

**Comment (for World TB Day March 24<sup>th</sup> 2018)**  
**Nature Reviews Drugs Discovery**

**Title:**

**Accelerating development and evaluation of new drugs and combination regimens for drug-resistant tuberculosis**

**Authors:**

**Michael J. Vjecha<sup>1</sup>, Simon Tiberi<sup>2</sup> and Alimuddin Zumla<sup>3,4\*</sup>**

**Institutional affiliations:**

<sup>1</sup>CDC TB Trials Consortium (TBTC) Core Science Group, Veterans Affairs Medical Center, Washington, DC, USA. (Dr Michael J Vjecha MD. Email: [michael.vjecha1@va.gov](mailto:michael.vjecha1@va.gov))

<sup>2</sup>Division of Infection, Royal London Hospital, Barts Health NHS Trust, London, United Kingdom (Dr Simon Tiberi MD. Email: [Simon.Tiberi@bartshealth.nhs.uk](mailto:Simon.Tiberi@bartshealth.nhs.uk))

<sup>3</sup>Division of Infection and Immunity, University College London, and <sup>4</sup>NIHR Biomedical Research Centre, UCL Hospitals NHS Foundation Trust, London, UK (Professor Alimuddin Zumla. Email: [a.i.zumla@gmail.com](mailto:a.i.zumla@gmail.com))

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**Other:** Online Appendix and links to drug development websites

**Correspondence:**

**Professor Sir Alimuddin Zumla** PhD.MD.FRCP  
Division of Infection and Immunity, University College London and NIHR Biomedical Research Centre, UCL Hospitals NHS Foundation Trust, London, United Kingdom  
**Email:** [a.i.zumla@gmail.com](mailto:a.i.zumla@gmail.com)

**Abstract (53 words)**

Recent progress in discovery, development and evaluation of new drugs and combination regimens for drug-resistant tuberculosis and more collaborative approaches by pharma, funders, advocates and researchers provides renewed hope for overcoming the challenges of improving the high death rates, reducing duration of therapy, improving patient adherence and curtailing the global spread of drug resistance.

Tuberculosis (TB) remains a global emergency and is now the most important infectious disease cause of death. In 2016, 10.4 million people developed active tuberculosis, of whom 1.7 million died. An estimated 490,000 had multi-drug-resistant TB (MDR-TB) and 6% had extensively-drug-resistant (XDR) TB. Currently available treatment regimens cure just over 50% of patients with MDR-TB, and only 30% of XDR-TB patients. These regimens are of long duration, have severe and at times irreversible side effects, and are associated with poor patient adherence, treatment failure, further acquisition of drug resistance, and high mortality. The novel and repurposed TB drug and combination regimen development pipeline has grown in recent years, spearheaded by the regulatory approval of two novel drugs, the diarylquinoline bedaquiline in 2012 and the nitroimidazole delamanid in 2014.

### **Growing pipeline of new TB drugs**

Recent concerted efforts of funders, pharma, advocates and researchers are accelerating development of new drugs and regimens for DR-TB (**Supplemental Figure 1**). Currently 17 new anti-TB drugs, including bedaquiline and delamanid, that are currently being studied in phase 1, 2, or 3 trials or that will enter phase 1 trials in 2018 (**Supplemental Table 1**). These drugs target mycobacterial energy production (diarylquinolines, imidazopyridines, riminophenazines); cell wall synthesis and energy production (nitroimidazoles, with differing actions in replicating vs. persistent bacilli); cell wall synthesis (ethylene diamines, DrpE1 inhibitors, including the benzothiazinones); or mycobacterial protein synthesis (oxazolidinones, oxaboroles – a new class, and carbo-styryl derivatives).

Repurposed drugs which are being included in several regimens for DR-TB include: clofazimine (a riminophenazine traditionally used to treat leprosy, prolonged use of which can lead to irreversible skin discolouration), levofloxacin or moxifloxacin (fluoroquinolones, often used for respiratory and other infections, with increasing prevalence of resistance), linezolid (an oxazolidinone developed for skin and soft tissue infections, with dose- and duration-dependent bone marrow and nerve toxicity), and pyrazinamide (for which point-of-care resistance testing is not readily available).

### **New combination regimens - trials and tribulations**

Since 2012, eleven phase 2 or 3 clinical trials of new drugs and regimens for DR-TB have been initiated, some with support from pharma (**Supplemental Table 2**). The Global Alliance for TB Drug Development has prioritized development of a common design is to randomize participants with DS-TB to two or more arms and to enrol participants with DR-TB in a single arm, possibly with an additional drug or a longer duration of treatment. The phase 2 NC-005 trial, begun in November 2014, contained a DR-TB arm with bedaquiline, pretomanid,

moxifloxacin and pyrazinamide. Final results are expected later in 2018. The phase 3 NC-006 or STAND trial, begun in February 2015, enrolling participants with DR-TB to 6 months of 200 mg daily pretomanid (vs. two lower doses of daily pretomanid in the two DS-TB arms), moxifloxacin and pyrazinamide. The study was put on hold in October 2015 after 3 participants developed severe hepatotoxicity. Follow-up of all 284 participants is continuing and will end in May 2018. After the accrual hold was lifted in 2016, the TB Alliance decided not to reopen STAND, and shifted their focus to developing regimens containing both bedaquiline and pretomanid. The single-arm NiX-TB trial, begun in March 2015 in persons with XDR-TB, reported dramatic preliminary results in 2017 with a high rate of relapse-free cure and low rates of mortality and irreversible toxicity after 6 to 9 months of treatment with bedaquiline, pretomanid, and high dose linezolid (which was dose-adjusted following toxicity). In November 2017, the TB Alliance closed accrual to NiX and transitioned to NC-007 or ZeNiX, a phase 3 four-arm trial of bedaquiline, pretomanid, and linezolid, testing two doses (1200 mg or 600 mg) and durations (6 months or 2 months) of daily linezolid in 180 persons with XDR-TB. The NC-008 or SimpliciTB trial will open in August 2018 enrolling 150 DS-TB participants to 4 months of bedaquiline, pretomanid, moxifloxacin, and pyrazinamide vs. standard 6 months of therapy, and a DR-TB arm with 6 months of the same four drugs. Data are being collated on long-term safety outcomes in participants who have received bedaquiline both receiving the drug both in clinical trials or through compassionate use/expanded access programs. There is increasing assurance that there is no signal for increased risk of mortality, though pharmacovigilance will continue considering the drug's long half-life and prolongation of the Qtc.

There are several other ongoing trials of bedaquiline and delamanid in new combination regimens in patients with MDR- and XDR-TB. The phase 2/3 NExT-5001 trial, opened in October 2015 in Cape Town, South Africa, randomizing participants to bedaquiline, linezolid, levofloxacin, pyrazinamide for 6 to 9 months vs. other non-bedaquiline-containing regimens. Unitaid with Partners in Health at Harvard and Médecins sans Frontières (MSF) began the phase 3 endTB trial in December 2016, an all-oral five-arm adaptive design study of various combinations of 9 months of bedaquiline, linezolid, moxifloxacin, clofazimine, and delamanid in 750 participants with fluoroquinolone-sensitive MDR-TB in Georgia, Kazakhstan, Kyrgyzstan, Lesotho and Peru. TB-PRACTECAL is a two-stage 5-arm phase 2/3 study begun in January 2017 of 6 months of various combinations of bedaquiline, pretomanid, moxifloxacin, linezolid, and clofazimine compared to standard WHO treatment, conducted by MSF in 630 participants with MDR or XDR-TB in Belarus, South Africa, and Uzbekistan.

Otsuka completed its phase 3 trial of 6 months of delamanid in addition to background regimen in June 2016 and reported results in November 2017 confirming efficacy and an improved safety profile over phase 2 trial results. The endTB trial includes delamanid in two arms, with

and without bedaquiline, with results expected in September 2021. AIDS Clinical Trials Group protocol A5343 assesses Qtc prolongation, safety, tolerability, and pK of bedaquiline and delamanid and will complete accrual in 2018. Such drug-drug interaction (DDI) studies are critical to document safety to study participants and patients as new TB drugs are included in large phase 3 trials and rolled out in country programmes.

### **Alternate approach to developing MDR-TB regimens**

In October 2016, WHO updated guidelines for treatment of drug-resistant TB, recommending a shorter regimen of 9 -12 months in patients with no documented resistance to fluoroquinolones or second-line injectables, rather than the standard 20-month treatment. This change was based in part on results from a prospective observational study in Bangladesh aiming to develop a safer, more patient compliant, effective, and inexpensive regimen. Moving away from classic single drug evaluation, the study used treatment outcomes and drug side effects to make adjustments in individual drug components of standard MDR-TB treatment regimen. The 9-month 'Bangladesh regimen' led to the STREAM trial, a phase 3 non-inferiority trial began in July 2012, treated with either 9 months of moxifloxacin, clofazimine, pyrazinamide and ethambutol and 4 months of high-dose isoniazid, injectable kanamycin, and prothionamide or the WHO standard of care.

Given the limitations of evaluating single drugs, and the success of the Bangladesh, a regimen-based approach is now favored in which new, old and re-purposed drugs are given in various combinations in order to identify a drug combination that can be used for treating TB and MDR-TB. Janssen Pharmaceuticals partnered with STREAM investigators to launch Stage 2 in April 2016, adding two new arms containing either 6 or 9 months of bedaquiline with a new target accrual of 1,155. STREAM Stage 1 trial preliminary results (November, 2017) indicate that the shorter regimen was almost as effective as the standard WHO regimen, though the lower confidence interval just crossed the margin of non-inferiority. STREAM Stage 2 is the largest trial of DR-TB ever to be conducted and is the first phase 3 randomized trial of bedaquiline. Results are expected in 2021.

### **Latent TB Infection**

Novel regimens to prevent development of TB in persons with latent TB infection are being tested. Three randomized controlled trials of treatment of latent TB infection (LTBI) in close contacts of patients with DR-TB are underway in both children and adults, comparing 6 months of daily levofloxacin vs. placebo or 6 months of daily delamanid vs. 9 months of daily isoniazid. As the incidence of DR-TB increases, so does the risk of transmission of resistant organisms to others, particularly young children.

## **Advances in pre-clinical and early developmental pipelines**

A number of new drugs are in late pre-clinical and early clinical development and have improved potency, bioavailability, and less toxicity than previous agents in their class (**Supplemental Table 1**). New agents targeting mycobacterial energy production, include the imidazopyridine Q203, which has completed phase 1 testing and enters phase 2 trials conducted by the PanACEA consortium in 2018. A new riminophenazine, TBI-166, developed by Institute Materia Medica in Beijing, China, will entire phase 1 testing as a less toxic alternative to clofazimine. A new potent new diarylquinoline, TBAJ-587, which has less Qtc prolongation than bedaquiline is being developed by The TB Alliance.

SQ109 is an ethylene diamine (same class as ethambutol), an inhibitor of cell wall synthesis, that was studied in the PanACEA MAMS-TB-01 trial of high-dose rifampicin, in which the two SQ109 arms were dropped before the trial was completed. Sequella has partnered with Infectex to conduct larger phase 2/3 studies at sites in Russia.

More promising is the development of four new DprE1 inhibitors of cell wall synthesis. PBTZ169, a benzothiazinone developed by Nearmedic, is entering phase 2 trials conducted by iM4TB based in Switzerland with funding from the Bill and Melinda Gates Foundation (BMGF). The TB Alliance will begin phase 1 trials of TBA7371 in 2018. Otsuka, with funding from BMGF, have phase 1 trials of OPC-0167832, for demonstrating synergy with delamanid. PanACEA consortium are planning phase 1 trials of BTZ-043, a benzothiazinone developed at the University of Munich.

Four new oxazolidinones and an oxaborole, an entirely new class of anti-TB drug are among the new agents that target mycobacterial protein synthesis. Sequella and now the TB Alliance are collaborating to renew commercial development of the oxazolidinone, Sutezolid, (initially developed by Pfizer) which appears to be much less toxic and more tolerable than linezolid. LegoChem Biosciences has begun phase 2 trials of delpazolid (LCB01-0371). MicuRX is in phase 1 trials of contezolid. The TB Alliance will begin phase 1 studies of Institute Materia Medica's TBI-223. Finally, GlaxoSmithKline will begin phase 2 studies of GSK 3036656, an oxaborole that is potent in combination with bedaquiline and pretomanid. All of these new agents in early clinical development offer the promise of greater potency, safety and tolerability, and reduced drug-drug interactions that may greatly expand the horizon of effective combination treatment for all forms of TB.

## **Unmet and longer-term needs**

Despite good progress in the TB drug pipeline there remain several key unmet needs and challenges: drug-resistant TB needs a more effective fully oral, shorter, less toxic and safer therapy; HIV co-infection needs minimal TB drug interactions with antiretrovirals; latent TB infection needs shorter and safer therapy; and accurate information is also required on drug–drug interactions, and their use in specific patient groups, such as children, HIV-co-infected individuals and pregnant women. Furthermore, there are up to 2 billion people with latent *Mycobacterium tuberculosis* (*Mtb*) infection (LTBI) of which between 5–15% will progress to develop active TB disease during their lifetime due to a range of risk factors including lower socioeconomic groups, homelessness, HIV, and immunosuppression due to any cause including HIV and renal transplantation. The mechanisms of antibiotic tolerance and survival of the bacteria in macrophages remain to be defined, and developing a means of inhibition requires investigation. Development of effective new TB drugs will need to define dynamic nature of the host–pathogen interaction during latent TB infection, identification of specific bacterial and host markers of this progression and the determinants of progression to active TB disease.

As more drug candidates become available for evaluation in trials, increased investments are required for: basic TB drug research discovery such as high throughput screening to find lead compounds acting against well-validated *Mycobacterium tuberculosis* targets; taking promising leads and expand the pipeline and facilitating promising new compounds from the preclinical to the clinical stages of development; defining new biomarkers for early prediction of long-term treatment outcome for accelerating clinical development and evaluation of short regimens using novel trial designs, and predicting quantitative relationships between phase 2 readouts of sputum culture conversion, phase 3 readout of cure, and duration of therapy. More creative solutions for efficient clinical trial designs and creative ways to test “new regimens” not just one drug at a time, are required.

Inadequate global capacity to perform controlled clinical trials to support registration of new regimens for treatment of tuberculosis in high-TB endemic regions is becoming problematic as more drug candidates progress into clinical trials. Phase 3 trials are always complex, expensive, and take longer to complete than anyone expected. Major limitation of TB drug development research and trials is the continuing dominance by western groups, the lack of funding, inadequate human capacity and required expertise, poor infrastructure, and limited career opportunities. Capacity building and knowledge transfer, infrastructure upgrading to good clinical and good laboratory practice standards is required and international agencies, national governments and communities should come together to develop innovative funding and market

incentive mechanisms to promote and support new TB drug development and rapid adoption of new regimens which provide a net overall benefit to the patient, and health service.

### **Concluding remarks**

There has been good progress since 2012 in development of new and repurposed TB drugs and combination regimens enriching the phase 1/2/3 trials pipeline. Whilst collaborative work between researchers, pharma and funders is increasing, vital challenges remain. The fragmentation of TB drug development and research together with inadequate investments in TB drug trials capacity high TB endemic countries leaves major gaps in coordination between TB stakeholders globally. Recent increase in political will arising from the Moscow declaration to end TB and the forthcoming United Nations General Assembly high-level meeting on TB in September 2018 brings renewed hope for increased resources for TB drug development through innovative financing mechanisms.

### **ACKNOWLEDGMENTS**

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### **CONFLICTS OF INTEREST**

All authors have ongoing research activities on various treatment aspects of TB.

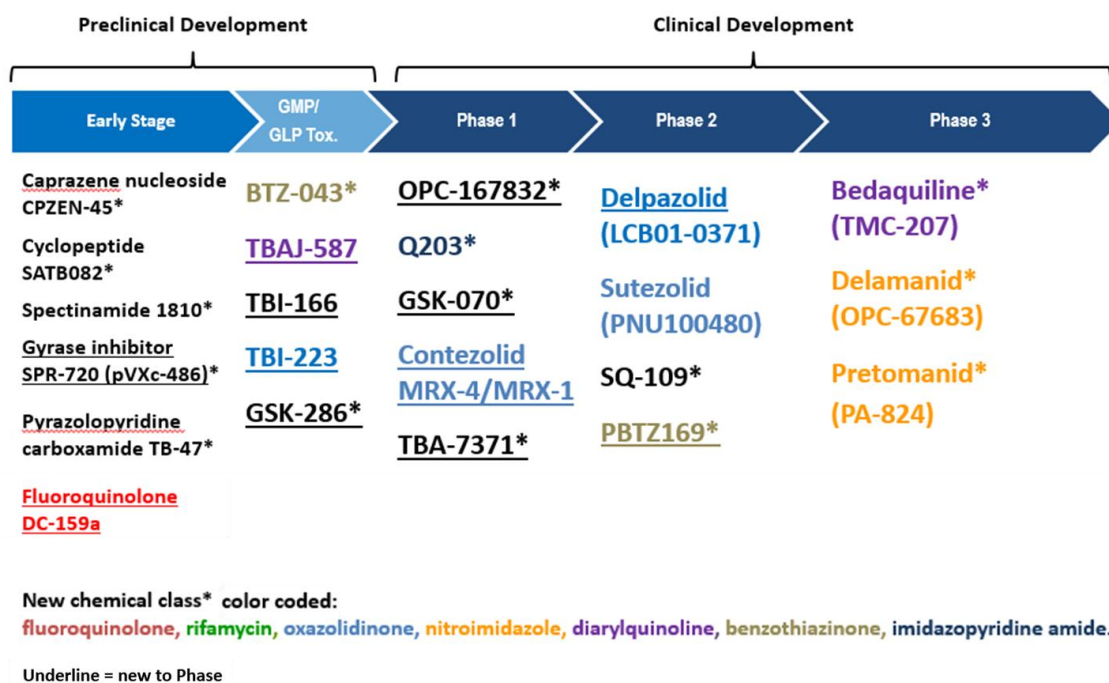


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## Supplemental material

**Figure 1: New TB Drugs Development Pipeline**

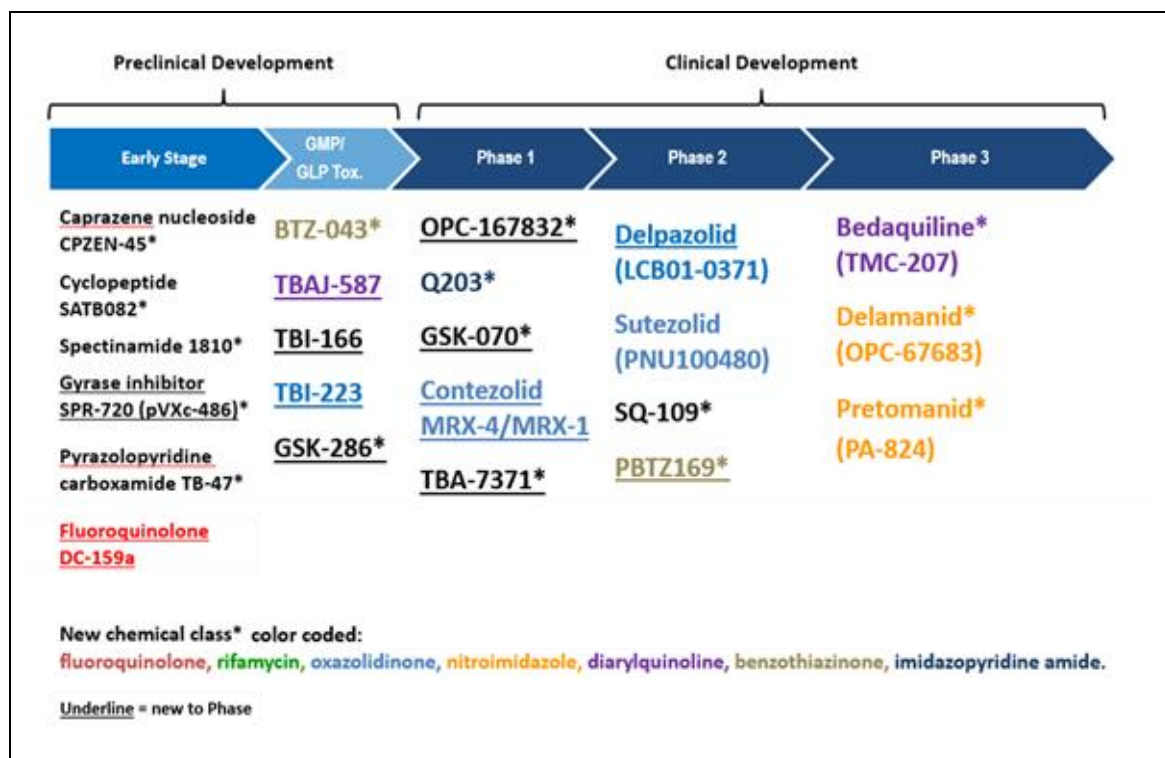


Courtesy of the WHO Stop TB Partnership's Working Group on New TB Drugs (WGND).  
<https://www.newtbdrugs.org/> <https://www.newtbdrugs.org/pipeline/clinical>

## Supplemental material

### Supplemental Figure 1

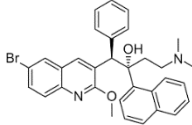
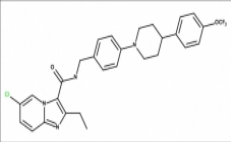
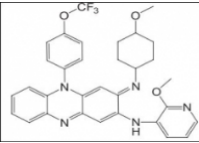
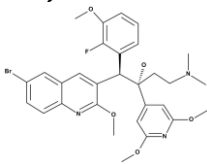
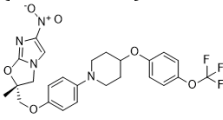
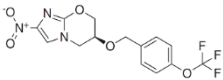
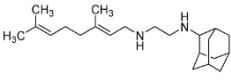
#### New TB Drugs Development Pipeline

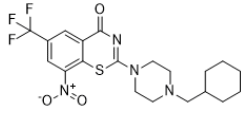
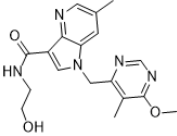
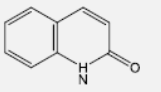
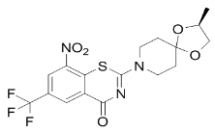
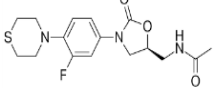
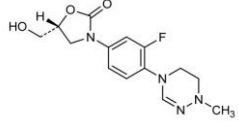
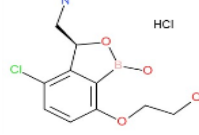
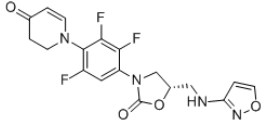


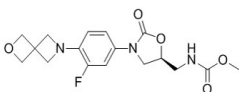
Courtesy of the WHO Stop TB Partnership's Working Group on New TB Drugs (WGND)  
<https://www.newtbdrugs.org/pipeline/clinical>

## Supplemental Table 1

### New TB drugs in clinical development

Drug	Class	Mechanism of Action	Evaluation Phase	Notes [sponsor]
<b>Target: Energy</b>				
<b>Bedaquiline (TMC-207, Sirturo)</b> 	Diarylquinoline	Inhibits ATP synthase and bacterial respiration	Phase 3	Conditional marketing approval, long half-life, ECG Qtc prolongation  [Janssen, TB Alliance, NIAID, SAMRC, the Union, Unitaid, USAID]
<b>Q203</b> 	Imidazopyridine	Inhibits mycobacterial QcrB cytochrome and bacterial respiration	Phase 1/2	Phase 1 studies underway, phase 2 studies planned for 2018, long half-life  [Qurient, Infectex, PanACEA]
<b>TBI-166</b> 	Riminophenazine	Inhibits ion transport and bacterial respiration	Phase 1	Potentially less toxic alternative to clofazimine  [Institute of Materia Medica]
<b>TBAJ-587</b> 	Diarylquinoline	Inhibits ATP synthase and bacteria respiration	Pre-Phase 1	IND filing late 2018, greater potency/efficacy, less Qtc prolongation than bedaquiline  [Janssen, Merck, TB Alliance]
<b>Target: Cell Wall Synthesis and Energy</b>				
<b>Delamanid (OPC-67683)</b> 	Nitroimidazole	Inhibits cell wall synthesis and bacterial respiration	Phase 3	Conditional marketing approval, phase 3 trial showed efficacy and better safety profile, twice daily oral dosing  [Otsuka, NIAID, Unitaid]
<b>Pretomanid (PA-824)</b> 	Nitroimidazole	Inhibits cell wall synthesis and bacterial respiration	Phase 3	Potent bactericidal and sterilizing activity in murine models  [TB Alliance]
<b>Target: Cell Wall Synthesis</b>				
<b>SQ109</b> 	1,2-ethylene diamine	Inhibits cell wall synthesis (MmpL3)	Phase 2/3	Possible synergy with bedaquiline  [Sequella, Infectex, PanACEA]

<b>PBTZ169</b> 	DprE1 inhibitor	Inhibits cell wall synthesis	Phase 2	Benzothiazinone, synergy with bedaquiline and clofazimine  [Nearmedic, iM4TB, BMGF]
<b>TBA7371</b> 	DprE1 inhibitor	Inhibits cell wall synthesis	Phase 1	Potential to shorten treatment for all TB, phase 1 trials underway  [TB Alliance]
<b>OPC-167832</b>  (Carbostyryl base)	DprE1 inhibitor	Inhibits cell wall synthesis	Phase 1	3,4-carbostyryl derivative, Synergy with delamanid  [Otsuka, BMGF]
<b>BTZ 043</b> 	DprE1 inhibitor	Inhibits cell wall synthesis	Phase 1	Benzothiazinone, synergy with rifampicin, low toxicity, no interaction with hepatic enzymes  [University of Munich, PanACEA]
<b>Target: Protein Synthesis</b>				
<b>Sutezolid (PNU-100480)</b> 	Oxazolidinone	Inhibits protein synthesis (23S ribosome)	Phase 1/2	Potentially less toxic than linezolid, renewed commercial development  [Pfizer then Sequella, TB Alliance]
<b>Delpazolid (LCB01-0371)</b> 	Oxazolidinone	Inhibits protein synthesis (23S ribosome)	Phase 2	Potentially less toxic and more potent than linezolid  [LegoChem Biosciences]
<b>GSK 3036656 (GSK 070)</b> 	Oxaborole	Inhibits protein synthesis (leucyl-tRNA synthetase)	Phase 2a	New chemical class, low oral daily dose, potent with bedaquiline/pretomanid, phase 2a studies mid-2018  [GSK]
<b>Contezolid (MRX-4/MRX-1)</b> 	Oxazolidinone	Inhibits protein synthesis (23S ribosome)	Phase 1	Potentially less toxic than linezolid  [MicuRX]

<p><b>TBI-223</b></p> 	Oxazolidinone	Inhibits protein synthesis (23S ribosome)	Pre-Phase 1	<p>IND filing late 2018, potent, bioavailable, oral single daily dose, no interaction with hepatic enzymes, no bone marrow toxicity (animal studies)</p> <p>[Institute of Materia Medica, TB Alliance]</p>
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**Abbreviations:** BMGF: Bill and Melinda Gates Foundation; GSK: GlaxoSmithKline PLC; iM4TB: Innovative Medicines for Tuberculosis (Switzerland); NIAID: National Institute of Allergy and Infectious Diseases (US); PanACEA: Pan African Consortium for the Evaluation of Antituberculosis Antibiotics; SAMRC: South African Medical Research Council; The Union: International Union Against Tuberculosis and Lung Disease; USAID: U.S. Agency for International Development

**Supplemental Table 2**  
**Advanced-stage clinical trials of new regimens for drug-resistant TB**

<b>Trial Name NCT Number</b>	<b>Experimental Arm(s)</b>	<b>Target Accrual</b>	<b>Trial Phase</b>	<b>Study Start and Completion Dates</b>
<b>Otsuka 213</b> NCT01424670	DLM + OBR	511	3	Sep 2011 –Jun 2016 (results announced IUATLD Oct 2017)
<b>STREAM Stage 1</b> NCT02409290	MOX, CFZ, EMB, PZA, INH, KAN, PRO	424	3	Jul 2012 –Jul 2018 (interim results announced IUATLD Oct 2017)
<b>NC-005</b> NCT02193776	BDQ, PRE, MOX, PZA	60	2	Nov 2014 –Mar 2018
<b>NC-006 STAND</b> NCT02342886	PRE, MOX, PZA	13 (of 300)	3	Feb 2015 –Mar 2018 (accrual stopped early October 2015)
<b>NiX-TB</b> NCT02333799	BDQ, PRE, LZD	109 (of 200)	3	Mar 2015 –Nov 2017 (transition to ZeNiX)
<b>NExT-5001</b> NCT02454205	BDQ, LZD, LVX, PZA + [ETH or INH or TRZ]	300	2/3	Oct 2015 –Jan 2019
<b>MDR-END</b> NCT02619994	DLM, LZD, LVX, PZA	238	2	Jan 2016 –Dec 2019
<b>STREAM Stage 2</b> NCT02409290	MOX, CFZ, EMB, PZA, INH, KAN, PRO BDQ, CFZ, LVX, EMB, PZA, INH, PRO BDQ, CFZ, LVX, PZA, INH, KAN	1155	3	Apr 2016 –Apr 2021

<b>endTB</b> NCT02754765	There are 5 experimental arms, three with bedaquiline and three with delamanid (one arm with both). BDQ, LZD, MOX, PZA BDQ, LZD, LVX, PZA, CFZ BDQ, LZD, LVX, PZA, DLM DLM, LZD, LVX, PZA, CFZ DLM, MOX, CFZ, PZA	750	3	Dec 2016 –Sep 2021
<b>TB-PRACTECAL</b> NCT0258972	BDQ, PRE, LZD, MOX BDQ, PRE, LZD, CFZ BDQ, PRE, LZD	630	2/3	Jan 2017 –Mar 2021
<b>NC-007 ZeNiX</b> NCT03086486	BDQ, PRE, LZD (dose range)	180	3	Nov 2017 –Jan 2022
<b>NC-008 SimpliciTB</b> NCT03338621	BDQ, PRE, MOX, PZA	150	2c/3	Aug 2018 –Mar 2022

**Abbreviations:**

BDQ: bedaquiline; CFZ: clofazimine; DLM: delamanid; EMB: ethambutol; ETH: ethionamide; INH: isoniazid; IUATLD: International Union against TB and Lung Disease Conference, Guadalajara, Mexico, October, 2017; KAN: kanamycin (injectable); LVX: levofloxacin; LZD: linezolid; MOX: moxifloxacin; OBR: optimized background regimen; PRE: pretomanid; PRO: prothionamide; PZA: pyrazina