IMI2

16th Call for proposals

Annex III to the 3rd amended IMI2 JU Annual Work Plan and Budget for 2018 approved by the IMI2 JU Governing Board on 13 July 2018 per Decision n° IMI2-GB-DEC-2018-23

Document reference: IMI2/INT/2018-01072

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Introduction

The Innovative Medicines Initiative is a jointly funded partnership between the European Union, represented by the European Commission, and the European Federation of Pharmaceutical Industries and Associations (EFPIA).

The Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) has been created[1] following the principles below:

Research related to the future of medicine should be undertaken in areas where societal, public health and biomedical industry competitiveness goals are aligned and require the pooling of resources and greater collaboration between the public and private sectors, with the involvement of Small- and Medium-sized Enterprises (SMEs).

The scope of the initiative should be expanded to all areas of life science research and innovation.

The areas should be of public health interest, as identified by the World Health Organisation (WHO) report on priority medicines for Europe and the World[2].

The IMI2 JU objectives are usually implemented through Research and Innovation Actions (RIAs), and Coordination and Support Actions (CSAs) where public and private partners collaborate, joining their expertise, knowledge and resources.

The initiative should therefore seek to involve a broader range of partners, including mid-sized companies[3], from different sectors e.g. biomedical imaging, medical information technology, diagnostic and/or animal health industries. Involving the wider community in this way should help to advance the development of new approaches and technologies for the prevention, diagnosis and treatment of diseases with high impact on public health.

The IMI2 Strategic Research Agenda (SRA)[4] is the main reference for the implementation of research priorities for IMI2 JU. The scientific priorities for 2018 for IMI2 JU have been prepared based on the SRA.

Applicant consortia are invited to submit a proposal for each of the topics that are relevant for them. These proposals should address all aspects of the topic to which the applicant consortia are applying. The size and composition of each consortium should be adapted so as to respond to the scientific goals and the expected key deliverables.

Applicant consortia, during all stages of the evaluation process, must consider the nature and dimension of the IMI2 JU programme as a public-private collaboration.

While preparing their proposals, applicant consortia should ensure that the needs of patients are adequately addressed and, where appropriate, patient involvement is encouraged. Applicants should ensure that gender dimensions are also considered. Synergies and complementarities with other national and international projects and initiatives should be explored in order to avoid duplication of efforts and to create collaboration at a global level to maximise European added value in health research. Where appropriate, the involvement of regulators is also strongly encouraged.

[1] Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU).
[2] http://www.who.int/medicines/areas/priority_medicines/en/
[3] Under IMI2 JU, mid-sized companies having an annual turnover of EUR 500 million or less not being affiliated entities of companies with an annual turnover of more than 500 million; the definition of 'affiliated entities' within the meaning of Article 2(1)(2) of Regulation (EU) No 1290/2013 applies mutatis mutandis. Where established in an EU Member State or an associated country, are eligible for funding.
[4] http://www.imi.europa.eu/sites/default/files/uploads/documents/About-IMI/research-agenda/IMI2_SRA_March2014.pdf

Applicant consortia shall ensure that where relevant their proposals are in compliance with the General Data Protection Regulation (EU) 2016/679[5] and Clinical Trial Regulation (EU) 536/2014[6] (and/or Directive 2001/20/EC[7)] and any relevant legislation[8].

Before submitting a proposal, applicant consortia should familiarise themselves with all Call documents such as the IMI2 JU Manual for evaluation, submission and grant award[9], and the IMI2 evaluation criteria. Applicants should refer to the specific templates and evaluation procedures associated with the topic type Research and Innovation Actions (RIA).

[5] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) , OJ L 119, 4.5.2016, p. 1–88.

[6] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, *OJ* L 158, 27.5.2014, p. 1-76.

[7] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (the "Clinical Trials Directive), *OJ* L 121, 1.5.2001, p. 34.

[8] Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and the free movement of such data and implementing national laws: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:31995L0046

[9] http://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2_ManualForSubmission_v1.6_October2017.pdf

Introduction to the IMI2 Antimicrobial Resistance (AMR) Accelerator programme

Background and problem statement

The discovery and development of new preventions and treatments to address antimicrobial resistance (AMR) is an undisputed European and global challenge that is compounded by a low return on investment (RoI) for the pharmaceutical sector driven largely by the lack of established reimbursement models and standard methods to express the true societal value for new technologies addressing AMR. This has subsequently led to a reduction in resources applied across the pharmaceutical industry and a decline in scientific discoveries. Overall this situation has compromised the delivery of new options to treat and prevent resistant infections. This was highlighted in the European One Health Action Plan against Antimicrobial Resistance (for more info please visit the following link: https://ec.europa.eu/health/amr/sites/amr/files/amr_action_plan_2017_en.pdf). Beyond Europe, it is of note that AMR is one of four public health concerns that has been raised to the level of discussion at the UN General Assembly (September 2016), putting it on par with subjects such as HIV and Ebola. Additionally, drug resistant tuberculosis (TB), the largest single contributor to AMR health, mortality, and economic impact, is scheduled to be discussed by heads of state at the UN General Assembly (September 2018).

There are significant scientific challenges to the discovery and development of new agents to treat and prevent AMR infections, including those caused by Gram-positive and Gram-negative bacteria, *Mycobacterium tuberculosis*, and non-tubercular mycobacteria (NTM). As an example, despite there being an extensive number of essential bacterial targets, no novel mechanism antibiotics for Gram-negative infections have been approved in 40 years.

Furthermore, despite some recent progress, we have a poor understanding of how to rationally design potent small molecules that are optimised to treat life threatening multi-drug resistant (MDR) Gram-negative pathogens. Models, approaches, and tools developed by large pharma or public entities to support antibiotic drug development need to be validated and shared more widely to serve the AMR community at large. At the same time, alternative approaches to treating infections require robust validation. The same is true for platforms that enhance the success of vaccines and monoclonal antibodies, or new imaging platforms to measure pharmacodynamic responses at the site of action.

In TB, the world's leading infectious disease killer with 1.7 million deaths in 2016, (from WHO TB report 2017 Executive Summary at the following link, http://www.who.int/tb/publications/global_report/Exec_Summary_13Nov2017.pdf) there is an acute need for the development of a novel combination regimen with an indication for the treatment of any form of TB ('pan-TB regimen') that will be more effective, shorter, and safer than current existing options. This applies to all types of TB (drug-sensitive (DS), multi-drug resistant (MDR) and extensively-drug resistant (XDR-TB)). A pan-TB regimen would encompass at least three new chemical entities, with properties better suited to protect against emerging resistance both individually as well as in combination. Many scientific hurdles must be overcome to understand how multiple chemical entities can be combined most successfully, keeping synergistic drug activity, drug-drug interactions, and translational aspects in mind. Regimen development in TB has provided and will continue to lead to learnings that will help to develop new treatments, including combination regimens, for other infections that have relied on mono-therapy thus far.

Overall objectives of the AMR Accelerator

The aim of the AMR Accelerator is to progress a pipeline of potential medicines, including but not limited to new antibiotics, to treat patients with resistant bacterial infections in Europe and across the globe or to prevent them. Specifically, if successful, projects in the Accelerator are expected to deliver up to >10 new preclinical candidates and >5 'phase 2-ready' assets over a roughly six-year period.

The AMR Accelerator will provide, under one operational structure, a wide-ranging series of projects that will address many of the scientific challenges in AMR. The scientific scope will be broad, including prevention (vaccines, mAbs, immunoprophylaxis, other means) and treatment (new antibiotics, non-antibiotic alternatives, and combinations). For clarity, the term 'AMR' should be interpreted to include Gram-positive and Gram-negative

bacteria, tuberculosis (TB) and non-tubercular mycobacteria (NTM). Within this broad scope, projects in the Accelerator will develop new pre-clinical tools and methods, validate alternative or 'non-traditional' approaches, progress potential new treatments through phase 1-3 clinical trials, and analyse data from EFPIA-funded clinical trials to assist in the translation of preclinical data to clinical results of novel anti-infective agents and vaccines. The Accelerator will also potentially generate new clinical/regulatory phase 2-3 pathways. Over the past years, IMI's New Drugs for Bad Bugs (ND4BB) programme has created a vibrant drug discovery and development network in AMR, and met important milestones. The AMR Accelerator will complement and augment the capabilities of the IMI ND4BB programme.

Progression of successful assets beyond the scope of the Accelerator (pillar-dependent, see below) may occur, as appropriate, by other mechanisms such as EU funding programmes within Horizon 2020 (including SME instruments) or future framework programmes, InnovFin instruments, Structural Funds, venture capitals, other internal R&D funding mechanisms, etc. In addition, the applicable principles from the Davos Declaration on Antimicrobial Resistance– January 2016 or the Industry Roadmap for Progress on Combatting Antimicrobial Resistance – September 2016 (https://www.ifpma.org/wp-content/uploads/2016/09/Roadmap-for-Progress-on-AMR-FINAL.pdf[10]) should be taken into account.

The Accelerator will contribute to one of the three pillars of the European One Health Action Plan against Antimicrobial Resistance 'Boosting research and development and innovation in AMR' (June 2017: https://ec.europa.eu/health/amr/sites/amr/files/amr_action_plan_2017_en.pdf). The Accelerator will also directly address the IMI2 JU objective of 'develop new therapies for diseases for which there is a high unmet need, such as Alzheimer's disease and limited market incentives, such as antimicrobial resistance' (Article 2(b)(iii) of the Council Regulation establishing IMI2 JU: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32014R0557)

AMR Accelerator programme structure

The AMR Accelerator programme consist of three pillars under which multiple actions are expected:

- **Pillar A:** Capability Building Network (CBN)
- **Pillar B:** Tuberculosis Drug Development Network (TBDDN)
- **Pillar C:** Company-specific Portfolio Building Networks (PBNs)

The two-stage IMI2 JU Call 15[11] includes two topics (topic 7 and topic 8) to launch Pillar A and Pillar B of the AMR Accelerator, respectively. The single-stage IMI2 JU Call 16 includes seven topics under Pillar C.

Applicants may submit a proposal to any of the topics under the different pillars and are not obliged to apply for all. If applicants wish to submit for more than one topic under the same or different pillars, separate proposals should be submitted.

For the two topics for Pillars A and B, launched as part of IMI2 JU Call 15:

- the indicative EFPIA in-kind contribution will be EUR 71 200 000
- the indicative Associated Partner in-kind contribution will be EUR 67 000 000

The EFPIA and Associated Partner in-kind contribution will be matched by IMI2 JU funding across the whole of the Accelerator and not necessarily 1:1 on an individual project or pillar basis.

The overall IMI2 JU financial contribution to the AMR Accelerator topics under Pillars A, B and C of IMI2 JU Call 15 and IMI2 JU Call 16 will be a maximum of EUR 144 730 000.

[10] For example, points 3 and 4 from the 'Roadmap for Progress'.
[11] http://ec.europa.eu/research/participants/data/ref/h2020/other/call_fiches/jtis/h2020-call-fiche18-15-imi2-ju_en.pdf

Future call for proposals could be launched at a later stage to select under each pillar additional research projects or networks depending on developing scientific needs and objectives in AMR research.

Pillar A: Capability Building Network (CBN) to accelerate and validate scientific discoveries.

The CBN will: 1) create a coordination and support group to assist in the effective management of projects across the Accelerator and; 2) deliver pre-competitive science to accelerate scientific discoveries in AMR, the results of which will be disseminated widely. The CBN will include projects to further basic science and discoveries to enable future drug discovery and development in the prevention (vaccines, mAbs, immunoprophylaxis, and others) and treatment of MDR bacterial infections including tuberculosis (TB), and non-tubercular mycobacteria (NTM). Although most research in the Accelerator related to TB will be conducted in the TBDDN (below), TB projects could occur in the CBN if the scientific concepts are of broader applicability (e.g. immunoprophylaxis).

The initial action in the CBN resulting from topic 7 in IMI2 JU Call 15 will implement a coordination and support group that will support operations of all projects in the AMR Accelerator with effective management, communication, and data capture capabilities. The initial CBN action also will focus on the collection, sharing, and analysis of vaccine and/or antibacterial clinical trial data and the optimisation of animal infection models for bacterial infections.

Pillar B: Tuberculosis Drug Development Network (TBDDN) to accelerate and validate scientific discoveries and advance the R&D pipeline of new and innovative agents to address the global TB epidemic.

The TBDDN will work to address the innovation gap in the discovery and development of a pan-TB regimen by combining access to novel drug candidates with innovative tools and incorporation of clinical trial data to accelerate the discovery of new combination regimens for the treatment of TB.

The platform will be self-sustained and independent from other similar activities (Integrated Research Platform (IRP), TB Drug Accelerator (TBDA)). It is anticipated that there will be linkages with the TBDA (for more info on TBDA please visit: http://partnerships.ifpma.org/partnership/tb-drug-accelerator-program). It will provide ready-to-use services for rapid progression of available (1st line) new and innovative candidates. The platform will be partly supported by the coordination and support group from Pillar A but will include management resources to self-sustain its scientific and financial reporting as well as innovation management procedures.

Topic 8 of IMI2 JU Call 15 will result in an action that will create a group to profile and progress anti-TB compounds from advanced lead through phase 1 and to collect, share, and analyse TB clinical trial data. Additionally, it will address the development of new alternative anti-tubercular drugs (for example, host-defence or virulence approaches).

Pillar C: Portfolio Building Networks (PBN) to advance the R&D pipeline of new and innovative agents to address AMR.

As in the CBN, the overall scientific scope in the PBN will be broad, including prevention (vaccines, mAbs, immunoprophylaxis, and others) and treatment (new antibiotics, non-antibiotic alternatives, formulation strategies, and combinations). Within this broad scope, the PBN will provide a mechanism for dedicated partnerships between EFPIA companies and SMEs and/or academic teams for the discovery and development of new antibacterial assets, including in select cases TB and NTM. Assets and projects can originate from SMEs, academia, or EFPIA companies, and will be jointly progressed or studied, including both pre-clinical work and potentially phase 1-3 clinical development. The PBN will also potentially be useful to generate new clinical/regulatory phase 3 pathways for pathogens such as NTM and to conduct phase 2 trials in TB.

Consortia selected under this pillar may have a limited number of partners, and will require the participation of an EFPIA partner (e.g. 1 EFPIA partner + 1 SME/academic partner)[12]. IMI2 JU Call 16, the first call under Pillar C, is divided in several topics, each dedicated to specific individual asset or research area. Additional single-stage calls, one or two per year, may be launched in the future pending available budget. A total of at least 8-10 grant agreements are anticipated in the PBN (indicative number only).

[12] See 'Applicant consortium' section of IMI2 JU Call 16 topic text (Pillar C, "Portfolio Building Networks").

Collaboration agreements

To ensure smooth operation of the projects in the AMR Accelerator, the grant agreement of the first CBN action (selected under Pillar A from IMI2 JU Call 15 topic 7, and containing the coordination and support group[13]) will be complementary to all the grant agreements of actions selected under Pillars B and C (via IMI2 JU Call 15 topic 8 and IMI2 JU Call 16 topics, and potential future additional calls for proposals), as well as probable future grant agreements from actions selected under Pillar A. In addition, grant agreements of actions under pillar B, if more than one, will be complementary between them. The respective options of Article 2, Article 31.6 and Article 41.4 of the IMI2 JU Model Grant Agreement[14] will be applied. Accordingly, the consortia selected under Pillars A, B, and C will conclude collaboration agreements with the CBN consortium selected from IMI2 JU Call 15 topic 7. These collaboration agreements will provide the framework for the CBN to provide day-to-day support of projects in the Accelerator, and will ensure exchange of relevant information, exploration of synergies, collaboration where appropriate, and avoid duplication of efforts.

Furthermore, a memorandum of understanding (MoU) will be pursued between the Pillar B TBDDN action(s) and the Integrated Research Platforms (IRP) action of IMI2 JU Call 15 topic 1 to cover collaboration and sharing of information on TB-related activities. The MoU should constitute one deliverable of the action resulting from topic 8 of IMI2 JU Call 15. Similarly, when reasonable, a MoU should be pursued between potential TB-focused actions under Pillar C of the Accelerator (resulting from IMI2 JU Call 16) and TBDDN action(s), as well as the IRP action of IMI2 JU Call 15 topic 1, with appropriate provisions to protect confidentiality and intellectual property of the interactions between those consortia.

Need and opportunity for public-private collaborative research

The discovery and development of new antibiotics and alternative treatment and prevention options for multi-drug resistant infections is a high medical and societal need. The AMR Accelerator will address multiple challenges in a coordinated programme, which offers excellent opportunities for collaborative work between different sectors and disciplines. Moreover, operating with the support of the coordination and support group in the CBN will allow for greater efficiency, by reducing the need for duplicative management structures or processes.

Due to the current low return on investment that developers can expect for agents to address AMR, this scientific area has not received the investment that was seen in the ‘call to action’ to address HIV/AIDS and on par with the public health threat. Consequently, public-private partnerships (PPPs) such as the framework provided by the IMI2 JU continue to be critical to that effort.

Excellent examples have been the previous and current investments by the European Union and IMI (ND4BB, Model-based preclinical development of anti-tuberculosis drug combinations (PreDiCT-TB), More Medicines for Tuberculosis (MM4TB), Open Collaborative Model for Tuberculosis Lead Optimisation (ORCHID), anTBiotic), the NIH (Tuberculosis Research Units Network, TBRU-N) and the Bill & Melinda Gates Foundation (TB Drug Development Accelerator and TB Alliance discovery portfolio)). Multiple new drug candidates are in the pipeline for the treatment of TB for the first time in decades, and are reaching or about to reach the clinic. Existing drugs are being repurposed or optimised for TB with the potential of shortened treatment duration for drug-sensitive TB and safer, shorter treatments for MDR-TB. In ND4BB, immense progress has been made from basic science to discovery of novel lead molecules through to running interventional clinical trials.

However, more work is critical to continue to address the constantly emerging global challenge of AMR. For example, there is a challenge of maturing the TB pipeline from the selection of candidates to progression through phase 1 studies, in addition to parallel studies to determine the optimal combinations to create new pan-TB regimens. Also, the ever-evolving resistance landscape requires additional investment to validate new tools and approaches, in addition to progressing potential new therapies to prevent and treat bacterial infections.

[13] For additional details see the topic 7 “Capability Building Network” of IMI2 JU Call 15.
[14] See: https://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/h2020-mga-imi_en_v5.pdf

Acting to address these challenges in a single, coordinated Accelerator offers excellent opportunities for collaborative work between different sectors and disciplines on an area of critical scientific need.

The development of the Accelerator will contribute to a vibrant AMR community in Europe and will offer potential opportunities for individual partners, such as:

- Capability Building Network:
  - play key role in a EU AMR programme with connectivity into the broader global agenda on AMR;
  - enable SME, and/or academic groups to progress pre-competitive basic science project in the AMR field;
  - opportunity to work within a broad network of researchers focused on AMR science and gain additional experience in AMR science and drug discovery.
- Tuberculosis Drug Development Network:
  - enable SME and/or academic groups to progress pre-competitive basic science project in the TB field;
  - enable SME and/or academic groups to progress potential drugs from pre-candidate status through to 'ready for phase 2' status, including, but not limited to GLP and GMP scale up, formulation, toxicology studies, and phase 1 clinical studies, including preclinical combinations of drugs;
  - opportunity to work within a broad network on researchers focused on TB drug discovery.
- Portfolio Building Network:
  - opportunity for SMEs and/or academic groups to partner with EFPIA companies to enable progression of promising assets or technologies to key milestones, creating value, and sharing risk. There will be both potential to further extend such partnerships with EFPIA companies beyond the scope of the Accelerator following completion of project;
  - will allow a vibrant partnering ecosystem that will benefit SMEs or academics with early stage assets based on pre-agreed conditions and milestone decision points.

Applicants to Calls launched as part of the Accelerator should consult the IMI2 JU Model Grant Agreement and IMI2 JU Annotated Model Grant Agreement, as well as a short questions and answers document available at https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/Questions_and_answers_on_the_AMR_accelerator_programme.pdf.

AMR Accelerator Programme – Pillar C: Portfolio Building Networks to advance the R&D pipeline of new and innovative agents to address AMR Topics:

Topics:

Topic 1: Progress new assets (one pre-new molecular entity (preNME) and one first-time-in-human (FTIH) start) for tuberculosis (TB) that act synergistically with bedaquiline, cytochrome bc or cytochrome bd inhibitors

Topic 2: Progress novel assets (one FTIH start) for non-tubercular mycobacteria (NTM) that may act synergistically with bedaquiline and cytochrome bc drugs

Topic 3: Discover and progress novel assets with new mechanisms of action (one preNME for TB and one preNME for NTM) and biomarkers for TB and NTM infection

Topic 4: Determination of gepotidacin levels in tonsils and prostatic tissue

Topic 5: Infection site targeting, antibiotic encapsulated in nanoparticles for treating extracellular bacterial infections

Topic 6: Functional Ethionamide boosters: a novel combination for tuberculosis therapy

Topic 7: Intravenous treatments of serious infections (urinary tract infections (UTI), intra-abdominal infections (IAI) & hospital-acquired pneumonia/ventilator associated pneumonia (HAP/VAP)) caused by Gram(-) bacteria (Enterobacteriaceae +/- *Pseudomonas* and/or *Acinetobacter*)

Topic details

Topic code	IMI2-2018-16-01 IMI2-2018-16-02 IMI2-2018-16-03 IMI2-2018-16-04 IMI2-2018-16-05 IMI2-2018-16-06 IMI2-2018-16-07
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	single-stage

Specific challenges to be addressed

The Portfolio Building Network (PBN), Pillar C of the IMI2 JU AMR Accelerator programme, will address the limited pipeline of treatments and preventions for AMR infections by enabling vibrant and nimble collaborations between EFPIA companies and small and medium-sized enterprises (SMEs) and/or academics that will advance the R&D pipeline of new and innovative agents to address AMR.

Scope

The PBN will provide a mechanism for partnerships between EFPIA constituent and affiliated entities and SMEs and/or academic teams for the discovery and development of new antibacterial assets to address the broad topic of AMR including Gram-positive and Gram-negative bacteria, including tuberculosis (TB) and non-tubercular mycobacteria (NTM) and prevention (vaccines/mAbs, immunoprophylaxis and others) and treatment (new antibiotics, non-antibiotic alternatives, and combinations) approaches. Assets and projects can originate from SMEs, academia, or EFPIA companies, and will be jointly progressed, including potentially pre-clinical and clinical development work. The potential generation of new clinical pathways, or the potential contribution to regulatory pathways for pathogens such as NTM is included in the scope, as is the conduct of phase 2 TB trial(s). Consortia arising from the IMI2 JU Call 16 topics may have a limited number of partners, and will require the participation of an EFPIA partner (e.g. 1 EFPIA partner + 1 SME/academic partner) (see details under the section '*Applicant consortium*').

There are seven topics under the current single-stage Call topic described below. Additional single-stage Calls may be published in the future.

Topics 1-3: Advancing a portfolio of novel compounds with the potential to treat TB and NTM

The goal of these actions is to develop and advance a portfolio of anti-TB drugs that may be used in combination with bedaquiline and cytochrome bc inhibitors to shorten treatment regimens and improve safety and efficacy.

Bedaquiline, currently in Phase 3 clinical development, is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in the treatment of adults with pulmonary multi drug resistant tuberculosis (MDR TB). It specifically inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase, by binding to subunit c of the enzyme that is essential for the generation of energy in *Mycobacterium tuberculosis*. The cytochrome bc inhibitor 901 is in the late lead optimisation phase.

IMI2 JU Call 16, topics 1-3 target different innovative novel assets, mechanisms and combinations for TB.

Topic 1: Progress new assets (one preNME and one FTIH start) for TB that act synergistically with bedaquiline, cytochrome bc or cytochrome bd inhibitors

These compounds can target any stage of energy metabolism, including ATP synthase, cytochrome bc and bd, NDH-2, menaquinone synthesis, but also glycolysis and the citric acid cycle, or any other metabolic pathway. Other assets, targeting the host cell instead of the bacilli itself, are also potentially interesting to combine with energy metabolism inhibitors.

The scope of this topic will be to identify and progress novel lead compounds towards design and implementation of phase 1.

As part of the project objectives, several models and tools are needed to further profile the targets of the respiratory chain and evaluate the effect of the combinations, that include but are not limited to:

Evaluation in several *in vitro* and *in vivo* models including but not limited to dormancy models, models to characterise the response to the antibiotic in real time, models to study the interaction between *M. tuberculosis* and human bronchial epithelial cells, evaluation of infected macrophage models and animal zebrafish larvae pharmacokinetics / pharmacodynamics (PK/PD), animal mouse infection models as follows:

- perform structural characterisation of cytochrome bd and bc targets;
- generation/access to a library of MTB mutants to profile cytochrome bc and bd inhibitors;
- progress assets to FTIH by evaluation of the toxicology profile, performing formulation development (including exploration of long-acting formulation and fixed dose combination), screening, selection and characterisation of solid form, screening of synthetic pathways and GMP scale-up, synthesis of impurities, and performing non-GLP and GLP toxicology studies in several species (including but not limited to evaluation of mitochondrial toxicity);
- design and implementation of phase 1 studies towards the development of TB candidates.

Topic 2: Progress novel assets (one FTIH start) for non-tubercular mycobacteria (NTM) that may act synergistically with bedaquiline, and cytochrome bc drugs

The project goal is to develop and advance a portfolio of anti-NTM drugs that may be used in combination with bedaquiline and cytochrome bc inhibitors to shorten treatment regimens and improve safety and efficacy.

The EFPIA partner's internal assets as well as external compounds will be profiled alone and in combination. The scope of this topic will be to progress novel lead compounds by performing medicinal chemistry optimisation, *in vitro* and *in vivo* characterisation, as well as PK, toxicology studies, formulation and CMC (chemistry, manufacturing and controls) studies. The scope also includes implementation of phase 1 studies towards the development of novel NTM candidates. For this topic, expertise in the field of NTM is necessary. The activities of this topic include but are not limited to:

- generation/access to a library of NTM mutants and access to an extensive panel of NTM isolates to profile cytochrome bc and bd inhibitors;
- *in vitro* and *in vivo* efficacy testing (including but not limited to determination of minimal inhibitory concentration (MIC), minimal bactericidal concentration (MBC) and time-kill kinetics), animal mouse infection models, animal zebrafish larvae PK/PD, and profiling of new agents/combinations in a panel of NTM clinical isolates and in Gram negative and Gram positive bacteria;
- progress assets to FTIH by determining the toxicology profile, performing formulation development (including exploration of long-acting formulation and fixed dose combination), screening, selection and characterisation of solid form, screening of synthetic pathways and GMP scale-up, synthesis of impurities, and performing non-GLP and GLP toxicology studies in several species (including but not limited to the evaluation of mitochondrial toxicity);
- design and implementation of phase 1 studies towards the development of NTM candidates;
- expertise (key opinion leaders (KOL)) in clinical treatment of NTM and treatment outcomes is crucial.

Topic 3: Discover and progress novel assets with new mechanisms of action (one preNME for TB and one preNME for NTM) and biomarkers for TB and NTM infection

Novel assets with new mechanisms of action will be identified through high throughput screening campaigns for TB and NTM, with a special focus on *M. avium* complex. Novel screening platforms and tools are needed for this evaluation. The resulting hits will be profiled and further optimised *in vitro* and *in vivo*. In addition, a better understanding of the host-mycobacteria interaction and the impact of coexisting viral infections can provide insights about biomarkers and new targets for mycobacteria**.**

The objectives include, but are not limited to the following.

- The development of high throughput assays to test TB and NTM in *in vivo* relevant conditions. Target identification and characterisation including exploration of mechanism of action by transcriptomics and the generation of resistant mutants.
- *In vitro* and *in vivo* efficacy testing (including but not limited to determination of minimal inhibitory concentration (MIC), minimal bactericidal concentration (MBC) and time-kill kinetics), animal mouse infection models, animal zebrafish larvae PK/PD, and profiling of new agents and combinations in a panel of clinical isolates and in Gram negative and Gram positive bacteria as appropriate.
- Progress assets to FTIH by determining the toxicology profile, performing formulation development (including exploration of long-acting formulation and fixed dose combination), screening, selection and characterisation of solid form, screening of synthetic pathways and GMP scale-up, synthesis of impurities, and performing non-GLP and GLP toxicology studies in several species (including but not limited to the evaluation of mitochondrial toxicity).

Topic 4: Determination of gepotidacin levels in tonsils and prostatic tissue

Gepotidacin (GSK2140944) is a novel antibiotic that selectively inhibits bacterial DNA gyrase and topoisomerase IV by a unique mechanism, which is not utilised by any currently approved human therapeutic agent. Structural data with a type II topoisomerase, DNA gyrase, reveals the novel binding mode of the triazaacenaphthylene class and distinguishes it from the binding mode of the quinolone antibacterials. As a consequence of its novel mode of action, gepotidacin is active *in vitro* against most target pathogens carrying resistance determinants to established antibacterials, including fluoroquinolones. Gepotidacin has broad Gram positive activity and selective Gram negative activity.

With increasing antimicrobial resistance, there are fewer options to treat gonorrhoea (Centers for Disease Control and Prevention (CDC) and World Health Organisation (WHO) urgent need, in particular at the pharyngeal site where tissue penetration is essential to activity and extended spectrum beta-lactamases (ESBL)/MDR (CDC and WHO serious need) urological infections due to *Escherichia coli*. In addition, few orally available agents have favourable penetration characteristics which are essential to activity.

The topic goal would be to assess penetration of gepotidacin in the following groups.

- Tonsils following elective tonsillectomy in adults aged >18 years or adolescents aged 12-17 years. 20 evaluable subjects willing to participate would receive a single oral or intravenous dose of gepotidacin at defined timepoints prior to tonsillectomy. Gepotidacin levels will be measured in homogenates or extracellular fluid using validated methods that may include *ex vivo* microdialysis.
- Prostatic tissue following elective prostate biopsy or TURP in adult males. 20 evaluable subjects willing to participate would receive a single oral dose of gepotidacin at defined timepoints prior to TURP or prostate biopsy. Gepotidacin levels will be measured in homogenates or extracellular fluid using validated methods that may include *ex vivo* microdialysis.

Topic 5: Infection site targeting, antibiotic encapsulated in nanoparticles for treating extracellular bacterial infections

The topic goal would be threefold:

- to identify a bacterium or infection site targeting ligand (small molecule preferred);
- to incorporate this ligand into a nanoparticle system which can be retained selectively in infected tissues for long periods;
- to encapsulate an appropriate antibiotic into the targeted nanoparticle and confirm improved efficacy over the free antibiotic and non-targeted encapsulated antibiotic, driven by higher local concentration at the infection site, in addition to other criteria such as reduced toxicity or side effects, longer half-life, etc.

Topic 6: Functional Ethionamide Boosters: a novel combination for tuberculosis therapy

The topic goal is to generate a small molecule clinical candidate that can boost the activity of Ethionamide and revert the existing resistance to this drug, by acting on bacterial transcriptional regulators. The associated, dose dependant side effects for Ethionamide observed at the currently required human doses together with the high pre-existing levels of resistance in patients has limited the use of Ethionamide as a TB front-line agent. However, Ethionamide is considered an essential drug for MDR-TB treatment even today and could well be positioned back into first line, replacing Isoniazid as the ‘fast killing’ agent acting on mycolic acid synthesis, once the bio-activation of Ethionamide is optimal. This project aims at identifying novel small molecules that are capable of:

a) increasing the level of bioactivation of Ethionamide, therefore reducing the levels of ETH required to achieve maximal efficacy both *in vitro* (>10-fold) and *in vivo* (>3-fold);

b) revert pre-existing ETH clinical resistance using a very low oral dose.

This will make it possible to open up the scope of the ETH field of use to both drug sensitive and multi-drug-resistant (MDR) patients. This project intends to progress these new compounds from the candidate selection stage to a proof of concept as Ethionamide booster in TB patients.

Topic 7: Intravenous treatments of serious infections (urinary tract infections (UTI), intra-abdominal infections (IAI) & hospital-acquired pneumonia/ventilator associated pneumonia (HAP/VAP)) caused by Gram(-) bacteria (Enterobacteriaceae +/- *Pseudomonas* and/or *Acinetobacter*

In the various threats encompassed in the global AMR crisis, Gram(-) bacteria and especially ESBL-producing and carbapenemases-producing *Enterobacteriaceae* consistently rank among the most problematic organisms for which novel ways of managing the infections they cause are lacking. The scope of this topic will be to progress novel lead compounds against these organisms by performing medicinal chemistry optimisation, *in vitro* and *in vivo* activity characterisation, as well as PK, ADMET, formulation and CMC studies. A particular focus will be on compounds identified from phenotypic screens of natural product extracts / libraries, and on compounds identified through non-traditional phenotypic screens (i.e. screens in non-traditional rich media and/or screens where a proxy for bacterial cell death is employed). These require specific areas of expertise in natural products (fermentation, dereplication and microbial genetics), as well as medicinal chemistry applied to natural products (including hemi-

synthesis), for instance. In addition, expertise in novel approaches to de-orphan lead compounds and strong translational capabilities will be particularly useful to progress these compounds and evaluate potency as well as toxicity and resistance liabilities

Expected key deliverables

Topic 1: Progress new assets (one preNME and one FTIH start) for TB that act synergistically with bedaquiline, cytochrome bc or cytochrome bd inhibitors

- one preNME candidate for TB;
- profiling and phase 1 studies of a novel TB preclinical candidate to deliver a phase 2 ready TB asset.

Topic 2: Progress novel assets (one FTIH start) for non-tubercular mycobacteria (NTM) that may act synergistically with bedaquiline, and cytochrome bc drugs

- profiling and phase 1 studies of a novel NTM preclinical candidate to deliver a phase 2a ready NTM asset.

Topic 3*:* Discover and progress novel assets with new mechanisms of action (one preNME for TB and one preNME for NTM) and biomarkers for TB and NTM infection

- two preNME candidates, one for TB and one for NTM.

Topic 4: Determination of gepotidacin levels in tonsils and prostatic tissue

- plasma samples, tissues homogenates and possibly extracellular unbound levels of novel antibacterial in the tonsils following oral or intravenous dosing;
- pharmacokinetic analysis to evaluate penetration and exposure in the tonsils;
- plasma samples, tissue homogenates and possibly extracellular unbound levels of novel antibacterial in the prostate following oral dosing;
- pharmacokinetic analysis to evaluate penetration and exposure in the prostate.

Topic 5: Infection site targeting, antibiotic encapsulated nanoparticles for treating extracellular bacterial infections

- one candidate-selection of an infection site targeting, antibiotic encapsulated nanoparticle system for treatment of extracellular bacterial infections.

Topic 6: Functional Ethionamide boosters: a novel combination for TB therapy

- clinical candidate ready to enter into phase 2 for the treatment of tuberculosis;
- preclinical candidate backup on a different chemical series.

Topic 7: Intravenous treatments of serious infections (UTI, IAI & HAP/VAP) caused by Gram(-) bacteria (Enterobacteriaceae +/- Pseudomonas and/or Acinetobacter

- up to two NMEs having completed preclinical profiling, including GLP toxicity studies so as to be ready to enter into phase 1 studies;
- up to four NMEs having completed lead optimisation process (showing acceptable in vitro and in vivo activities and toxicity/resistance profiles) so as to be ready to enter phase 1 enabling studies such as GLP toxicity studies.

Expected impact

The expected impact of actions selected under this Call will be to:

- contribute to the development of a vibrant AMR research environment in the EU and strengthen the competitiveness and industrial leadership of Europe;
- contribute to the EU's ambition of being a 'best practice region' for addressing AMR;
- enhance the overall pipeline of medicines for patients with AMR infections and advance new and innovative agents.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

Example of relevant IMI/IMI2 JU and non-IMI projects include:

- aspects of the research of ND4BB TRANSLOCATION (http://www.nd4bb.eu/) (e.g. the ND4BB Information Centre as a possible framework for data sharing);
- ND4BB ENABLE project (http://nd4bb-enable.eu/);
- ND4BB COMBACTE projects and iABC Programme, (https://www.combacte.com; http://www.iabcproject.com) in particular in relation to networks (CLIN-NET, LAB-NET, STAT-NET and EPI-NET);
- projects funded by other organisations/programmes supporting AMR R&D e.g. the EU Framework Programmes for Research and Innovation FP7 and Horizon 2020, the Joint Programming Initiative AMR, Wellcome Trust, Biomedical Advanced Research and Development Authority (BARDA), Medical Research Council (MRC), CARB-X, Global Antibiotic Research and Development Partnership (GARDP), National Institute of Allergy and Infectious Diseases (NIAID), TB Alliance and TB Drug Accelerator etc. to ensure synergy and avoid duplication of research.

Indicative duration of the actions

The indicative duration of the actions under the different topics is shown below. Due to the uncertain nature of drug discovery and development, a shorter duration could be envisioned depending on the scientific progress of the project.

Topic 1: 72 months

Future project expansion: Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking may, if exceptionally needed, publish at a later stage another Call for proposals restricted to the consortium already selected under this topic, in order to enhance and progress the results and achievements by extending the duration and funding by means of another grant agreement. The consortium will be entitled to open to other beneficiaries as it sees fit. The scope of such potential future extension would be to develop further an agent/ combination successful in phase 1.

Topic 2: 72 months

Future project expansion: Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking may, if exceptionally needed, publish at a later stage another Call for proposals restricted to the consortium already selected under this topic, in order to enhance and progress the results and achievements by extending the duration and funding by means of another grant agreement. The consortium will be entitled to open

to other beneficiaries as it sees fit. The scope of such potential future extension would be to develop further an agent/ combination successful in phase 1.

Topic 3: 72 months

Future project expansion: Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking may, if exceptionally needed, publish at a later stage another Call for proposals restricted to the consortium already selected under this topic, in order to enhance and progress the results and achievements by extending the duration and funding by means of another grant agreement. The consortium will be entitled to open to other beneficiaries as it sees fit. The scope of such potential future extension would be to develop further an agent/ combination successful in phase 1.

Topic 4: 18 months

Topic 5: 36 months

Topic 6: 48 months

Topic 7: 72 months

Indicative budget

The IMI2 JU financial contribution is a maximum of EUR 46 900 000 for this Call. The IMI2 JU maximum financial contribution for each topic is:

Topic 1: EUR 6 840 000

Topic 2: EUR 5 690 000

Topic 3: EUR 1 770 000

Topic 4: EUR 7 300 000

Topic 5: EUR 6 000 000

Topic 6: EUR 7 000 000

Topic 7: EUR 12 300 000

Proposals will be ranked under each topic separately. Under each topic, only the top ranked proposal will be selected for funding within the budget available under each topic.

Applicant consortia

The applicant consortia will be selected based on submitted proposals. Each applicant consortium must include at least one EFPIA constituent or affiliated entity, i.e. EFPIA company. This requirement is justified by the particular nature of the scientific challenge to be addressed under these topics. One of the goals of the European One Health Action Plan against AMR is ‘to increase the development and availability of new effective antimicrobials inside and outside the EU’. EFPIA companies are uniquely placed to have the capability to ensure that during the rapid progression of new compounds and candidate drugs and vaccines in the projects to be selected, all the relevant regulatory and other requirements from jurisdictions around the world are appropriately considered, so that the data generated can be used when regulatory filings will be made.

The applicant consortia (e.g. EFPIA company + SME) may be limited in size but they must involve at least two independent legal entities established in different EU Member States, or countries associated to Horizon 2020[15], while addressing all of the objectives and having the necessary expertise to produce the deliverables and ensure the expected impact of the topic they are applying to. The condition for having a minimum of two legal entities is justified by the specificity of the AMR return on investment (RoI) where small consortia are sufficient to rapidly progress towards the development of new compounds while maintaining the agility of operations.

Applicants are expected to take advantage of and exploit support from different stakeholders with the necessary expertise, including the mobilisation of funds through the inclusion of contributing partners under the IMI2 JU framework of public-private consortia. Such contributing partners may include, in addition to EFPIA companies (i.e. its constituent or affiliated entities), Associated Partners to IMI2 JU.

Topics 1-3: Advancing a portfolio of novel compounds with potential to treat TB and NTM

To achieve the scientific objectives of topics 1-3, each applicant consortium is expected to mobilise as appropriate, and taking into account the scope of the different topics as described above, the following capabilities:

- Discovery capabilities including but not limited to:
    - development of animal infection models, to improve reproducibility and predictability for both single drugs and combinations;
    - development of dormancy models, such as RPF-dependent mycobacteria, low-oxygen recovery assay, nutrient starvation;
    - development of *in vitro* models to characterise the response to antibiotics in real time, such us reported-based growth inhibition and time-kill kinetics, and real-time single-cell analysis in a microfluidic device;
    - development of infected macrophage models to study the effect of single drugs and combinations, including direct antibacterials and host-directed compounds, as well asexploration of the secretome of lung epithelial cells upon interaction with mycobacteria to identify new targets and biomarkers;
    - exploration of mechanism of action, transcriptomics, generation of resistant mutants and characterisation of targets: purification, crystallisation and modelling;
    - profiling new inhibitors/ combinations in a panel of clinical isolates, and in Gram negative and Gram positive bacteria;
    - expertise in high throughput screening campaigns.
- Basic preclinical research capabilities to be able to develop and conduct specific PK/PD studies/models and tolerability studies including toxicology profiling, non-GLP and GLP toxicology profiling.
- PDMS (GMP manufacturing and formulation development) including capacity for long acting formulations of agents and combinations, and also including scale-up synthesis of non GMP and GMP selected candidates.
- In addition, applicants should have access to a network of patients of different socio-economic backgrounds on mycobacterial therapy and/or paediatric patients with underlying lung disease and carrying a mycobacterial infection.
- In depth infectious disease (TB, NTM) expertise, operational and quality capabilities required to design, implement, conduct, collect and analyse full data (bio, microbiology and clinical), and draft/finalise clinical study reports. Significant documented track record on the conduct of registrational phase 1 clinical studies in healthy volunteers, TB and/or NTM patients is mandatory.
- To achieve the objectives of topics 1-3, bedaquiline and cytochrome bc/bd inhibitors could be brought to the combination, as well as expertise in discovery and development activities.
- Access to compounds in the field of TB/NTM.

[15] http://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/3cpart/h2020-hi-list-ac_en.pdf

Topic 4: Determination of gepotidacin levels in tonsils and prostatic tissue

To achieve the scientific objectives of the topic, each applicant consortium is expected to mobilise as appropriate, the following capabilities:

- access to patients undergoing tonsillectomy;
- access to patients undergoing TURP or prostate biopsy;
- experience with clinical trials;
- training in International Council of Harmonisation (ICH) guidelines and good clinical practice (GCP);
- expertise and capacity to perform PK analysis.

Topic 5: Infection site targeting, antibiotic encapsulated nanoparticles for treating extracellular bacterial infections

To achieve the scientific objectives of the topic, each applicant consortium is expected to mobilise as appropriate, the following capabilities:

- experience with bacterial or infection site targeting;
- experience with nanoparticles with clear regulatory path, e.g. nanoparticles that have reached suitable levels of drug development (e.g. phase 3 or marketed, for any indication, not necessarily for infectious disease) as a demonstration that there are no insurmountable technical or regulatory challenges;
- experience with the incorporation of surface modifications of nanoparticles;
- experience in production, characterisation, and scale-up of nanoparticles, including preferably GMP-production;
- experience and capacity to run in vivo animal models of infection;
- experience in running rodent toxicology studies, including immunotoxicology, with nanoparticle agents;
- experience with preclinical PET imaging;
- experience working with regulators.

Topic 6: Functional Ethionamide boosters: a novel combination for TB therapy

To achieve the scientific objectives of the topic, each applicant consortium is expected to mobilise as appropriate, the following capabilities:

- experience with the use of bacterial transcriptional regulators;
- experience with bacterial or infection site targeting;
- experience setting up, validating, and running In vitro biochemistry assays;
- experience in using HPLC/mass spectrometry for the identification of metabolites;
- experience and capacity to run Mycobacterium tuberculosis animal models of infection including PK/PD;
- experience in running toxicology, pharmacokinetics and pharmaceutical development studies, including human dose projection;
- experience with preclinical PET imaging;
- experience in active pharmaceutical ingredient (API) production;
- experience working with regulators;
- GMP manufacturing / CMC / clinical experience;
- medicinal chemistry experience.

Topic 7: Intravenous treatments of serious infections (UTI, IAI & HAP/VAP) caused by Gram(-) bacteria (Enterobacteriaceae +/- Pseudomonas and/or Acinetobacter

To achieve the scientific objectives of the topic, each applicant consortium is expected to mobilise as appropriate, the following capabilities:

- compounds and expertise in novel phenotypic screening assays, including the expertise in new natural products (fermentation, extract purification, dereplication);
- expertise in technologies necessary to quickly de-orphan hits from phenotypic screens;
- expertise in approaches and techniques to translationally validate novel mode of action to the clinical situation; expertise and capacity in medicinal chemistry, microbiology, pharmacology and early ADMET optimisation programmes as well as pharmaceutical development techniques to maximise the evaluation of the therapeutic index of novel compound;
- expertise in innovative PK/PD approaches, including hollow-fibre models;
- expertise in development of companion diagnostics and biomarkers, enabling special stratification and/or monitoring of treatment response such as, for instance, antibody-focused and/or broader immune profiling of patients.
- ability to perform preclinical development studies (e. g. GLP toxicity studies, formulation, synthesis of material of clinical degree);
- ability to undertake first into human studies (FTIH) on heathy volunteers to determine key pharmacokinetic parameters in humans.

Note that, as stated above, the scope of this topic will be to progress novel ead compounds. These lead compounds should be proposed by the applicant consortium and might come either from the EFPIA company or from any other partner of the consortium. Thus, in addition to or in place of novel compound(s), novelty brought in by the applicant consortium might be new tools, new competence and/or specific knowledge in a novel targeted pathway that are applicable to the progression of an EFPIA compound.

Note regarding all topics

Note that for all topics, most day-to-day management such as rigorous project, programme, and alliance management (including but not limited to supporting the coordinator in the management of scientific and financial reporting, prosecution of legal agreements such as confidentiality agreements (CDA), material transfer agreements (MTA), meeting facilitation and secretariat) of projects across the Accelerator will be supported by the coordination and support group within the CBN (established through the IMI2 JU Call 15, topic 7 action). Therefore only minimal project and financial management capabilities will be required from the applicant consortium in the PBN.

In addition, representatives from all selected projects will contribute to an advisory and communications board (containing independent experts and representatives from all the projects running in the AMR Accelerator) created as part of the coordination and support group within the CBN. This group will meet regularly to share summary level, non-confidential progress reports on projects and where appropriate make recommendations to the AMR Accelerator overall.

Suggested architecture of the full proposal

The applicant consortia should suggest complete architectures in the submitted proposals.

Decision making: Each applicant consortium must agree on a fair and robust go/no-go decision-making process to ensure that only the most promising compounds or approaches are pursued. Note that go / no go milestones will need to be proposed in each proposal and later formalised in the relevant Annex 1 of the Grant Agreement, and consortium agreement. These milestones will then assist in the decision-making process to help ensure that projects funded under the PBN remain dynamic.

Each consortium's decision making would be governed by a committee whose makeup will take into account the nature and scope of the work planned, and be detailed in the respective consortium agreement and agreed to by all partners. The committee must include at least one independent expert to be selected by a process established by the full consortium and to be detailed in the consortium agreement. This committee will track the progress of the

project against its own internal milestones and will be empowered (as outlined in each project's consortium agreement) to make recommendations for progression/stopping tasks based on each consortium's pre-agreed go / no go milestones in an e.g. quarterly, streamlined, single-meeting process. It is anticipated that the consortium agreements will be structured such that independent experts can recommend termination or continuation of a project, but they cannot force a project to continue if all partners suggest termination. The decision-making process by the committee may result, in case of 'no-go' decision, in the recommendation from the committee/consortium to IMI2 JU for terminating the grant based on Art. 50.3.1 (h) of IMI2 JU MGA. The final decision about the project continuation or termination will be taken by the IMI2 JU in line with the provisions of the Grant Agreement. However, the JU may also make such a decision without prejudice to any decision-making process at the level of the consortium, i.e., even without the aforementioned recommendation.

Applicants to Calls launched as part of the Accelerator should consult the IMI2 JU Model Grant Agreement and IMI2 JU Annotated Model Grant Agreement, as well as a short questions and answers document available at https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/Questions_and_answers_on_the_AMR_accelerator_programme.pdf.

Conditions for this Call for proposals

All proposals must conform to the conditions set out in the H2020 Rules for Participation (https://ec.europa.eu/research/participants/portal/doc/call/h2020/common/1595113-h2020-rules-participation_oj_en.pdf) and the Commission Delegated Regulation with regard to IMI2 JU http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0622&from=EN.

The following conditions shall apply to this IMI2 JU Call for Proposals:

Applicants intending to submit a proposal in response to the IMI2 Call 16 should read this topics text, the IMI2 JU Manual for submission, evaluation and grant award and other relevant documents (e.g. IMI2 JU Model Grant Agreement).

Call Identifier	**H2020-JTI-IMI2-2018-16-single-stage**
Type of actions	**Research and Innovation Action (RIA)**
Publication Date	**18 July 2018**
Submission start date	**18 July 2018**
Submission deadline	**24 October 2018 (17:00:00 Brussels time)**
Indicative Budget	
From EFPIA companies and IMI2 JU Associated Partners	To be defined based upon submitted proposals
From the IMI2 JU	EUR 46 900 000

Call Topics

IMI2-2018-16-01 **Progress new assets (one pre-new molecular entity (preNME) and one first-time-in-human (FTIH) start) for TB that act synergistically with bedaquiline, cytochrome bc or cytochrome bd inhibitors**	The indicative contribution from EFPIA companies is to be defined based upon submitted proposals The financial contribution from IMI2 JU for is EUR 6 840 000	Research and Innovation Action (RIA) Single-stage submission and evaluation process. Under each topic, proposals submitted will be evaluated and ranked in one single list.
IMI2-2018-16-02 **Progress novel assets (one FTIH start) for non-tubercular mycobacteria (NTM) that may act synergistically with bedaquiline and cytochrome bc drugs**	The indicative contribution from EFPIA companies is to be defined based upon submitted proposals The financial contribution from IMI2 JU for is EUR 5 690 000	Research and Innovation Action (RIA) Single-stage submission and evaluation process. Under each topic, proposals submitted will be evaluated and ranked in one single list.

IMI2-2018-16-03 **Discover and progress novel assets with new mechanisms of action (one preNME for TB and one preNME for NTM) and biomarkers for TB and NTM infection**	The indicative contribution from EFPIA companies is to be defined based upon submitted proposals The financial contribution from IMI2 JU for is EUR 1 770 000	Research and Innovation Action (RIA) Single-stage submission and evaluation process. Under each topic, proposals submitted will be evaluated and ranked in one single list.
IMI2-2018-16-04 **Determination of gepotidacin levels in tonsils and prostatic tissue**	The indicative contribution from EFPIA companies is to be defined based upon submitted proposals The financial contribution from IMI2 JU for is EUR 7 300 000	Research and Innovation Action (RIA) Single-stage submission and evaluation process. Under each topic, proposals submitted will be evalutated and ranked in one single list.
IMI2-2018-16-05 **Infection site targeting, antibiotic encapsulated in nanoparticles for treating extracellular bacterial infections**	The indicative contribution from EFPIA companies is to be defined based upon submitted proposals The financial contribution from IMI2 JU for is EUR 6 000 000	Research and Innovation Action (RIA) Single-stage submission and evaluation process. Under each topic, proposals submitted will be evalutated and ranked in one single list.
IMI2-2018-16-06 **Functional Ethionamide boosters: a novel combination for tuberculosis therapy**	The indicative contribution from EFPIA companies is to be defined based upon submitted proposals The financial contribution from IMI2 JU for is EUR 7 000 000	Research and Innovation Action (RIA) Single-stage submission and evaluation process. Under each topic, proposals submitted will be evalutated and ranked in one single list.
IMI2-2018-16-07 **Intravenous treatments of serious infections (urinary tract infections (UTI), intra-abdominal infections (IAI) & hospital-acquired pneumonia/ventilator associated pneumonia (HAP/VAP)) caused by Gram(-) bacteria (Enterobacteriaceae +/- Pseudomonas and/or Acinetobacter)**	The indicative contribution from EFPIA companies is to be defined based upon submitted proposals The financial contribution from IMI2 JU for is EUR 12 300 000	Research and Innovation Action (RIA) Single-stage submission and evaluation process. Under each topic, proposals submitted will be evalutated and ranked in one single list.

The following general conditions shall apply to the IMI2 JU Calls for Proposals. They are based on the General Annexes to the Horizon 2020 – Work Programme 2018-2020[16].

[16] http://ec.europa.eu/research/participants/data/ref/h2020/other/wp/2018-2020/annexes/h2020-wp1820-annex-ga_en.pdf

LIST OF COUNTRIES AND APPLICABLE RULES FOR FUNDING

By way of derogation[17] from Article 10(1) of Regulation (EU) No 1290/2013, only the following participants shall be eligible for funding from the Innovative Medicines Initiative 2 Joint Undertaking:

(a) legal entities established in a Member State or an associated country, or created under Union law; and

(b) which fall within one of the following categories:

(i) micro, small and medium-sized enterprises and other companies with an annual turnover of EUR 500 million or less, the latter not being affiliated entities of companies with an annual turnover of more than 500 million; the definition of 'affiliated entities' within the meaning of Article 2(1)(2) of Regulation (EU) No 1290/2013 shall apply *mutatis mutandis*;

(ii) secondary and higher education establishments;

(iii) non-profit organisations, including those carrying out research or technological development as one of their main objectives or those that are patient organisations.

(c) the Joint Research Centre;

(d) international European interest organisations.

Participating legal entities listed in (b) above established in a third country may receive funding from the IMI 2 JU provided their participation is deemed essential for carrying out the action by the IMI 2 JU or when such funding is provided for under a bilateral scientific and technological agreement or any other arrangement between the Union and the country in which the legal entity is established[18].

STANDARD ADMISSIBILITY CONDITIONS, PAGES LIMITS AND SUPPORTING DOCUMENTS

Part B of the General Annexes to the Horizon 2020 – Work Programme 2018–2020 shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

In addition, page limits will apply to proposals as follows:

For a single stage call the limit for RIA/IA proposals is 70 pages.

STANDARD ELIGIBILITY CONDITIONS

Part C of the General Annexes to the Horizon 2020 – Work Programme 2018–2020 shall *apply mutatis mutandis* for the actions covered by this Call for proposals.

Furthermore, in the context of the IMI2 JU 16 Call for proposals, (single-stage calls for proposals), the following conditions apply:

- The additional condition for participation[19] that each applicant consortium must include at least one EFPIA constituent or affiliated entity. This requirement is justified by the particular interest in establishing a mechanism for dedicated partnerships between EFPIA constituent or affiliated entities, and SMEs and/or academic teams,

[17] Pursuant to the Commission Delegated Regulation (EU) No 622/2014 of 14 February 2014 establishing a derogation from Regulation (EU) No 1290/2013 of the European Parliament and of the Council laying down the rules for participation and dissemination in 'Horizon 2020 — the Framework Programme for Research and Innovation (2014-2020)' with regard to the Innovative Medicines Initiative 2 Joint Undertaking
[18] In accordance with Article 10(2) of the Regulation (EU) No 1290/2013 and Article 1 of Commission Delegated Regulation (EU) No 622/2014
[19] Article 9(5) of the Regulation (EU) No 1290/2013 of the European Parliament and of the Council of 11 December 2013 laying down the rules for participation and dissemination in "Horizon 2020".

for the discovery and development of new antibacterial assets to address antimicrobial resistance (AMR). AMR is a major European and global challenge and a major public health concern. One of the goals of the European One Health Action Plan against AMR is "to increase the development and availability of new effective antimicrobials inside and outside the EU". EFPIA constituent entities or affiliated entities are uniquely placed to have the capability to ensure that during the rapid progression of new compounds and candidate drugs and vaccines in the projects to be selected under IMI2 JU Call 16 all the relevant regulatory and other requirements from jurisdictions around the world are appropriately considered, so that the generated data can be used when regulatory filings will be made;

- In derogation[20] to the eligibility conditions for participation established under Part C of the General Annexes to the Horizon 2020 – Work Programme 2018–2020, the minimum conditions for applicant consortia for Research & Innovation Actions (RIA) under Call 16 shall be of at least two legal entities, independent from each other, established in different EU Member States or countries associated to Horizon 2020. The limited size of the applicant consortia is justified by the specificity of the AMR research space where small consortia operate to rapidly progress towards the development of new compounds while maintaining operation agility.

TYPES OF ACTION: SPECIFIC PROVISIONS AND FUNDING RATES

Part D of the General Annexes to the Horizon 2020 – Work Programme 2018–2020 shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

TECHNOLOGY READINESS LEVELS (TRL)

Part G of the General Annexes to Horizon 2020 – Work Programme 2018–2020 shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

EVALUATION RULES

Part H of the General Annexes to the Horizon 2020 – Work Programme 2018–2020 shall apply *mutatis mutandis* for the actions covered by this Call for proposals with the following additions:

Award criteria and scores:

Experts will evaluate the proposals on the basis of criteria of “Excellence”, “Impact” and “Quality and efficiency of the implementation” according to the submission stage and type of action, as follows:

Type of action	Excellence	Impact	Quality and efficiency of the implementation
RIA Single stage	The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the call for proposals and referred to in the IMI2 Annual Work	The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or International level: The expected impacts of the proposed approach as	The following aspects will be taken into account: Coherence and effectiveness of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and budget;

[20] Article 9(5) of the Regulation (EU) No 1290/2013 of the European Parliament and of the Council of 11 December 2013 laying down the rules for participation and dissemination in “Horizon 2020”.

Type of action	Excellence	Impact	Quality and efficiency of the implementation
	plan and is consistent with the stage 1 proposal: Clarity and pertinence of the proposal to meet all key objectives of the topic; Credibility of the proposed approach; Soundness of the concept, including trans-disciplinary considerations, where relevant; Extent that proposed work is ambitious, has innovation potential, and is beyond the state of the art; Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders.	mentioned in the call for proposals; Added value from the public private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant; Enhancing innovation capacity and integration of new knowledge; Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges; Improving European citizens' health and wellbeing and contribute to the IMI2 objectives;**Error! Bookmark not defined.** Any other environmental and socially important impacts; Effectiveness of the proposed measures to exploit and disseminate the project results (including management of IPR), to communicate the project, and to manage research data where relevant.	Complementarity of the participants within the consortium (where relevant); Clearly defined contribution to the project plan of the industrial partners (where relevant); Appropriateness of the management structures and procedures, including manageability of the consortium, risk and innovation management and sustainability plan.

These evaluation criteria include scores and thresholds. Evaluation scores will be awarded for the criteria, and not for the different aspects listed in the above table. For all evaluated proposals, each criterion will be scored out of 5. Half marks may be given.

For the evaluation of proposals under a single-stage submission procedure, the threshold for individual criteria is 3. The overall threshold, applying to the sum of the three individual scores is 10.

Following the evaluation, applicants will receive an ESR (Evaluation Summary Report) regarding the respective evaluated proposal.

The full evaluation procedure is described in the IMI2 JU Manual for submission, evaluation and grant award in line with the H2020 Rules for Participation.[21]

[21] http://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2_ManualForSubmission_v1.6_October2017.pdf

Proposals will be ranked under each topic separately. Under each topic, only the top ranked proposal will be selected for funding within the budget available under each topic.

As part of the panel deliberations, the IMI2 JU may organise hearings with the applicants to:

- clarify the proposals and help the panel establish their final assessment and scores, or
- improve the experts' understanding of the proposal.

INDICATIVE TIMETABLE FOR EVALUATION AND GRANT AGREEMENT

	Information on the outcome of the evaluation (single stage, or first stage of a two-stages)	Information on the outcome of the evaluation (second stage of a two stages)	Indicative date for the signing of grant agreement
Single-stage	Maximum 5 months from the submission deadline at the single stage.	N/A	Maximum 8 months from the submission deadline.

BUDGET FLEXIBILITY

Part I of the General Annexes to the Horizon 2020 – Work Programme 2018–2020 shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

ACTIONS INVOLVING FINANCIAL SUPPORT TO THIRD PARTIES

Part K of the General Annexes to the Horizon 2020 – Work Programme 2018–2020 shall apply *mutatis mutandis* for the actions selected under topics covered by this Call for proposals.

CONDITIONS RELATED TO OPEN ACCESS TO RESEARCH DATA

Part L of the General Annexes to the Horizon 2020 – Work Programme 2018–2020 shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

However, should a project "opt-out" of these provisions, a Data Management Plan must still be prepared. A template for the Data Management Plan is available under:

http://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/oa_pilot/h2020-hi-oa-data-mgt_en.pdf

SUBMISSION TOOL

Proposals in response to a topic of the IMI2 JU Call for proposals must be submitted on-line, before the call deadline, by the coordinator via the Electronic Submission Service of the Participant Portal:

http://ec.europa.eu/research/participants/portal/desktop/en/home.html

No other means of submission will be accepted.

OTHERS

For proposals including clinical trials/studies/investigations, a specific template to help applicants to provide essential information on clinical studies in a standardised format is available under:

http://ec.europa.eu/research/participants/data/ref/h2020/other/legal/templ/h2020_tmpl-clinical-studies_2018-2020_en.pdf

In a single-stage evaluation procedure involving clinical studies, the use of this template is mandatory in order to provide experts with the necessary information to evaluate the proposals. The template may be submitted as a separate document.

Ethical issues should be duly addressed in each submitted proposal to ensure that the proposed activities comply with ethical principles and relevant national, Union and international legislation. Any proposal that contravenes ethical principles or which does not fulfil the conditions set out in the H2020 Rules for Participation, or in the IMI2 JU Call for proposals shall not be selected.[22]

In order to ensure excellence in data and knowledge management consortia will be requested to Disseminate scientific publications on the basis of open access[23] (see "Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020").

To ensure actions are implemented properly, at the time of the signature of the grant agreement, each selected consortia must have agreed upon a consortium agreement, i.e. the internal arrangements regarding their operation and co-ordination.

Single-stage proposals must contain a draft plan for the exploitation and dissemination of the results.

Applicants intending to submit a proposal in response to the IMI2 JU Calls should also read the topic text, the IMI2 JU Manual for submission, evaluation and grant award, and other relevant documents[24] (e.g. IMI2 JU model Grant Agreement).

[22] Article 19 of Horizon 2020 Framework Programme and Articles 13 and 14 of the Horizon 2020 Rules for Participation.
[23] Article 43.2 of Regulation (EU) No 1290/2013 of the European Parliament and of the Council laying down the rules for participation and dissemination in "Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020)" and repealing Regulation (EC) No 1906/2006
[24] http://www.imi.europa.eu/apply-funding/call-documents/imi2-call-documents

LIST OF ACRONYMS

Acronym	Meaning
AD	Alzheimer's disease
ADMET	absorption, distribution, metabolism, and excretion
AIDS	Acquired Immune Deficiency Syndrome
AMR	Antimicrobial Resistance
API	Application Programming Interface
ATP	adenosine 5'-triphosphate
AWP2018	Annual Work Plan 2018
CBN	Capability Building Network
CDC	Centers for Disease Control and Prevention
CMC	Chemistry, manufacturing and controls
CNS	Central Nervous System
CSA	Coordination and Support Action
DMP	Data Management Plan
DNA	Deoxyribonucleic acid
DS	Drug Sensitive
EC	European Commission
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHR	Electronic Health Record
EMA	European Medicines Agency
ESBL	Extended spectrum beta-lactamases
ETH	Ethionamide
EU	European Union
FDA	Food and Drug Administration
FP	Full Proposal
FTIH	First-time-in-human
GA	Grant Agreement
GB	Governing Board
GDPR	General Data Protection Regulation
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
H2020	Horizon 2020 is the financial instrument implementing the Innovation Union, a Europe 2020 flagship initiative aimed at securing Europe's global competitiveness. For more information, click here: http://ec.europa.eu/programmes/horizon2020/en/what-horizon-2020
HAP/VAP	hospital-acquired pneumonia/ventilator associated pneumonia
HD	Huntington's Disease
HIV	Human Immunodeficiency Virus
HPLC	High-performance liquid chromatography

Acronym	Meaning
IAI	Intra-abdominal infections
ICH	International Council of Harmonisation
IMI	Innovative Medicines Initiative
IMI1 JU	Innovative Medicines Initiative 1Joint Undertaking
IMI2 JU	Innovative Medicines Initiative 2Joint Undertaking
IMI JU	Innovative Medicines Initiative Joint Undertaking
IMI PreDICT	Model-based preclinical development of anti-tuberculosis drug combinations
IP	Intellectual property
IRP	Integrated Research Platform
IT	Information Technology
JU	Joint Undertaking
KM	Knowledge Management
KOL	Key Opinion Leaders
MAbs	Monoclonal antibodies
MDR	Multi-drug resistance
MDR-TB	Multi-drug-resistant tuberculosis
MM4TB	More Medicines for Tuberculosis
MoU	Memorandum of Understanding
MRC	Medical Research Council
MS	Multiple sclerosis
MTA	Material transfer agreement
MTB	Mycobacterium tuberculosis
ND4BB	New Drugs for Bad Bugs
NIH	National Institutes of Health
Non-GLP	Non Good Laboratory Practices
NTM	Non-tubercular mycobacteria
ORCHID	Open Collaborative Model for Tuberculosis Lead Optimisation
PBNs	Company-specific Portfolio Building Networks
PD	Pharmacodynamics
PD	Parkinson's Disease
PDMS	Polydimethylsiloxane
PET	Positron emission tomography
PK	Pharmacokinetic
POC	Proof of Concept
PPPs	Public-private partnerships
PreDICT-TB	Model-based preclinical development of anti-tuberculosis drug combinations
preNME	Pre-new molecular entity
R&D	Research and development
RIA	Research and Innovation Action

Acronym	Meaning
RoI	Return on investment
SME	Small and Medium-Sized Enterprise
SP	Short Proposal
SRA	Strategic Research Agenda
TB	Tuberculosis
TBDA	TB Drug Accelerator
TBDDN	Tuberculosis Drug Development Network
TBRU-N	Tuberculosis Research Units Network
TI	therapeutic index
TRL	Technology Readiness Level
TURP	Transurethral resection of the prostate
UTI	Urinary tract infections
XDR-TB	Extensively-drug resistant
WHO	World Health Organisation
WP	Work package