A new dawn in the fight against Tuberculosis

UNITE4TB, the largest public-private collaboration in tuberculosis drug development, announces start of clinical trials

8 November 2023. Today, UNITE4TB, an international public-private partnership striving to fast-track the development of innovative Tuberculosis (TB) treatments, announced the start of its phase 2B/C clinical trial program with the first participant enrolled at its trial site in Cape Town, South Africa. The announcement is a major milestone for the project and the TB community as a whole, helping to advance TB science and enhance the efficiency with which new treatments are delivered.

The TB challenge

TB is a major threat to public health, being among the leading causes of death worldwide. In 2021, the disease claimed the lives of 1.6 million people, making it the second leading infectious killer after COVID-19.[1] Drug-resistant TB and long treatment regimens have increased the urgency for action and investment in TB research.

For people affected by TB, the most important outcome is rapid access to better regimens of shorter treatment duration and with fewer side effects. UNITE4TB is engaging with key societal stakeholders to ensure that its novel regimens will be made available as efficiently as possible.

Exploring new frontiers

UNITE4TB's innovative phase 2B/C trials will test 14 combinations of nine existing drugs, as well as two newly developed candidates (GSK656[2] and BTZ-043[3]). The ultimate aim is to create regimens that can further improve multidrug-resistant (MDR) treatment, and also be effective for drug-sensitive TB.

UNITE4TB's explorative regimens have been constructed by combining the novel compounds GSK656 and BTZ-043 with the most recently licensed drug classes: diarylquinoline (bedaquiline) and nitroimidazoles (delamanid or pretonamid). Apart from DECISION, a BTZ-043 dose evaluation in combination study, the UNITE4TB trial program includes PARADIGM4TB, a phase 2B/C platform trial to evaluate multiple regimens and durations of treatment in Pulmonary Tuberculosis. PARADIGM4TB will establish which fourth drug (either moxifloxacin, linezolid, or pyrazinamide) can be added as the optimal component to a bedaquiline, delamanid, BTZ-043 or GSK656 regimen. The trial will also explore the efficacy of a totally new combination of GSK656 and BTZ-043 together with bedaquiline and delamanid.

[1] https://www.who.int/en/news-room/fact-sheets/detail/tuberculosis

[2] GSK656 is a 3-aminomethyl 4-halogen benzoxaboroles, a new class of antibiotics that inhibit leucyl-tRNA synthetase (LeuRS), an essential enzyme for mycobacterial protein synthesis

[3] BTZ-043 is a benzothiazinone, a new class of anti-tuberculosis compounds that inhibit *Mycobacterium tuberculosis* cell wall synthesis by blocking the decaprenyl- phosphoribose-2'-epimerase (DprE1), necessary for the arabinan biosynthesis

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 101007873. The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA, Deutsches Zentrum für Infektionsforschung e. V. (DZIF), and Ludwig-Maximilians-Universität München (LMU). EFPIA/AP contribute to 50% of funding, whereas the contribution of DZIF and the LMU University Hospital Munich has been granted by the German Federal Ministry of Education and Research.

Expert insights

Commenting on the trial design, UNITE4TB Scientific Leader, Prof. Michael Hoelscher of LMU University Hospital Munich said: *"There are three major steps in TB regimen development: the establishment of the optimal dose for each individual drug, the identification of the right combination of four different drugs and the shortest possible treatment duration of the regimen of choice. In UNITE4TB, we are addressing these aspects via the most efficient trial designs possible."*

The South African trial site, part of the clinical research institute TASK, where the first participant in the UNITE4TB trial program has been enrolled, is one of several selected for the project. The sites were chosen based on TB prevalence. Other high-burden countries on the trial site list include Tanzania, Uganda, Vietnam, and the Philippines.

Prof. Andreas Diacon, Chairman and CSO TASK and CEO TASK Europe, said: *"At TASK, we conduct all stages of clinical trials, from first in human trials all the way through to licensing. We are thrilled to be kicking off the UNITE4TB clinical trial program here in Cape Town and are proud to be part of this important clinical research project."*

Reflecting on this latest milestone, Prof. Martin Boeree, UNITE4TB project coordinator from Radboudumc said: *"Today's announcement marks an exciting moment for TB research. The world needs new drugs for TB but also new ways to run clinical studies. Our public-private partnership sets a new standard in this regard. If successful, our work will deliver a new treatment regimen of shorter duration that can be used to fight all types of tuberculosis."*



View this video marking the start of the UNITE4TB phase 2B/C clinical trial program, which kicked off at the trial site in Cape Town, South Africa (copyright: UNITE4TB)

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For the media (not for publication)
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Press photo caption: UNITE4TB Phase 2B/C clinical trial program gets underway at trial site in Cape Town, South Africa (Copyright: UNITE4TB)

Notes to editors

1. **About UNITE4TB**
   UNITE4TB is a public-private partnership with representation from academic institutions, small- and medium-sized enterprises (SMEs), public organizations, and pharmaceutical companies. Over a project term of 7 years, the consortium aims to accelerate and set a new standard for the clinical evaluation of novel compounds and combinations of drugs to develop new and highly active anti-tuberculosis (TB) treatment regimens for drug-resistant (DR) and -sensitive (DS) TB. The consortium will deliver an efficient, global clinical trials (CTs) network equipped to implement phase 2A and 2B/C trials that conform to the highest regulatory standards. These trials will integrate state-of-the-art adaptive designs with conventional and new biomarkers of treatment success and employ advanced pharmacokinetic (PK) and pharmacodynamic (PD) modelling techniques as well as artificial intelligence (AI) and machine learning (ML) techniques.

   Launched in July 2021, the €185 million project is funded by the Innovative Medicines Initiative (IMI) Joint 2 Undertaking. With 30 partners from 13 countries, it is the largest public-private partnership on clinical TB drug development in the history of the European Union. For more information, visit the consortium website: www.unite4tb.org

2. **About tuberculosis**
   Tuberculosis (TB) is a global threat and one of the leading infectious disease killers worldwide. The World Health Organization (WHO) reported that 1.6 million people died from TB in 2021.[4] 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).[5] 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 strategy.[6]

[4] https://www.who.int/en/news-room/fact-sheets/detail/tuberculosis
[5] WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment - Drug-Resistant Tuberculosis Treatment, available in https://www.who.int/publications/i/item/9789240063129
[6] Implementing the end TB strategy: the essentials, 2022 update: https://www.who.int/publications/i/item/9789240065093

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3. Consortium partners

Academic/SME partners

- **Stichting Radboud Universitair Medisch Centrum (Radboudumc)** (The Netherlands) – Project Coordinator
- **London School of Hygiene and Tropical Medicine (LSHTM)** (United Kingdom)
- **University of Oxford** (United Kingdom)
- **Forschungszentrum Borstel, Leibniz Lungenzentrum** (Germany) – Clinical Leader
- **Lygature** (The Netherlands)
- **University of Cambridge** (United Kingdom)
- **University College London** (United Kingdom)
- **TASK** (South Africa)
- **Vita-Salute San Raffaele University (UniSR)** (Italy)
- **Helmholtz Zentrum München** (Germany)
- **KNCV Tuberculosis Foundation (KNCV)** (The Netherlands)
- **Critical Path Institute, Limited** (Ireland)
- **European Lung Foundation** (United Kingdom)
- **Instituto de Saude Publica da Universidade do Porto (ISPUP)** (Portugal)
- **University of Liverpool** (United Kingdom)
- **Institut de Recherche Pour le Developpement** (France)
- **University of Hamburg** (Germany)
- **University of California San Francisco (UCSF)** (USA)
- **TB Alliance** (USA)
- **FIND** (Switzerland)
- **University of Milano (UMIL)** (Italy)
- **University St Andrews** (United Kingdom)
- **Uppsala University** (Sweden)
- **European Respiratory Society** (Switzerland)
- **TBnet** (Germany)

EFPIA/Associated Partners

- **GlaxoSmithKline Investigación y Desarrollo S L (GSK)** (Spain) – Project Leader
- **Janssen Pharmaceutica NV** (Belgium)
- **Otsuka Novel Products GmbH** (Germany)
- **Deutsches Zentrum für Infektionsforschung** (Germany)
- **LMU University Hospital Munich** (Germany) – Scientific Leader

View a detailed overview of all partner information on the UNITE4TB website

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4. **About the UNITE4TB clinical trial phase 2B/C program**

The UNITE4TB clinical trial program is made up of the DECISION and PARADIGM4TB trials. The trial sponsor for DECISION is LMU University Hospital Munich. For PARADIGM4TB, the trial sponsor is University College London.

DECISION (BTZ-043 **D**ose **E**valuation in **C**omb**I**nation and **S**elect**ION**) is a phase 2B, dose-finding study, comparing the safety and efficacy of different doses of BTZ-043 administered with a backbone of bedaquiline and delamanid, in participants with drug-sensitive tuberculosis. Participants will be assigned to receive either one of three BTZ-043-containing regimens or a comparator regimen of bedaquiline, delamanid and moxifloxacin. The objective is to find the optimal dose of BTZ-043 to be used in subsequent studies. Further information about the study is available at: https://clinicaltrials.gov/study/NCT05926466

PARADIGM4TB is an innovative seamless phase 2B/C platform trial that will be active in approximately 30 trial sites on four continents (Europe, Asia, Africa and South America), with the goal of delivering novel phase 2B/C clinical trials that will accelerate the development of new TB drugs and regimens with a higher probability of success in subsequent phase 3 clinical trials.

5. **Acknowledgement of support**

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