



6th Call for proposals 2012

Innovative Medicines Initiative

Version 1.3

Table of Contents

GENERAL PRINCIPLES	2
COMBATING ANTIBIOTIC RESISTANCE: NEWDRUGS4BADBUGS (ND4BB)	6
TOPIC 1 - INNOVATIVE TRIAL DESIGN & CLINICAL DRUG DEVELOPMENT	15
SUBTOPIC 1A	20
SUBTOPIC 1B	23
SUBTOPIC 1C ¹	33
TOPIC 2 - LEARNING FROM SUCCESS AND FAILURE & GETTING DRUGS INTO BAD BUGS	42

¹ To be launched later this year under a new Call by IMI JU

GENERAL PRINCIPLES

The Innovative Medicines Initiative Joint Undertaking (IMI JU) is a unique pan-European public private partnership between the European Commission and EFPIA² 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 6th Call 2012 for proposals consists of one Theme: Combating Antibiotic Resistance: NewDrugs4BadBugs (ND4BB) which falls under one of the new key research priorities: 'infectious diseases', which is correlated to the following Area of Interest: Disease Drug Efficacy.

Alignment with the EU strategy and action plan on anti-microbial resistance (AMR)

Antimicrobial resistance (AMR) is now a major global public health threat. 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. Despite the recognized need for new antimicrobials for clinical use, the reality is that only two new classes of antibiotics have been brought to market in the last 30 years and many drug developers have left the field.

ND4BB is part of the "Action plan against the rising threats from Antimicrobial Resistance" adopted by the European Commission³ 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:

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 programme for research on new antibiotics aimed at improving the efficiency of research and development of new antibiotics through unprecedented open sharing of knowledge. [...]

The current Call is fully in line with the announced action plan and aims to join forces between public and private partners in order to bring new antimicrobials closer to patients, to share information and to boost research on improving the uptake (and decreasing the efflux) of antibiotics into Gram-negative bacteria which is one of the greatest challenges facing drug discovery for Gram-negative pathogens.

² European Federation of Pharmaceutical Industries and Associations – www.efpia.eu

³ http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf

The current Call includes the first projects to be funded under this initiative. Future Calls will also include projects focused on the discovery of novel agents targeting Gram-negative pathogens.

The IMI 6th Call 2012 consists of two topics:

- Topic 1 : Innovative Trial Design & Clinical drug development
 - Subtopic 1A: Workpackages 1-4 (WP1-4)
 - Subtopic 1B: Workpackage 5 (WP5)
- Topic 2 : Learning from success and failure & Getting Drugs into Bad Bugs

Applicant Consortia are invited to submit expressions of interest to any of the above mentioned (sub)topics (i.e. Topic 1 Subtopic 1A, Topic 1 Subtopic 1B and/or Topic 2), but will not be obliged to apply for the other (sub)topics.

For Topic 1, at the second stage the successful Applicant Consortium for each subtopic will merge with the EFPIA consortium to prepare the full project proposal. All participants working under Topic 1 will be part of the same Grant Agreement.

The expressions of interest should address all aspects of the (sub)topic to which the Applicant Consortia are applying.

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

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 6th Call 2012 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.

Please note that Topic 1 Subtopic 1C (WP 6&7) as outlined in the present Call text will be launched later this year under a new Call for Proposals by the IMI JU. Further details will be provided in the specific text of this future Call.

Future Calls by the IMI JU addressing further research topics in relation to antimicrobial resistance with a specific focus on tackling Gram-negative pathogens will follow.

DURATION OF THE PROJECTS

The indicative duration of the project for Topic 1 is up to 7 years and for Topic 2 is 5 years.

FUNDING OF THE PROJECTS

For this Call:

- the total available financial contribution from the IMI JU to participants eligible for funding will be a maximum of 95 % of the amounts that the research-based

companies that are members of the European Federation of Pharmaceutical Industries and Associations (EFPIA) will contribute as 'in kind'⁴ contribution.

- the indicative EFPIA in kind contribution will be EUR 114 700 000.
- the IMI JU financial contribution will be up to EUR 109 000 000.

The indicative IMI JU contribution will be divided between the two Topics as follows:

Topic 1: Innovative Trial Design & Clinical drug development: up to EUR 93 million

- Subtopic 1A: WP1-4 (EUR 5M)
- Subtopic 1B: WP5 (EUR 88M)

Topic 2: Learning from success and failure & Getting Drugs into Bad Bugs: up to EUR 16 million

This Call will result in specific projects, for which costs incurred by EFPIA companies for prospective research activities carried out outside a Member State or an associated country (hereinafter referred as to “non-EU EFPIA in kind contributions”) will be considered as part of the EFPIA in kind contribution to the IMI research activities. As a rule for special projects derived from topics of interest for 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 research into rare diseases or disease areas of high public interest where creation of a critical mass of research is needed. The Special Clause 13b) applicable to the IMI model Grant Agreement, according to which there is no maximum limit of 10% per project but a global cap at the IMI programme level of 30% of the total committed EFPIA in kind contribution, shall apply to the grant agreements to be signed between the successful full consortia and the IMI JU.

The Applicant Consortia shall keep in mind that the budget of each expression of interest should 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 6th Call is 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.

In preparing their EoIs, the Applicant Consortia should carefully consider the research contribution that an EFPIA Consortium will make to a given project as well as the expectations from the Applicant Consortia, as outlined in the topic texts below.

⁴ In kind contribution is e.g. personnel, clinical research, equipment, consumables.

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

For Topic 1, the Applicant Consortia with the highest ranked EoI(s) for each subtopic (Subtopic 1A and Subtopic 1B) will be invited to merge and to jointly develop a full project proposal together with the EFPIA Consortium.

It should be noted that in accordance with the *“IMI JU Rules for submission, evaluation and selection of Expressions of Interest and Full Project Proposals”*, any arrangements for clustering or merging expression of interest may be dealt with at the stage of the full project proposals.

For Topic 2, the Applicant Consortium with the highest ranked EoI for each topic will be invited to jointly develop a full project proposal together with the EFPIA Consortium.

For both topics, 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* published on the IMI JU website www.imi.europa.eu at the launch of the 6th Call.

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* 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 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* (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.

COMBATING ANTIBIOTIC RESISTANCE: NEWDRUGS4BADBUGS (ND4BB)

BACKGROUND

Antimicrobial resistance (AMR) is now a major global public health threat. 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 ECDC/EMA joint technical report "The bacterial challenge: time to react", 2009).

Despite the recognized need for new antimicrobials for clinical use, the reality is that only two new classes of antibiotics have been brought to market in the last 30 years and many drug developers have left the field. This is largely driven by the fact that development of antibiotics for the treatment of resistant infections is not a financially viable option for drug developers. Due to the potential low level use of some antibiotics, companies are unable to recoup their costs as they are effectively generating drugs to support society that will only be used under limited circumstances resulting in the cost of development often being greater than the potential return. This has led to few companies remaining dedicated to addressing this essential societal need. If this situation continues with no intervention there will even fewer companies left focusing on AMR thus leaving society in a situation where prescribers will face few, if any, therapeutic options to treat bacterial infections. For the sake of maintaining quality of life, it is essential that the antibiotic research community works together to ensure that societal needs for novel and effective antibiotics remain fulfilled for the foreseeable future.

In view of the enormity of this global health threat the European Commission is committed to combating AMR which is outlined in its recent communication to the European Parliament and Council entitled 'Action plan against the threats from antimicrobial resistance' (COM (2011) 748) (http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf). The European Federation of Pharmaceutical Industries and Associations (EFPIA) share the views of the EC, and recognize that although a number of activities have already been undertaken at the EU (including FP7 funded activities) and international level, including the Trans-Atlantic Task Force on Antimicrobial Resistance, more concrete actions need to be materialized to make a meaningful change. Both parties agree that in order to make significant progress in this field there is a need of an unprecedented level of collaborative research and development.

ND4BB therefore forms an integral part of the broad EU strategy and action plan on anti-microbial resistance adopted by the EU with the support of Member States. Action 6 reads:

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 programme for research on new antibiotics aimed at improving the efficiency of research and development of new antibiotics through unprecedented open sharing of knowledge. [...]

The current Call presents the first projects to be funded under this initiative and is an example of the type of studies that will be conducted. Future Calls will also include projects focussed on the discovery of novel agents targeting Gram-negative pathogens.

THE SPECIFIC OBJECTIVES OF ND4BB

The goal of this new research programme is to create an innovative and collaborative public-private partnership (PPP)-based approach that will positively impact all aspects of antimicrobial resistance (AMR), from the discovery of novel products to Phase 1, Phase 2, and Phase 3 clinical trials. This will increase the probability of success of developing new and effective antibiotics for the treatment or prevention of infections caused by resistant pathogens as well as the consequences of those infections.

The focus of the work in the entire ND4BB programme will be on products targeting treatment, prevention, or management of the sequelae of infections due to resistant priority bacterial pathogens (e.g. one or more of the following: Enterobacteriaceae (specifically *E. coli*, *K. pneumoniae* and *Enterobacter* species), *Acinetobacter*, *Pseudomonas*, *Clostridium difficile*, or methicillin-resistant *Staphylococcus aureus* (MRSA)).

An important aim of ND4BB is also to develop a data repository that is sustainable beyond the life of the current programme, so that ND4BB will provide a key information base for research projects focused on antibiotic resistance. All consortia participating in projects running under the ND4BB research programme will be expected to deposit data in the ND4BB data hub and work together to share data and experience as widely as possible amongst all programme members and the antibiotic community as a whole.

Finally, ND4BB will establish a network of investigators that will exist beyond the life of these particular IMI Calls.

Programme Architecture

Under the research programme on antimicrobial resistance, NewDrugs4BadBugs (ND4BB), the present Call consists of 2 topics:

- **Topic 1: Innovative Trial Design & Clinical Drug Development**
 - **Subtopic 1 A: WP 1-4** (€ 3M EFPIA/€ 5M IMIJU)
 - **Subtopic 1B: WP5** (€ 103.7M EFPIA/€ 88M IMIJU)
- **Topic 2: Learning from success and failure & Getting Drugs into Bad Bugs** (€ 8M EFPIA/€ 16M IMIJU)

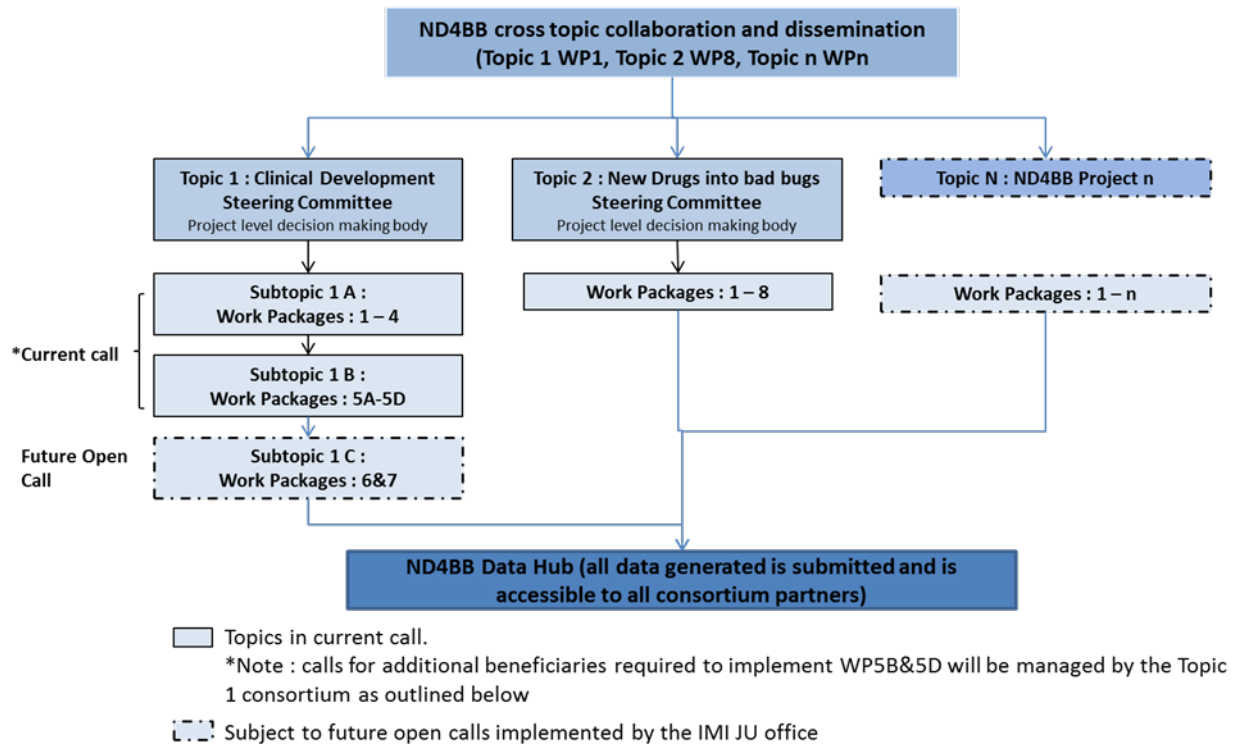
Future Additional Calls

A further subtopic forming part of Topic 1 will be launched later by the IMI JU under a new open Call: **Subtopic 1C - Topic 1: WP6&7**: (indicatively € 276M EFPIA/€ 92M IMIJU)

Applicants for the current Call should not present at this stage a proposal for this subtopic 1C as outlined in WP6&7 however it is already described in this document as it forms an integral part of the planned overall ND4BB programme combating AMR: Innovative Trial Design & Clinical Drug Development and will form part of the same Grant Agreement as subtopic 1A and 1B

The ND4BB programme is also expected to be expanded in the future Calls with further research topics that will include the discovery of new molecular entities for the treatment of Gram-negative pathogens, and may include discovery of robustly validated host (human) targets for bacterial infections, regulatory/responsible use of antibiotics, and additional clinical development programmes.

Summary of the overall research programme architecture



Points of note:

- An Applicant Consortium can apply for one of the topics of the Call and will not be obliged to apply for the other topics.
- For Topic 1 an Applicant Consortium is invited to submit an expression of interest (EoI) to any of the subtopics but will not be obliged to apply for both. At the second stage the successful Applicant Consortium for each subtopic will merge with the EFPIA consortium to prepare the full project proposal. All participants working under Topic 1 (i.e. subtopics 1A, 1B and later on 1C) will be part of the same Grant Agreement.
- Applicants for Topic 1 subtopic 1B (WP 5), should bring forward proposals for investigating novel endpoints/biomarkers with the understanding that gathering these endpoints must be successfully combined with the pre-defined primary outcome data.
- An Applicant Consortium is expected to address all WPs for the chosen Topic or subtopic.
- All Applicant Consortia should include provision of plans and resources to support collaboration between projects funded under ND4BB. A dedicated workpackage has been allocated to this task in both Topic 1 and Topic 2. It is envisaged that this will be a shared activity across the projects generated by the current Call and also for those in future ND4BB projects.
- All Consortia participating in topics running under the ND4BB research programme will be expected to deposit data in the ND4BB data hub and to participate in cross project team meetings as appropriate to ensure

learnings, knowledge and skill sets are maximized across the ND4BB teams.

- Funding for the clinical trials running under Topic 1 will be allocated in a stepwise manner including additional Calls for beneficiaries or following milestone review as outlined in the workpackage description. Where, following milestone reviews, for the running of the clinical trials outlined in the WP(s) description additional expertise is required for their implementation, open and competitive Calls for selecting additional beneficiaries will be organized by the consortium according to the Call process hereafter described.

PROBLEM STATEMENT

Despite the recognized need for new antimicrobials for clinical use, 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

- 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 preventing 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 it an unattractive area for drug developers therefore limiting the future antibiotic pipeline.

Major pharmaceutical companies are leaving antibiotic drug discovery

The size and cost of an antibacterial clinical trial is dictated by the need to enroll enough patients to ensure a meaningful number of patients with resistant infections are encompassed in the trial. As enrolment must often be on an empirical basis, this dictates large trials which significantly drive up the overall development costs for new antibiotics targeting resistant pathogens. Coupled with the designs for equivalence studies having to target a 10% delta for the lower limit of the confidence interval the cost and also the practicalities of running such studies has contributed to a significant decrease in the number of antibiotics currently under development. This is largely driven by the fact that development of antibiotics for the treatment of resistant infections is not a financially viable option for drug developers. Due to the potential low level use of some antibiotics, companies are unable to recoup their costs as they are effectively generating drugs to support society that will only be used under limited circumstances resulting in the cost of development often being greater than the potential return. This has led to few companies remaining dedicated to addressing this essential societal need. If this situation continues with no intervention there will be even fewer companies left focusing on AMR thus leaving society in situation where prescribers will face few, if any, therapeutic options to treat bacterial infections. For the sake of maintaining quality of life, it is essential that the antibiotic research community works together to ensure that societal needs for novel and effective antibiotics remain fulfilled for the foreseeable future.

Pharmacokinetic/pharmacodynamic modeling, optimal patient selection and innovative trial design all have the potential to result in smaller, more efficient clinical trials thus reducing the cost of antibiotic development. In order to achieve this it is essential to

combine data from clinical studies conducted using an array of study designs and the knowledge and experience of investigators regularly involved in running clinical trials to support registration of new drugs. Topic 1 of this Call aims to address this problem.

Resistance is continually emerging: MRSA

Methicillin-resistant *Staphylococcus aureus* (MRSA) remains worldwide a major threat, and is the most important cause of antibiotic-resistant healthcare-associated infections worldwide. Infections with MRSA result in prolonged hospital stay and increased mortality rates. Although some European countries have reported decreasing trends for MRSA in recent years, the opposite trend is observed in other countries, and the proportion of invasive *S. aureus* isolates that are MRSA remains above 25% in more than one quarter of EU countries (ECDC data).

Given the fact that it takes at least 10 years to deliver efficacious medicines to patients it is crucial that the research delivers agents able to address any future unpredictable epidemiology changes in Europe such as increases in the prevalence of MRSA, increase in resistance to current MRSA agents and the emergence of other resistances in *S. pneumoniae* (eg quinolone resistance). Through Topic 1 ND4BB aims to develop new oral agents targetting MRSA infections and other multi-resistant pathogens which will provide prescribers with the much needed range of therapeutic options to treat bacterial infections.

Resistance is continually emerging: Gram-negative pathogens

A major challenge in the discovery of new agents against Gram-negative pathogens is their inherent low permeability coupled with multiple mechanisms for rapid efflux of agents out of the cell. This results in the need for high doses of drug to be administered to achieve efficacious intracellular concentrations, thus leaving a very small therapeutic range where efficacy can be achieved in the absence of toxicity. This represents real, unsolved problems for drug discovery efforts, wherein increased knowledge of either process could greatly facilitate the development of next-generation antibiotics for Gram-negative infections. One already well-studied example of such an approach is combining siderophores with known antibacterial scaffolds. The siderophore portion of the drug binds iron, which is then recognized by cellular uptake machinery in bacterial cells. The result is much more efficient penetration of the agent into the cell where it can have its antibacterial effect, thereby increasing the potency of a given antibacterial agent. Although this example can be productive it is not generally applicable to antibiotic drug discovery. Efforts are therefore required to study these processes and apply learnings to drug discovery efforts in a practical way. Through Topic 2, ND4BB aims to identify other approaches for hijacking uptake pathways and create a more robust understanding of how to rationally design compounds with improved penetration and decreased efflux. This work will provide key fundamental science to increase the success of creating a more robust pipeline of new Gram-negative targeted antibacterials to meet the ever-growing unmet medical need.

Future topics developed for launch under the ND4BB programme will focus on developing novel agents for Gram-negative infections.

Downstream sequelae of resistant infection

Control of the bacterial infection is not always adequate to save a patient's life. Uncontrolled bacterial infections may also trigger the syndrome of sepsis, the body's response to infection. The accompanying syndrome of sepsis triggered by the infection adds to the morbidity and mortality of both antibiotic-resistant and –susceptible infections. Sepsis arises through the body's response to infection and covers a diverse spectrum of illness ranging in severity from mild systemic inflammation to multi-organ

system failure in septic shock and progression is in proportion to the lack of control of the infection which is more pronounced when initial empiric antibiotic therapy is unsuccessful. Furthermore antibiotic-resistant infections may benefit especially from adjunct measures to control sepsis.

Although it is thus possible that patients with drug-resistant bacterial infections may receive more benefit from the availability of a sepsis therapy, patients with infections of any type (both drug-resistant and –susceptible) will benefit. More rapid control of sepsis should reduce the need for extended courses of antibiotics, thus addressing the broad stewardship goals of the antibiotic community.

The consequences of sepsis can be prolonged and uncontrolled sepsis can be fatal even as the underlying infection is coming under control. Thus through Topic 1, ND4BB also supports a programme focused on a novel therapy for this problem.

In addition, including AZD9773 in ND4BB supports growth of the investigator network. The study of AZD9773 requires investigators capable of doing hospital-level research in critically ill patients - the same type of patients most at risk for drug-resistant bacterial infections.

A platform for collaboration

A general challenge in many areas of drug development is a lack of mechanisms through which investigators 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 development process. A common element in both Topic 1 and Topic 2 is to drive the sharing of data and knowledge to increase the probability of success in the development, thus accelerating the delivery of quality medicines to patients.

NEED FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

The extent of action required to significantly impact the challenges facing the discovery and development of novel antibacterial agents is too great for any single entity; collaboration is essential. Furthermore the diversity of skill sets 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 that the industry faces and consequently a framework for sharing knowledge and resources across companies, SMEs and academia is needed to increase the success of antibiotic R&D.

Specific approach for accepting non-EU contribution 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, 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” published on the IMI website www.imi.europa.eu).

The benefit to Europe of implementing Special Clause 13b)

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 in the EU. This does not only cover funding for the implementation of

clinical trials but also a substantial budget to support innovative research in to biomarker/diagnostic development as well as discovery activities to be conducted in Topic 2.

The opportunity to build a network of investigators through which pharmaceutical and biotechnology companies can advance the clinical development of new assets will attract future clinical trials to Europe. Indeed 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: The opportunity to work with leading experts in the field to tackle major bottlenecks such as influx and efflux from Gram negative pathogens, clinical trial design and implementation and the development of a clinical trial network to support future clinical trials

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

The proposed topics address areas for which there are complementarities/synergies with other initiatives on AMR in particular:

- Joint Programming Initiative AMR
- 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>
- NIH initiative to set up a clinical research network on antimicrobial resistance: <http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-12-019.html>
- Potential synergies may be developed with existing IMI projects such as RAPP-ID. This project deals with the development of rapid point-of-care test platforms for infectious diseases and will tackle the problem of early diagnosis of microbial resistance. The work of RAPP-ID will bring important contributions to the testing of new antibiotics in clinical trials.
- Portfolio of FP7-funded projects in the area (see http://ec.europa.eu/research/health/infectious-diseases/antimicrobial-drug-resistance/index_en.html)

The expressions of interest should clearly outline the unique properties of the proposed plan of work and also how potential interaction with these initiatives would be managed, avoiding at the same time potential duplications and overlaps of activities.

TOPIC 1

Innovative Trial Design & Clinical Drug Development

Activities to be undertaken in Topic 1 will be staged according to pre-defined milestones. Applicants for the current Call should propose innovative research approaches to WPs 1-4 (subtopic 1A) and/or WP5 (subtopic 1B). Applicants applying for subtopic 1A are not obliged to apply for subtopic 1B and vice versa. The decision to fund WP5B and WP5D will depend on the outcomes of WP5A and WP5C and may be subject to additional Calls from within the consortium for additional beneficiaries required to perform this work.

Subtopic 1C (WPs 6 & 7) will be subject to further Calls to be launched by the IMI JU – applicants should not propose a plan of work to address WP6&7 at this stage.

Subtopic 1A

- WP1 Project Management, Collaboration and Dissemination
- WP2 Establishment & Training of an Investigator Network
- WP3 *In vitro* microbiology Surveillance and Epidemiology dataset
- WP4 Improvements in data-driven design of Phase 2 and 3 clinical trials

Subtopic 1B

- WP5 Conduct of Clinical Trials supporting the development of GSK1322322:
 - WP5A: Evaluation of GSK1322322 in acute bacterial skin and skin structure (ABSSSI) (M1-21);
 - WP5B: GSK1322322 Phase III Trial: IV treatment of ABSSSI with oral step down (M18-M38);
 - WP5C: Phase 2IIb: GSK Compound GSK1322322 for hospitalised CABP (M1-M21)
 - WP5D: GSK1322322 Phase III Pivotal hospitalized CABP Trials (M20-M44)

Subtopic 1C - To be launched later as new Call by the IMI JU:

- *WP6: Conduct of Clinical Trials supporting the development of MEDI4893, a monoclonal antibody targeting S. aureus alpha toxin:*
 - *WP6A : Epidemiologic Surveillance of Surgical Site Infections in the European Union ; WP6B : Prospective observational study to evaluate the natural history of Staphylococcus aureus (including MRSA) surgical site infections (SSIs) in the European Union;*
 - *WP6C : Phase 1b/2 randomized, placebo-controlled, single-dose, dose ranging study to evaluate the safety, pharmacokinetics and efficacy of MEDI4893 for prevention of Staphylococcus aureus (including MRSA) ventilator associated pneumonia (VAP));*
 - *WP6D : Phase 1b/2 randomized, placebo-controlled, single-dose, dose ranging study to evaluate the safety, pharmacokinetics and efficacy of MEDI4893 for prevention of surgical site infections (SSIs) attributable to Staphylococcus aureus;*
- *WP7: Conduct of Clinical Trials supporting the development of AZD9773, a polyclonal ovine FaB fragment directed at tumor necrosis factor alpha (TNF-α) for the treatment of the severe sepsis, including septic shock ;*

OVERALL OBJECTIVES OF TOPIC 1

- Increase the efficiency of antibiotic R&D through analysing pre-clinical and clinical data sets shared and making recommendations for the development of novel antibiotic agents. In particular to define and standardize the most clinically relevant pre-clinical assays, to enhance the application of PK/PD to pre-clinical data to improve the ability of pre-clinical data to inform clinical study design and to utilize comparator data to inform novel clinical trial design to reduce the burden on Phase 2 and Phase 3 trials, therefore making the development of antimicrobial products more feasible.
- Establish investigator networks and surveillance programmes to support antibacterial clinical development
- Conduct prospective clinical trials with novel trial designs to deliver safety, pharmacology, and proof of efficacy data for novel agents directed towards treatment, prevention or sequelae of infections due to priority pathogens and if possible to validate novel bacterial identification diagnostics or clinical endpoints with the aim of reducing the size and cost of clinical trials.

OVERALL EXPECTED DELIVERABLES OF TOPIC 1

- Successful Phase 1, Phase 2, and/or Phase 3 clinical trials demonstrating the pharmacology, safety, and efficacy of new antibiotics against priority pathogens.
- Global surveillance and epidemiological data relevant to the future use and development of novel products
- Good Clinical Practice (GCP)-qualified investigational centers (with a focus on European geographic regions with high levels of resistance) with all necessary training, test materials, and instrumentation to conduct clinical studies of drugs and diagnostic devices
- Functioning investigator network(s) for the conduct of antibacterial clinical trials and non-interventional trials,
- Novel clinical trial design proposals
- Novel diagnostics and/or endpoints

INDICATIVE DURATION OF THE PROJECT

The indicative duration will be 7 years, but may be less depending on the eventual study designs implemented. Current estimated start dates and WP durations are indicated in the text below.

INDICATIVE BUDGET

Subtopic 1A: WP1-4: Indicative in kind contribution from the EFPIA companies is estimated at approximately € 3 M and IMI JU contribution will be € 5M.

Subtopic 1B: WP5A-5D: Indicative in kind contribution from the EFPIA companies is estimated at approximately € 103.7 M and IMI JU contribution will be € 88 M (of which: €15-20M for biomarker/diagnostic research (i.e. 3-4M per study) - € 68-73M for the clinical studies per se).

Approximately 23% (about € 20 M) of the available funding for Subtopic 1B should be allocated to subcontracting a CRO to implement and monitor the clinical trials. This represents approximately 11% of the total clinical study costs and approximately 10% of the current total requested IMI JU budget for ND4BB. Overall GSK will fund 64% of the total CRO costs. Applications should assume the requirement for subcontracting to a CRO in compliance with applicable rules and regulations. In order to cover the funding gap arising out of the maximum 75% reimbursement of research activities, GSK will provide as part of its in kind contribution a direct financial contribution to concerned beneficiaries.

*For Subtopic 1C to be launched later under a new Call by the IMI JU:
WPs 6 & 7: Indicative in kind contribution from the EFPIA companies
for WPs 6 & 7 is estimated at approximately € 276 Million and IMI JU
contribution will be € 92 Million.*

*The Call text will provide further details of the requirements from
beneficiaries, recruitment requirements and study design and outline
how new beneficiaries will be expected to provide input into WP1-4
(subtopic 1).*

Allocation of funding and milestone/progression decisions for WP5 (Subtopic 1B)

The Applicant Consortium should initially apply with proposals to address **WP5A and WP5C** including suggestion for additional endpoints or for collection of samples for diagnostic or biomarker analysis with the understanding that gathering these endpoints must be successfully combined with the pre-defined primary outcome data.

It should be noted that approximately € 3-4M per study is available for biomarker/diagnostic research. Drug discovery is a highly risky business with only very few potential candidates making it all the way through clinical development. Due to this inherent risk, funding for WP5B and WP5D will be released following successful milestone completion. The decision making criteria to be used at each of these milestones will be included in the full project proposal and therefore subject to peer review to ensure transparency of the decision making process.

Specifically for GSK1322322 the decision to progress to funding of WPs 5B and 5D:

- The initiation of WP5B will be dependent on successful completion of WP5A demonstrating non-inferiority to the comparator linezolid, and positive results /trends in WP5C demonstrating the GSK1322322 shows strong promise as a CABP antibacterial agent.
- The key criteria for WP5D will be successful completion of WP5C & WP5A. Successful completion will be primarily defined as comparable safety and tolerability to the control treatment arm of the trial and similar efficacy.

If required, additional Calls will be launched from within the consortium to identify additional beneficiaries required to ensure successful delivery of WPs 5B and 5D.

Irrespective of the therapeutic area drug discovery has unpredictable risks and consequently there are contingency plans in the event that GSK 1322322 fails for scientific reasons during development. In such a scenario, GSK intends to replace this with a molecule being developed for CABP, ABSSI (currently in Phase 1 clinical trials) or a compound being developed for prevention or treatment of other severe hospitalised infections such as complicated urinary tract infections (UTI), hospital-acquired pneumonia, ventilator associated pneumonia or intra – abdominal infections. The proposal for introduction of this molecule would form part of the milestone review and subsequent release of funding. The full details of these molecules will be included in the full project proposal where scenario planning will be presented.

The open Call process for additional beneficiaries to perform tasks in WP5 (Subtopic 1B)

Call process

When open Calls from within the existing consortium are required to engage additional beneficiaries, these will be handled by the consortium with guidance from the IMI JU. The consortium will propose procedures for implementing open and competitive Call(s) in order to recruit investigators for the conduct of clinical trials as required in response to protocol requirements. The procedures will be based on the below guiding principles and will comply with the conditions established in the IMI model grant agreement⁵:

- 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 at least in 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:

⁵ The IMI model grant agreement (IMI-GB-DEC-2012-8) will be amended in order to introduce the specific provisions establishing the process for launching open and competitive calls for the selection of additional beneficiaries.

- 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 45 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.

EFPIA PARTICIPANTS

GlaxoSmithKline, AstraZeneca, Janssen R&D, Sanofi

PROPOSED PROJECT OUTLINE

Subtopic 1A

Key objectives

- To establish investigator networks and surveillance programmes to support antibacterial clinical development
- To increase the efficiency of antibiotic R&D through analysing pre-clinical and clinical data sets shared and making recommendations for the development of novel antibiotic agents. In particular to define and standardize the most clinically relevant pre-clinical assays, to enhance the application of PK/PD to pre-clinical data to improve the ability of pre-clinical data to inform clinical study design and to utilize comparator data to inform novel clinical trial design to reduce the burden on Phase 2 and Phase 3 trials, therefore making the development of antimicrobial products more feasible.

WP1: ND4BB Project Management, Collaboration and Dissemination

The main purpose of this WP will be to ensure effective Project Management, manage the process for additional Calls from within the consortium, ensure collaboration between Topic 1 investigators, additional ND4BB projects and those in other consortiums AMR research area/ND4NN programme and ensure coherent dissemination of ND4BB results to the broader scientific community.

In order to ensure effective communication and collaboration between projects funded under the ND4BB programme, a dedicated team will work with members of the other Topic teams to:

- Develop standard communication tools for all the projects funded under the AMR research area/ND4BB programme, e.g. standard templates, externally facing website etc.
- Ensure ND4BB dissemination to the external community is coherent and aligned across all projects /website strategy etc
- Ensuring data from all projects is deposited in the ND4BB data hub in accordance to the ND4BB framework
- Arrange bi-annual meetings between all ND4BB investigators
- Establish a ND4BB Scientific Advisory Board consisting of leading academics and key stakeholders

In addition, the workpackage will be responsible for developing and implementing a Call process for additional beneficiaries as required to conduct the clinical trials outlined in WPs 5B and 5D.

This WP should be co-led by project Leaders from projects funded under the ND4BB programme.

EFPIA Partner Contribution: Project/Alliance Management personnel, meeting facilities, communication expertise.

WP2: Establishment & Training of an Investigator Network

This workpackage will build a network of investigators targeting areas of high resistance with shared interest and expertise in specific clinical infections (e.g. pneumonias, urinary, skin, intra-abdominal & bloodstream infections) who are specialists in the conduct of clinical trials for regulatory approval of new antibiotic

agents. It is expected that in collaboration with EFPIA partners, experienced clinical investigators will function as coordinators and mentors within this network, facilitating the sharing of appropriate information between network members and providing training to new investigators. The aim will be to establish a network of investigators and sites with 1) experience and know how to conduct clinical trials in compliance with Good Clinical Practice standards (this would include having a high quality Clinical Microbiology Laboratory that can meet study requirements); and 2) an excellent understanding of international regulatory processes and the evolving regulatory landscape. Investigators will also function as a network as regards to sharing of information related to clinical care of specific diseases, assisting in the design and execution of clinical trials for compounds in clinical development and supporting interested new investigators to become part of the network. The establishment of this network is independent of the conduct of clinical trials as outlined below and should not be limited to the investigators of the consortium who implement the studies in WP4 Topic 1. It is envisioned that this Investigator Network will serve as a potential source of future investigator consortia who would apply for subsequent workpackages involving clinical trials.

Epidemiological research studies (sometimes also called Phase 0 studies) are needed to describe the burden of disease and support the design of Phase 1, 2, and 3 clinical studies. Implementation of such studies in Topic 1 will provide members of the investigator network with opportunities for training and experience in data collection and epidemiological research. Furthermore, these studies will promote the standardization of collection methods and instruments for these data and, as a consequence, describe the frequency and determinants of disease across the EU, in spite of country-specific differences.

EFPIA member contribution: Provision of workshops/seminars/Q&As. Sharing of learnings from HIV clinical networks and running clinical trials in emerging economies. Information/expertise in clinical trial design, regulatory requirements, Clinical Microbiology requirements and data quality standards.

WP3: *In vitro* microbiology Surveillance and Epidemiology dataset

Clinical trials for both therapeutic and prophylactic agents could be more effectively designed and executed if pre-existing detailed microbiology surveillance and epidemiology data (including specimen type, associated clinical information, institutional antibiotic use restrictions, etc) was available throughout Europe. Antimicrobial susceptibility surveillance data as well as molecular epidemiology data on resistant pathogens is limited in some EU geographic regions, particularly in Eastern Europe. An assessment of pre-existing resistance to current agents as well as new antibiotics is needed. Developing data on clinical consequences of some microbiological observations (e.g., frequency of clinical infections requiring therapy in patients colonized with selected organisms) might also be useful.

It is envisaged that the consortium would create study protocols and determine the pathogens, antimicrobial agents, clinical correlates (if appropriate), and analysis of the data.

The critical goal of this work will be to assess the activity of novel antibiotics that are not yet in clinical use against very large and diverse collection of pathogens from different countries to inform the extent of pre-existing resistance which could also identify countries which higher resistance rates which could inform the

use of the drug in those countries. Additional useful data will also be created in these studies. For example as a set of standard of care antibiotics will be used as controls and comparators in these studies, data on these established antibiotics will further inform resistance trends and augment any ongoing EU resistance surveillance programmes.

All data generated will be gathered in the ND4BB data hub and disclosed publically through the ND4BB website.

EFPIA member contribution: To provide clinical microbiology expertise in designing the surveillance programme and framework of data to be collected. To contribute to protocols and provide new antimicrobial agents targeting priority pathogens for *in vitro* MIC testing as well as standard of care agents.

WP4: Improvements in data-driven design of Phase 2 and 3 clinical trials

This workpackage will deliver strategies that may yield more effective Phase 2 and 3 clinical trial programmes in support of antibacterial drug development efforts. Examples of research questions that could inform these strategies include

- How can the extensive knowledge base of preclinical *in vitro* microbiological and *in vivo* animal infection data be used to inform the prior distributions describing patient efficacy in disease models supporting Bayesian-based Phase 2b or Phase 3 dose-finding or efficacy trials?
- Given that suboptimal dosing cannot be studied in patient clinical trials, what dose response design optimally informs the decision of a dose to progress into Phase 3?
- How can historical clinical trial data on an active comparator as well as Phase 2 trial data on the test agent and the active comparator be used to reduce the burden on Phase 3 trials?

Any agreement on use of these approaches will rely on existing data (from industry or public partners) demonstrating such an approach is appropriate. Therefore, data will be needed from preclinical experiments (i.e., PK/PD drivers, PD target values and % Target Attainment values) as well as historical clinical trial data. The consortium will compile a set of data for all indications to help this assessment and provide a central data repository (as formed in Topic 2). In addition, it will be necessary to develop specific proposals on how the various pieces of information may be utilised to support regulatory filings. These proposals will be discussed in the first instance with the ND4BB Scientific Advisory Board which will be nominated during the full project proposal drafting stage. An alternative to formal quantification, where there is focus on the overall weight of evidence from the PK/PD information (Phase 1 trials) and supportive Phase 2 and microbiological data when assessing the Phase 3 programme requirements will also be considered.

EFPIA Partner Contribution: Data, statistical (i.e., Bayesian) and PK/PD modeling and simulation expertise.

Subtopic 1B

Key objective

- To conduct prospective clinical trials with novel trial designs to deliver safety, pharmacology, and proof of efficacy data for novel agents directed towards treatment, prevention or sequelae of infections due to priority pathogens and if possible to validate novel bacterial identification diagnostics or clinical endpoints with the aim of reducing the size and cost of clinical trials.

WP5: Conduct of Clinical Trials supporting the development of GSK1322322

GSK1322322 is an antibacterial agent currently in development that inhibits bacterial peptide deformylase (PDF) function, a clinically unexploited target. GSK1322322 demonstrates targeted antibacterial activity against multi-drug resistant respiratory and skin pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), and represents a new antibiotic class with a novel mode of action. The major unique attribute of the antibiotic is that it provides an oral treatment for MRSA which is a major pathogen in acute bacterial skin and skin structure infections (ABSSSI), VABP (ventilator-associated bacterial pneumonia, and associated with high mortality in hospitalised community-acquired bacterial pneumonia (CABP). Therefore, the clinical development programme is targeting studies to support the clinical use in both skin infections and severe/moderate lower respiratory tract infections, where MRSA can be a significant concern. GSK1322322 has demonstrated efficacy via oral administration against MRSA infections in a Phase 2 skin infection trial and will now be evaluated for efficacy in hospitalised CABP and further trials of ABSSI. Although MRSA will only be detected in a few patients in the Phase 2 hospitalised CABP trial, success in such patients and other patients with bacterial pneumonia will demonstrate the utility of the drug in covering MRSA in hospitalized patient with CABP and trigger the progression of IV & oral GSK1322322 in Phase 3 pneumonia clinical trials. A summary of protocols and a summary of the results of studies that have been completed previously with GSK1322322 can be found at: (<http://www.gsk-clinicalstudyregister.com/quick-search-list.jsp?item=GSK1322322&type=Compound&letterrange=G-K&studyType=All&phase=All&population=All&marketing=All>)

In all cases clinical trial designs for studies conducted under ND4BB will undergo scientific advice from the EMA and/or FDA prior to study initiation.

Evaluation of GSK1322322 in acute bacterial skin and skin structure infections (ABSSSI)

Clinical efficacy, defined as non-inferiority in the intent to treat (ITT) and the clinically evaluable (CE) population of 2 pivotal Phase III studies (WP5A is the first and WP5B the second), and non-inferiority in a combined analysis of modified intent to treat (MITT) population will serve as the basis for approval of a marketing authorization of GSK1322322 for ABSSSI. Based on recent guidance from the US FDA, the primary timepoint for analysis will be clinical improvement measuring change in entry criteria of fever, lesion size, and purulence at Day 3 or 4 (after at least 72 hours of therapy, though a co-primary endpoint will occur at the Test of cure visit (TOC) 10 to 14 days after the end of therapy in line with

EMA guidance. Photographs will be taken before treatment, and at end of therapy, and lesions size and fever will be recorded daily until the primary endpoint at Day 3. The total duration of therapy should be 7 to 10 days. **The Applicant Consortium is invited to suggest additional endpoints or propose collection of samples for diagnostic or biomarker analysis with the understanding that gathering these endpoints must be successfully combined with the pre-defined primary outcome data.**

The subjects must have either: severe cellulitis / erysipelas, (defined by size and accompanying signs of fever or adenopathy), a secondary wound infection, a major cutaneous abscess (enrollment of this group limited to 25% of total) or infected non life-threatening burns.

**WP5A GSK1322322 Phase III Trial: intravenous (IV) treatment of ABSSSI with oral step down option
(Estimated start: 1Q2013 – Duration: Month 1-21)**

Study preparation: Month 1-4

Study recruitment: Month 5-14

Study close out and report generation: Month 15-21

The Applicant Consortium should focus on site recruitment within the EU, i.e. those sites eligible for IMI JU funding. A total of **80 patients** should be recruited for this study in Europe as part of the global Phase III study. The other 552 patients will be recruited in the rest of the world and funded directly by GSK. **In addition the consortium should bring forward proposals for investigating novel endpoints/biomarkers with the understanding that gathering these endpoints must be successfully combined with the pre-defined primary outcome data.**

Objective: Pivotal global study to determine safety, tolerability and efficacy in subjects hospitalized with acute bacterial skin and skin structure infection (ABSSSI). Pharmacokinetic analysis in subset of subjects.

Design: Comparator-controlled (linezolid), double-blind, double dummy, randomized, parallel group, non-inferiority study in subjects ≥ 18 years of age with ABSSSI. IV to oral step down therapy.

Primary endpoint: clinical response at day 3-4 in ITT population

Co-primary endpoint: clinical response at TOC visit in the ITT and CE population

Non-inferiority margin: 10%

Sample size: clinical success rate in ITT population is assumed to be 82% in the sample size estimation. Using a randomization ratio of 1:1, the total sample size becomes **632**. If the pathogen recovery rate is 50% then two studies will have 632 subjects in MITT population. Using the same non-inferiority margin at 10%, this will ensure at least 90% power as long as the response rate in MITT population is 82% or higher.

Primary analysis population must receive a minimum of 24 hours (i.e., 2 doses) IV therapy, but no more than 10 days (20 doses) therapy. Limit the enrollment

of abscess with surrounding cellulitis to no more than 25% of total enrolment. Enrich MRSA yield by allowance of Hep C (+) and HIV infected (CD4 count greater than 200) into the study. Subjects can present with community onset ABSSSI, or nosocomial ABSSSI (must be culture positive for MRSA or MSSA only for nosocomial infections).

EFPIA contribution: Knowledge and expertise on GSK1322322. All study-implementation-related processes (study drug, regulatory support, project management, pharmacovigilance, clinical expertise etc). Direct financial contribution by the sponsoring EFPIA company to supplement the CRO subcontracting costs incurred by public partners ensuring that 100% of these costs will be reimbursed. Direct funding for the CRO.

WP5B: GSK1322322 Phase III Trial: IV treatment of ABSSSI with oral step down option
(Estimated start: 3Q2014 – Duration: Month 18-38)

The WP5B is subject to the outcome of WP5A and may be subject to an open call for including additional partners later based on milestones completion.

Study preparation: Month 18-21

Study recruitment: Month 22-32

Study close out and report generation: Month 32-38.

The Applicant Consortium should focus on site recruitment within the EU, i.e. those sites eligible for IMI JU funding. At total of **400 patients** should be recruited for this study in Europe. The other 232 patients will be recruited in the rest of the world and funded directly by GSK. **In addition the consortium should bring forward proposals for investigating novel endpoints/biomarkers with the understanding that gathering these endpoints must be successfully combined with the pre-defined primary outcome data.**

Objective: Pivotal global study to determine safety, tolerability and efficacy in subjects hospitalized with acute bacterial skin and skin structure infection (ABSSSI). Pharmacokinetic analysis in subset of subjects

Design: As in WP5A - Comparator to be selected.

EFPIA contribution: Knowledge and expertise on GSK1322322. All study-implementation-related processes (study drug, regulatory support, project management, pharmacovigilance, clinical expertise etc). Direct financial contribution by the sponsoring EFPIA company to supplement the CRO subcontracting costs incurred by public partners ensuring that 100% of these costs will be reimbursed. Direct funding for the CRO.

WP5C: Phase 2b: GSK Compound GSK1322322 for hospitalised CABP
(Estimated start: 1Q2013 - Duration: Month 1-21)

Study preparation: Month 1-2

Study recruitment: Month 3-15

Study close out and report generation: Month 16-21.

The Applicant Consortium should focus on site recruitment within the EU, ie those sites eligible for IMI JU funding. A total of **300 patients** should be recruited for this study in Europe. In total 300 patients are required for this study which is likely to require approximately 50-60 sites from the northern hemisphere to ensure adequate recruitment. In addition the consortium should bring forward proposals for investigating novel endpoints/biomarkers with the understanding that gathering these endpoints must be successfully combined with the pre-defined primary outcome data.

The ITT and clinically evaluable (CE) will be the primary populations, with co-primary endpoints of clinical success at Day 4, and at test of cure (TOC). Clinical efficacy measurement will include improvement in 4 pivotal symptoms (cough, purulence, chest pain, and dyspnea/ tachypnea) at the Day 4 timepoint, and overall clinical assessment at the TOC visit. The duration of therapy is 5- 10 days, with all patients initiating IV therapy, and allowed to switch to oral therapy after 4 doses (2 days) if clinical assessment allows it.

Objective: Dose range finding study to allow for selection of dose to progress into pivotal Phase III CABP studies. Study will further help to determine safety, tolerability and efficacy in subjects hospitalized with Community acquired bacterial pneumonia (CABP), as well as model the statistical effect of using a day 4 efficacy endpoint, based on pivotal symptoms, as it has been recently promoted by some authorities (US FDA). There will also be pharmacokinetic analysis in subset of subjects.

Design: Comparator-controlled (probably fluoroquinolone, such as levofloxacin), double-blind, double dummy, randomized, parallel group, non-inferiority study in subjects ≥ 18 years of age with hospitalized CABP treated with IV to oral step down therapy.

Primary endpoint: clinical response at day 4 in ITT population

Co-primary endpoint: clinical response at TOC visit in the ITT and CE population

Non-inferiority margin: 10%.

Sample size: Using hypothesis GSK1322322 and 1 arm utilizing levofloxacin will provide a power of 43.5% non-inferiority if the success rate at day 4 is 80%.

Further, as an additional goal of the study is to explore the effect of using Day 4 as a primary endpoint, based on the 4 pivotal symptoms, it may be more relevant to define the sample size based on the estimation purpose. 100 patients per arm is a good start for this purpose. Under this sample size, the precision is about 8%, which means a 95% confidence interval of (72%-88%) when the actual response rate is 80%.

EFPIA Partner Contribution: Knowledge and expertise on GSK1322322. All study-implementation- related processes (study drug, regulatory support, project management, pharmacovigilance, clinical expertise etc). Direct financial contribution by the sponsoring EFPIA company to supplement the CRO subcontracting costs incurred by public partners ensuring that 100% of these costs will be reimbursed. Direct funding for the CRO

**WP5D: GSK1322322 Phase III Pivotal hospitalized CABP Trials
(Estimated start: 1Q2015 – Duration: Month 26-60)**

The WP5D is subject to the outcome of WP5C may be subject to an open call for including additional partners later based on milestones completion.

In addition to the Phase III ABSSSI trials, two Phase III CABP trials will be conducted as pivotal registration studies. These trials will be conducted conditional upon the successful completion and evaluation of the Phase IIb CABP trial as well as the completion of at least one of the Phase III ABSSSI trials. In addition the consortium should bring forward proposals for investigating novel endpoints/biomarkers with the understanding that gathering these endpoints must be successfully combined with the pre-defined primary outcome data.

The Phase III CABP studies will be similar in design to the Phase IIb trial with details regarding the comparator and sample size not yet described. Data from the Phase IIb trial will be evaluated to optimize the design of these studies. However current estimates for the number of patients to be included in the CABP Phase 3 studies: each trial will have approximately 800 patients in total, 500 from Europe and 300 from the rest of the world.

In general terms, the study population will consist of subjects with moderate to moderately severe CABP (defined as PORT class III or IV) who require hospitalization.

The protocol will consist of IV to oral step down, with subjects requiring at least 72 hours of IV therapy. Subjects can be treated with oral therapy after that time, but, must be still be hospitalized for at least the first 48 hours of therapy.

These Phase III CABP studies will be comparator controlled double blinded, double dummy comparing the safety and efficacy of GSK1322322 to an acceptable comparator. Subjects will be required to have a clinical diagnosis of CABP (by standard criteria involving a combination of at least 2 of the following: increased cough; sputum (purulence) production; chest pain; and/or dyspnea or shortness of breath). All enrolled must also have a new infiltrate on chest x-ray, The CABP must be of such severity (as calculated by the Pneumonia Severity Index (PSI)) as to be a PORT class III or IV illness, and to require hospitalization. Subjects will be randomized to either IV (or oral) GSK1322322 or a comparator for at least 48 hours of hospitalized therapy. Therapy can be changed to oral whenever the subject is clinically improved, but, they must receive at least 2 days (4 doses) of total IV therapy, and at least 5 but no more than 10 days of total therapy.

EFPIA Partner Contribution: Knowledge and expertise on GSK1322322. All study-implementation- related processes (study drug, regulatory support, project management, pharmacovigilance, clinical expertise etc). Direct financial contribution by the sponsoring EFPIA company to supplement the CRO subcontracting costs incurred by public partners ensuring that 100% of these costs will be reimbursed. Direct funding for the CRO.

EXPECTATIONS FROM THE APPLICANT CONSORTIUM

The Applicant Consortium applying for this Topic should include the following:

Subtopic 1 A: WP1-4

- Expertise in developing mechanisms and procedures for engaging across network(s) to share information regarding local/regional standard of care, clinical trial activities, etc
- Hospital and healthcare institutions to join a clinical trial network with capability to run Phase 1, Phase 2, and Phase 3 clinical trials.
- Information/expertise in current standard of care for patients with specific clinical conditions
- SMEs with experience in supplying training at sites to ensure compliance for clinical trials and suitability of clinical microbiology laboratories to support the clinical trial site.
- Participants with expertise in coordinating global surveillance programmes.
- Surveillance experts to create study protocols and determine the pathogens, antimicrobial agents, clinical correlates (if appropriate), and analysis to be performed in support of the surveillance WP
- Hospital and healthcare institutions providing bacterial isolates and associated microbiological and epidemiologic data to a central regional lab.
- Expert labs to act as central regional labs with expertise at performing standardized *in vitro* MIC testing.
- Expertise in establishing standards for data extraction and data privacy principles
- Data from existing clinical studies to incorporate into the data sharing aspect of ND4BB
- Expertise in clinical trial design.
- Expertise in statistics and specific pre-clinical PK/PD modeling approaches.
- Project Management/communication expertise.

Subtopic 1B: WP5⁶,

The Applicant Consortium must ensure that the expression of interest describes for each site the ability to recruit and retain the targeted patient population in addition to describing recent clinical experience conducting randomized comparator controlled antibacterial studies. Sites should conduct trials in accordance with the ethical principles in the Declaration of Helsinki, and be consistent with ICH GCP and the applicable local regulations.

- 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 protocol outlined in WP5A and 5C in the first instance.
- Hospital and healthcare institutions with expertise in running clinical trials for hospital based infection to GCP standards.
- Participants with novel diagnostics/biomarkers to be included in the clinical trial designs. Inclusion should be based on diagnostics very close to validation with sufficient turnaround time (<60min) to identify patients with relevant infections for enrollment and/or biomarkers which can be incorporated onto the trial design with little or no impact on the collection of study data required for regulatory submissions.
- Participants able to fulfil the recruiting requirements of the studies **within the indicated time frame.**

⁶ and later-on for subtopic 1C (WPs 6 & 7)

More specifically, the sites must demonstrate and/or certify in the EoI the following characteristics:

1. Clinical study experience with antibacterial treatments, preferably with the capability of administering parallel infusions to maintain double-blinding of studies and with the ability to follow patients upon discharge.
2. Demonstrated ability to recruit patients with the target characteristics (e.g., PORT Grade 3 or 4 community acquired bacterial pneumonia requiring hospitalization for studies of hospitalized CABP, acute bacterial skin and soft tissue infections requiring initial intravenous therapy for the ABSSI studies, nosocomial pneumonia [including ventilator associated bacterial pneumonia], complicated urinary tract infections and or complicated intra-abdominal infections).
3. In order to ensure recruitment goals for the trial can be met, the clinical research sites potentially to be recruited must demonstrate capacity to recruit and provide follow-up care in the proposed clinical trial, to at least 5 eligible patients over a 12 month period. 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. Sites should be able to comply with procedures for data recording, reporting and retention.
4. 24 hour availability of an un-blinded pharmacist/third party for preparation and dispensing of IV infusions and trained blinded staff to administer IV infusions.
5. Minimum clinical microbiology laboratory requirements include:
 - Laboratory accreditation by a country specific agency
 - Documentation of appropriate quality control/quality assurance programme
 - Ability to process (plate on appropriate media and incubate) all skin swab, abscess fluid, skin curettage or biopsy specimens (ABSSI studies) or respiratory specimens including sputum, endotracheal aspirate, bronchoalveolar lavage or protected brush (CABP studies), and blood cultures within 2 hours from collection time if specimen is kept at room temperature or within 24 hours of collection if stored at 2-8°C
 - Ability to perform Gram stain on abscess fluid or skin swab specimens and report number of white blood cells (WBC) per 100x field, and bacteria (semi-quantitation and morphology) per 1000x field
 - Ability to perform Gram stain on respiratory specimens and report number of white blood cells (WBC) and epithelial cells per 100x field, and bacteria (semi-quantitation and morphology) per 1000x field
 - Ability to report the growth of bacteria semi-quantitatively as growth per corresponding quadrant on agar media (i.e. 1+, 2+, 3+, etc.)
 - Ability to subculture any isolated pathogens and send to a central laboratory for further testing (i.e. identification confirmation, susceptibility testing, etc.)
 - Ability to collect and have results for procalcitonin values within 24 hours (for CABP studies)
 - Ability to process respiratory, blood and urine specimens for shipment to central laboratory for urine antigen and/or atypical pathogen culture and serology testing (for CABP studies)
 - Ability to properly store any isolated pathogens and Gram stain slides until instructed by study monitor to discard

- Ability to collect and process stool samples for *C. difficile* culture or antigen testing
- Other study specific laboratory requirements (e.g., a study may require the ability to store specimens)
- Laboratory results reported to the investigator via electronic data capture, hard copy or fax

GENERAL PRINCIPLES FOR ALL CLINICAL STUDIES CONDUCTED UNDER ND4BB

Study Management

In the case of the clinical trials, protocol compliance data quality and data integrity is essential to avoid the risk of a failed regulatory process. If a trial is non-compliant, this can severely jeopardise regulatory approval and poses ethical issues related to informed consent agreements with patients. Therefore all clinical studies conducted in ND4BB will be conducted to Good Clinical Practice (GCP) standards in order to ensure no process or data quality issues arise that would jeopardize the outcome of the trials.

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 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 two possible scenarios for the selection of the CRO:

- 1) The public entities recruit subcontractors under full respect of all applicable rules and regulations. In order to make up the funding gap arising out of the maximum 75% reimbursement of research activities, EFPIA companies foresee to provide a direct financial contribution to concerned beneficiaries.
- 2) 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 company according to normal internal procurement practices. The EFPIA company must be able to demonstrate 'value for money' to satisfy external auditors otherwise this cannot be counted as contribution in kind.

The criteria for selection of the CRO and its identification will be agreed 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 in place with the CRO 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 will be responsible for ensuring coordination across all clinical trial sites (ie those funded directly by the EFPIA Sponsor as well as those engaging as part of the Applicant Consortium). This relationship will be governed through a specific Clinical Trial Agreement between 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 institution shown via site visits

to be sufficiently compliant to be able to fulfill all aspects of the protocol to GCP standards will be permitted to recruit patients into the study.

Monitoring

Site Compliance

The EFPIA company who 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. The Topic 1 Steering Committee will be notified of any decisions to terminate or change a study in response to emerging safety data.

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 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.

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 is presented and communicated in a responsible way by ensuring that efficacy data is 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 such activities are 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 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

On the other hand, some types of data are very compound specific, may have special handling and reporting requirements due to regulatory concerns, and do not provide generalized insight useful for other development programmes. 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 an accurate and balanced presentation of its data. As such for all clinical trials being run 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, to post 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.
- Proposals for additional analyses and reporting of either aggregate or subject level data pre- or post-approval are assessed for scientific merit, impact, and reporting concerns by the Topic 1 Steering Committee and EFPIA Sponsor and will only be undertaken following final approval by the Sponsor. As noted above, reporting is legally required to be presented and communicated in a responsible way such that efficacy data are presented with a balanced understanding and communication of the adverse event profile or other safety risks. Such work is generally undertaken as collaborations between the clinical trial Sponsor and the proposer, with all analyses being reviewed and approved by the Sponsor prior to publication to ensure Sponsor policies regarding responsible communication are regarded (i.e. to ensure that the data is being used for appropriate scientific purposes in line with the original informed consents in addition to all local and national data privacy and data transparency policies).

In general terms, summary data from all clinical trials being run under the ND4BB programme must be publicly posted within a reasonable period following study completion (typically considered the date of the last subject last visit) or completion of the Clinical Study Report. Once a clinical trial has completed and the database locked for subsequent statistical analysis 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. Broad dissemination of any clinical trial data to investigators or other public entities will be made only as outlined above, as such data dissemination "pre-approval" is considered as promotional and violates several regulatory statutes.

**Subtopic 1C - to be launched later under a new Call by IMI JU
(the text is indicative and therefore may be subject to
change)**

Key objective

To conduct prospective clinical trials with novel trial designs to deliver safety, pharmacology, and proof of efficacy data for novel agents directed towards treatment, prevention or sequelae of infections due to priority pathogens and if possible to validate novel bacterial identification diagnostics or clinical endpoints with the aim of reducing the size and cost of clinical trials.

Cost and timelines estimates are only approximate and are subject to revision prior to launch of the new Call.

WP6: Conduct of Clinical Trials supporting the development of MEDI4893, a monoclonal antibody targeting *S. aureus* alpha toxin

S. aureus can induce substantial tissue and organ damage through its toxins; therefore, targeting these toxins preemptively may prevent serious *S. aureus* (including MRSA) disease in high-risk patients, independent of the antimicrobial resistance status. MEDI4893 is a potent human IgG1 that binds to *S. aureus* alpha toxin. In-house data in animal models has shown that MEDI4893 can prevent lethal *S. aureus* (including MRSA) pneumonia, reduce pathology associated with infection and accelerate pulmonary bacterial clearance even in the absence of concurrent antimicrobial therapy. In addition, prophylactic use of this human antibody could reduce use of antimicrobial agents, thereby helping to avoid the development of antimicrobial resistance and perhaps even improve the outcome of patients.

WP6A: Epidemiologic Surveillance of Surgical Site Infections in the European Union (Month 3-14)

The focus will be on site recruitment within the EU, ie those sites eligible for IMI JU funding and further details will be described in the new Call.

Study Rationale

*Surgical Site Infections (SSI) cause considerable morbidity and mortality among surgical patients. The majority of SSI are due to *S. aureus* (including MRSA). Surgical failures due to SSI contribute significantly to the financial burden of the healthcare system. The epidemiology of SSI in the European Union (EU) has not been fully described, partly because of the use of fundamentally different case definitions and surveillance systems by member states. In addition, because of temporal and geographic variation in SSI risk, standardized assessment of SSI measures in hospitals of different countries is warranted. The proposed study will systematically assess the impact of patient and contextual factors on SSI incidence with the goal of identifying patient subgroups, which bear a disproportionate burden.*

Study Population

The study will target patients undergoing types of surgery which are associated with high rates of SSI (to be determined).

Study Design

The proposed study is a prospective observational study, with passive follow-up of all surgical patients undergoing selected procedures in participating hospitals. The study will identify SSI among surgical patients. Samples will be collected and tested for the etiologic agent. Data regarding patients (e.g., demographics, co-morbidities) and hospitals (e.g., annual number of surgeries by type, infection control protocol, SSI rate vs. the study median) will be collected for the entire study population and participating sites. Follow-up patients after exposure (i.e., surgery) will be performed. Cases and non-cases will be compared to assess factors associated with infection and long-term outcomes.

Objectives

The proposed study will address the incidence of and risk factors associated with SSI

Collaboration and Information Sharing

This study will be conducted in close collaboration with EU Member State investigators having particular expertise in SSIs. Every effort will be made to incorporate existing Member State-specific surveillance networks and European Centre for Disease Prevention and Control (ECDC). Results will be disseminated widely in an effort to promote standardization of existing systems. The network created under the auspices of this study may participate in future clinical trials regarding SSI and can be leveraged for future public health initiatives.

Study details

The proposed study intends to include 10-20 hospital networks in 6-12 EU countries (no world-wide sites). The number of surveillance sites is dependent on the number of sites per participating network. These networks and participating sites would have either been part of the Hospitals in Europe Link for Infection Control through Surveillance (HELICS) network or have demonstrated the ability to implement HELICS protocols. The study is expected to initiate data collection in 1Q2013 and complete such collection in 1Q2014. A passive follow-up period will follow in order for long-term outcomes to be captured.

EFPIA contribution: *All study-implementation-related processes (study drug, regulatory support, project management, pharmacovigilance, clinical expertise etc). Direct financial contribution by the sponsoring EFPIA company to supplement the CRO subcontracting costs incurred by public partners ensuring that 100% of these costs will be reimbursed. Direct funding for the CRO.*

WP6B: Prospective observational study to evaluate the natural history of *Staphylococcus aureus* (including MRSA) surgical site infections (SSIs) (Month 3-18)

*The focus will be on site recruitment within the EU, i.e. those sites eligible for IMI JU funding. At total of **40-60 patients /6-8 sites** should be*

recruited for this study in Europe. The other 40-60 patients /6-8 sites will be recruited in the rest of the world and funded directly by AZ. Estimated study duration: 12 months enrollment.

Study Rationale

Staphylococcus aureus (including MRSA) causes significant morbidity among patients undergoing certain high-risk surgeries (e.g., orthopedic, cardiothoracic, neurosurgery/spine). *S. aureus* secretes several toxins and virulence factors that are responsible for tissue and organ damage and promote dissemination from the primary site of infection. Antimicrobial agents do not specifically address disease manifestations caused by secreted factors. Therefore therapeutic interventions targeting these toxins may prove useful for prevention of serious *S. aureus* (including MRSA) disease. Data in animal models have shown that targeting the *S. aureus* alpha toxin can prevent lethal *S. aureus* infections, reduce pathology and accelerate bacterial clearance, in the absence of concurrent antimicrobial therapy. Understanding the role and kinetics of expression of toxins and selected virulence factors in the onset or prevention of SSIs is central to development of effective immunoprophylactic monoclonal antibodies for use in surgical populations.

Study Population:

The study will enroll patients diagnosed with SSIs attributable to *S. aureus* (including MRSA) subsequent to high-risk surgeries (to be determined) at major surgery and trauma centers in Europe. Controls, defined as patients not having an *S. aureus* SSI, will be matched to cases.

Study Design:

The proposed study is a prospective cohort study, with active follow-up of surgical patients diagnosed with *S. aureus* SSI and matched controls. Serum samples will be compared across cases and controls in order to study the host antibody responses against selected *S. aureus* toxins such as alpha toxin. Bacterial isolates will be collected to study the expression of various toxins and virulence factors. A nested case-control analysis will be performed.

Objectives:

The proposed study will address the role and kinetics of expression of toxins and selected virulence factors in the onset or prevention of SSIs

Collaboration and Information Sharing:

This study will be conducted in close collaboration with EU member state investigators having particular research and clinical expertise in surgical site infections. Results will be shared with investigators. The network of centers created in this study may participate in future clinical studies regarding prevention of *S. aureus* SSIs.

Study details

Key endpoint:

Compare *S. aureus* SSI group with non-SSI controls for serum Alpha Toxin and serum Anti-Alpha Toxin Ab titers

Sample size: Approximately 100 subjects (40-60 patients /6-8 sites in EU. The other 40-60 patients /6-8 sites outside EU).

EFPIA contribution: All study-implementation-related processes (study drug, regulatory support, project management, pharmacovigilance, clinical expertise etc). Direct financial contribution by the sponsoring EFPIA company to supplement the CRO subcontracting costs incurred by public partners ensuring that 100% of these costs will be reimbursed. Direct funding for the CRO.

WP6C: Phase 1b/2 randomized, placebo-controlled, single-dose, dose ranging study to evaluate the safety, pharmacokinetics and efficacy of MEDI4893 for prevention of Staphylococcus aureus (including MRSA) ventilator associated pneumonia (VAP) (Month 18-36)

The focus will be on site recruitment within the EU, i.e. those sites eligible for IMI JU funding. At total of **390 patients /25 sites** should be recruited for this study in Europe. The study will be better defined during 2H2012. Estimated study duration: 12-15 months enrollment.

Study Rationale

Staphylococcus aureus is a major bacterial pathogen worldwide, associated with significant morbidity and mortality in diverse patient populations. Patients in the intensive care unit (ICU) are at an extremely high risk for developing severe *S. aureus* (including MRSA) infection, such as pneumonia, bacteremia, and sepsis. Treatment with antimicrobial agents has driven the emergence of strains resistant to methicillin (MRSA) and glycopeptides (GISA, hGISA and GRSA), which has limited the antimicrobial therapeutic options. *S. aureus* can induce substantial tissue and organ damage through its toxins; therefore, targeting these toxins preemptively may prevent serious *S. aureus* (including MRSA) disease in high-risk patients, independent of the antimicrobial resistance status. MEDI4893 is a potent human IgG1 that binds to *S. aureus* alpha toxin. In-house data in animal models has shown that MEDI4893 can prevent lethal *S. aureus* pneumonia, reduce pathology associated with infection and accelerate pulmonary bacterial clearance even in the absence of concurrent antimicrobial therapy. In addition, prophylactic use of this human antibody could reduce use of antimicrobial agents, thereby helping to avoid the development of antimicrobial resistance and perhaps even improve the outcome of patients.

Study Population:

The proposed study population consists of patients admitted to the ICU who are at increased risk (to be determined) of developing *S. aureus* (including MRSA) pneumonia and who also require mechanical ventilation.

Study Design:

Phase 1b/2 randomized, placebo-controlled, dose ranging study in mechanically ventilated ICU patients.

Objectives:

Recipients of MEDI4893 or placebo who are mechanically ventilated and at risk for *S. aureus* (including MRSA) pneumonia will be followed and assessed for:

- 1- Safety and PK

- 2- Incidence of *S. aureus* pneumonia
- 3- Measures of *S. aureus* disease severity (eg. ventilator free days, ICU-free days)
- 4- Biomarkers

Collaboration and Information Sharing:

*This study will be performed in collaboration with top experts in the fields of pulmonary medicine, critical care medicine and infectious disease at major research centers in Europe. This study will also contribute to the training of other clinical investigators. Results of the study will be shared with the investigators and the wider scientific community in Europe to promote better understanding of the clinical and biological markers of disease development, progression and severity in mechanically ventilated ICU patients at risk for developing *S. aureus* VAP.*

Study details

*Key efficacy endpoint: Reduction in incidence of *S. aureus* ventilator associated pneumonia*

Key safety endpoints: Safety, PK and anti-drug antibody (ADA)

Sample size: approximately 390 subjects in Europe.

EFPIA contribution: *All study-implementation-related processes (study drug, regulatory support, project management, pharmacovigilance, clinical expertise etc). Direct financial contribution by the sponsoring EFPIA company to supplement the CRO subcontracting costs incurred by public partners ensuring that 100% of these costs will be reimbursed. Direct funding for the CRO.*

WP6D: Phase 1b/2 randomized, placebo-controlled, single-dose, dose ranging study to evaluate the safety, pharmacokinetics and efficacy of MEDI4893 for prevention of surgical site infections (SSIs) attributable to *Staphylococcus aureus* (Month 18-42)

*The focus will be on site recruitment within the EU, i.e. those sites eligible for IMI JU funding. At total of **150 patients /12-15 sites** should be recruited for this study in Europe. The other **150 patients /12-15 sites** will be recruited in the rest of the world and funded directly by AZ. The study will be better defined during 2H2012.*

Estimated study duration: 12-15 months enrollment.

Study Rationale

*Staphylococcus aureus causes significant morbidity among patients undergoing certain high-risk surgeries (to be determined). Certain subgroups such as those with prior *S. aureus* surgical infection are at a high risk of recurrent *S. aureus* SSI despite prolonged courses of systemic antistaphylococcal antibiotics prior to revision surgery. *S. aureus* can induce substantial tissue and organ damage through its toxins; therefore, targeting these toxins preemptively may prevent serious *S. aureus* disease in high-risk patients, independent of the antimicrobial resistance status. MEDI4893 is a potent human IgG1 that binds to *S. aureus* alpha toxin. Data in animal models have shown that targeting the *S. aureus* alpha toxin can prevent lethal *S. aureus* infections, reduce pathology and*

accelerate bacterial clearance, in the absence of concurrent antimicrobial therapy.

Study Population:

The proposed study population consists of surgical patients considered at high-risk for developing *S. aureus* surgical site infections (to be determined). These subjects have to be free of any clinical and laboratory signs of active *S. aureus* disease for enrollment in the study.

Study Design:

Phase 1b/2 randomized, placebo-controlled, dose ranging study in surgical patients at high-risk of *S. aureus* SSI, who are currently free of *S. aureus* disease. Subjects will be evaluated for safety, PK and efficacy.

Objectives:

Recipients of MEDI4893 or placebo will be followed and evaluated for:

1. Safety and PK
2. Incidence of *S. aureus* SSI
3. Measures of *S. aureus* severity
4. Biomarkers

Collaboration and Information Sharing:

This study will be performed in collaboration with top experts in the fields of surgery and SSIs at major surgical centers in Europe. This study will contribute to the training of clinical investigators for future studies evaluating SSIs. This study will also offer avenues for collaboration with European experts studying *S. aureus* virulence factors in SSI population. Results of the study will be shared with the investigators and the wider scientific community in Europe to promote better understanding of the clinical and biological markers of disease development, progression and severity in surgical patients at risk for developing *S. aureus* SSIs.

Study details

Key efficacy endpoint: Reduction in incidence of *S. aureus* surgical site infection

Key safety endpoints: Safety, PK and anti-drug antibody (ADA)

Sample size: approximately 300 subjects. Total of **150 patients /12-15 sites** should be recruited within EU and the other **150 patients /12-15 sites** will be recruited in the rest of the world.

EFPIA contribution: All study-implementation-related processes (study drug, regulatory support, project management, pharmacovigilance, clinical expertise etc). Direct financial contribution by the sponsoring EFPIA company to supplement the CRO subcontracting costs incurred by public partners ensuring that 100% of these costs will be reimbursed. Direct funding for the CRO.

Allocation of funding and milestone/progression decisions for WP6

The launch of WP6 work is subject to successful completion of the ongoing Phase 2 studies and internal governance reviews.

WP7: Conduct of Clinical Trials supporting the development of AZD9773, a polyclonal ovine FaB fragment directed at tumor necrosis factor alpha (TNF- α) for the treatment of the severe sepsis, including septic shock (Month 6-36)

WP7 is subject to the successful completion of the Phase 2 b trial and results will be available in 2H2012. For WP7, it is estimated that 25% of patients will be recruited within EU, 75% ex-EU.

Bacterial infections due to both susceptible and resistant organisms may trigger the syndrome of sepsis. Sepsis arises through the body's response to infection and covers a diverse spectrum of illness ranging in severity from mild systemic inflammation to multi-organ system failure in septic shock. There are currently no specific treatments for severe sepsis and it remains the most common cause of death in the intensive care unit (ICU) with mortality between 20 to 50% for severe sepsis and 45 to 80% for septic shock (CHMP/EWP/4713/03).

AZD9773 is in clinical development for the treatment of severe sepsis and septic shock. It is an ovine-derived polyclonal antibody fragment of IgG directed against human TNF- α . AZD9773 drug product is presented as a sterile lyophilised powder purified from the serum of sheep immunised with recombinant human TNF- α (rhTNF- α).

Early studies of AZD9773 were conducted with D-CytoFab, a form of AZD9773 manufactured under small scale conditions, with TNF- α affinity chromatography at its core. D-CytoFab has shown promising efficacy signals in small clinical trials of severe sepsis. The most notable results were from a randomised double-blind multi-centre Phase 2b trial in 81 patients (Rice et al, Crit Care Med 2006) where, compared to Standard of Care (SoC) alone, D-CytoFab significantly reduced time on ventilator, and ICU-stay. In addition, D-CytoFab showed an 11% numerical reduction in 28 day all-cause mortality, but this was not statistically significant. These signals of clinical efficacy were accompanied by a neutralization of TNF- α in plasma, and the drug was well tolerated.

Following the completion of the original Phase 2b trial, the manufacturing process was successfully changed to a commercially viable process, with Fc affinity chromatography at its core. For clarity, material manufactured by the new manufacturing process is referred to as AZD9773 and the material used in the original Phase 2b trial as D-CytoFab.

Pre-clinical, clinical and CMC comparability for AZD9773 and D-CytoFab has been established and on the basis of these comparability studies, AZD9773 entered a Phase 2 programme in 2010. The Phase 2 programme, which contains 2 studies (see below) that has now completed recruitment:

- 1.) A twenty patient Phase 2 study in Japan, to facilitate Japanese participation in the global Phase 3 programme
- 2.) A 3-arm, Phase 2b study (100 patients per arm, 300 in total) studying 2 doses of AZD9773 (given in addition to SoC) vs. placebo. Patients have been recruited in Australia, Belgium, Canada, Czech Republic, Finland, France, and Spain. Data is expected from this study before end of 2012.

Study Rationale

The release of cytokines into the circulation is an essential part of the inflammatory cascade that underlies sepsis. Experimental and clinical data have shown that the pro-inflammatory cytokine TNF- α is a principal initiator of this cascade. TNF- α is the first cytokine to be released by macrophages in response to infection, and once in the circulation, it causes systemic inflammation through stimulating the widespread release of "downstream" cytokines such as interleukin-6 (IL-6) and interleukin-8 (IL-8) in uninfected tissues. In experimental models, injection of TNF- α recreates the entire pattern of sepsis. In human studies, injection of minute quantities of TNF- α creates the cardiovascular changes of early sepsis. Given its important role as an early mediator in the inflammatory response, TNF- α is an appropriate target for the treatment of sepsis.

Data from earlier clinical studies with D-CytoFab have demonstrated a potential therapeutic benefit of treating patients with severe sepsis with polyclonal F(Ab) fragments targeted against TNF- α (as above). An ongoing Phase 2b study of AZD9773 (described above) is expected to report before the end of 2012. A strongly positive signal from the Phase 2b study will warrant further investigation of the drug in a Phase 3 programme.

Study Population:

The Phase 3 study is likely to be conducted in the same severe sepsis or septic shock target patient population as that treated in the Phase 2b study, a population very similar to the patient population treated in the D-Cytofab Phase 2 study.

Study Design:

In this workpackage, either one large or two smaller (but identical) Phase 3 studies of AZD9773 vs. placebo will be conducted in patients with severe sepsis or septic shock. Current estimates suggest that the required number of patients will be in the range of 2,400 to 3,200 across either one or two clinical trials. The sample size and number of trials will be determined once the Phase 2b study results are known and also pending final regulatory consultations.

Objectives:

Recipients of AZD9773 or placebo will be followed and compared for:

- 1. 28-day all-cause mortality*
- 2. Ventilator-free days*
- 3. ICU-free days*
- 4. Other measures of co-morbidity relating to severe sepsis*

Collaboration and Information Sharing:

This study will be performed in collaboration with top experts in the fields of pulmonary medicine, critical care medicine and infectious disease at major research centers in Europe and across the world. This study will also contribute to the training of other clinical investigators. Results of the study will be shared with the investigators and the wider scientific community in Europe and elsewhere to promote better understanding of the clinical and biological markers and mechanisms of severe sepsis and septic shock.

EFPIA contribution: All study-implementation-related processes (study drug, regulatory support, project management, pharmacovigilance, clinical expertise etc). Direct financial contribution by the sponsoring EFPIA company to supplement the CRO subcontracting costs incurred by public partners ensuring that 100% of these costs will be reimbursed. Direct funding for the CRO.

TOPIC 2

LEARNING FROM SUCCESS AND FAILURE & GETTING DRUGS INTO BAD BUGS

EFPIA PARTICIPANTS

GlaxoSmithKline R&D, AstraZeneca, Janssen R&D, Sanofi, Basilea

KEY OBJECTIVES

Improving permeability of drugs into Gram-negative bacteria

- Gain an increased level of overall understanding of penetration into and efflux out of Gram-negative bacterial cells, and knowledge to improve template selection for novel drug discovery efforts.

Increasing the efficiency of antibiotic R&D through knowledge and data sharing

- Form a data repository (with variable levels of access, e.g. consortium only and consortium plus public) for archived data available from consortium partners and in the public domain and for data generated throughout the life of the project and beyond
- Develop the business model required to support the sharing of data amongst consortium partners and the wider antibiotic research community throughout the life of the project and beyond

EXPECTED KEY DELIVERABLES

Improving permeability of drugs into Gram-negative bacteria

- High throughput assays to determine the degree of penetration into and efflux out of bacterial cells; preliminary output of screening selected compound collections describing templates or SAR which generally leads to improved cellular residence time.
- Improved understanding of porin structure and function and how it could be related to drug discovery efforts.
- Information on bacterial uptake pathways beyond iron-uptake which could be used as delivery systems applied to drug discovery programmes to improve activity or spectrum.
- Increased knowledge on druggable adjuvant targets which could increase penetration or decrease efflux, leading to a combination antibacterial with improved activity or spectrum.
- Design and synthesis of compounds that have enhanced antibacterial activity via hijacking uptake pathways
- Improved understanding of features that promote good penetration into and reduce efflux out of key multi-resistant Gram-negative pathogens.

Increasing the efficiency of antibiotic R&D through knowledge and data sharing

- More efficient overall use of antibacterial R&D resource
- A repository of clinical and preclinical data for future research use

Through the sharing and analysis of high level summary data in the data repository, a better understanding of:

- What is successful (and not successful) in terms of lead identification strategies, including recommendations of a best practice for future efforts.

- Why lead optimization programmes and preclinical or clinical compounds fail.
- Better overall understanding of target tractability—which targets or approaches are more likely to give leads.
- Information on the state-of-the-art animal infection models and clinical active comparator data which will be applied to future clinical study designs (eg Bayesian). This will be done in collaboration with Topic 1.

INDICATIVE DURATION OF THE PROJECT

The indicative duration of the project will be 5 years.

INDICATIVE BUDGET

Indicative in kind contribution from EFPIA companies: € 8M; Indicative IMI JU contribution: € 16M

PROPOSED PROJECT OUTLINE

Several related avenues of research will be undertaken, all with a primary focus on application to drug discovery against multi-resistant pathogens, e.g. one or more of the following: Enterobacteriaceae (specifically *E.coli*, *K.pneumoniae* and *Enterobacter* species), *Acinetobacter*, *Pseudomonas* and *Clostridium difficile*. It is envisaged that in all cases, the details of learnings and novel assays developed will be made publically available to support drug discovery across the antibiotic community.

WP 1: Development of assays to study penetration and efflux in multi-resistant Gram-negative pathogens

In order to improve our ability to develop novel antibiotics with good intrinsic bacterial permeability and minimal intrinsic efflux it is essential to develop novel assays to support drug screening and selection. This workpackage will focus on the development of assays to measure the penetration and/or efflux of agents into and out of bacterial cells. These assays should be sufficiently sensitive and reproducible to allow differentiation between agents with known intrinsic permeability. Assays should be developed and validated (i.e. with respect to reliability, variability, signal: noise and Z' values) with the aim of scale up for high throughput screening (HTS) of novel antibiotics. Once validation is complete, assays should be scaled up and validated to enable the support of drug screening activities.

EFPIA Partner Contribution: experience and knowledge of the development of HTS, expertise in computational modeling and systems biology, medicinal chemistry expertise, drug supply, bacterial strains.

WP2: Understanding the impact of Porin structure and intrinsic permeability

This workpackage will focus on identifying the aspects of porin structure and function with the goal of enhancing permeability into multi-resistant Gram-negative pathogens. More specifically efforts should focus on specific examples beyond currently well understood systems (e.g. further work on ampicillin or related drugs is of less interest) or, if possible, the concept of increasing porin permeability to potentially act as an adjunct to a wide variety of antibiotics. Using molecules with various levels of intrinsic permeability computational modeling or experimental techniques will be applied to understand which chemical templates or series may have intrinsically better porin permeability. Once key factors

affecting porin permeability are established, learnings will be broadly communicated and applied to new or ongoing drug discovery efforts.

EFPIA Partner Contribution: assay development experience, expertise in computational modeling and systems biology, medicinal chemistry expertise, drug supply, bacterial strains.

WP3: Pro-drugging permeability (hijacking bacterial transport mechanisms)

This work would aim to expand the overall understanding of lesser known uptake mechanisms such as sugar or nitrogen phosphotransferase pathways, peptide uptake systems, the various ABC and TRAP transporters, etc., or the discovery of novel uptake mechanisms and how these pathways may be exploited to enhance the penetration of antibacterial compounds into Gram-negative bacteria. In addition, expansion of the fosfomycin entry factor and/or iron-uptake systems (beyond application to beta-lactams) would be of interest. A key point is that these studies lead to druggable features or targets, e.g. where the structural features required for transport could be readily included in the structure of a small molecule drug. It is expected that EFPIA partners and consortium members would apply this information by designing novel features into known or novel antibacterials that would be recognized by uptake pathways and thus increase their antibacterial activity and/or spectrum.

EFPIA Partner Contribution: assay development expertise, expertise in computational modeling and systems biology, medicinal chemistry expertise, supply of lead molecules to build in recognition features for uptake pathways,, bacterial strains.

WP4: Genetic approach to novel penetration / efflux targets

Using innovative genetic tools, work will be undertaken to identify molecular targets within bacterial cells which can be modified to either improve penetration / permeability into or reduce efflux out of bacterial cells. Another aspect of this work would be to identify novel, selective agents that alter outer membrane permeability (regardless of target), thus improving overall drug penetration. Any potential novel targets identified should be rigorously validated using a well defined series of studies with the aim of eventually screening those validated novel targets against libraries of small molecules to identify novel starting point(s) for a novel, adjuvant treatment of bacterial infections.

EFPIA Partner Contribution: expertise in computational modeling and systems biology, medicinal chemistry expertise, drug supply, bacterial strains.

WP5: Modeling and simulation

In addition to analysis conducted in each individual WP this WP will focus on using a systems biology approach to interrogate all the data obtained from each WP. Data from each of the WPs will be integrated to fully understand interrelationships that exist between key penetration and efflux mechanisms. A systems biology approach will be taken to identify the overall features or property space that is advantageous for the development of antibacterials for multi-resistant Gram-negative pathogens.

EFPIA Partner Contribution: expertise in computational modeling, medicinal chemistry expertise, system biology expertise

WP6: ND4BB Data Hub: Governance Structure and software development

This workpackage will deliver i) a framework governing data sharing within and outside of the ND4BB consortium; ii) a software solution with a supporting IT infrastructure to create an appropriate database to house and support the interrogation of the various forms of data to be gathered from different sources contributing to ND4BB.

The framework will be built on a 'data life cycle' platform with two primary components. These components will consist of (i) the content and format of the data warehouse and (ii) the access privileges to the content. Database content and format will be defined by the specific data to be aggregated into the warehouse. To control the size, scope, and development costs of the warehouse, the specific data targeted for aggregation will be limited to metadata (i.e., metacontent) describing drug discovery and development efforts. Metadata (metacontent) are defined as data providing information about one or more aspects of the data, such as the means of creation of the data, purpose of the data, date of creation, creator or author of data, placement on a [computer network](#) where the data is stored, and [standards](#) used.

The software solution will govern the gated access to data stored within the warehouse and should be capable of supporting public sharing as well as sharing restricted within the ND4BB consortium

The data to be shared are the metadata and documents describing such drug discovery and development efforts as high-throughput screening (e.g., targets, assay formats, general strategy, high level outcomes); terminated efforts (e.g., target and essential SAR information for discontinued lead optimization, preclinical or clinical efforts, including key hurdles and reasons for termination); and ongoing clinical efforts (target, structure, intended use). Archived data surrounding standard animal models use, clinical comparator data (identified in Topic 1) as well as all data generated during the duration of ND4BB will also be housed here. Rather than aggregating large volumes of raw data, a framework will be put in place to allow investigators the opportunity to request additional data (e.g. structures of leads) for clearly defined research purposes.

Database access will be governed by rules to be established jointly by the Topic 1 and Topic 2 consortia. These rules will form the underpinnings of a solution that accounts for data privacy, ethics, standards as well as legal and information technology (IT) issues surrounding the use and re-use of clinical data. The solution will provide options for gated access to the data warehouse such that some datasets are accessible only to consortium members while other datasets will be publically available.

EFPIA Partner Contribution: Knowledge of business models employed in similar projects, information regarding the data sets available within EFPIA companies, knowledge of formats most routinely used in industry, experience in data sharing and privacy requirements. Knowledge in web-based data warehouse construction and deployment

WP7: Combining R&D experience to develop best practice and avoid duplication

This workpackage will focus on the analysis of the data sets gathered in WP6 and on all data generated as part of the ND4BB programme to deliver recommendations that will lead to more efficient antibacterial drug discovery and

development efforts. Academic and industry scientists will work side by side to mine the data accumulated from both public and private partners to identify:

- What factors are common to failed lead optimization efforts?
- What data as well as tools and procedures should be put into practice so that a lead optimization team can confidently discriminate among lead candidates to progress toward early clinical development?
- Best practice for predicting resistance in the clinic
- Based on analysis of all available data sets which animal infection models best predict clinical outcome?

These proposed research questions should be considered in the first instance, other questions will also be considered if fully justified. Once datasets are gathered, these data will be brought to bear against research questions to produce answers that could be practically applied to ongoing or future drug discovery efforts. Output of this analysis will be disseminated widely through scientific conferences, dedicated seminars, scientific papers or summaries on, for example, the ND4BB externally facing website.

It is anticipated that newly identified tools, new animal model paradigms etc should be validated using a set of well characterised compounds made available from the EFPIA partners to test the hypothesis generated through data mining.

EFPIA Partner Contribution: Data, data visualization and mining expertise, computational and statistical analysis expertise, PK/PD modeling and simulation expertise, well characterized antibiotic molecules to validate hypothesis

WP8: ND4BB Collaboration and Dissemination

The main purpose of this WP will be to ensure effective Project Management, ensure collaboration between Topic 1 investigators and those in other Topic consortium and ensure coherent dissemination of ND4BB results to the broader scientific community.

In order to ensure effective communication and collaboration between projects funded under the ND4BB programme, a dedicated team will work to:

- Develop standard communication tools for all the projects funded under, e.g. standard templates, externally facing website etc.
- ensure ND4BB dissemination to the external community is coherent and aligned across all projects /website strategy etc
- Ensuring data from all projects is deposited in the ND4BB data hub in accordance to the ND4BB framework
- Arrange bi-annual meetings between all ND4BB investigators
- Establish a ND4BB Scientific Advisory Board consisting of leading academics and key stakeholders

This WP should be co-led by project Leaders from projects funded under the ND4BB programme.

EFPIA Partner Contribution: Project/Alliance Management personnel, meeting facilities, communication expertise

INDICATIVE EXPECTATIONS FROM THE APPLICANTS:

The Applicant Consortium applying for this Topic should include the following:

WP1-5

- Expertise in a variety of projects related to bacterial cell penetration and efflux, including but not limited to: novel & known uptake mechanisms that could be exploited to enhance uptake of antibacterials
- Knowledge of the structure, mechanism and SAR of porin penetration,
- Knowledge of mechanisms underlying permeability differences across pathogens, and efflux from multi-resistant Gram-negatives organisms
- Assay development expertise to determine penetration / efflux
- Expertise in computational modeling and medicinal chemistry to build in recognition features into antibacterial leads

WP6-8

- expertise in IT to develop infrastructure and framework to allow for collation and sharing of the data being pooled
- web design and maintenance
- scientific and media communications expertise