

Ground Breaking Advancement in TB Treatment Regimen

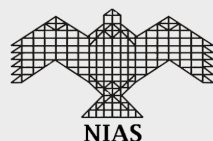
1Shingar Sharma* & 2Pawan Sharma

1. Formerly Grant Advisor, WT-DBT India Alliance, New Delhi (shingar.sharma@gmail.com)
2. Formerly Senior Research Scientist, ICGEB, New Delhi (pawan37@gmail.com)

A six-month-long duration of TB treatment under the DOTS programme is fraught with issues like non-compliance by patients, mix up of drugs, etc., contributing to the emergence of multi-drug-resistant TB. Shortening the duration of treatment has been a priority area in the TB drug discovery research efforts. In a recent Phase 3 clinical trial (Study 31/A5349), a 4-month regimen is as efficacious as the 6-month regimen for treatment of drug-susceptible tuberculosis in patients. This landmark breakthrough is expected to strengthen the global efforts for the elimination of TB by 2030.



Volume:1



Shingar Sharma* & Pawan Sharma

Ground Breaking Advancement in TB Treatment Regimen



Ground Breaking Advancement in TB Treatment Regimen

Issue:2

Dec 2020

According to the WHO Global TB report, there were an estimated 10 million new cases of TB worldwide in 2019 and approximately 1.5 million people died due to the disease. India accounted for 26% of the global TB burden, the highest among all countries. Though the numbers have been falling over the past years, the progress is too slow. Disruptions in health services and case reporting due to the COVID-19 pandemic have caused a setback in the efforts to achieve the Sustainable Development Goals and can derail the ambitious End TB Strategy which aims to reduce TB deaths by 90% by the year 2030. The ongoing Covid-19 pandemic has not only laid bare the abject unpreparedness of countries across the world to effectively deal with such a massive health emergency but also poses a grave threat to the gains made in combating other major global diseases, such as Tuberculosis (TB). TB continues to be a leading cause of death worldwide and has not halted its grim march even as Covid-19 is taking a toll on health systems everywhere.

The need to find game-changing yet feasible solutions to overcome the TB problem has taken on even greater importance in unprecedented times like these. Drug-resistant TB remains a formidable threat and radical approaches are required to stem its onslaught. India had the largest number of drug-resistant cases in 2019, amounting to 27% of the global burden (WHO report 2020)¹. Although the current new TB drug pipeline reflects impressive international effort in developing new anti-TB drugs {*Table*}, research on cutting down the duration of a long treatment schedule is equally important.

Putative New TB Drug Pipeline 2020 : Based on www.newtbdrugs.org/pipeline/discovery

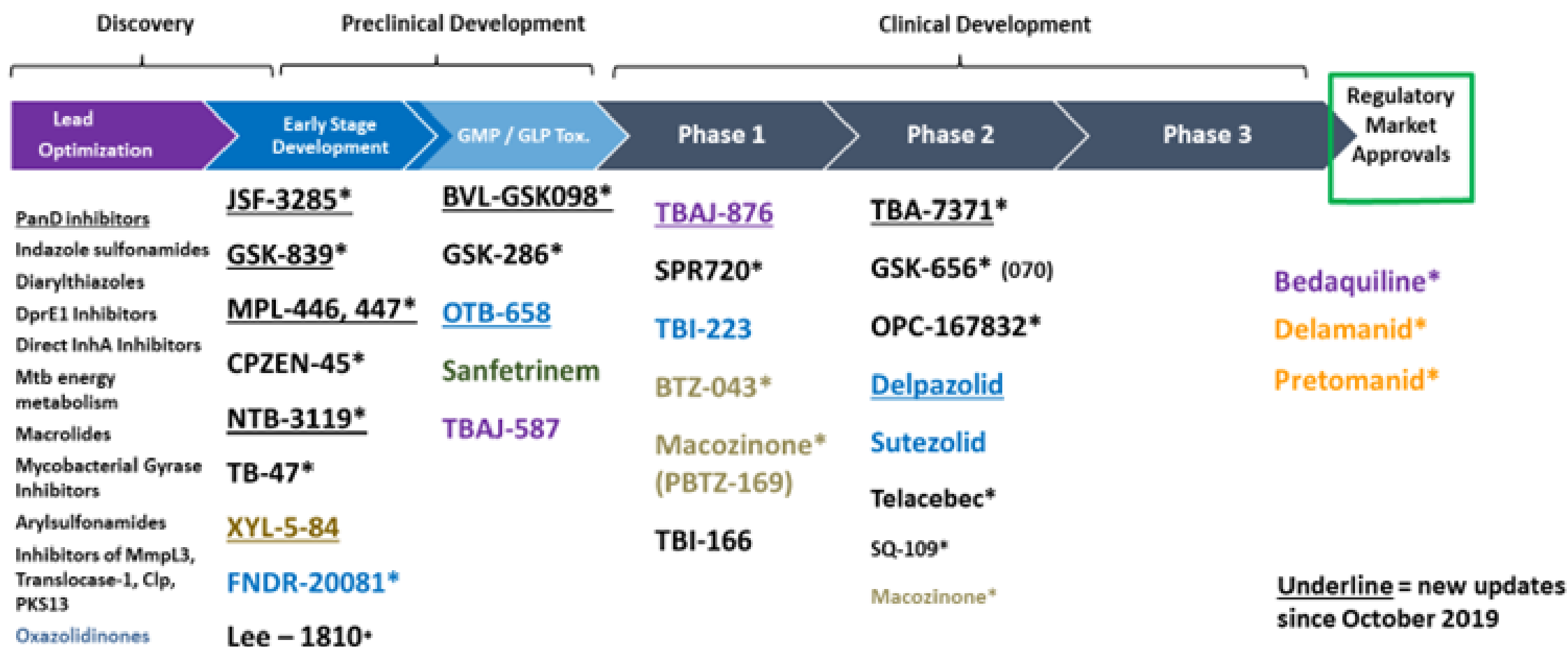
Pre-clinical	Phase 1	Phase 2	Phase 3
Sanfetrinem GlaxoSmithKline, Bill & Melinda Gates Foundation BVL-GSK098 BioVersys AG, GlaxoSmithKline GSK-286 GlaxoSmithKline, TB Drug Accelerator, Bill & Melinda Gates Foundation TBAJ-587, Diarylquinoline TB Alliance, University of Auckland, Merck & Co., Inc. Spectinamide 1810 Microbiotix, Inc.	TBI-223 TB Alliance, Institute of Materia Medica SPR720 Spero Therapeutics, LLC, Bill & Melinda Gates Medical Research Institute Phase 1 Safety, Tolerability, and Pharmacokinetics of SPR720 BTZ-043 University of Munich, Hans-Knöll Institute, Jena, German Center for Infection Research (DZIF), European and Developing Countries Clinical Trials Partnership (EDCTP), Radboud University BTZ-043 Multiple Ascending Dose / EBA TBAJ-876 Diarylquinoline TB Alliance, University of Auckland Evaluate Safety, Tolerability, PK of TBAJ-876 in Healthy Adults TBI-166 Institute of Materia Medica, CAMS & PUMC TBA-7371 TB Alliance, Bill & Melinda Gates Medical Research Institute, Foundation for Neglected Disease Research Phase 1 Study to Evaluate Safety, Tolerability, PK, and PK Interactions of TBA-7371 Macozinone (MCZ, PBTZ-169) iM4TB - Innovative Medicines for Tuberculosis, Bill & Melinda Gates Foundation	Telacebec (Q203) Qurient Co., Ltd, Qurient Co. Ltd. / LLC "Infectex", a portfolio firm of Maxwell Biotech Venture Fund Q203 Phase 1b Q203-TB-PI-US002 Phase 2 Telacebec (Q203) EBA Rifampicin PanACEA, EDCTP, NIAID, NIH, DHHS, USAID ReDEFINE High-Dose RIF for Meningitis High-Dose Rifampin Macozinone (MCZ, PBTZ-169) Nearmedic Plus LLC Phase 2a Study of PBTZ169 OPC-167832 Otsuka Pharmaceutical Development & Commercialization, Inc. OPC-167832 Phase 1 / 2 EBA GSK 3036656 GlaxoSmithKline, European Union Horizon 2020, NIAID, NIH, DHHS EBA, Safety and Tolerability of GSK3036656 in Subjects With Drug-sensitive Pulmonary Tuberculosis Bedaquiline, Pretomanid, Moxifloxacin, Pyrazinamide (BPamZ) TB Alliance SimpliciTB SQ109 Sequella, Inc Sutezolid	TRUNCATE-TB University College, London, SPRINT TB (National University of Singapore) Delamanid Otsuka Pharmaceutical Development & Commercialization, Inc. Delamanid with OBR for MDR TB Pediatric PK and Safety Trial Delamanid in MDR TB OPC-167832 Phase 1 / 2 EBA Bedaquiline Janssen Research & Development, LLC STREAM Trial Stage 2 Nix-TB (B-Pa-L) SimpliciTB Rifapentine CDC TBTC, Sanofi TBTC Study 31 ACTG 53494-month treatment regimens BEAT-TB Bedaquiline - Pretomanid - Linezolid TB Alliance Nix-TB (B-Pa-L) ZeNix (B-Pa-L) NC-007 endTB Médecins Sans Frontières Clofazimine Novartis Rifampicin St. George's Hospital University of London RIFASHORT Bedaquiline - Linezolid
Volume:1	Issue:2		Dec 2020

	Sequella, Inc, TB Alliance <u>Delpazolid (LCB01-0371)</u> LegoChem Biosciences, Inc. ·NCT02836483 A Prospective, Randomized, Open, Active-controlled, Interventional, Exploratory, Phase II Trial of LCB01-0371. <u>TB-PRACTECAL</u> Médecins Sans Frontières <u>Auranofin</u> The Aurum Institute NPC, Calibr, The Scripps Research Institute ·TB Host Directed Therapy (TBHDT) <u>PredictTB</u> NIAID, NIH, DHHS, Bill & Melinda Gates Foundation, EDCTP <u>Levofloxacin</u> CDC TBTC, NIAID, NIH, DHHS, Boston University ·TBTC Study 32, Opti-Q <u>INH, RIF, PZA, MOX</u> ·NexGen EBA <u>Bedaquiline - Delamanid with MBT for MDR</u> ·ACTG 5343 Bedaquiline - Delamanid with MBT for MDR	<u>ifampicin</u> St. George's Hospital University of London RIFASHORT <u>Bedaquiline - Linezolid - Levofloxacin with OBR</u> ·Bedaquiline - Linezolid with OBR MDR (NExT Trial) <u>Pretomanid, Moxifloxacin, Pyrazinamide (PaMZ)</u> TB Alliance ·STAND
--	--	--

Current treatment regimens for TB are prolonged, intensive and complex, and often result in mismanagement by healthcare providers (the wrong combination of drugs prescribed or inappropriate length of treatment) or non-compliance by patients. In some regions, drugs may not be readily available or maybe of poor quality. These issues of mismanagement and non-compliance have given rise to several drug-resistant strains of *Mycobacterium tuberculosis*. Given this situation, there is a great emphasis on developing shorter regimens. Though research on this front has been going on for several decades, it is only this year that a major breakthrough has been reported. An international, randomized, Phase 3 clinical trial called Study 31/A5349, has shown that a shortened four-month daily treatment regimen is as safe and effective as the standard six-month daily drug therapy. The trial, led by the U.S. Centers for Disease Control and Prevention's (CDC) Tuberculosis Trials Consortium (TBTC) in collaboration with the AIDS Clinical Trials Group (ACTG) was conducted at 34 clinical sites in 13 countries with more than 2,500 participants, including 214 people with HIV. The study tested the safety and efficacy of two four-month regimens containing high doses of rifapentine to treat drug-susceptible TB. Out of the two regimens, the one that included moxifloxacin (2PHZM/2PHM) showed promise. It included eight weeks of daily treatment with high-dose rifapentine, isoniazid, pyrazinamide, and moxifloxacin and nine weeks of daily treatment with rifapentine, isoniazid, and moxifloxacin. The treatment was well-tolerated and found to be non-inferior in efficacy to the standard six-month regimen (2RHZE/4RH) which includes eight weeks of daily treatment with rifampin, isoniazid, pyrazinamide, and ethambutol and 18 weeks of daily treatment with rifampin and isoniazid.

These findings, presented at the 51st Union World Conference on Lung Health², (held virtually on Oct. 20-24, 2020), are nothing short of ground-breaking. A shortened course would be more convenient, economical and most likely boost patient compliance. The shorter duration would hopefully mitigate the dire consequences of interruptions in the longer standard regimen and thus prevent emergence of drug-resistant cases. However, it remains to be seen how well these findings translate to actual clinical practice. It would be important to examine the safety and efficacy of the short-course treatment in different ethnicities and more vulnerable populations. TB disease is a wide spectrum and manifests in highly varied forms in individuals. Moreover, the current uncertainty and socio-political instability in many parts of the world can also have an enormous impact on the ability of countries to implement new treatment regimens for the masses. Nevertheless, the success of this trial will surely generate immense buzz in the TB research community and also serve to strengthen the hope that other advancements in TB treatment are still very much possible even if the journey is extremely arduous. The TB drug clinical pipeline has many candidates, existing and novel, as well as novel regimens being tested in various trial phases. The outcomes of these trials are eagerly anticipated and further success could tremendously bolster TB control programmes around the world, especially in high burden countries like India.

Draft 2020 Global New TB Drug Pipeline ¹



*New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

¹ New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at <http://www.newtbdrugs.org/pipeline/clinical>

Ongoing projects without a lead compound series identified: <http://www.newtbdrugs.org/pipeline/discovery>



www.newtbdrugs.org

Updated: October 2020

References:

1. WHO(2020). Global tuberculosis report 2020. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.
2. <https://www.youtube.com/watch?v=ODoatOOYKwY&list=PLn2oAgU-emcXJWNhCVeTUmX3v0QIEn8P3&index=8>