Pipeline Report » 2019

Tuberculosis Treatment

TAG
Treatment Action Group

The Tuberculosis Treatment Pipeline

By Lindsay McKenna

Introduction

The past two years have been transformative for the tuberculosis (TB) treatment pipeline. New compounds with novel mechanisms of action or advantaged properties advanced to phase I and II clinical studies, replenishing a clinical pipeline that has seemed bare for the greater part of the last decade. Results were reported from a number of important trials, including two phase III clinical trials.[1] Program data transformed World Health Organization (WHO) guidelines and the global standard of care for rifampin-resistant/multidrug-resistant tuberculosis (RR-/MDR-TB), elevating all-oral bedaquiline- and linezolid-containing regimens in treatment hierarchy. The U.S. Food and Drug Administration (FDA) approved pretomanid in the Nix-TB regimen for extensively drug-resistant TB (XDR-TB) and treatment-intolerant and nonresponsive (TI/NR) MDR-TB, making pretomanid the fourth TB medicine to be approved by a stringent regulatory authority (SRA) in the past 40 years.

These advances have pushed the field forward and raised a number of important research and access issues. As new compounds advance, collaboration among drug sponsors and research funding institutions will be critical to expedite studies to inform the independent contribution and optimal role and combination(s) of new TB drugs. Research funders, including governments, must ensure that research initiatives are relevant, are rigorous, are adequately resourced, and incorporate the views and priorities of affected communities. As many privately held products in the pipeline will benefit from significant public and philanthropic funds, donors need to ensure that these investments are made according to a set of shared principles that promote transparency, equity, and access. Finally, as ongoing trials produce results and as data from programs and other cohorts continue to emerge, policymakers will need to adapt to accommodate more frequent changes to normative guidance and, in doing so, establish a more efficient process for implementation and uptake at the national level.

Updates On Influential Treatment Studies And Data Sets

The data discussed in this section were foundational to the 2019 updates to the *WHO Consolidated Guidelines on Drug-resistant Tuberculosis Treatment*, which revolutionized the standard of care for RR-/MDR-TB by recommending all-oral, bedaquiline- and linezolid-based regimens.[2] Ongoing trials (see Table 2), operational research initiatives, data from national TB programs, and interim data from the Nix-TB study are expected to inform further updates to WHO guidelines in the first half of 2020.

Study 213 (Otsuka Pharmaceutical Development & Commercialization Inc.; NCT01424670)

Otsuka's phase III superiority study of delamanid—Study 213—compared an optimized background regimen given with six months of delamanid or placebo. Neither time to sputum culture conversion over six months (the primary endpoint of the trial) nor final treatment outcomes (cure or mortality) differed between

participants receiving delamanid and participants receiving placebo.[3] The incidence of serious treatment-emergent adverse events was similar between treatment groups (89/341, or 26.1%, for delamanid and 47/170, or 27.6%, for placebo), as was the proportion of deaths related to treatment-emergent adverse events (15/341, or 4.4 %, for delamanid and 6/170, or 3.5%, for placebo).[4] Importantly, the effect of delamanid on the QT or QTcF interval (the amount of time between heartbeats, a risk factor for life-threatening cardiac events) was lower than in previous studies (prolonged by 5.9 milliseconds, on average, compared to 12.1 ms) and did not result in any clinically associated serious adverse events.[5]

These results are disappointing but not unexpected given the design of the study, which added a single agent to an effective regimen and underestimated how well an optimized background regimen with placebo would perform in the context of a clinical trial. Success rates among participants in Study 213 treated with an optimized background regimen plus placebo (78%) were remarkably higher than success rates historically reported by national TB programs using similar treatment regimens (55%). As a result, Study 213 was underpowered to detect differences in efficacy between the delamanid and placebo arms.

The investigators concluded that delamanid is safe and well tolerated but that further research is needed to understand the role of delamanid in the treatment of MDR-TB. Delamanid is a component of multiple investigational drug-resistant TB treatment-shortening regimens and is being studied for TB prevention among household contacts of people with MDR-TB. These studies will be critical to confirming delamanid's impact on a clinical endpoint and determining its optimal role in a rapidly evolving standard of care for drug-resistant TB. In the meantime, despite its favorable safety profile, the WHO has recommended delamanid as a group C medicine, to be used when a regimen containing four effective medicines cannot otherwise be constructed using medicines from groups A (bedaquiline, linezolid, levofloxacin/or moxifloxacin) and B (clofazimine and cycloserine).[6]

STREAM Stage I (International Union Against Tuberculosis and Lung Disease; NCT02409290)

Stage I of the Union's phase III STREAM study found the nine- to 11-month standardized shorter regimen* to be noninferior to longer (20-month) regimens composed according to the WHO treatment guidelines from 2011, which did not include new and repurposed TB medicines such as linezolid, clofazimine, bedaquiline, or delamanid. The STREAM investigators reported favorable treatment outcomes among 78.8% of participants who received the shorter regimen compared with 79.8% of participants randomized to the longer regimen.[7]

Loss to follow-up was more common among participants treated with the longer regimen (2.4% vs. 0.4%). Severe adverse events were more common among participants treated with the shorter regimen (48.2% vs. 45.4%), as were instances of bacteriologic reversion during, or relapse after the treatment period (10.6% vs. 5.6%). Prolongation of the QT or QTcF interval developed in more participants receiving the short regimen than the long regimen (11% vs. 6.4%, P = 0.14), as did alanine aminotransferase (liver enzyme) levels exceeding five times the upper limit of normal (a marker of damage to the liver), reported among 6.6% of participants in the short-regimen group compared with 1.4% of participants in the long-regimen group (P = 0.03). Though not statistically significant, more deaths were reported among people

* The nine- to 11-month standardized shorter regimen studied in stage I of the STREAM trial comprises four months of clofazimine, high-dose moxifloxacin, ethambutol, pyrazinamide, high-dose isoniazid, prothionamide, and kanamycin (the intensive phase), followed by five months of clofazimine, high-dose moxifloxacin, ethambutol, and pyrazinamide. The intensive phase could be extended to five or six months for participants who did not culture convert by four or five months, respectively.

receiving the shorter regimen, with the difference more pronounced among people with HIV (17.5% of HIV-positive participants in the short-regimen group died compared with 8% in the long-regimen group [HR 2.23; 95% CI: 0.76–6.60]).[8]

These data have helped policymakers refine which patient populations are eligible to receive the standardized shorter regimen and what types of adverse events should be monitored to protect patients from avoidable harm, such as hearing loss induced by the injectable agents (a core element of the standardized shorter regimen).[9] As the RR-/MDR-TB treatment landscape has changed dramatically since STREAM I was initiated, we don't know how the standardized shorter regimen compares with the contemporary standard of care: all-oral, bedaquiline- and linezolid-containing regimens. Stage II of the STREAM study, which is ongoing, compares the nine- to 11-month standardized shorter regimen (with levofloxacin in place of moxifloxacin) to an all-oral nine- to 11-month standardized shorter regimen with bedaquiline given in place of the injectable agent (see Table 2).

South African National TB Program Data

A retrospective analysis of patient data from the South African RR-TB case and national vital statistics registers compared all-cause mortality between patients who received bedaquiline and patients who did not from July 2014 through March 2016. The analysis included 19,617 patients. Four percent (743) of 18,542 patients with RR-/MDR-TB and 25.4% (273) of 1,075 patients with XDR-TB received a bedaquiline-containing regimen (a total of 1,016 patients). Bedaquiline was associated with a three- and fourfold reduction in risk of all-cause mortality for patients with RR-/MDR-TB (HR: 0.35; 95% CI: 0.28–0.46) and XDR-TB (HR: 0.26; 95% CI: 0.18–0.38), respectively.[10]

In contrast with initial concerns about excess mortality with bedaquiline that emerged from Janssen's phase IIb study,[11] this retrospective analysis suggests that bedaquiline offers a mortality *benefit*. These findings are especially notable given the high rates of HIV coinfection and second-line drug resistance among the patients treated under the public health system in South Africa and included in the Schnippel et al. analysis. In light of possible bias introduced by the retrospective nature of the study—specifically that the cohort may represent patients with a survival advantage over those who did not survive to receive bedaquiline—it will still be important to confirm these findings via a randomized controlled trial. Stage II of the STREAM study, the phase III randomized controlled trial sponsored by the Union and required by the FDA and European Medicines Agency (EMA) as a condition of bedaquiline's approval in the United States and Europe, will further inform this question.

In the meantime, these data have had a direct impact on policy in South Africa and globally. From 2013 to 2018, the WHO had recommended that bedaquiline be restricted to treating MDR-TB when there was resistance to or intolerance of other TB medicines.[12,13] In 2018, the WHO evaluated the growing body of evidence demonstrating the safety and effectiveness of bedaquiline and broadened its indication, strongly recommending bedaquiline as a core component of treatment regimens for RR-/MDR-TB and establishing all-oral regimens as the new global standard of care.[14]

Individual Patient Data Meta-analysis

The aforementioned 2018 WHO guideline review relied on findings from a meta-analysis performed on individual patient data (IPD) from studies published from 2009 to 2016. These results support the use of new and repurposed TB medicines and challenge the effectiveness of second-line medicines that have served as the cornerstone of treatment for drug-resistant TB for decades. The meta-analysis included data from 12,030 patients from 25 countries. In subgroup analyses, the later-generation fluoroquinolones (moxifloxacin and levofloxacin), bedaquiline, and linezolid were associated with significantly greater treatment success and lower mortality. Amikacin was associated with modest benefits, whereas the two other commonly used second-line injectable agents, kanamycin and capreomycin, were associated with worse outcomes. Other commonly used second-line medicines such as pyrazinamide, ethionamide, prothionamide, and para-aminosalicylic acid (PAS) were associated with no benefit.[15] The analysis found that outcomes were consistently better with the use of drugs to which patient isolates were susceptible compared with resistant isolates, calling into question the practice of giving certain drugs, such as pyrazinamide, in spite of possible or documented resistance.

The IPD meta-analysis has a number of limitations, including its predominant reliance on data from observational studies and constrained ability to examine the effect of changes in patient characteristics and regimens during treatment.[16] Still, these findings have important implications and support the new all-oral global standard of care for drug-resistant TB treatment. In the absence of data from randomized clinical trials, policymakers and clinicians have historically relied on such IPD meta-analyses and expert opinion to inform treatment guidelines. Moving forward, policymakers will need to determine how to balance issuing (provisional) recommendations based on data emerging from national TB programs and other observational cohorts (and induce improvements in data quality and methods that can enhance the inference that can be drawn from these resources) and delaying such recommendations until data emerge from ongoing and planned phase III randomized controlled trials (see Table 2).

The DELIBERATE Trial (ACTG A5343; NCT02583048)

The phase II AIDS Clinical Trials Group (ACTG) study DELIBERATE determined that bedaquiline and delamanid—two medicines that can prolong the QT interval—can be safely used together for the treatment of people with MDR-TB. The ACTG randomized 84 adults with MDR-TB from South Africa and Peru to receive a multidrug background regimen with bedaquiline, delamanid, or both bedaquiline and delamanid for 24 weeks. Electrocardiograms were performed at baseline, every two weeks for 24 weeks and at week 28. The investigators concluded that the combined effect on the QT interval of co-administering bedaquiline and delamanid is “clinically modest and no more than additive” and that the study “demonstrates the cardiac safety of the combined use of these drugs” for MDR-TB.[17]

The Guideline Development Group that met in July 2018 to update the WHO treatment guidelines for RR-/MDR-TB reviewed these data, but the *2019 WHO Consolidated Guidelines on Drug-resistant Tuberculosis Treatment* do not include an explicit recommendation supporting use of bedaquiline and delamanid together. The Guideline Development Group scheduled to meet in November 2019 will reconsider this question by reviewing these data again in conjunction with other data on concomitant use of these drugs.

TAG and the Global TB Community Advisory Board (TB CAB) have called for data on concomitant use of these drugs since 2011, when bedaquiline and delamanid were in mid-stage clinical development.[18,19] Bedaquiline and delamanid received stringent regulatory approval and entered the global market seven and five years ago, respectively. We finally have evidence that these two new drugs can be used in combination, but these findings and their translation into policy come far later than they should have.[20] Moving forward, drug developers and sponsors and funding organizations need to plan earlier for and move faster to answer questions about whether new drugs can be used together and in combination with other drugs with overlapping toxicity profiles.

Nix-TB (TB Alliance; NCT02333799)

In August 2019, the FDA approved a new TB drug, pretomanid, with existing drugs bedaquiline and linezolid (commonly referred to as the Nix-TB or BPaL regimen[†]) for the treatment of XDR-TB and TI/NR MDR-TB. Pretomanid is only the second new TB drug approved by the FDA in the past two decades, and it is the first sponsored by a nonprofit organization, the TB Alliance. A shorter, simpler treatment for the most difficult forms of drug-resistant TB is a welcome development. But the limited evidence supporting pretomanid's contribution to the Nix-TB regimen and the small, uncontrolled design of the trial on which the FDA's decision was based have left many questions about pretomanid and the Nix-TB regimen unanswered.[21]

The three-drug regimen was administered for six months (or for nine months in patients without culture conversion by month four). The primary endpoint was incidence of bacteriologic failure, relapse, or clinical failure (including death) until six months after the end of treatment. According to interim results presented at the 2018 Union World Conference on Lung Health and submitted to the FDA, 66 of 75 participants (88%) had a favorable outcome.[22] These findings are encouraging, but in the absence of comparison to a control regimen, they require additional context and careful interpretation.

The Nix-TB study was designed in the pre-bedaquiline era when as many as 73% of people with XDR-TB treated with WHO-recommended regimens died within five years.[23] Over the course of the study, the standard of care and prognosis for XDR-TB and TI/NR MDR-TB changed dramatically. The previously described retrospective analysis of patients with RR-TB treated with bedaquiline in South Africa showed that bedaquiline's inclusion in a regimen was associated with a 41% increase in treatment success and a fourfold reduction in mortality compared with regimens that did not contain bedaquiline.[24]

In its public communications and submission to the FDA, the TB Alliance compares successful treatment outcomes among people with XDR-TB enrolled in Nix-TB (88%) to those observed among people with XDR-TB treated under program conditions in South Africa from 2008 to 2012 (16% treatment success).[25] However, more recent data, including from cohorts in South Africa and Belarus, indicate that treatment success for patients with XDR-TB with reported final outcomes ranges from 65% to 93% with the implementation of existing bedaquiline-based regimens.[26,27] These contemporary cohorts offer a more relevant comparison for the Nix-TB regimen, which is especially important in the absence of a control arm.

[†] Please note that in Tables 1 and 2, bedaquiline is represented by "J" not "B."

The TB CAB publication *Research, Regulatory, and Access Considerations Regarding Pretomanid* summarizes well the issues raised by and risks of using nonrandomized, historic controls. It states that:

> Byar et al. warned that non-randomized, historic control participants may differ from patients receiving the new treatment in several ways, including that patients may not receive the same care and support.[28] This could be the case with the Nix-TB study; in fact, other recent phase III MDR-TB trials have already demonstrated this risk: the control arms in both phase I of the STREAM study and Otsuka 213 performed surprisingly well compared to outcomes observed in program settings. In each study, roughly 80 percent of participants randomized to the control regimen had a favorable treatment outcome.[29,30] In contrast, data from patients treated under program conditions indicate just 55–70 percent of patients treated for MDR-TB have a successful treatment outcome.[31] If STREAM and Otsuka 213 were conducted as single arm studies and compared to historic controls (like Nix-TB), the effect of each intervention compared to the existing standard of care for MDR-TB would be dramatically overstated relative to the actual differences observed between the experimental and control arms in these trials.
>
> It is unknown whether a similar effect would have been observed in the context of a [randomized controlled trial] comparing the pretomanid-containing Nix-TB regimen to the pre-bedaquiline standard of care for XDR-TB and [TI/NR MDR-TB]. Any comparisons made between the outcomes observed in the Nix-TB study and those observed under program conditions in the pre-bedaquiline era should be interpreted with the above risks in mind. The meaningful comparison regulators [and policymakers] should consider today is how the Nix-TB regimen compares to other regimens that contain bedaquiline and linezolid as these make up the current standard of care for DR-TB.[32]

The testimony TAG delivered to the FDA Antimicrobial Drugs Advisory Committee in June 2019 builds on the TB CAB's position by highlighting a number of critical research needs, including:

> (1) a randomized controlled trial comparing the Nix-TB regimen to the global standard of care for the treatment of drug-resistant TB (18–20 months of bedaquiline, linezolid, moxifloxacin [or levofloxacin], clofazimine and/or cycloserine, or the highest available standard of care pending further guidance from WHO); (2) a randomized controlled trial comparing pretomanid to delamanid, a drug from the same class as pretomanid that has completed a phase III trial, is SRA-approved and WHO-recommended, and is being rolled out for the treatment of DR-TB; and (3) a randomized study to determine the optimal dose and duration of linezolid, a critical component of the Nix-TB regimen, and whether other oxazolidinones in development improve the tolerability of the regimen without compromising efficacy.[33]

Two ongoing phase III trials provide opportunities to answer some of these questions. TB-PRACTECAL will compare the Nix-TB regimen to the local standard of care for M/XDR-TB (see Table 2) and ZeNix will evaluate different doses and durations of linezolid within the Nix-TB regimen (see Table 1). Like Nix-TB, however, ZeNix is uncontrolled. The endTB trial (see Table 2) includes a secondary randomization to one of two reduced linezolid doses (300 mg daily or 600 mg intermittently) after four months of linezolid exposure or linezolid-dose-limiting toxicity. TAG has emphasized the importance of ensuring that the approval of pretomanid in the Nix-TB regimen based on such limited data not be considered precedential and that rigorous, randomized controlled trials be upheld as the evidentiary standard upon which the approvals of future TB drugs and regimens are based.[34]

Optimizing The Use Of Approved And Repurposed Drugs

Efforts continue to optimize existing and repurposed compounds (see Table 1) and to shorten treatment for drug-sensitive and drug-resistant TB (see Table 2), including by prospectively testing whether tailoring treatment duration according to risk factors can improve outcomes.[35]

Table 1. Trials to optimize existing and repurposed drugs for TB

Study Name	Experimental Arms [Control]	For Treatment of	Number of Participants	Phase	Estimated Completion Date
ACTG A5312 NCT01936831	H: 5, 10, 15 mg/kg [currently dosed at 5 mg/kg, Hd: 10-15 mg/kg]	HR-TB (inhA mutation)	265	I	Oct 2019
HR1 Extension NCT01392911	R: 20, 25, 30, 35, 40, 45, 50, 55 mg/kg [currently dosed at 10 mg/kg]	DS-TB	128	II	Nov 2018
TBTC Study 32/ Opti-Q NCT01918397	Lx: 14, 17, 20 mg/kg [currently dosed at 11 mg/kg]	MDR-TB	111	II	Mar 2020
ZeNix NCT03086486	$6JPaLz_{1200}$ $2JPaLz_{1200}$/4JPa $6JPaLz_{600}$ $2JPaLz_{600}$/4JPa [none]	XDR-TB TI/NR MDR-TB	180	III	Dec 2021

Table 2. Trials to shorten treatment for TB

Study Name	Experimental Arms [Control]	For Treatment of	Number of Participants	Phase	Estimated Completion Date
ACTG A5362/ Clo-FAST	2CHPZE/1CHPZ (C_{300} for first 2 weeks followed by C_{100}) [2HRZE/4HR]	DS-TB	185	IIc	Protocol in development
ACTG 5373/ FIRST	$6H_{Hd}RZE$ [2RZELx/4RLx]	HR-TB	556	III	Protocol in development
ACTG A5384/ IMAG-INE-TB	$6R_{Hd}H_{Hd}Lz$ [2HRZE/7HR]	TBM	300	II	Protocol in development
APT NCT02256696	2PaBHZ/1PaBH 2PaRHZ/1PaRH [2HRZE/1HR]	DS-TB	183	II	Sep 2021

BEAT TB CTRI/2019/01/017310	6-9JDLzC [none]	Pre-XDR XDR-TB	165	III	Jan 2023
BEAT-Tuberculosis NCT04062201	6JDLz (Lx, C or both) [9mo RSA SOC]	RR-TB MDR-TB FQ-R MDR-TB	400	III	Mar 2023
DRAMATIC	$4JDCLxLz_{8wk}$ $6JDCLxLz_{8wk}$ $8JDCLxLz_{8wk}$ $10JDCLxLz_{8wk}$	MDR-TB	180	II	Protocol in development
endTB NCT02754765	9JLzMZ 9JLzLxCZ 9JLzLxDZ 9DLzLxCZ 9DMCZ [9–20mo local SOC]	MDR-TB	750	III	May 2022
endTB-Q NCT03896685	6JDLzC 9JDLzC [9–20mo local SOC]	FQ-R MDR-TB	500	III	Dec 2022
MDR-END NCT02619994	9–12DLzLxZ [20mo SLI-containing local SOC]	MDR-TB	238	II/III	Jun 2021
NEXT NCT02454205	6–9JLzLxZ(Eto or H_{Hd} or Tzd) [12–24mo SLI-containing local SOC]	MDR-TB	154	III	Dec 2020
Nix-TB NCT02333799	JPaL [none]	XDR-TB TI/NR MDR-TB	109	III	Oct 2021
RIFASHORT NCT02581527	$2HR_{1200}ZE/2HR_{1200}$ $2HR_{1800}ZE/2HR_{1800}$ [2HRZE/4HR]	DS-TB	654	III	Dec 2020
SimpliciTB NCT03338621	4JPaMZ [2HRZE/4HR]	DS-TB MDR-TB	450	III	Jan 2022
STREAM stage II NCT02409290	$4JCLxEZH_{Hd}Pto/5JCLxEZ$ $2JCLxZH_{Hd}K/4JCLxZ$ [$4CLxEZH_{Hd}KPto/5CLxZE$]	MDR-TB	530	III	Jun 2022
TB-PRACTECAL NCT02589782	6JPaMLz 6JPaLzC 6JPaLz [9–20mo local SOC]	MDR-TB XDR-TB	630	II/III	Mar 2021
TBTC CURE-TB	2HPZE 2HPZE/2HP 2HPZE/4HP [2HRZE/4HR]	DS-TB	1,800	III	Protocol in development

TBTC Study 31/ A5349 NCT02410772	2HPZE/2HP 2HPZM/2HPM [2HRZE/4HR]	DS-TB	2,516	III	Dec 2020
TRUNCATE-TB NCT03474198	$2HR_{Hd}ZELz$ $2HR_{Hd}ZEC$ 2HPZLzLv 2HZELzJ [2HRZE/4HR]	DS-TB	900	II/III	Mar 2022

In Tables 1 and 2, unless otherwise indicated (i.e., mg/kg), numbers represent the duration of treatment (in months). Letters represent the individual drugs comprising each regimen. Slashes are used to separate intensive and continuation phases of treatment.

B = rifabutin
C = clofazimine
D = delamanid
DS-TB = drug-sensitive TB
E = ethambutol
Eto = ethionamide
FQ-R = fluoroquinolone resistant
H = isoniazid
Hd = high dose
HR-TB = isoniazid mono-resistant TB
J = bedaquiline
K = kanamycin
Lx = levofloxacin
Lz = linezolid
M = moxifloxacin
MDR-TB = multidrug-resistant TB
mo = month
P = rifapentine
Pa = pretomanid
Pto = prothionamide
R = rifampin
RSA = South Africa
SLI = second-line injectable
SOC = standard of care
TBM = tuberculous meningitis
TI/NR = treatment-intolerant or non-responsive
Tzd = terizidone
XDR-TB = extensively drug-resistant TB
Z = pyrazinamide

Updates On New Compounds In Development

Novel compounds, including from new classes or that may prove to be safer alternatives to existing powerful TB medicines, are advancing through the development pipeline (see Table 3). Compounds from new classes (i.e., that have new targets and/or mechanisms of action) are important for constructing effective regimens and staying ahead of drug resistance. The TB drugs highlighted in Table 3 work by inhibiting four processes: energy production, cell wall synthesis, protein synthesis, and DNA synthesis. These processes are key targets for medicines, as interrupting them affects the TB bacteria's ability to survive and/or replicate.

Table 3. Drugs in development for TB

Drug	Class	Mechanism of Action	Sponsor	Phase	Clinical Trial(s)
Energy Production					
bedaquiline	diarylquinoline	Inhibits ATP synthase and bacterial respiration	Janssen	III	see Table 2
pyrifazimine (TBI-166)	rimino-phenazine	Inhibits ion transport and bacterial respiration	IMM/CAMS/PUMC	I	ChiCTR1800018780
telacebec (Q203)	imidazopyridine	Inhibits ATP synthesis (QcrB) and bacterial respiration	Qurient/ Infectex	IIa	NCT02530710 NCT02858973 NCT03563599

Cell Wall Synthesis					
BTZ-043	benzothiazinone	Inhibits cell wall synthesis (DprE1)	University of Munich/DZIF	Ib/IIa	NCT03590600 NCT04044001
delamanid	nitroimidazole	Inhibits cell wall synthesis and bacterial respiration	Otsuka	IV	see Table 2
macozinone (PBTZ169)	benzothiazinone	Inhibits cell wall synthesis (DprE1)	iM4TB/Nearmedic	Ib	NCT03423030 NCT03776500
OPC-167832	carbostyril	Inhibits cell wall synthesis (DprE1)	Otsuka	Ib/IIa	NCT03678688
pretomanid	nitroimidazole	Inhibits cell wall synthesis and bacterial respiration	TB Alliance	III	see Table 2
SQ109	1,2-ethylene diamine	Inhibits cell wall synthesis (MmpL3)	Sequella	IIb	NCT01585636 NCT00866190 NCT01358162 NCT01218217 NCT01785186
TBA-7371	azaindole	Inhibits cell wall synthesis (DprE1)	TB Alliance	Ia/Ib	NCT03199339
Protein Synthesis					
contezolid acefosamil (MRX-4)	oxazolidinone	Inhibits protein synthesis (23S ribosome)	MicuRx	II	NCT03033342 NCT03033329 NCT03747497
delpazolid (LCB01-0371)	oxazolidinone	Inhibits protein synthesis (23S ribosome)	LegoChem Biosciences	IIa	NCT01554995 NCT01842516 NCT02540460 NCT02836483
sutezolid (PNU-100480)	oxazolidinone	Inhibits protein synthesis (23S ribosome)	Sequella/TB Alliance	IIb	NCT00871949 NCT00990990 NCT01225640 NCT03199313 NCT03959566
TBI-223	oxazolidinone	Inhibits protein synthesis (23S ribosome)	TB Alliance/IMM	Ia	NCT03758612
GSK3036656 (GSK-070)	oxaborole	Inhibits protein synthesis (LeuRS)	GSK	IIa	NCT03075410 NCT03557281
DNA Synthesis					
SPR720	benzimidazole	Inhibits bacterial DNA synthesis (GyrB)	Spero Therapeutics/ BMG MRI	Ia/Ib	NCT03796910

Phase listed represents the most advanced trial that is ongoing/completed.

CAMS: Chinese Academy of Medical Sciences
DZIF: German Center for Infection Research
BMG MRI: Bill & Melinda Gates Medical Research Institute
GSK: GlaxoSmithKline
iM4TB: Innovative Medicines for Tuberculosis
IMM: Institute of Materia Medica, China
PUMC: Peking Union Medical College, China

Energy Production

Pyrifazimine (TBI-166)

Pyrifazimine is a member of the riminophenazine class, like clofazimine—a medicine derived from a red dye and used to treat leprosy that has been repurposed for the treatment of drug-resistant TB. Pyrifazimine is less lipophilic (fat-soluble) and has a shorter half-life than clofazimine, which may reduce drug-induced discoloration of the skin.[36] A phase I study of pyrifazimine opened in China in January 2018.

Telacebec (Q203)

Telacebec is a first-in-class drug candidate sponsored by Qurient, a small biotech company based in South Korea. In July 2018, Qurient opened a phase IIa early bactericidal activity (EBA) study to evaluate the safety, pharmacokinetics, and bactericidal activity of telacebec administered at different doses (100, 200, 300 mg) for 14 days to participants with drug-sensitive TB in South Africa. The study completed in the third quarter of 2019. According to Qurient, telacebec demonstrated good dose-dependent EBA.[37] Qurient is planning a phase IIb study to evaluate telacebec given in combination with other TB medicines for two months or longer to people with drug-resistant and/or drug-sensitive TB.[38]

Cell Wall Synthesis

BTZ-043

BTZ-043 is from a new class of drugs (benzothiazinones) under investigation for TB. A phase Ia single ascending dose (SAD) study to evaluate the safety of increasing single oral doses (125–2,000 mg) of BTZ-043 administered to healthy volunteers in Germany was completed in March 2019. Investigators from the Ludwig-Maximilians-University of Munich and German Center for Infection Research (DZIF) found that BTZ-043 was safe and well tolerated at doses up to 500 mg. Following better-than-expected bioavailability, which met a preset pharmacokinetic threshold, dose escalation was stopped early. Higher doses will be evaluated in a phase Ib/IIa study.[39]

A phase Ib/IIa multiple ascending dose (MAD)/EBA study to evaluate the safety, pharmacokinetics, and bactericidal activity of BTZ-043 administered at different doses (250–2,000 mg) once daily for 14 days to participants with drug-sensitive TB is expected to open in South Africa in November 2019. This study will be conducted in two stages and will include assessments of food effects and the potential for drug-drug interactions.[40] Results are expected after November 2020.

Macozinone (PBTZ169)

Macozinone is an optimized derivative of BTZ-043. In February 2019, Innovative Medicines for Tuberculosis (iM4TB) opened a phase Ib MAD study to evaluate the safety and pharmacokinetics of macozinone administered at different doses once or twice daily (up to 600 mg) for 14 days to healthy male volunteers in Switzerland. Results are expected after October 2019.

In 2018, Nearmedic—the company leading development for Russia and countries that make up the Commonwealth of Independent States—terminated early its phase IIa EBA study of different doses (160–640 mg) of macozinone administered daily for 14 days to participants with drug-sensitive TB in Russia and Belarus (NCT03334734). The reason for early termination of the study listed on ClinicalTrials.gov is "slow enrollment."

OPC-167832

In 2017, Otsuka—also the sponsor of delamanid—completed a phase Ia SAD study to evaluate the safety of increasing single doses (30–480 mg) of OPC-167832 administered to healthy volunteers. No safety signals were observed.[41]

In October 2018, Otsuka opened a phase Ib/IIa MAD/EBA study to evaluate the safety, pharmacokinetics, and early bactericidal activity of OPC-167832 administered at different doses (10–270 mg) once daily with and without 200 mg delamanid for 14 days to participants in South Africa with drug-sensitive TB. The first two cohorts have completed enrollment, and full results are expected after December 2020.[42]

With support from the Bill & Melinda Gates Foundation, Otsuka plans to develop OPC-167832 in combination with delamanid as the backbone of a "pan-TB regimen."[43]

SQ109

Sequella, a small biotech company based in the United States, has leveraged the resources and infrastructure of the U.S. National Institute of Allergy and Infectious Diseases (NIAID) and the European and Developing Countries Clinical Trials Partnership-funded Pan-African Consortium for the Evaluation of Antituberculosis Antibiotics (PanACEA) to advance the development of SQ109.

In May 2012, PanACEA completed a phase IIa EBA study to evaluate the safety, pharmacokinetics and bactericidal activity of SQ109 administered at different doses (75, 150, 300 mg) with or without rifampin for 14 days to participants with drug-sensitive TB in South Africa. The investigators found that while SQ109 was generally safe and well tolerated, the drug did not appear to be active alone or to enhance the activity of rifampin during the study period.[44] The relationship between early bactericidal activity (EBA) and sterilizing activity is not so apparent. EBA may measure well the ability of a drug to kill actively replicating TB but may not predict the ability of a drug to kill dormant TB (sterilizing activity), which is important for achieving relapse-free cure.[45,46] Clofazimine, a core component of treatment for drug-resistant TB, has no EBA. Rifampin and pyrazinamide, core components of treatment for drug-sensitive TB, and bedaquiline, a core component of treatment for drug-resistant TB, have delayed bactericidal activity.

In March 2015, PanACEA completed a multiple-arm multiple-stage (MAMS) phase IIb study to evaluate the safety, pharmacokinetics, and efficacy of 300 mg SQ109 administered for four months in combination with isoniazid, pyrazinamide, and standard or high-dose rifampin to participants with drug-sensitive TB in South Africa and Tanzania. At the recommendation of the independent data-monitoring committee after the first scheduled interim analysis, the investigators terminated the SQ109-containing arms of the study, which failed to meet a prespecified threshold for time to culture conversion.[47]

SQ109 and rifampin demonstrate synergy in mice,[48] but according to Sequella, unpublished pharmacokinetic data from the phase IIa EBA study suggest a potential drug-drug interaction between SQ109 and rifampin.[49] Once these and other pharmacokinetic data are made public and undergo peer review, the research community will be better positioned to discuss the most appropriate next step for the further research and development of SQ109.

In the meantime, Sequella is preparing a phase III trial protocol and planning to register SQ109 with the FDA as a Qualified Infectious Disease Product (QIDP). Medicines designated as a QIDP are eligible for fast-track designation and priority review, intended to expedite the development and review of new products that are intended for the treatment of serious or life-threatening conditions and/or that demonstrate potential to address unmet medical needs.

In Russia, the development of SQ109 appears to be further along and focused on MDR-TB. In 2016 at a conference in Moscow, Infectex—the company to which Sequella licensed the rights to develop SQ109 in Russia—reported top-line results from a phase IIb/III trial of SQ109 for the treatment of MDR-TB.[50] In 2018, final results were published in Russian.[51] According to Sequella, Infectex's phase IIb/III trial, which enrolled 140 participants, was designed to compare 300 mg SQ109 to placebo, each given daily with an optimized background regimen for six months, followed by the optimized background regimen alone for another six months (drugs available at the time of the study and eligible for inclusion in the optimized background regimen included pyrazinamide, ethambutol, amikacin, capreomycin, kanamycin, streptomycin, levofloxacin, ofloxacin, cycloserine, ethionamide, PAS). The trial was powered to detect a difference in the proportion of participants with negative cultures at six months of treatment. Sequella reports that 80% of participants treated with SQ109 achieved cure, compared with 61% of participants treated with placebo.[52] Sequella also reports faster time to culture conversion among participants treated with SQ109 compared with placebo (8 vs. 12 weeks, respectively).[53]

TBA-7371

In July 2018, the TB Alliance completed a phase Ia/Ib SAD/MAD and drug-drug interaction study of TBA-7371. Phase Ia evaluated the safety and pharmacokinetics of increasing single doses (100–1,500 mg) of TBA-7371 administered to healthy volunteers in the United States. Phase Ib evaluated the safety and pharmacokinetics of TBA-7371 administered at different daily doses (100–400 mg) for 14 days to healthy volunteers in the United States. A drug-drug interaction study looked at the pharmacokinetic effects of multiple doses of TBA-7371 on two probe medications (midazolam and bupropion) to predict how TBA-7371 might affect drugs metabolized by CYP3A and CYP2B6 enzymes. Further development will be undertaken in partnership with the Bill & Melinda Gates Medical Research Institute.[54]

Protein Synthesis

Linezolid—an oxazolidinone—is a core component of treatment regimens for drug-resistant TB but has severe side effects (myelosuppression and peripheral and optic neuropathy) limiting tolerability and often requiring early discontinuation. Given linezolid's efficacy against TB, much work is underway to optimize the duration and dose of linezolid (see Table 1) and to advance other drugs from the oxazolidinone class as potential safer alternatives (see below).

Contezolid acefosamil (MRX-4)

MicuRx is developing an oxazolidinone, contezolid acefosamil (MRX-4)—a prodrug of contezolid (MRX-1)—for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and diabetic foot infections caused by multidrug-resistant Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci in China and the United States.[55] In 2019, MicuRx completed a phase II study in the United States to evaluate the safety and efficacy of contezolid acefosamil (MRX-4) compared with linezolid administered orally and intravenously for 10–14 days for ABSSSI.[56] The proportion of participants with a favorable response after 10–14 days of treatment with contezolid acefosamil (MRX-4) was similar to that of participants treated with linezolid (76.3% vs. 73.8%, respectively). Treatment emergent adverse events were also similar between study arms, though there was fewer participants with lower than normal neutrophil and platelet values in the contezolid acefosamil (MRX-4) arm, suggesting that contezolid acefosamil (MRX-4) may have a better safety profile than linezolid.[57]

Contezolid (MRX-1) has demonstrated promising in vitro and in vivo activity against TB (comparable to that of linezolid),[58] but MicuRx does not have any current plans for its development, or for that of the prodrug (MRX-4), for TB.[59]

Delpazolid (LCB01-0371)

LegoChem Biosciences, a biopharmaceutical company based in South Korea, is developing an oxazolidinone, delpazolid, for the treatment of TB. A phase Ia SAD study to evaluate the safety of increasing single oral doses (50–3,200 mg) of delpazolid administered to healthy male volunteers in South Korea was completed in February 2013 and found that delpazolid was well tolerated up to 2,400 mg.[60] The study also found that delpazolid is cleared from plasma more rapidly than linezolid, potentially lowering the risk of mitochondrial toxicity, the symptoms of which include peripheral neuropathy.[61]

A phase Ib MAD study to evaluate the safety and pharmacokinetics of delpazolid administered twice daily (400–1,600 mg) for seven days to healthy male volunteers in South Korea was completed in December 2013 and found that twice-daily doses of delpazolid up to 1,200 mg were well tolerated.[62] A second phase Ib MAD study to evaluate the safety and pharmacokinetics of delpazolid administered at 800 mg once or twice daily or 1,200 mg twice daily for 21 days to healthy male volunteers in South Korea was completed in January 2015 and found that doses up to 1,200 mg twice daily were well tolerated.[63]

A phase IIa EBA study to evaluate the safety, pharmacokinetics, and bactericidal activity of delpazolid administered at different doses once or twice daily (up to 1,600 mg) for 14 days to participants with drug-sensitive TB opened in South Korea in December 2016. An interim analysis showed that when administered twice daily, 800 mg delpazolid exposures were 7–8 times lower than 600 mg once-daily linezolid exposures but demonstrated similar bactericidal activity.[64] Final results are expected after February 2020. Next, LegoChem Biosciences plans to evaluate the safety and efficacy of delpazolid administered at 1,200 mg once daily and 800 mg twice daily for six months.[65]

Sutezolid

From 2009 to 2011, Pfizer completed several studies of sutezolid.[66,67] However, sutezolid's development has been stuck in phase IIa since 2011, when Pfizer exclusively licensed the rights to sutezolid to Sequella (see section on SQ109).

Johns Hopkins University shared rights with Pfizer to develop sutezolid in combination with other medicines, and in January 2017, the university licensed these rights to the Medicines Patent Pool (MPP). The MPP then granted a sublicense to the TB Alliance. In December 2017, the TB Alliance completed a phase Ia SAD study to evaluate the safety and pharmacokinetics of increasing oral doses (300–1,800 mg) of sutezolid administered to healthy volunteers in the United States. The TB Alliance's plans to further develop sutezolid, however, are in flux after a six-month, repeat-dose toxicology study in rats conducted by SRI International with funding support from NIAID and study drug and technical expertise from Sequella. In the study, convulsions were observed in a limited number of non-ovariectomized female rats when handled (picked up).[68] Any further development by the TB Alliance will be done in partnership with the Gates Medical Research Institute.[69]

Sequella asserts that the observed convulsions—hypothesized to be a consequence of drug-induced serotonin syndrome—may be species- and sex-specific.[70] Following a green light from the FDA, PanACEA (in partnership with Sequella) is enrolling a phase IIb dose-finding study called SUDOCU to evaluate the safety, pharmacokinetics, and exposure-response relationship of different doses of sutezolid administered once or twice daily (up to 1,200 mg) for three months in combination with bedaquiline, delamanid, and moxifloxacin to participants with drug-sensitive TB in South Africa and Tanzania. Results are expected in 2020 and will inform the sutezolid dose to be evaluated in a future phase IIc study of four months of sutezolid, bedaquiline, delamanid, and moxifloxacin for the treatment of drug-sensitive TB. Additional preclinical research may be required by regulatory authorities before sutezolid can be studied in humans for durations greater than three months.

TBI-223

While the TB Alliance's investigations of sutezolid may have been temporarily paused, they are moving forward with the development of another oxazolidinone, TBI-223. In January 2019, the TB Alliance opened a phase Ia SAD study to evaluate the safety and pharmacokinetics of increasing oral doses (50–1,400 mg) of TBI-223 administered to healthy volunteers in the United States. The study is ongoing, and results are expected after May 2020.

GSK3036656 (GSK-070)

Similar to oxazolidinones, GSK3036656—an oxaborole sponsored by GlaxoSmithKine (GSK)—acts by inhibiting protein synthesis.

In August 2017, GSK completed a phase Ia/Ib SAD/MAD study of GSK3036656. Phase Ia evaluated the safety and pharmacokinetics of increasing single doses (5, 15, 25 mg) of GSK3036656 administered to healthy volunteers in the United Kingdom. Phase Ib evaluated the safety and pharmacokinetics of GSK3036656 administered at different daily doses (5 or 15 mg) for 14 days to healthy volunteers in the United Kingdom. GSK3036656 was well tolerated after single and multiple doses with no reports of serious adverse events.[71]

In March 2019, GSK initiated a phase IIa EBA study to evaluate the safety, pharmacokinetics, and bactericidal activity of GSK3036656 administered at different doses (starting at 5 mg) for 14 days to participants with drug-sensitive TB in South Africa. Results are expected after September 2020.

DNA Synthesis

SPR720

In December 2018, Spero Therapeutics Inc. opened a phase Ia/Ib SAD/MAD study of SPR720. Phase Ia will evaluate the safety and pharmacokinetics of increasing single oral doses (100–3,000 mg) of SPR720 administered to healthy volunteers in the United Kingdom. Phase Ib will evaluate the safety and pharmacokinetics of SPR720 administered at different doses (500–1,500 mg) for seven days to healthy volunteers in the United Kingdom. Results were expected after June 2019; the study is listed as recruiting on ClinicalTrials,gov.

Spero Therapeutics is developing SPR720 for nontuberculous mycobacterial infections, and in 2019, the company granted the Gates Medical Research Institute an exclusive license to develop, manufacture, and commercialize SPR720 for TB in low- and middle- income countries.[72]

Conclusion

The TB treatment pipeline is increasingly dynamic and the healthiest it's been in decades. As the research community works to better understand and optimize the use of existing medicines, new drugs with novel mechanisms of action or the potential to offer safer alternatives to existing medicines are advancing through early stage clinical trials. Now more than ever, the field needs increased resources, community engagement, collaboration, and commitment to a set of shared principles that promote rigorous science, transparency, equity, and access.

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TAG

Treatment Action Group

www.treatmentactiongroup.org

90 Broad Street, Suite 2503
New York, NY 10004
Tel 212.253.7922, Fax 212.253.7923

tag@treatmentactiongroup.org

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