

PAN-TB Collaboration to Advance Investigational Tuberculosis Drug Regimens to Phase 2 Clinical Trials

Public-private collaboration to evaluate five antimicrobial agents across two combination regimens for treating both drug-susceptible and drug-resistant forms of TB with shorter treatment durations

August 17, 2022 – The Project to Accelerate New Treatments for Tuberculosis (PAN-TB) collaboration announced today the execution of a joint development agreement (JDA) supporting the progression of two investigational tuberculosis (TB) combination treatment regimens into phase 2 clinical development. The collaboration will evaluate whether the novel regimens, which combine registered products and new chemical entities (NCEs), can effectively treat all forms of active pulmonary TB using substantially shorter treatment durations than existing drug regimens, with the goal of identifying a regimen suitable for phase 3 development.

TB is a major global cause of illness, disability and catastrophic household costs, and is one of the leading causes of death from an infectious disease worldwide, responsible for an estimated 1.5 million deaths per year. A shorter drug regimen that can treat both drug-susceptible and drug-resistant forms of TB in potentially three months or less could provide a significant benefit to both patients and health systems and may overcome the need for accompanying drug-resistance testing.

Recognizing that no single organization produces the full range of drugs needed to respond to TB, the PAN-TB collaboration brings together philanthropic, non-profit and private sector organizations to accelerate the development of novel, shorter drug regimens to treat all forms of TB. The five antimicrobial agents to be evaluated under the new JDA, and the organizations contributing them, include:

- Bedaquiline; registered product for multidrug-resistant TB, Janssen Pharmaceutica NV, part of the Janssen Pharmaceutical Companies of Johnson & Johnson, and NCE for drug-sensitive TB, TB Alliance¹
- Delamanid; registered product, Otsuka Pharmaceutical Co., Ltd.
- Pretomanid; registered product, TB Alliance
- OPC-167832; NCE, Otsuka
- Sutezolid; NCE, TB Alliance, Medicines Patent Pool, Bill & Melinda Gates Medical Research Institute

The two investigational drug regimen combinations to be evaluated include:

- DBOS – delamanid, bedaquiline, OPC-167832 and sutezolid
- PBOS – pretomanid, bedaquiline, OPC-167832 and sutezolid

The planned phase 2 trials that will be supported by the JDA were designed by the PAN-TB collaboration and informed by the World Health Organization's (WHO) recently published position statement on the design of clinical trials for novel TB therapies.

¹ Janssen provided the exclusive rights for developing and marketing bedaquiline for drug-sensitive TB to the TB Alliance in 2009

New treatment regimens could help transform TB care. The most commonly used drug regimen for the treatment of drug-sensitive TB requires patients to take multiple drugs for up to six months with routine clinical monitoring. Patients with drug-resistant forms of TB can face longer and more complex treatment journeys, often with significant side effects that require increased monitoring. Accurate and rapid drug resistance testing is essential for early diagnosis of both drug-sensitive and drug-resistant TB, but access to testing can be limited due to high costs, technical challenges and other barriers.

The PAN-TB collaboration is a first-of-its-kind effort to accelerate development of a drug regimen capable of treating all forms of TB (a “pan-TB” regimen), focusing on advancing research through phase 2 clinical studies and identifying promising regimens for further development. The collaboration comprises Evotec, GSK, Janssen Pharmaceutica NV, Otsuka, TB Alliance, the Bill & Melinda Gates Medical Research Institute (Gates MRI) and the Bill & Melinda Gates Foundation. The JDA announced today is among the four collaborators contributing drugs – Janssen Pharmaceutica NV, Otsuka, TB Alliance and the Bill & Melinda Gates Medical Research Institute. Gates MRI will also conduct the clinical studies.

Masanori Kawasaki, Global TB Project Leader, Otsuka Pharmaceutical Co. Ltd., said: “We are extremely proud to be moving forward within this unique collaboration towards the phase 2 b/c trial of a new universal treatment regimen. We are excited to be working closely with our colleagues in the Bill & Melinda Gates Medical Research Institute, Janssen Pharmaceutica NV and the TB Alliance to do all we can to bring a new treatment to patients whose options are limited. Otsuka is dedicated to research and development to eliminate tuberculosis. We extend our thanks to the Bill & Melinda Gates Foundation for bringing together leaders in the field of TB, towards the goal of ending TB for good.”

Ruxandra Draghia-Akli, MD, PhD, Global Head of Global Public Health R&D, Janssen Research & Development, LLC, said: “The Janssen Pharmaceutical Companies of Johnson & Johnson remain steadfast in our commitment to advancing research and development to create next-generation TB treatment regimens, as guided by our 10-year initiative to discover and develop new drugs to help end TB. Today, our medicine has become the backbone of WHO-recommended all-oral treatment regimens for nearly all DR-TB patients, and this agreement will allow us to explore further our medicine’s potential to help transform TB treatment for patients in need while maintaining its long-term effectiveness in the face of rising antimicrobial resistance.”

Mel Spiegelman, MD, President and CEO, TB Alliance, said: “TB is becoming a greater and greater global health emergency. We are proud to be a member of the PAN-TB consortium to advance novel drug regimens that can much more effectively combat this deadly pandemic and save lives. This initiative is a significant advancement of our pioneering efforts that introduced and validated the concept of regimen development in TB.”

Emilio Emini, PhD, CEO, the Bill & Melinda Gates Medical Research Institute, said: “The Bill & Melinda Gates Medical Research Institute team looks forward to working with its PAN-TB collaboration partners in the execution of the phase 2 clinical studies evaluating the first two TB drug regimens for further development as potentially improved TB treatment options.”

Werner Lanthaler, PhD, CEO, Evotec, said: “Tuberculosis still has a significant impact on global health that needs to be addressed. The PAN-TB research group brings together global leaders in their particular fields. As Evotec we are dedicated to contributing to the research through our expertise and multi-modality platform, which can help validate drug candidates.”

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About the Project to Accelerate New Treatments for Tuberculosis

The Project to Accelerate New Treatments for Tuberculosis (PAN-TB) is a first-of-its-kind collaboration among philanthropic, non-profit and private sectors that aims to accelerate the development of an investigational drug regimen capable of treating all forms of tuberculosis.

The PAN-TB collaboration will leverage members' collective assets, resources and scientific expertise to identify and evaluate new drug regimens with an acceptable safety profile, that have the potential to treat both drug-sensitive and drug-resistant TB, and are better-tolerated, shorter in duration and simpler to use than existing options. The collaboration will focus on advancing research through phase 2 clinical efficacy studies in order to identify promising regimens for further development.

The PAN-TB collaboration plans to work closely and transparently with the European Regimen Accelerator for Tuberculosis (ERA4TB), which was launched in January 2020. New molecular entities identified by ERA4TB that show promise in initial human studies could later be incorporated into the PAN-TB collaboration's later-stage, clinical research. Several organizations, including Evotec, GSK and Janssen Pharmaceutica NV, are members of both projects, which will help to ensure coordination across collaborations toward the common goal of advancing TB drug and regimen development.

The founding members of the PAN-TB collaboration are Evotec, GSK, Janssen Pharmaceutica NV, Otsuka Pharmaceutical Co., Ltd., based in Japan, the Bill & Melinda Gates Medical Research Institute and the Bill & Melinda Gates Foundation. Additional members may be announced in the future.

About Evotec SE

Evotec is a life science company with a unique business model that delivers on its mission to discover and develop highly effective therapeutics and make them available to the patients. The Company's multimodality platform comprises a unique combination of innovative technologies, data and science for the discovery, development, and production of first-in-class and best-in-class pharmaceutical products. Evotec leverages this "Data-driven R&D Autobahn to Cures" for proprietary projects and within a network of partners including all Top 20 Pharma and over 800 biotechnology companies, academic institutions, as well as other healthcare stakeholders. Evotec has strategic activities in a broad range of currently underserved therapeutic areas, including, e.g., neurology, oncology, as well as metabolic and infectious diseases. Within these areas of expertise, Evotec aims to create the world-leading co-owned pipeline for innovative therapeutics and has to-date established a portfolio of more than 200 proprietary and co-owned R&D projects from early discovery to clinical development. Evotec operates globally with more than 4,500 highly qualified people. The Company's 16 sites offer highly synergistic technologies and services and operate as complementary clusters of excellence. For additional information please go to www.evotec.com and follow us on Twitter [@Evotec](https://twitter.com/Evotec) and [LinkedIn](https://www.linkedin.com/company/evotec).

About GSK

GSK is a global biopharma company with a purpose to unite science, technology, and talent to get ahead of disease together. Find out more at gsk.com/company.

About the Janssen Pharmaceutical Companies of Johnson & Johnson

At Janssen, we're creating a future where disease is a thing of the past. We're the Pharmaceutical Companies of Johnson & Johnson, working tirelessly to make that future a reality for patients everywhere by fighting sickness with science, improving access with ingenuity, and healing hopelessness

with heart. We focus on areas of medicine where we can make the biggest difference: Cardiovascular, Metabolism, & Retina; Immunology; Infectious Diseases & Vaccines; Neuroscience; Oncology; and Pulmonary Hypertension.

Learn more at www.janssen.com. Follow us at www.twitter.com/JanssenGlobal. Janssen Research & Development, LLC and Janssen Pharmaceutica NV are part of the Janssen Pharmaceutical Companies of Johnson & Johnson.

About Otsuka Pharmaceutical Co., Ltd.

Otsuka is a global healthcare company with the corporate philosophy, *Otsuka-people creating new products for better health worldwide*. Otsuka researches, develops, manufactures and markets innovative products, focusing on pharmaceutical products to meet unmet medical needs and nutraceutical products for the maintenance of everyday health. In pharmaceuticals, Otsuka is a leader in the challenging area of mental health and also has research programs in several under-addressed diseases including tuberculosis, a significant global public health issue.

About TB Alliance

TB Alliance is a not-for-profit organization dedicated to finding faster-acting and affordable drug regimens to fight TB. Through innovative science and with partners around the globe, we aim to ensure equitable access to faster, better TB cures that will advance global health and prosperity. TB Alliance operates with support from Australia's Department of Foreign Affairs and Trade; Bill & Melinda Gates Foundation; Foreign, Commonwealth and Development Office (United Kingdom); Cystic Fibrosis Foundation; Germany's Federal Ministry of Education and Research through KfW; Global Disease Eradication Fund (Korea); Global Health Innovative Technology Fund; Indonesia Health Fund; Irish Aid; Korea International Cooperation Agency; Medical Research Council (United Kingdom); National Institute of Allergy and Infectious Diseases; Netherlands Ministry of Foreign Affairs; Republic of Korea's Ministry of Foreign Affairs; and the United States Agency for International Development. For more information, visit www.tballiance.org.

About the Bill & Melinda Gates Medical Research Institute

The Bill & Melinda Gates Medical Research Institute is a non-profit organization dedicated to the development and effective use of novel biomedical interventions addressing substantial global health concerns, for which investment incentives are limited – malaria, tuberculosis, enteric and diarrheal diseases, and diseases that impact maternal, newborn, and child health. For further information please visit www.gatesmri.org.

About the Bill & Melinda Gates Foundation

Guided by the belief that every life has equal value, the Bill & Melinda Gates Foundation works to help all people lead healthy, productive lives. In developing countries, it focuses on improving people's health and giving them the chance to lift themselves out of hunger and extreme poverty. In the United States, it seeks to ensure that all people—especially those with the fewest resources—have access to the opportunities they need to succeed in school and life. Based in Seattle, Washington, the foundation is led by CEO Mark Suzman, under the direction of co-chairs Bill Gates and Melinda French Gates and the board of trustees. For further information please visit www.gatesfoundation.org.

About Bedaquiline

Bedaquiline, developed by Janssen Pharmaceutica NV, part of the Janssen Pharmaceutical Companies of Johnson & Johnson, was the first targeted medicine for TB with a novel mechanism of action to be

introduced in over 40 years when it received accelerated approval by the U.S. Food and Drug Administration in 2012. Today, it is recommended by the World Health Organization (WHO) as a core component of all-oral treatment regimens for nearly all DR-TB patients and is included on the WHO Model List of Essential Medicines. It is indicated in the U.S. and European Union for use as part of combination therapy in the treatment of adult and pediatric patients (5 years and older and weighing at least 15 kg) with pulmonary multidrug-resistant tuberculosis (MDR TB). In total, 156 countries are accessing the medicine today, including the 30 countries with the highest burdens of TB. To learn more about how Johnson & Johnson is working to enable access to this medicine, visit [JNJ.com/TB](https://www.jnj.com/tb).

About Delamanid (Delyba)

Delamanid is a compound created by Otsuka Pharmaceutical with a mechanism of action showing anti-mycobacterial activity that occurs through inhibition of the synthesis of mycolic acid, an essential component of mycobacterial cell walls.¹ To date, delamanid (50 mg film-coated tablets) is approved in 47 countries for treatment of patients with MDR-TB. It was added to the WHO Model List of Essential Medicines in 2015 and to date has been used to treat patients with MDR-TB in more than 122 countries.

In 2020, in the European Union, approval was granted for Delyba 50 mg film-coated tablets to be used in children and adolescents weighing at least 30 kg.² In 2021, a 25 mg dispersible tablet formulation was approved in the European Union for children with pulmonary MDR-TB weighing at least 10 and below 30 kg as part of an appropriate combination regimen, when an effective treatment regimen cannot otherwise be composed for reasons of resistance and tolerability.²

¹ Matsumoto M, *et al.* OPC-67683, a nitro-dihydro-imidazooxazole derivative with promising action against tuberculosis in vitro and in mice. *PLoS Med.* 2006; 3(11): e466

² Delyba (delamanid) EU Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/delyba-epar-product-information_en.pdf

About OPC-167832

OPC-167832 is an anti-TB compound discovered and currently under investigation by Otsuka. It inhibits the enzyme decaprenylphosphoryl- β -D-ribose 2'-oxidase (DprE1), which is connected to synthesis involving mycobacterial cell walls. This is a different mechanism of action from other currently available anti-TB drugs. In vivo studies in mice suggest that OPC-167832 plus delamanid-containing regimens have the potential to shorten therapy and improve outcomes in drug-susceptible TB and multidrug-resistant TB (MDR-TB).¹

¹ Hariguchi N, *et al.* OPC-167832, a Novel Carbostyryl Derivative with Potent Antituberculosis Activity as a DprE1 Inhibitor. *Antimicrob Agents Chemother.* 2020 May 21;64(6):e02020-19.

About Pretomanid:

Pretomanid is a new chemical entity and a member of a class of compounds known as nitroimidazooxazines. Pretomanid was developed by TB Alliance as an oral tablet formulation for the treatment of tuberculosis in combination with other anti-tuberculosis agents. One such combination is the BPaL regimen, consisting of bedaquiline, pretomanid, and linezolid, which received its first regulatory approval in 2019. In 2022, the World Health Organization issued a rapid communication on forthcoming TB treatment guidelines that will allow for the programmatic implementation of treating almost all forms of drug-resistant TB with six-month, BPaL-based regimens.

About Sutezolid

In October 2019, The Medicines Patent Pool (MPP) and Pfizer entered into a license agreement which granted MPP rights to sublicense to third parties the patents and information relating to sutezolid. In December 2020, MPP and Gates MRI signed an agreement to advance the development of this investigational drug from the oxazolidinone class, for use in low- and middle-income countries.

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