Summary of the context and overall objectives of the project

The anTBiotic consortium aims to fuel the long-term Tuberculosis (TB) clinical pipeline while also immediately offering new options to clinicians when confronted with multidrug-resistant (MDR)-TB.

More specifically, the proposed studies aim to:

- Establish the proof of concept of anti-TB efficacy in humans of a pioneering, first-in class, low dose oxaborole clinical drug candidate.
- Identify a combination of β-lactam antibiotics suitable for the treatment of MDR TB orally or as a once daily intravenous or intramuscular application.
- Explore personalized treatment with biomarker-guided duration of salvage regimens incorporating β-lactams for patients with extensively drug-resistant (XDR)-TB
- Identify optimal pathways through early phase TB drug development using biomarkers and in silico dose modelling approaches

TB is the leading cause of death from infectious diseases. The number of TB patients has never been higher and the growing proportion of drug-resistant TB is threatening control strategies. Given the increasing incidence of MDR/XDR-TB cases worldwide, effective drugs are urgently needed for incorporation into new regimens that can improve outcomes and potentially shorten treatment

The consortium will undertake novel Early Bactericidal Activity Phase IIa studies with the objectives of:

- Renewing the pipeline: GSK´656 is an exciting new molecule, with a novel mechanism of action that has no pre-existent resistance in the field and the

potential to be developed into an oral drug as part of future drug combination regimens.

- Repurposing an optimized combination of meropenem or ertapenem and amoxicillin-clavulanate for MDR/XDR TB chemotherapy. The repurposing strategy of β-lactam combinations is based on a positive proof concept generated within FP7 and EDCTP-funded projects for the combination of meropenem with amoxicillin-clavulanate.
- Re-establishing the efficacy of rifampicin for the treatment of MDR/XDR-TB. Despite its wellestablished status as the cornerstone of TB chemotherapy, resistance to rifampicin is becoming progressively more common. The β-lactam class has been shown to act with synergy when combined with rifampicin in vitro and we hypothesize that this effect will translate into the clinic.

The partners aim also to:

- Explore personalized treatment with biomarker-guided duration by comparing therapy outcomes of MDR-TB patients (receiving β-lactam-containing treatment) with biomarker defined therapy durations vs. standard of care. This approach has the potential to significantly shorten drug-exposure whilst also reducing adverse events and costs. The identification of patients being at risk for therapy failure may improve patient outcomes.
- Explore the predictive potential of Positron Emission Tomography (PET) integrated with computed tomography (CT) as a non-invasive approach to evaluate drug action to complement the more traditional CFU (colony forming units) and TTP (time to culture positivity) EBA sputum markers. Should a correlation between early PET/CT signals and the sterilizing potential of individual drugs or drug regimens be confirmed, this would impact future clinical trial design, shortening clinical development timelines and lowering the associated uncertainties.
- Validate new EBA biomarkers as surrogates for treatment outcome. The identification of biomarkers that reflect the early therapy-induced immunological and bacteriological changes could lead to improved treatment monitoring, better prediction of treatment response and a better classification of patients demanding longer treatments.
- The project will also seek to develop and validate in silico predictions that could be used to shorten the drug development cycle. Mathematical models can inform optimal dosing strategies from data collected in preclinical development and address bottlenecks between early clinical development and phase III, where TB relapse is assessed. A new in silico approach connecting processes within single bacteria with the dynamics of entire bacterial populations within patients, enables the extrapolation of basic molecular mechanisms of drug action into response signals to treatment.

Work performed and main results achieved so far

By the end of the second reporting period, the consortium has completed enrollment to the initially planned six arms of the 2-weeks EBA study with β-lactam antibiotics, aiming to identify a combination suitable for the treatment of MDR TB that could be administered once day either orally, intravenously or intramuscularly. Given the positive results of the study, a new arm is being added to refine the dose and simplify the once-daily administration of meropenem plus clavulanic acid, to improve the utility for the patient and the clinic.

PET/CT scan images from participants in this trial, as well as blood and urine samples have been collected and will be analyzed with the objective of validating biomarkers that accurately reflect the early therapy-induced immunological, radiological and bacteriological changes. Following this objective and based on the recent results obtained by one of the partner´s work, the consortium is also preparing a clinical trial that will compare therapy outcomes of patients with biomarker-guided therapy durations vs. standard of care, aiming for individualized treatment shortening.

The EBA study that aims to establish proof of concept of anti-TB efficacy in humans of a low-dose oxaborole clinical drug candidate is close to completing recruitment of the first cohort (lowest dose).

Finally, the project modeling work aims to find optimal dosing and identify promising combination regimens to be further developed. The team has completed the development of a mathematical model that is able to describe the interaction of two drugs with their respective targets. The preliminary mathematical model developed to predict optimal dosing, based on novel models that incorporate chemical reaction kinetics of an antibiotic with its target, has been now fit and validated with timekill curves information for two project drugs.

Expected results

- A novel chemical entity that could be ready for progression to Phase IIb clinical trials, towards becoming a new TB drug within a suitable combination.
- Optimised drug regimen options for the treatment of MDR/XDR-TB with agents that are presently out of patent protection and available in the market.
- A defined set of biomarkers to guide individualized treatment duration able to improve patient outcomes by enabling personalized treatment-shortening.

Expected impacts

This project will contribute to address major challenges and needs identified for TB treatment, namely:

- Addressing the large mortality and morbidity associated with drug resistant TB by providing novel and repurposed drugs for new combination therapies

- Contributing to the TB treatment shortening agenda, one of the main goals pursued by major TB stakeholders (WHO, TB Alliance, Stop TB Partnership, etc).
- Developing innovative tools that could improve TB clinical practice.
- Shorten future TB drug development cycles by identifying biomarkers with the potential to predict phase 3 endpoints at earlier phases.
- Contributing to ending the TB epidemic by 2030, which is one of the targets of the Sustainable Development Goals (SDGs) of the United Nations.
- Making efficient use of limited funding, one of the main obstacles for TB drug development.

This project has received funding form the European Union´s Horizon2020 research and innovation programme under Grant Agreement No. 733079