Accelerating the development of new treatment regimens for Tuberculosis
Tuberculosis is among the leading causes of death worldwide

THE TB CHALLENGE
With 1.5 million people dying and 10 million affected each year worldwide, tuberculosis (TB) is a leading cause of death and suffering from an infectious disease. According to a 2021 report by the World Health Organization (WHO), the COVID-19 pandemic has reversed years of global progress in tackling TB with TB deaths increasing for the first time in over a decade.

In recent years, the public health challenge of multidrug-resistant TB (MDR-TB) – the largest concern in the control of antimicrobial resistance (AMR) globally – has triggered renewed scientific efforts in anti-TB drug research and development (R&D).

An integrated approach to anti-TB drug R&D is still lacking with the recent clinical trial designs generally focused on developing single drugs rather than drug combinations. With current methodology, it is estimated it will take 15-20 years to develop a new 3-4 drug combination regimen to treat all forms of TB, including the most drug-resistant strains.

Consequently, new drugs and shorter regimens for the treatment of TB, and their rapid uptake, are urgently needed if we are to reach the ambitious targets of 95% death reduction and 90% incidence decline by 2035 set by the WHO in its End TB global strategy.

UNITE4TB aims to deliver more effective and shorter regimens through innovative clinical trial designs that conform to the highest regulatory standards.

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1 WHO 2021 Global TB report: https://www.who.int/publications/i/item/9789240037021
2 WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment - Drug-Resistant Tuberculosis Treatment, available in https://www.who.int/publications/i/item/9789240007048

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UNITE4TB is a public-private partnership with representation from academic institutions, small- and medium-sized enterprises (SMEs), patient-led organisations, and pharmaceutical companies.

With 30 partners from 13 countries, UNITE4TB aims to accelerate and improve the clinical evaluation of novel compounds and drug combinations to develop new and effective anti-TB treatments for drug-resistant (DR) and drug-sensitive (DS) TB.

Over a project term of 7 years, UNITE4TB will be active in four WHO regions (Europe, Asia, Africa and South America), with the goal of delivering novel phase 2 clinical trials that will accelerate the development of new anti-TB drugs and regimens.

Achieving this goal will facilitate fulfillment of one of the main unmet needs in the TB field: well-tolerated drug regimens of shorter duration that can be deployed to tackle TB across various DR patterns and co-morbidities.
### CONCEPT & METHODOLOGY

To address the challenge of developing new anti-TB treatment regimens, UNITE4TB follows a concept that is analogous to a car racetrack.

The project will ensure access to the most innovative anti-TB compounds (the key car parts) tested during phases 1 and 2A (the pitstop) before being assembled into a new treatment regimen (the race car) to be launched into a clinical trial platform covering four continents (the racetrack).

New car parts (drugs) and cars (regimens) may enter the race when ready, making this a state-of-the-art adaptive trial design with conventional and new biomarkers of treatment success. Advanced pharmacokinetic and pharmacodynamic modelling techniques as well as artificial intelligence and machine learning techniques will be employed to select, test and deliver novel combination regimens with a high probability of success in subsequent phase 3 trials.

### Overview

- **APP/LUP compounds are colored red, bold and underlined.**
- **DR drug**
- DprE1 inhibitor (OPC-167832, BTZ-043, Macozinone, TBA7371)
- Respiratory chain inhibitor/energy metabolism (TBAJ-587, TBAJ-876, Telacebec)
- Cell wall inhibitor (Sanfetrinem)
- Protein synthesis inhibitor (KRS (DDU-1), OTB658, GSK656, TBI-223, Delpazolid, Sutezolid)
- Exporter of mycolic acid (MMPL3 (TBA3) & SQ109)
- Cholesterol metabolism (GSK286)
- Ethionamide booster (BVL-GSK098)
- Tryptophane synthase enzyme (GSK3778839A (GSK2))
- Fatty acid biosynthesis pathway (KasA inh (GSK3))
- Unknown (MV46 (DDU2) & TBI-166)

**Global TB drug pipeline (October 2020), with UNITE4TB EFPIA/AP drug candidates in red (EFPIA/AP = European Federation of Pharmaceutical Industries and Associations/Associated Partners).**

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### Timeline

- **START PHASE 2B/C**
- **FIRST INTERIM ANALYSIS**
- **PITSTOP**
- New regimen(s) phase 3 ready
- Improved trial design
- Knowledge on TB treatment and geographic dependencies
- International network of TB experts and patient advocates
- New data for further analyses

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### UNITE4TB

**First interim analysis**
- Nutrition optimisation
- Feeding/trial design
- Ethionamide booster
- Treatment regimen visualised as race-cars

**Second interim analysis**
- Treatment regimen re-adjusted
- Advanced pharmacokinetic and pharmacodynamic modelling
- Artificial intelligence and machine learning
- Selection of compound combinations
- Dose adjusting (phase 2A)

**End phase 2B/C**
- New regimen(s) phase 3 ready
- Improved trial design
- Knowledge on TB treatment and geographic dependencies
- International network of TB experts and patient advocates
- New data for further analyses

**Process test track**
- Intermediate checks
- Treatments (cars) re-adjusted at the pitstop
Providing new tools and knowledge of how to progress TB science

Developing an innovative clinical trial design

Contributing to the development of a vibrant TB research environment

Improving current practices through contributing to new policy recommendations

Collaborating with other consortia to accelerate the development of new anti-TB drug regimens

Enabling the progression of new, safe and affordable treatment solutions that are well tolerated, shorter in duration and highly effective

Improving the lives of people living with TB

The consortium intends to have an impact on a number of critical issues within TB drug development by:

The ambition of UNITE4TB is to connect with policymakers, funders, and agencies at both national and international levels to ensure that all necessary viewpoints are collected. By doing so, we aim to progress the development and implementation of new and better drug regimens to treat TB.

Through collaboration we can:

1. Share state-of-the-art knowledge and expertise to progress new TB treatment innovations
2. Ensure engagement of civil society, decision-makers, and other key stakeholders, so that the people affected by TB are at the heart of the project
3. Support affected communities with easier, faster, more effective regimens

The UNITE4TB consortium has the expertise, capacity, and influence to change the paradigm of clinical TB drug R&D.

We have a vision for UNITE4TB to be the start of a major new enterprise. In collaboration with centers of excellence around the world, we hope to secure sustained investment in TB drug development in the years to come, so that the elimination of TB as a public health problem can finally be achieved.

For more information, visit the UNITE4TB website:

www.unite4tb.org
Contact information
If you have general questions about the project, please send an email to: office@unite4tb.org
For more information, visit the UNITE4TB website: www.unite4tb.org

Facts & figures

Who’s involved? 30 partners from 13 countries
Participating countries Belgium, France, Germany, Ireland, Italy, Netherlands, Portugal, South Africa, Spain, Sweden, Switzerland, United Kingdom, USA
Start date 1 June 2021
End date 31 May 2028
Project coordinator RadboudUMC
Project lead GSK
Scientific lead LMU
Clinical lead (rotating representatives) UOXF; FZB; LSHTM
Total budget 185M Euro

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