and biofilm); Imaging technologies and LCI (lung clearance index) as exploratory endpoints.

Timelines WP3A:

Estimated Start: Q1 2017
Estimated duration: 3 years

Budget:

For WP3A, the indicative EFPIA in kind contribution will be EUR 2 800 000 and the IMI JU funding will be up to EUR 2 200 000.

WP3B: CLINICAL DEVELOPMENT OF A NOVEL INHALED ANTIBIOTIC (BAL30072); PHASE 1/2 STUDIES

Rationale

Inhaled BAL30072 provides a unique opportunity to address the need to treat respiratory infections caused by Gram-negative multi-drug-resistant (MDR) pathogens that show carbapenem-resistance or resistance to other antibiotics, such as tobramycin, aztreonam, ciprofloxacin or colistin.

The development of inhaled BAL30072 for the treatment of respiratory infections with MDR Gram-negative pathogens, especially infections caused by Gram-negative non-fermenters including *Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Burkholderia spp., Acinetobacter spp., Achromobacter (or Alcaligenes) xylosoxidans, Ralstonia spp. and Pandoraea spp*, is of high medical interest, since despite their rarity, some of these pathogens have been noted with increasing frequency in patients with cystic fibrosis (CF), and some are associated with poor outcome.

WP3B focuses on the development of long term inhaled treatment (rather than short-term intravenous treatment) in specific patient groups such as CF. The clinical development of BAL30072 will further expand research addressing the challenge of MDR Gram-negative pathogens, and will supplement previous topics (e.g., Topic 5) under the ND4BB programme.

Objectives for WP3B:

The key objective of WP3B is the conduct of an adaptive clinical trial programme with designs to deliver data on the safety, pharmacology, and efficacy of BAL30072 in healthy subjects and in patients with CF.

Study design of Phase 1 studies:

Pharmacokinetics and safety in healthy subjects

A randomised, double-blind, placebo-controlled, multiple-ascending dose study at 3 dose levels of inhaled BAL30072, and administered over 3 days will be conducted in healthy adults ≥ 18 years.

The main objectives of this study are:

- To assess the maximum tolerated dose of multiple-dose inhaled BAL30072.
- To assess the pharmacokinetics (plasma-levels) of inhaled BAL30072.
- To assess the safety and tolerability of inhaled BAL30072 (versus inhaled placebo).

The estimated sample size is 6 subjects on inhaled BAL30072, and 2 subjects on inhaled placebo per dose cohort. Total N=24 (3 cohorts).
Description of the method:

- The study will be performed in a single center.
- The study is planned to include 3 sequential dose cohorts starting with the lowest dose level in the first cohort. Blood samples for PK will be collected periodically and up to 24 hours after the last study drug administration.
- Adverse events, vital signs, ECG, safety laboratory parameters, and pulmonary function tests will be recorded until study day 4.
- The maximum tolerated dose (MTD) will be defined based on adverse events, change in pulmonary function or oxygenation.

Pharmacokinetics and safety in adult and adolescent patients with CF

A randomised, double-blind, placebo-controlled, multiple-ascending dose study at 3 dose levels of inhaled BAL30072, and administered over 3 days will be conducted in adults ≥ 18 years and in adolescents ≥ 12 to ≤ 17 years with CF.
The main objectives of this study are:

- To assess the maximum tolerated dose of multiple-dose inhaled BAL30072.
- To assess the pharmacokinetics (plasma and sputum) of multiple-dose inhaled BAL30072.
- To assess the safety and tolerability of multiple-dose inhaled BAL30072 (versus inhaled placebo).
- To assess the change in the number of colony-forming units (CFUs) of MDR Gram-negative pathogens in the sputum from baseline to day 4.

The estimated sample size is 16 patients in each dose cohort (12 patients on inhaled BAL30072, and 4 patients on placebo). Total N=96 (6 dose cohorts).
Description of the method:

- The study will be performed as multicenter study.
- The study is planned to include 6 dose cohorts (3 sequential dose cohorts in adults, and 3 sequential dose cohorts in adolescents), starting with the lowest dose level in the first cohort. Enrolment of adolescent patients in a dose cohort may be initiated once the respective dose level has been shown as safe and well tolerated for adults.
- Blood samples for PK and sputum will be collected periodically and up to 24 hours after the last study drug administration.

- Adverse events, vital signs, ECG, safety laboratory parameters, and pulmonary function tests will be recorded until study day 4.
- The maximum tolerated dose (MTD) will be defined based on adverse events, change in pulmonary function or oxygenation.

Study design of the Phase 2 study:

Efficacy and safety in adult and adolescent patients with CF

A randomised, double-blind, placebo-controlled, parallel-group study at 2 dose levels of inhaled BAL30072, and administered over 14 days will be conducted in patients with CF ≥ 12 years with CF and Gram-negative pathogens including MDR pathogens.

The main objectives of this study are:

- To assess the change of pulmonary function of patients treated with inhaled BAL30072 from baseline to day 14.
- To assess the change of pulmonary function in patients treated with multiple-dose inhaled BAL30072 from baseline to day 7 and day 28.
- To assess the change in the number of CFUs of MDR Gram-negative pathogens in the sputum from baseline to day 7, day 14 and day 28 (the assessment of virulence factors will also be explored).
- To assess the change in health-related quality of life (HrQoL) by day 14 and day 28.
- To assess the change in exercise tolerance from baseline to day 7, day 14 and day 28.
- To assess the safety and tolerability of multiple-dose inhaled BAL30072 (versus inhaled placebo).

The estimated sample size is 35 patients each on inhaled BAL30072 in dose cohort 1, dose cohort 2, and on placebo. Total N=105 (3 dose cohorts).

Description of the methods:

- Adult and adolescent patients with CF will be randomised to 14-day treatment in 1 of 3 treatment groups. The treatment groups are: inhaled BAL30072 at dose level 1 inhaled BAL30072 at dose level 2, inhaled placebo.
- Pulmonary function testing, the number of CFUs of Gram-negative including MDR pathogens, HrQoL and exercise tolerance will be determined at baseline and at various post-baseline timepoints up to day 28.
- Blood samples for PK and sputum will be collected periodically.

- Adverse events, vital signs, ECG, safety laboratory will be assessed up to study day 28.

EFPIA consortium contribution:

Project management and the management of the clinical trial will be performed by the EFPIA partners; the EFPIA partners will also assume clinical trial sponsor obligations, regulatory oversight and safety reporting to health authorities (e.g. DSURs, expedited safety reporting of individual cases etc.); the EFPIA partners will provide clinical and medical expertise and oversight and will also be responsible for database cleaning, database lock and preparation of the clinical study reports and their submission to health authorities and ethic committees; the monitoring of the Phase 1 trials will be done by the EFPIA partner; Study drug will be provided by the EFPIA partner; direct financial contribution by the sponsoring EFPIA company to supplement the study costs (up to 25%) including CRO subcontracting if any, incurred by public partners ensuring that 100% of these costs will be reimbursed.

Applicant consortium contribution:

The applicant consortium with a track record in running operations of phase 1 and phase 2 clinical trials is welcome to propose alternative study designs and endpoints for discussion within the full consortium, and is invited to propose a plan for the operational running of the studies proposed above. This includes clinical trial applications and full study site management as well as monitoring of the phase 2 study.
The applicant consortium is expected to contribute expertise in the fields of pharmacokinetic analysis of blood samples and microbiological analysis of the sputum samples.

Timelines

Estimated start: Q1 2017
Estimated duration: 3 years

Budget:

For WP3B, the indicative EFPIA in-kind contribution will be EUR 3 050 000 and the IMI JU funding will be up to EUR 3 050 000.

WP4: ANTIBACTERIALS IN PATIENTS WITH NON-CF BE (CLINICAL STUDIES)

WP4A: CLINICAL DEVELOPMENT OF A NEW INHALED ANTIBIOTIC (BAL30072); PHASE 1 STUDY

Rationale:

This work package focuses on the development of long-term inhaled treatment (rather than short-term intravenous treatment) in patients with non-CF BE including patients with BE who have Chronic Obstructive Pulmonary Disease (COPD). The key objective is the conduct of a clinical trial programme with novel designs to deliver data on the safety, pharmacology, and efficacy of inhaled BAL30072.

Objectives of WP4A:

The key objective of WP4A is the conduct of an adaptive clinical trial program with designs to deliver data on the safety, pharmacology, and efficacy of BAL30072 in patients with non-CF BE.

Study design of the Phase 1 study:

Pharmacokinetics and safety in adult patients with non-CF BE

A randomised, double-blind, placebo-controlled, multiple-ascending dose study at 3 dose levels of inhaled BAL30072, and administered over 3 days will be conducted in adults ≥ 18 years with non-CF BE including BE due to COPD.

The main objectives are:

- To assess the maximum tolerated dose (MTD) of multiple-dose inhaled BAL30072.
- To assess the PK (in plasma and sputum) of multiple-dose inhaled BAL30072.
- To assess the safety and tolerability of multiple-dose inhaled BAL30072 (versus inhaled placebo).
- To assess the change in the number of CFUs of MDR Gram-negative pathogens in the sputum from baseline to day 4.
- The estimated sample size is 16 patients in each dose cohort (12 patients on inhaled BAL30072, and 4 patients on placebo). Total N=48 (3 dose cohorts).

Description of the method:

- The study will be performed as multicenter study.
- The study is planned to include 3 sequential dose cohorts in adults with non-CF BE including BE due to COPD, starting with the lowest dose level in the first cohort.

- Blood samples for PK and sputum will be collected periodically up to 24 hours after the last study drug administration.
- Adverse events, vital signs, ECG, safety laboratory parameters, and pulmonary function tests will be recorded until study day 4.
- The MTD will be defined based on adverse events, change in pulmonary function and/or oxygenation.

EFPIA contribution:

Project management and the management of the clinical trial will be performed by the EFPIA partners; the EFPIA partners will also assume clinical trial sponsor obligations, regulatory oversight and safety reporting to health authorities (e.g. DSURs, expedited safety reporting of individual cases etc.); the monitoring of the Phase 1 trial will be done by the EFPIA partners; the EFPIA partners will provide clinical and medical expertise and oversight and will also be responsible for database cleaning, database lock and preparation of the clinical study reports and their submission to health authorities and ethic committees; study drug will be provided by the EFPIA partners; direct financial contribution by the sponsoring EFPIA company to supplement the study costs (up to 25%) including CRO subcontracting if any, incurred by public partners ensuring that 100% of these costs will be reimbursed.

Applicant consortium contribution:

The applicant consortium is welcome to propose alternative study designs and endpoints for discussion within the full consortium, and is invited to propose a plan for running the phase 1, study operations**.** This will include clinical trial applications, full study site management.

The applicant consortium is invited to contribute expertise in performing the PK analysis of blood samples and microbiological analysis of the sputum samples.

The applicant consortium should provide the necessary expertise in bioanalytics and in the microbiological analysis including highly specialized characterization of pathogens in human sputum samples.

Timelines:

Estimated start: Q1 2017

Estimated duration: 3 years

Budget:

Indicative Budget for WP 4A: Total EUR 1 700 000 (EFPIA in-kind contribution EUR 850 000; IMI JU funding will be up to EUR 850 000).

WP4B: CLINICAL DEVELOPMENT OF TOBRAMYCIN POWDER FOR INHALATION (TIP) IN NON-CF BE; PHASE 2 AND PHASE 3 STUDIES

Rationale

Bronchiectasis (BE) is a chronic disease characterised by a vicious cycle of chronic inflammation and infection that ultimately results in irreversible dilatation of bronchi with destruction of elastic and muscular components of the bronchial walls and is diagnosis by HR-CT of the lung. Approximately two thirds of patients with bronchiectasis are infected with Gram-negative pathogens, *P. aeruginosa* (Pa) being the most difficult to treat and having a faster decline in lung function and more frequent exacerbations. There is a need to reduce in non-CF BE the number and severity of exacerbations, the length and number of costly hospitalisations and to provide relief of symptoms. An effective antibiotic targeting the endobronchial space (site of infection) with low systemic side effects specifically approved to reduce exacerbations has the potential to be a significant benefit for the patients. There is no approved inhaled antibiotic for this indication and population, for whom an unmet medical need exists.

Objectives of WP4B

Tobramycin powder for inhalation (TIP) is already approved for the management of Cystic Fibrosis patients infected with Pa in over 55 countries worldwide. Pilot studies using inhaled tobramycin have been performed with non-CF BE patients, suggesting improvements in several outcome measures including bacterial load reduction, symptom improvement, fewer hospitalisations and reduced length of hospital stay. The efficacy and safety of inhaled tobramycin combined with the PulmoSphere technology has the potential to provide meaningful benefit in non-CF BE patients by reducing bacterial load, exacerbations (e.g., frequency, severity) and improving associated clinical outcomes.
In this work package the aim is to study TIP in a phase 2 dose finding study and phase 3 registration program assessing the efficacy and safety in non-CF BE patients with frequent exacerbations and infected with *Pseudomonas aeruginosa.*

Phase 2 dose finding study:

Efficacy and safety in patients with non-CF BE.
Design: Randomised, double-blind, placebo-controlled, parallel-group study (3 different dose levels of TIP, 28-day active treatment period (or 3 cycles of 28-day active treatment and 28-day off treatment, tbd))

The primary objectives of this study are:

1. To evaluate the effect of incremental doses of TIP on the relative change in the bacterial load in sputum as assessed by the change in colony forming units (CFUs) *P. aeruginosa*, from baseline to the end of the 28 days treatment period, compared to placebo
2. To assess the safety and tolerability of 28 days treatment with incremental doses of TIP at each visit of the treatment period and follow-up period compared to placebo

Estimated sample size: N=144 (36 patients on each TIP cohort and on placebo)
Brief description of methods:

- Adult patients with BE and documented *P.aeruginosa* cultures in the past 12-months will be randomised to one of the treatment groups
- *P.aeruginosa* CFUs, MIC, pulmonary function tests, and HrQoL will be assessed at baseline and post-dose
- Blood samples and sputum for PK will be collected periodically
- Adverse events, vital signs, safety laboratory will be assessed at baseline and periodically

Phase 3 efficacy and safety study(ies):

Design: 12 month randomised double-blind, placebo-controlled parallel group study
Estimated Sample Size: N = max. 500 patients (might be divided into 2 phase 3 studies depending on the regulatory requirements)

Primary Objectives:
Confirmation of safety, tolerability and efficacy of dose and dosing interval chosen from phase II.

Brief description of methods:

- Adult patients with BE, frequent exacerbations and documented *P.aeruginosa* cultures in the past 12-months will be randomized to one of the treatment groups
- Endpoints: Exacerbations, safety and tolerability, sputum and serum PK, hospitalization rate, change in MIC for Pa, other clinically relevant endpoints (symptom scores, sputum volume, HR-QoL)
- Adverse events, vital signs, safety laboratory will be assessed at baseline and periodically

EFPIA consortium contribution

Clinical supplies for TIP and placebo.
All activities related to sponsorship of phase 2 and phase 3 clinical trial including regulatory strategy and interactions with Health Authorities (HA), coverage of HA fees, safety reporting.

Expected Applicant consortium contribution:

The applicant consortium is welcome to propose alternative study designs and endpoints for discussion within the full consortium, and is invited to propose and execute a plan for the management of all aspects of the phase 2 and phase 3 clinical studies; clinical sites for conduct of the studies; collection and analysis of samples for microbiology and PK; central evaluation and adjudication of CT-scans; clinical expert opinion regarding endpoints for ph2 and ph3 to enable inclusion of rare PPMs (e.g. *Klebsiella* and *Proteus*) in the study for the purpose of indicating TIP for these rare PPMs.

Note: IP rights for TIP in non-CF BE will remain with Novartis Pharma AG in accordance with the IMI IP policy and will therefore require agreement by the whole consortium.

Timelines:

Estimated start: Q1 2015
Estimated duration: 5 years

Budget:

Indicative Budget for WP 4B: Total EUR 39 000 000 (EFPIA in kind contribution will be EUR 21 000 000; IMI JU contribution will be up to EUR 18 000 000).

WP4C: CLINICAL STUDIES COORDINATING CENTER

The coordinating center for clinical studies (WP3/4) will provide project management, coordination, and strategic alignment across the proposed WP3/4 clinical development studies and work in close interaction with the WP2 coordinating center, and with WP1 of ND4BB Topic 7.

Timelines:

Estimated start: Q1 2015
Estimated duration: 5 years

Budget:

The budget covering activities under this WP is covered by the budget estimations listed under WP3 and WP4. Applicant consortia are invited to plan accordingly.

WP5: SUPPORT OF AN EU-WIDE REGISTRY OF NON-CF BRONCHIECTASIS

Rationale

Non-CF bronchiectasis is a chronic debilitating condition increasingly being diagnosed. It is an underestimated disease, not only in its unknown and potentially increasing prevalence and incidence, but also in its ability to cause morbidity and mortality. Stimulating and improving research in non-CF BE clearly has enormous potential for society and public health benefits. Unlike CF bronchiectasis, there have been few randomised clinical trials to guide the evaluation and management of the disease. Similarly, there is a lack of real-world data from multicentre large prospective observational studies that could better describe its frequency across Europe, the considerable phenotypic diversity of the disease or contribute to generating evidence-based algorithms to better support the management and prognosis of the disease. Several countries participate in local registry initiatives for non-CF bronchiectasis, for example Spain and Germany, but there has been limited coordination of these registries to create a larger analysable database.

Objectives of WP5

1. To support alignment and coordination between current local efforts in Europe that have set up or are in the process of setting up registries of non-CF bronchiectasis. This may include identification of current or future pan-EU registries, and the exploration of potential collaboration and joint efforts taking into account data which may be already available and accessible. The goal would be to find solutions for connecting registries and sharing data, to formulate common design and data elements, written operating procedures and documented methodologies, in order to optimise the value of available information for further analyses.

   The collaborative effort may result in comprehensive information on:

a. Frequency of the disease, antimicrobial resistance, natural history of disease, aetiologies, microbiology, clinical characteristics, management, prognosis, resource utilization and quality of life.

b. Potential differences in the disease epidemiology, clinical characteristics, management and prognosis across Europe.

c. Evidence-based data on predictors of exacerbations, hospitalisations and survival in a large cohort of bronchiectasis patients.

2. To explore synergies with non-EU registry initiatives for non-CF bronchiectasis, e.g. the US Bronchiectasis Research Registry of the COPD Foundation.

3. To contribute to the generation of evidence-based recommendations on the management and control of patients with non-CF bronchiectasis.

4. To coordinate with ND4BB Topic 6 WP2 and the ND4BB Information Center in TRANSLOCATION in order to support public health and drug development priorities related to antimicrobials.

5. To investigate approaches to ensure that an EU-registry of non-CF BE will be accessible to the scientific community at large.

6. To disseminate knowledge and communicate research results at international conferences, e.g., European Respiratory Society/American Thoracic Society.

EFPIA contribution

EFPIA support for coordinating activities, regulatory support, and if requested, epidemiological, health outcomes and pharmacoeconomics support and advice.

Expected Applicant consortium contribution:

The applicant Consortium is invited to bring in expertise with data registries of non-CF BE and/or links with current local or pan-European registry initiatives; expertise in establishing and complying with standards for data collection, recording, database architecture, database analysis, and privacy principles.

Timelines

Estimated Start: Q2 2015
Estimated Duration: 5 years

Budget

The budget covering activities under this WP is covered by the budget estimations listed under WP4. Applicant consortia are invited to plan accordingly.

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8. ECORISKPREDICTION (ERP)

A methodology for the prediction of the potential environmental risk of pharmaceutical substances (EcoRiskPrediction, ERP)

BACKGROUND

Low levels of many active pharmaceutical ingredients (APIs) are detected in the aquatic environment. The dominant pathway for these residues is via the administration to patients and excretion of their residues or the breakdown products entering sewage treatment systems and, after incomplete elimination, surface waters.

Environmental risks of new medicinal products are currently assessed based on a regulatory guideline on a standardised assessment scheme (EMEA, 2006)[9], in order to fulfil the requirements for market approval. The present testing scheme, however, is not designed to take into account specific properties of pharmaceutical substances in environmental organisms and is typically conducted when a medicinal product is close to an application for market approval. Scientifically based information on potential environmental properties, however, may be required during the early development process of an API, in order to be prepared for specific environmental concerns and consequently, to design substance specific environmental testing strategies.

Currently, systematic approaches to investigate the responses of environmental organisms to substances with specific properties such as physico-chemical behaviour, pharmacological mode-of-actions and (mammalian) toxicity are lacking. Those that do exist lack sufficient data to allow the fullest possible assessment to be made. Therefore, a more fully developed methodological approach based on high quality data could support predictions of the potential environmental risks of un-tested APIs during early development or on the market. A new systematic approach could help to focus experimental research on ecotoxicological effects on specifically sensitive organisms, life-stages and specific test designs for critical endpoints (intelligent testing).

Newly introduced legislation (Directive 2010/84/EU, recital 6) requires the European Commission to evaluate whether amendments to Union legislation on medicinal products

[9] EMEA. Guideline on environmental risk assessment of medicinal products for human use. EMEA/CHMP/SWP/4447/00 corr 1, London, June 2006

or other relevant Union legislation are needed to deal with the issues of environmental impact of pharmaceuticals. Therefore there is an urgent need for the pharmaceutical industry and relevant stakeholders to provide a more systematic approach which can be employed to estimate the potential environmental risk of APIs. Thus, a project in this area could support the European Commission's initiative to analyse the risk of pharmaceuticals in the environment.

In summary the present environmental risk assessment procedures for human pharmaceuticals lack important approaches, including:

- an approach to determine a specific testing strategy for a certain pharmacological mechanism
- information, whether ecotoxicological hazards can be predicted based on specific properties of an API
- relevant scientific information to prioritise APIs (pre-2006 and in early development) for specific experimental approaches

In order to develop targeted testing schemes for environmental risk assessment, an effects-based methodology developed on pharmacological mode-of-actions could help to reduce unnecessary testing and provide more relevant data for ecological risk assessment.

As a result, the following key aspects should be addressed by EcoRiskPrediction (ERP):

- Identification of certain patterns of responses may help to support an environmental evaluation during early development of APIs. Defining parameters, which are useful for determining the environmental relevance of a certain product, could also help to prioritise old compounds which have been introduced into the market before the implementation of the Environmental Risk Assessment (ERA) in 2006.
- The proposed programme could address the question brought forward by many academic and regulatory scientists whether a validated methodology could support the evaluation of the ecotoxicological hazards of APIs during the early development process.
- It could take into account the public and regulatory concern that for many older pharmaceutical products information about their environmental risk is lacking and thus, by providing a methodology to prioritise the large number of non-evaluated APIs for a future assessment programme.

- Therefore to address this urgent need, ERP aims to develop a science based methodology to enable a more systematic approach to ecotoxicological risk assessment.

PROBLEM STATEMENT

There is an unmet need of methodologies to predict environmental hazards and risks of human pharmaceutical substances in the early development process, for defining targeted intelligent testing strategies and for prioritization of existing APIs for further experimental testing.

Traditionally, environmental testing is undertaken late in development such that there is little time to refine any identified risks before the regulatory submission. However, with the knowledge from clinical and preclinical studies, mode of action and epidemiology it should be possible to predict at an earlier stage whether or not a particular drug may have properties that could potentially harm the environment. Such knowledge could be used to develop predictive tools to help companies identify risks at an earlier stage and to tailor environmental testing programmes accordingly so that the risks can be refined as necessary throughout drug development process.

Additionally, such an innovative methodology could be used for prioritizing the vast number of APIs on the market, not yet assessed for their environmental risk. Thus, the methodology could be used for prediction of potential environmental hazards during the early development process of new APIs and for providing information on the relative environmental relevance of existing APIs.

NEED FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

In order to deliver the expected deliverables for this topic there is a need for many different stakeholders to share their data and work together. It is clear that a single entity or institution will not be able to develop the tools and methodologies required for a systematic approach. For the realization of the project, the inclusion of interested stakeholders is needed:

- SMEs to support the development of in-silico tools and the collection of public data in a data base with public data; and can provide project management services
- Academia to contribute by elaborating theoretical approaches and experimental testing programmes to define prioritization parameters

- Industry to provide input regarding their product portfolio in particular pre-clinical and clinical data, unpublished ecological information and the contribution to validation programmes for defining prioritization parameters.
- Regulatory Agencies (i.e., EMA, National Environment Agencies) to contribute with available information on registered APIs within existing ERAs
- European Regulators, such as the EMA and the European Commission (DG SANCO, DG-Environment) are key stakeholders for discussions in which way regulators can support intelligent testing strategies and what scientific information may be useful to get broad acceptance for a prioritization concept of old APIs.

The tools and methodologies developed during the lifetime of the project may be used by different stakeholders in assessing environmental impacts. Therefore it is important that those different stakeholders are involved in the definition and testing of the expected new tools, in order to ensure future consistency between approaches applied by different national and international agencies.

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

It is intended that ERP will collaborate with other IMI projects, particularly with eTOX. The eTOX project has already developed a toxicological database and a repository for in silico tools, which could be adapted and extended for the needs of ecotoxicological data. In addition, eTOX has developed an honest broker approach, which allows sharing confidential data among the projects' participants, which could also be valuable for ERP. The synergy of this collaboration is obvious, since researchers would only have to access one database and one system to perform read-across or to predict properties. A clear-cut synergy has been identified between eTOX and ERP with regard to database and repository for in silico tools. Relevant resources to support the activity have to be considered. This interaction will be developed more fully during the Full Project Proposal stage.

OVERALL OBJECTIVES

- Establishment of an ecotoxicological database for pharmaceuticals and a repository for predictive tools or models for environmental risk assessment
- Develop a validated methodology based on scientific information on specific properties of pharmaceutical compounds in order to predict a response in environmental organisms

- Evaluate existing proposals of parameters which can be used in such a methodology, e.g.:
    - similarities between pharmacological activity and response in environmental organisms
    - potency considerations for environmental organisms on similar acting compounds
    - uptake/response models in correlation to pharmacologically active plasma concentrations in mammalians/humans
- Useful indicators for exposure (sales, environmental behaviour and occurrence)
- An experimental testing programme of these parameters,
- To agree on a methodology for evaluating the reliability (quality and validity) of data to go into the underlying data base
- Recommendations for the use of the results of the project in early development programmes for new compounds and for prioritizing legacy products for experimental testing
- Recommendations for closing knowledge gaps and evaluating the issue of pharmaceuticals in the environment

EXPECTED KEY DELIVERABLES

- Literature evaluation of concepts for mode-of-action based approaches to environmental risk assessment (ERA)
- A data management system containing literature and industry owned data, focussing on links between environmental information and specific properties of APIs (synergies with IMI eTOX),
- Analysis of the data management system, for example: search for common mechanisms of ecotoxicity and information developed during the drug development process, such as physico-chemical properties, pharmacological and toxicological mode-of-action
- Delivery of predictive tools for early screening of hazardous environmental properties and validation of the tools through experimental research projects
- Guidance on how the tools can be used in early development programmes for new APIs
- Guidance on how the tools can be used to develop a prioritization process for existing APIs (legacy products)
- Recommendation for closing knowledge gaps and evaluation of the scale of the issue of pharmaceuticals in the environment

- Discuss the outcome of this programme with stakeholders

EFPIA PARTICIPANTS

Bayer Pharma (coordinator), Novartis (deputy coordinator), AstraZeneca (deputy coordinator), Roche, Johnson and Johnson, Merck (MSD), Pfizer, Sanofi.

INDICATIVE DURATION OF THE PROJECT

The indicative duration of the project is 4 years.

INDICATIVE BUDGET OF THE PROJECT

The indicative in kind contribution from the EFPIA companies is estimated at EUR 3 884 200.
The indicative IMI JU contribution will be up to EUR 3 000 000.

APPLICANT CONSORTIUM

The applicant consortium should consist of academic institutions, SMEs and regulatory bodies.
A track record in environmental risk assessments particularly in the assessment of pharmaceuticals, in developing and performance of data management systems, in statistical evaluations of large data bases, expertise in environmentally related in vitro and in vivo testing, environmental exposure and effect modelling are required. Regulatory bodies such as national agencies should have the resources to provide environmental and pharmacologically related information on collected and condensed information regarding registered pharmaceuticals.

PROPOSED ARCHITECTURE OF THE FULL PROJECT PROPOSAL

The Applicant Consortium is expected to address all the research objectives and make key contribution to the defined deliverables in synergy with the EFPIA consortium.

The architecture below for the full proposal is a proposal; different innovative project designs are welcome, if properly justified.

Apart from the participation of applicants and EFPIA industry, a stakeholder advisory group is planned to include international (EC, EMA) and national regulators, pharma

industry associations, and academic researchers to provide a transparent, widely accepted approach. This stakeholder advisory group is not part of the work packages but interaction between work package participants and the stakeholder advisory group is part of the project structure. The composition and organisation of such an advisory group will be determined at the Full Project Proposal stage after discussion between the EFPIA partners and the successful applicant consortium selected at Stage 1.

It is expected that management of the work packages will be coordinated by a steering committee consisting of the work package leaders along with their deputies (potentially one person from the applicant consortium and one from industry) and the project coordinator and deputy coordinators. However, the exact composition of the steering committee will be agreed by all partners at the FPP stage.

WORK PACKAGE 1: SCREEN EXISTING APIs FOR INFORMATION ON PROPERTIES AND PARAMETERS USEFUL FOR THE PREDICTION METHODOLOGY, PREPARE THOSE DATA TO GO INTO DATA BASE INCLUDING CRITERIA FOR VALIDITY AND QUALITY, REVIEW CONCEPTS FOR PREDICTION OF ENVIRONMENTAL HAZARDS AND RISKS

Expected Applicant Contribution

Expertise in environmental assessments in order to engage in literature searches. Selection of ecotoxicological parameters/endpoints which should go into data base, evaluation of identified environmental information with regard to validity and quality, identification of meaningful concepts for the evaluation of correlation patterns useful for prediction of ecotoxicological hazards and risks, network with organizations having developed or developing approaches for prediction of environmental risks of human pharmaceuticals. A number of prioritization methods have already been developed and applied around the world. These should be reviewed to identify good practice and limitations of methodologies already used.

EFPIA Contribution

Provide unpublished industry information on pharmaceuticals, cooperate on the selection process for parameters/endpoints, provide toxicological and pharmacological data and expertise to be used in data mining.

WORK PACKAGE 2: DEVELOP ALGORITHMS TO DETERMINE SIMILARITIES/CORRELATIONS BETWEEN DATA PARAMETERS (DATA MINING)

Expected Applicant Contribution

Expertise in data management systems in order to develop structures for data base input
Expertise in data management and statistical approaches for data mining,
Develop synergy with the toxicological prediction data management system developed in the IMI project eTOX[10].

EFPIA Contribution

Support the development of extraction and combination methods, develop proposal for experimental validation of identified correlations and similarities, coordinate with the eTOX project (IMI) to determine needs for further adaptation of the eTOX data management system

WORK PACKAGE 3: REVIEW EXPOSURE MODELS FOR PREDICTING ENVIRONMENTAL DISTRIBUTION OF PHARMACEUTICALS

Expected Applicant Contribution

Expertise in exposure modelling, develop criteria for use of exposure models including the sensitivity and specificity.
Review existing exposure models on the realistic prediction of environmental exposure (both aquatic and terrestric) of APIs.
Relate exposure models to hazard based prediction models in order to identify approaches to predict environmental risks.

EFPIA Contribution

Provide unpublished environmental exposure assessment data of human pharmaceuticals, provide expertise in exposure models such as PhATE.

[10] The eTOX data management system allows the compilation of diverse data. If regulators, academia and industry are enabled to directly contribute information on substances of their interest on a voluntary basis, it could generate an added value and trust building knowledge exchange. It is possible to also have a database structure that allows confidential information to be handled in a hidden part of the database.

WORK PACKAGE 4: EXPERIMENTAL VALIDATION OF PROPOSED CONCEPTS FOR PREDICTION METHODOLOGY: MOLECULAR, CELL BASED, ORGANISM BASED

This WP is designed to be split into several sub-packages with specific focus on experimental designs at different levels of organization, such as molecular, cell based, whole organisms based. These experimental approaches should serve the following objectives:

Specifying the mechanisms or properties to be experimentally validated, identification of typical markers for organism responses to specific groups of pharmaceutical substances in molecular and cell based systems,

Definition of the environmental relevance of those markers in whole organism tests,

Identification of experimental approaches to combine exposure and mechanism/property based models for effects

Expected Applicant Contribution

Laboratory expertise in molecular, cell based and ecotoxicological whole organism testing.

Develop targeted testing methodologies with reference to harmonised methods (e.g. OECD ecotoxicological testing methods) which could use information on sub-organism marker responses. Based on the information developed in WP2 and 3, specific mechanisms or properties potentially useful for identifying predictors of environmental hazards and risks are to be identified and tested in appropriate test systems.

EFPIA CONTRIBUTION

Provide experimental testing capacities in cooperation with the applicants.

WORK PACKAGE 5: DEVELOPMENT OF RECOMMENDATIONS HOW TO USE THE METHODOLOGY IN REGULATORY (LEGACY APIS, GENERAL PIE EVALUATION) AND RESEARCH AND DEVELOPMENT OF NEW APIS

Expected Applicant Contribution

Cooperate with stakeholder advisory group, evaluate results of in silico and experimental research of WP 2, 3 and 4 in order to come up with recommendations:

Determine the main parameters which are useful in predicting environmental hazards and risks,

Determine, whether a relationship exists between mechanisms/properties and exposure models of APIs and environmental risks determine whether a grouping approach is feasible, which parameters are needed for QSAR models in grouping,
Propose test species and endpoints which are useful predictors of relevant environmental effects for specific groups of APIs. Propose a methodology on prioritizing the universe of existing -and presently not tested- APIs for testing and which tests and testing methodology can be used to efficiently determine environmental risks

EFPIA Contribution:

Cooperate with successful applicant consortium partners and stakeholder advisory group in developing recommendations, illustrate realistic scenarios in API research and development

WORK PACKAGE 6: PROJECT MANAGEMENT

Expected Applicant Contribution:

Demonstrated success at managing large consortia particularly those at an international level is required for a project of this complexity, along with the ability to manage all administrative and coordination activities and to provide the best possible interaction of the applicant consortium with the EFPIA consortium. It is expected that the project management should also support the interaction with the stakeholder advisory group and the dissemination of project outcome information.

EFPIA Contribution:

The project coordinator and the deputy coordinators will cooperate with the project management to ensure that the project goals and timelines are fulfilled. The project coordinators and deputies will also coordinate the scientific information flow from the work packages and work together with the project management to organise appropriate fora for discussions and information exchange, such as meetings and telephone conferences.