

# Pipeline Report » 2020

Tuberculosis Treatment

**TAG**

Treatment Action Group

# The 2020 Tuberculosis Treatment Pipeline Report

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## INTRODUCTION

Despite COVID-19 related challenges and disruptions,<sup>1,2</sup> tuberculosis (TB) treatment research initiatives have managed to progress and produce results, among them: a large phase III trial to evaluate the ability of rifapentine- and moxifloxacin-containing regimens to shorten treatment for drug-sensitive TB from six to four months (TBTC Study 31/ ACTG A5349); and a randomized controlled trial to evaluate four versus six months of treatment for children with minimal drug-sensitive TB (the SHINE trial).

Global policymakers have also managed to keep pace with the evolving evidence base for the treatment of drug-resistant TB. In July 2020, the World Health Organization (WHO) issued updated guidelines establishing bedaquiline as a core component of all regimens recommended for the treatment of drug-resistant TB, and introducing the six- to nine-month pretomanid-containing BPaL or Nix-TB regimen for multidrug-resistant TB with additional fluoroquinolone resistance under conditions of operational research.<sup>3</sup>

Advances earlier in the clinical development pipeline for TB were more limited in 2020. Two new compounds—TBAJ-876 and GSK-286—entered phase I trials, bringing the total number of compounds in clinical development for TB to 14.<sup>4</sup> Though few of these compounds have advanced beyond the phase in which they were reported to be in during 2019,<sup>5</sup> previously nascent initiatives such as the Project to Accelerate New Treatments for Tuberculosis (PAN-TB collaboration) coordinated by the Bill and Melinda Gates Medical Research Institute (GMRI) and initiatives funded under the Innovative Medicines Initiative (IMI) Antimicrobial Resistance (AMR) Accelerator are expected to advance several compounds in the year ahead.<sup>6,7,8</sup>

Figure 1. TB Drugs and Research/ Product Sponsors by Phase of Development

		telacebec (Q203)		
	BTZ-043			
pyrifazimine (TBI-166)	macozinone (PBTZ-169)			
TBI-223	OPC-167832			
TBAJ-876			SQ109	bedaquiline
SPR720		TBA-7371	delpazolid (LCB01-0371)	delamanid
GSK2556286 (GSK-286)		GSK3036656 (GSK-656)	sutezolid (PNU-100480)	pretomanid
<b>PHASE IA</b>	<b>PHASE IB</b>	<b>PHASE IIA</b>	<b>PHASE IIB/C</b>	<b>PHASE III</b>
	IMI ERA4TB			
		IMI UNITE4TB		
	GMRI			
			PAN-TB	
			CDC TBTC	
			NIH ACTG	
			EDCTP PanACEA	
Pharmaceutical Companies (e.g., Otsuka, Janssen, GlaxoSmithKline, Qurient, LegoChem)				
Product Development Partnerships (i.e., TB Alliance)				

CDC TBTC: U.S. Centers for Disease Control and Prevention Tuberculosis Trials Consortium  
 EDCTP PanACEA: European and Developing Countries Clinical Trials Partnership Pan-African Consortium for the Evaluation of Anti-tuberculosis Antibiotics  
 GMRI: Bill and Melinda Gates Medical Research Institute  
 IMI ERA4TB: Innovative Medicines Initiative European Regimen Accelerator for Tuberculosis  
 IMI UNITE4TB: Innovative Medicines Initiative Academia and Industry United Innovation and Treatment for Tuberculosis  
 NIH ACTG: U.S. National Institutes of Health AIDS Clinical Trials Group  
 PAN-TB: Project to Accelerate New Treatments for Tuberculosis

The 2020 Tuberculosis Treatment Pipeline report offers summaries of influential treatment studies and data sets, and updates on new drugs and regimens in clinical development for TB.

## UPDATES ON INFLUENTIAL TREATMENT STUDIES AND DATA SETS

### TBTC Study 31/ ACTG A5349 (NCT02410772)

Results from a phase III randomized controlled study conducted by the U.S. Centers for Disease Control and Prevention (CDC) Tuberculosis Trials Consortium (TBTC) and the U.S. National Institutes of Health (NIH) AIDS Clinical Trials Group (ACTG)—S31/ A5349—were presented at the 51st Union World Conference on Lung Health. S31/A5349 compared two four-month regimens, both with rifapentine in place of rifampin, and one with moxifloxacin in place of ethambutol (2HPZE/2HP and 2HPZM/2HPM) to the six-month standard of care for drug-sensitive TB (2HRZE/4HR). S31/ A5349 is the largest TB treatment shortening trial to be conducted in the last two decades, enrolling 2,516 participants from 34 sites in 13 countries. S31/ A5349 may also be one of the most diverse trials conducted to date, allowing for the inclusion of adolescents down to 12 years of age (2.7%), people living with HIV with CD4 counts down to 100 cell/mm<sup>3</sup> (8.2%), as well as people with cavitory disease (72.6%).<sup>9</sup> S31/ A5349 was a noninferiority trial, meaning it tested whether the two experimental regimens were no worse than the control regimen by a prespecified amount. This prespecified amount is called a noninferiority margin and is set by the trial investigators based on the anticipated performance of the control regimen (in the case of S31/ A5349, based on the proportion of unfavorable outcomes observed among participants randomized to the control arms of prior drug-sensitive TB treatment shortening studies, i.e., RIFAQUIN, OFLOTUB, and REMoxTB) and what the investigators deemed to be an acceptable trade in efficacy for shorter treatment duration.<sup>10</sup> For this trial, the investigators chose a noninferiority margin of 6.6%. This means that an experimental regimen would be deemed no worse than the control if the upper bound of the 95% confidence interval for the **risk difference** between the experimental regimen and the control was less than 6.6%.

The S31/ A5349 investigators found the four-month rifapentine- and moxifloxacin-containing regimen (2HPZM/2HPM) **non-inferior** to the existing six-month standard of care.<sup>11</sup> S31/ A5349 offers the first advance over the existing standard of care for the treatment of drug-sensitive TB in 40 years. Non-inferiority was demonstrated in multiple analysis populations identified in the study protocol and statistical analysis plan, including the “microbiologically eligible” (risk difference: 1% [-2.6%, 4.5%]) and “assessable” (risk difference: 2% [-1.1%, 5.1%]) populations.<sup>12</sup> Both are modified intention-to-treat populations, but the “assessable” population excludes participants that experience an event that is unlikely related to TB disease or the intervention (e.g., death from violent or accidental cause, loss to follow up after completing treatment), whereas the “microbiologically eligible” population classifies these participants as having an unfavorable outcome (more similar to the intention-to-treat population).<sup>13</sup> The investigators also analyzed “PP75” and “PP95” populations – per protocol 75% and per protocol 95% populations – from which they excluded any participants that did not complete 75% and 95% of treatment as described in the study protocol, respectively. Non-inferiority was again demonstrated in both the PP75 (risk difference: 3.0% [0.8%, 5.2%]) and PP95 (risk difference: 3.1% [0.9%, 5.3%]) populations.<sup>14</sup>

Throughout this report regimens are represented in short form where numbers represent the duration of treatment in months, letters represent the individual drugs comprising each regimen (see Table 1), and slashes are used to separate the intensive and continuation phases of treatment. For example, 2HRZE/4HR represents the six-month standard of care regimen for drug-sensitive TB – 2 months of isoniazid, rifampin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampin. \*Please note that in the narrative text “B” represents bedaquiline, but in the tables “J” represents bedaquiline and “B” represents rifabutin.

**Risk difference** is the difference between the risk of an outcome in the experimental or exposed group and the control or unexposed group, or put differently, the excess risk of an outcome that can be attributed to the intervention or exposure.

In the case of S31/A5349, **noninferior** means that the intervention (2HPZM/2HPM) is no worse than the control (2HRZE/4HR). Testing noninferiority is different than testing for either superiority or equivalence.

Unfavorable treatment outcomes were defined as: absence of bacteriological cure (e.g., a sputum sample at or after week 17 that is culture positive, indistinguishable from the initial isolate, and confirmed by a second positive culture); death from any cause during study treatment; failure to complete treatment; positive culture when last seen, unless determined to be re-infection; and any one or more of the following: extension of treatment; re-start of treatment; a change in treatment for any reason other than re-infection, pregnancy, or temporary drug challenge.<sup>15</sup> In the “assessable” population the investigators reported unfavorable treatment outcomes among 11.6% (88/756) of participants who received the four-month rifapentine- and moxifloxacin-containing regimen compared with 9.6% (70/726) of participants who received the six-month standard of care regimen.<sup>16</sup> The observed treatment effect and non-inferiority was consistent across all primary, secondary, subgroup, and sensitivity analyses.<sup>17</sup>

S31/ A5449 is the first phase III study to identify a regimen capable of successfully shortening treatment for drug-sensitive TB from six to four months. Of note, the experimental arm in S31/ A5349 that failed to achieve non-inferiority (2HPZE/2HP), did perform well in certain subgroups, including those with indicators of less severe disease (without **cavitation** on chest X-ray, with low baseline acid fast bacilli [AFB] **smear grade**, with high time to detection [TTD] in liquid culture).<sup>18</sup> This upholds a pattern observed in drug-sensitive TB treatment shortening studies historically, including REMoxTB, OFLOTUB, and RIFAQUIN, in which experimental four-month regimens failed to demonstrate non-inferiority to the six-month standard of care but demonstrated efficacy in certain subgroups (participants with minimal disease defined by < 2+ sputum smear grade or non-cavitary disease), further buoying proposals to prospectively evaluate a stratified approach to TB treatment.<sup>19</sup>

**Cavitation** is the presence of thick walled, abnormal gas filled spaces within the lung created when dead or necrotic tissue tears and breaks down.

**Smear grade** is a ranked indicator (+4, +3, +2, +1) of how infectious an individual's TB is based on the number of bacilli observed in a sputum or other sample when examined under a microscope.

In terms of the primary and secondary safety outcomes for S31/ A5349, there were no significant differences between the investigational and control regimens. All-cause mortality during treatment was similar across arms, with just 0.4% of participants who received the four-month rifapentine- and moxifloxacin-containing regimen and 0.8% of participants who received the six-month standard of care dying from any cause.<sup>20</sup> Similarly, all-cause mortality during treatment and follow up was similar across arms, with just 1.5% of participants who received the four-month rifapentine- and moxifloxacin-containing regimen and 1.4% of participants who received the six-month standard of care dying from any cause.<sup>21</sup> The proportion of participants with any grade three or higher adverse events during treatment was similar across arms, with 18.8% of participants who received the four-month rifapentine- and moxifloxacin-containing regimen reporting grade three or higher adverse events compared to 19.3% of participants who received the six-month standard of care.<sup>22</sup> Treatment-related grade three or higher adverse events were experienced by 12.9% of participants who received the four-month rifapentine- and moxifloxacin-containing regimen compared to 9.8% of participants who received the six-month standard of care.<sup>23</sup> The proportion of

participants experiencing any serious adverse event during treatment was 4.4% among participants who received the four-month rifapentine- and moxifloxacin-containing regimen compared to 6.8% among participants who received the six-month standard of care regimen.<sup>24</sup> The proportion of participants discontinuing assigned treatment for any reason other than microbiological ineligibility—a marker of tolerability—was similar across arms, with 7.0% of participants who received the four-month rifapentine- and moxifloxacin-containing regimen discontinuing treatment compared to 7.9% of participants who received the six-month standard of care.<sup>25</sup> There was no observed increase in grade 3–5 **hepatotoxicity** between the experimental and control regimens during treatment (2.5% of participants who received the four-month rifapentine- and moxifloxacin-containing regimen compared to 4.5% of participants who received the standard of care regimen).<sup>26</sup>

**Hepatotoxicity:** drug-induced damage or injury to the liver.

The results of S31/ A5349 represent a watershed moment and will likely result in a major revision to a long-settled global standard of care for a condition affecting nearly 10 million people a year. While we can and should take a hard-earned and long-awaited moment to celebrate this important achievement, much work lies ahead for the benefits of this research to be enjoyed by all communities affected by TB. Of note, S31/ A5349 only enrolled people living with HIV on efavirenz-based regimens. The DOLPHIN Study (NCT03435146) determined that rifapentine at 900 mg once weekly (provided in the context of the **3HP** regimen for TB prevention) can be safely administered to people living with HIV on dolutegravir-based regimens without dose adjustments.<sup>27</sup> ACTG A5372 (NCT04272242) will evaluate whether dose adjustments are necessary when dolutegravir is given with 600 mg once daily rifapentine in the context of the **1HP** regimen for TB prevention. YODA (NCT03510468) will evaluate the effects of once-weekly rifapentine on tenofovir alafenamide fumarate (TAF) in healthy volunteers, and NCT03785106, a phase III study comparing 1HP to 3HP for TB prevention, includes a pharmacokinetic sub-study of rifapentine, dolutegravir, and tenofovir alafenamide fumarate (TAF). But data is not available to inform whether and how daily, high-dose (1,200 mg) rifapentine can be safely administered alongside integrase inhibitors and tenofovir alafenamide fumarate (TAF).

**3HP:** three months of once weekly rifapentine and isoniazid for TB prevention.

**1HP:** one month of daily rifapentine and isoniazid for TB prevention.

Existing pediatric formulations of rifapentine (a 150 mg/ 150 mg dispersible fixed-dose combination [FDC] of rifapentine and isoniazid, and 100 mg and 200 mg standalone dispersible tablets of rifapentine) are trial formulations developed for TBTC Study 35 (NCT03730181), an ongoing study to evaluate the safety and optimal dosing of 3HP in children under two years of age with and without HIV. A study to determine the safety and optimal dosing of 1HP for the prevention of TB among children with and without HIV is planned (IMPAACT P2024). However, in S31/ A5349 rifapentine is dosed daily at 1,200 mg (rather than 900 mg once weekly for 3HP or 600 mg daily for 1HP). At what dose rifapentine exposures in children will match those achieved in adults at 1,200 mg daily is suddenly a glaring knowledge gap that stands between children and access to this new four-month standard of care for drug-sensitive TB.

In addition to the aforementioned knowledge gaps among people living with HIV on certain antiretroviral (ARV) medications and children, the already limited global supply of rifapentine available to programs scaling up access to rifapentine-based TB preventive therapy, recently further compounded by nitrosamine impurities detected in samples of rifapentine,<sup>28</sup> can be anticipated as a barrier to expeditious adoption of the four-month rifapentine- and moxifloxacin-containing regimen as a new standard of care regimen for the treatment of drug-sensitive TB. In addition, the daily pill burden required to achieve a 1,200 mg dose of rifapentine using existing formulations (Sanofi: 150 mg rifapentine tablet; Macleods: 300 mg / 300 mg FDC tablet of rifapentine and isoniazid) and the current absence of FDCs that contain rifapentine and moxifloxacin are likely to present as challenges to acceptability by patients and providers alike, and subsequently may become another barrier to adoption.

### SHINE (ISRCTN63579542)

Though it may be some time before children can benefit from the four-month regimen (2HPZM/2HPM) proven as good as the six-month standard of care in S31/A5349, results from the SHINE trial support the more immediate use of another four-month regimen (2HRZE/2HR) in children with **minimal TB**. SHINE— a phase III trial to evaluate whether the continuation phase of treatment for drug-sensitive TB could be shortened by two months for children with minimal TB— enrolled 1,204 children under 16 years old, including 127 children living with HIV (10.5%), from sites in South Africa, Uganda, Zambia, and India.<sup>29</sup> Typically, in pediatric TB research, studies are focused on pharmacokinetics (PK) and safety, to identify the dose at which children achieve drug exposures similar to those that have been associated with efficacy in adults. SHINE did include nested PK studies to describe the PK of rifampicin, isoniazid, and pyrazinamide when administered as a fixed-dose combination (FDC) according to the WHO weight-band doses recommended in 2010, and to evaluate PK interactions with ARV medicines among co-infected children.<sup>30</sup> However, SHINE is special in that it was primarily a randomized controlled trial powered for efficacy. Using a non-inferiority margin of 6%, the SHINE investigators found the risk difference between the four- and six-month regimens to be 0 (-2.9–2.9), -0.3 (-2.3–1.6), and -0.6 (-2.5–1.4) across the intention to treat, modified intention to treat, and per protocol analyses, respectively.<sup>31</sup> More simply, the investigators found four months of treatment non-inferior to six months of treatment for minimal drug-sensitive TB in children, detecting no difference between the four- and the six-month regimen in terms of the proportion of children with an **unfavorable outcome** 72 weeks post randomization (3% vs. 3%).<sup>32</sup>

In terms of safety, there were few treatment-related grade three or higher adverse events in the study, with similar rates observed across arms. There were a total of 49 and 66 grade three or higher adverse events among children who received four and six months of treatment, respectively. Out of 16 adverse treatment reactions, 11 were raised liver enzymes, experienced among five and 11 children who

**Minimal TB:** TB which is both smear negative and non-severe in form (i.e., in lymph nodes outside of the chest or, if inside of the chest, confined to one lobe with no cavities or to lymph nodes without significant airway obstruction and no bilateral airway narrowing).

In the SHINE trial, **unfavorable outcomes** were defined as treatment failure, TB recurrence, death of any cause, or loss to follow up.

received four and six months of treatment, respectively.<sup>33</sup> There were a total of 17 deaths in the trial, a majority of which occurred within the first four months of treatment. There were eight deaths among children randomized to receive four months of treatment and nine deaths among children randomized to receive six months of treatment, with two of the deaths among children randomized to receive four months of treatment occurring after week 16, when treatment was completed.<sup>34</sup>

The four-month regimen is something that programs can move to implement right away, as they should already have access to the tools used in the trial to determine minimal/ non-severe TB (smear microscopy and X-ray) and to treat minimal TB according to the four-month regimen. The medicines and formulations required for the four-month regimen are exactly the same as those already in use for the six-month standard of care—the continuation phase of treatment just ends two months earlier. A sub study to evaluate the palatability and acceptability of the FDCs, and to describe challenges administering treatment to children in the SHINE study, found that the FDCs compared favorably to other formulations, albeit with some practical challenges to administration identified, and drug manipulation required by caregivers to administer treatment to children who found the formulations bitter and poorly palatable.<sup>35</sup> Ongoing work by the SHINE investigators to define minimal TB when molecular tests are used as the initial test (as opposed to smear microscopy) in line with WHO guidelines, will be important for implementation.

The SHINE findings are consistent with a pattern observed in prior treatment shortening studies conducted in adults, whereby shorter regimens performed better in subgroups with less severe disease. A trial being planned in adults (SPECTRA-TB) will prospectively evaluate a “stratified” approach to TB treatment, whereby regimen durations are adapted based on risk factors for poor outcomes, including disease severity, similarly measured by smear grade/ Xpert cycle threshold and extent of cavitation on X-ray. For the first time in the years-long game of catch-up played between the pediatric and adult TB treatment research communities, the roles have been reversed with children in a position to benefit from a new treatment strategy ahead of adults.

#### **ACTG A5312/ INHindsight (NCT01936831)**

Findings from ACTG A5312, a phase IIa, seven-day **early bactericidal activity study**, suggest that higher doses of isoniazid (10–15 mg/kg vs. 5 mg/kg) can overcome low level resistance mediated by *InhA* mutations.<sup>36</sup> ACTG A5312 enrolled 59 participants, 43 with *InhA*-mediated isoniazid resistance and 16 with drug-sensitive TB. The investigators found the bactericidal activity of high-dose isoniazid (10–15 mg/kg) against *InhA*-mediated isoniazid-resistant TB was similar to the bactericidal activity of standard-dose isoniazid (5 mg/kg) against drug-susceptible TB. Though evidence from cohort studies suggest that high-dose isoniazid provides some treatment benefit to people with drug-resistant TB,

**Early bactericidal activity (EBA) studies** evaluate the number of viable colony-forming units (CFUs) in sputum samples— a measure of TB bacterial growth— typically over the course of 7-14 days, and serve as an indicator of a drug or drug combination's ability to kill TB bacteria.

*InhA* is a regulatory region that encodes an enzyme that is the primary target of active isoniazid, as well as ethionamide and prothionamide.

more direct data from ACTG A5312 provides reassurance and expands the evidence base for the inclusion of high-dose isoniazid (10–15 mg/kg) in the standardized shorter regimen, as recommended by the WHO for RR-/MDR-TB. The next stage of A5312, currently open to enrollment, will look at the bactericidal activity of isoniazid at 15–20 mg/kg against **KatG**-mediated strains of isoniazid-resistant TB, which are more prevalent and confer higher level resistance.<sup>37</sup> Longer term studies, like ACTG A5373/ FIRST, which is currently in development (see Table 2), will be necessary to determine the safety and tolerability of higher isoniazid doses.

### Pretomanid

Interim findings from the Nix-TB study (NCT02333799) submitted to the U.S. Food and Drug Administration (FDA) were covered in the 2019 Pipeline Report and have since been published in a peer-reviewed journal.<sup>38</sup> Six-months after the end of treatment with the Nix-TB regimen, also referred to as **BPaL**, 90% (98/109) of participants had a favorable treatment outcome (i.e., resolution of clinical disease and negative culture status). Two participants, one with positive cultures at month four and the other with positive cultures at month five, had their treatment extended by three months (to nine months total); all other participants received six months of treatment. There were 11 unfavorable outcomes, including seven deaths (six of which occurred during treatment), two relapses during follow up, one withdrawal of participant consent, and one participant loss to follow up.

A total of 62 participants (57%) experienced adverse events of grade three or higher during treatment. **Peripheral neuropathy** occurred in 88 participants (81%) and **myelosuppression** in 52 participants (48%). Most participants had a linezolid dose reduction or interruption during treatment. In fact, only 37 participants (34%) completed six months of linezolid without any interruption, and only 16 participants (15%) completed six months of linezolid without interruption at a total daily dose of 1,200 mg. Eight participants had their treatment interrupted for hepatic adverse events, though all eventually resumed and completed treatment. Outcomes and adverse events were consistent irrespective of HIV-status.<sup>39</sup> Follow up to 24 months after the end of treatment was recently completed. Final results are expected in early 2021. Limitations of the Nix-TB study, including the lack of a randomized control group, are well described elsewhere.<sup>40,41</sup> Given “important residual concerns about the likelihood and severity of adverse events, possible reproductive toxicity signals in the pre-clinical data, limitations in the study design, and the overall very low certainty of the evidence”, the Nix-TB regimen is currently only recommended by the WHO for a limited population and under **conditions of operational research**.<sup>42</sup>

Several ongoing and planned studies provide opportunities to gather additional data necessary to answer outstanding questions about the Nix-TB regimen and pretomanid: ZeNix (NCT03086486), evaluating different linezolid doses (600 mg vs. 1,200 mg) and durations (two vs. six months) within the Nix-TB regimen,

**KatG** is a gene region that encodes an enzyme responsible for converting isoniazid to its biologically active form.

**BPaL** is the Nix-TB regimen, composed of 6-9 months of bedaquiline, pretomanid, and linezolid.

**Peripheral neuropathy**: nerve damage in the extremities, which can cause numbness and pain starting in the fingers and toes, spreading upwards.

**Myelosuppression**: a reduction in the production of blood cells from the bone marrow. This can manifest as anemia (red blood cells; causing fatigue), neutropenia (white blood cells; increasing risk of severe infection), or thrombocytopenia (platelets; leading to easy bruising or bleeding).

**Conditions of operational research** require that National TB Programs monitor TB treatment more carefully than under program conditions and collect additional data on the safety and efficacy of medicines and/or treatment regimens not yet proven or endorsed for broader programmatic use, and for which additional research is needed.

completed enrollment in December 2019; TB-PRACTECAL (NCT02589782), comparing BPaL regimens (albeit with modified linezolid dosing) with or without the addition of a fourth drug (moxifloxacin or clofazimine) to the local standard of care, is expected to enter its second stage in November 2020; and Mylan's phase III study for which the protocol is still in development is poised to fill a critical data gap by evaluating both the Nix-TB (BPaL) and SimpliciTB (BPaMZ) regimens against the all-oral 9- to 12-month standardized shorter regimen<sup>\*</sup> for the treatment of rifampicin- and multidrug-resistant TB (see Table 2). In addition to ZeNix, other ongoing clinical trials, including TB-PRACTECAL and endTB (NCT02754765), are poised to contribute additional data necessary to optimize linezolid dosing in the context of Nix-TB and other linezolid-containing regimens. In TB-PRACTECAL, linezolid will be administered at 600 mg daily for the first four months and then at 300 mg daily for the remaining two months. Similarly, the endTB trial 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.

Pediatric trial formulations of pretomanid have been developed and tested in healthy adult volunteers. In close collaboration with the TB Alliance, the IMPAACT network is developing a protocol to evaluate the pharmacokinetics and safety of a single dose of pretomanid in children receiving treatment for drug-resistant TB (CAP 556). This single dose study is expected to help inform the doses that will be evaluated in a future pediatric extended dosing study, which can only be initiated once a reproductive safety study is completed in male adults (PaSEM; NCT04179500; expected to start May 2021).

### Bedaquiline

The WHO conducted an analysis of non-randomized data from the South African National TB Program to compare 891 patients treated using the all-oral 9- to 12-month standardized shorter regimen (with bedaquiline given in place of the injectable agent) and 987 patients treated using the injectable-containing 9- to 12-month regimen. The all-oral 9- to 12-month regimen demonstrated improved treatment outcomes (73% vs. 60%; aOR success versus failure/recurrence: 2.1, 95% confidence interval [CI]: 1.1–4.0; aOR success versus death: 1.6, 95% CI: 1.2–2.1; aOR success versus failure/recurrence/death: 1.7, 95% CI: 1.3–2.2; and aOR success versus all unfavorable outcomes: 1.9, 95% CI: 1.6–2.4) and a reduction in loss to follow up (aOR loss to follow up versus all other outcomes: 0.5, 95% CI: 0.4–0.7) compared to the injectable-containing 9- to 12-month regimen.<sup>43</sup> These data underlie the changes made to the WHO treatment guidelines for RR-/MDR-TB in 2020. The 2020 update to the *WHO Consolidated Guidelines on Tuberculosis*,

An **aOR or adjusted odds ratio** is used to measure the strength of association between an exposure/intervention and outcome of interest, taking into account other variables that may influence the strength of association. An odds ratio greater than one demonstrates an association, with higher numbers meaning greater/stronger association; an odds ratio equal to one means there is no association; and an odds ratio less than one means there are low odds of there being an association.

<sup>\*</sup> Nine- to 12-months of clofazimine, levofloxacin (or moxifloxacin), ethambutol, and pyrazinamide; supplemented by bedaquiline for the first six months and high dose isoniazid, ethionamide (or prothionamide) for the first four- to six-months.

*Module 4: Treatment – Drug Resistant Tuberculosis Treatment* recommends the use of bedaquiline in place of the injectable agent in the 9- to 12-month standardized regimen and supports the use of other all-oral bedaquiline-based shorter regimens under conditions of operational research, making bedaquiline a core component of all regimens for the treatment of drug-resistant TB.<sup>44</sup>

STREAM II, which offers a randomized comparison of the bedaquiline vs. injectable-containing 9- to 12-month standardized regimens completed enrollment in January 2020. Results from STREAM II (18 months post randomization) are expected in late 2021.<sup>45</sup> Results from a number of other studies of bedaquiline-based drug-resistant TB treatment shortening regimens with the potential to further simplify and improve the standard of care are expected around the same time or shortly thereafter (see Table 2).

Data collected by the South African Medical Research Council on a cohort of 108 individuals with drug-resistant TB (81% HIV-positive), of whom 58 were treated with a bedaquiline-containing regimen during pregnancy between 2013 and 2017 in KwaZulu-Natal, also resulted in changes to the WHO treatment guidelines for RR-/MDR-TB in 2020. In terms of overall maternal outcomes, favorable treatment outcomes were reported in 72 (67%) women. Eight women died after childbirth (median 67 days after childbirth), with four deaths related to TB disease. In terms of overall pregnancy outcomes, 91% of the 109 fetuses (includes one set of twins), were born alive, but only 57 (52%) pregnancies had a favorable outcome according to the study criteria, which required pregnancies be carried to full term ( $\geq 37$  weeks), babies be born with normal birth weight ( $\geq 2,500$  grams), and babies be born alive and live for at least 28 days. Women living with HIV had a higher risk of unfavorable pregnancy outcome, with nine of 10 fetal deaths among pregnant women living with HIV. In terms of overall infant outcomes after 12 months (available for 86 of 99 live infants), favorable infant outcomes were documented in 72 (84%) of the liveborn infants. In terms of the impact of bedaquiline on all outcomes, Loveday et al. found no difference in pregnancy outcomes between women whose fetuses were exposed to bedaquiline in utero compared to those that were unexposed (49% vs. 57% favorable outcome,  $P = .312$ ). However, they did find a higher proportion of newborns exposed to bedaquiline in utero had a birth weight  $< 2,500$  grams (45% vs 24%;  $P = .034$ ). Finally, of infants exposed to bedaquiline, Loveday et al. found that 36 (88%) had a favorable infant outcome, compared to 36 (80%) infants not exposed ( $P = .136$ ). These data are limited but suggest that bedaquiline can be safely used during pregnancy, and is associated with good treatment, pregnancy, and infant outcomes.<sup>46</sup> The 2020 update to the *WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment – Drug Resistant Tuberculosis Treatment* supports the use of bedaquiline for the treatment of drug-resistant TB among pregnant women in the context of individualized regimens designed to include at least four medicines with established safety profiles and low teratogenic risks.<sup>47</sup>

**P values** measure statistical significance, or the likelihood that a detected difference between two groups or interventions is real rather than due to chance. A P-value equal to or less than .05 represents statistical significance.

In 2020, the WHO also recommended bedaquiline for use in children down to six years old.<sup>48</sup> Based on data from Janssen C211 (NCT02354014), in August 2019, the FDA approved bedaquiline for use in adolescents (12 ≤ 18 years old) and in May 2020, approved Janssen's 20 mg bedaquiline dispersible tablet for children 5 < 12 years old weighing at least 15 kg. C211 is currently recruiting children to the third of four cohorts (2 ≤ 5 years old) from clinical sites in Russia, South Africa, Uganda, the Philippines, and Mozambique.<sup>49</sup> IMPAACT P1108 (NCT02906007), which provides additional PK and safety data, including in children living with HIV, is currently enrolling its final two cohorts in parallel, children aged 2 < 6 years old and 0 < 2 years old.

### Delamanid

Given the disappointing results from Otsuka's Study 213 (NCT01424670), covered in the 2019 Pipeline Report, and the continued limited use of delamanid in program settings, few new data have emerged in the last year. During the 50th Union World Conference on Lung Health in 2019, the endTB project reported data on 1,082 patients that initiated a bedaquiline and/or delamanid-containing regimen as part of its observational study (NCT03259269) and that had final treatment outcomes available at the time of presentation, among which 32% of participants received a delamanid-containing regimen and 3% received a regimen containing both delamanid and bedaquiline. Overall, 77.6% (840/1,082) of participants achieved a favorable treatment outcome. Poorer outcomes were documented among people with more extensive TB disease (3+ smear grade with cavitation) and co-infected with hepatitis C virus.<sup>50</sup> In 2020, Seung et al. published six-month culture conversion data from 325 of 631 (51.5%) participants in the endTB observational study that initiated treatment with a delamanid-containing regimen. Among the 325 participants that initiated treatment with a delamanid-containing regimen and that had a positive baseline culture, 261 (80%) experienced culture conversion within six months (an interim marker of favorable treatment outcome) despite having more extensive drug resistance, comorbidities, including diabetes, hepatitis C and advanced HIV disease, and reporting drug or alcohol use.<sup>51</sup>

The endTB observational study also found delamanid and bedaquiline to be safe, with clinically relevant **QT-prolonging events** occurring infrequently (2.8%) even with concomitant use of multiple QT-prolonging drugs,<sup>52</sup> and no difference in the risk of QT-prolongation among patients who received bedaquiline and delamanid for longer than six months or in combination.<sup>53</sup> Based on these data and results from ACTG A5343/ DELIBERATE (NCT02583048), the latter of which was covered in the 2019 Pipeline Report, the 2020 update to the WHO guidelines for the treatment of drug-resistant TB says, "the data suggest no additional safety concerns regarding concurrent use of bedaquiline and delamanid" and that "[b]oth medicines may be used concurrently in patients who have limited other treatment

**QT prolongation** is a disturbance in the heart's electrical activity that can lead to serious (and sometimes fatal) rhythmic disturbances.

options available to them, provided that sufficient monitoring (including baseline and follow up ECG and electrolyte monitoring) is in place”.<sup>54</sup> Still, until additional data from trials of delamanid-containing regimens become available (see Table 2), delamanid is likely to remain categorized by the WHO 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). Future publications on end-of-treatment outcomes are expected from the endTB observational study in 2021, as are initial non-randomized data collected as part of the South African National TB Program’s Delamanid Clinical Access Program (D-CAP).<sup>55</sup>

Based on pediatric pharmacokinetic and safety studies conducted by Otsuka (Otsuka 232/ 233; NCT01856634/ NCT01859923), the WHO recommends that delamanid can be used to treat children down to three years old. In September, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion for the use of delamanid to treat pulmonary multidrug-resistant TB in adolescents and children weighing at least 30 kg.<sup>56</sup> Otsuka is expecting a positive EMA CHMP opinion for children weighing less than 30 kg in the coming months, and approval of its dispersible delamanid formulation in 2021.<sup>57</sup> Meanwhile, the IMPAACT network is currently enrolling P2005 (NCT03141060), a pharmacokinetic and safety study of delamanid administered in combination with an all oral regimen, which will provide data in HIV-positive children and may help to further refine delamanid dosing, especially in children 0-2 years old.

**Table 1. TB Medicines Abbreviations Cheat Sheet**

<b>amikacin</b>	Am	<b>linezolid</b>	Lzd, Lz
<b>bedaquiline</b>	J, Bdq	<b>meropenem</b>	Mpm
<b>clofazimine</b>	C, Cfz	<b>moxifloxacin</b>	M, Mfx, Mx
<b>cycloserine</b>	Cs	<b>p-aminosalicylic acid</b>	PAS
<b>delamanid</b>	D, Dlm	<b>pretomanid</b>	Pa
<b>delpazolid</b>	Dzd	<b>prothionamide</b>	Pto
<b>ethambutol</b>	E	<b>pyrazinamide</b>	Z, PZA
<b>ethionamide</b>	Eto	<b>rifabutin</b>	B
<b>high dose</b>	Hd	<b>rifampicin</b>	R, RIF
<b>imipenem-cilastatin</b>	Imp-Cln	<b>rifapentine</b>	P, RPT
<b>injectable agent</b>	IA	<b>streptomycin</b>	S
<b>isoniazid</b>	H, INH	<b>sutezolid</b>	Stz
<b>kanamycin</b>	K, Kan	<b>terizidone</b>	Trd, Tzd
<b>levofloxacin</b>	L, Lfx, Lx		

Table 2. Trials to Shorten Treatment for TB

Study Name	Experimental Arms [Control]	For Treatment of	Number of Participants	Phase	Estimated Completion Date
<b>Nix-TB</b> <a href="#">NCT02333799</a>	JPaL <sub>1200</sub> [none]	TI/NR MDR-TB Pre-XDR-TB XDR-TB	109	III	Results presented 2019 and published 2020
<b>TBTC Study 31/ A5349</b> <a href="#">NCT02410772</a>	2HPZE/2HP 2HPZM/2HPM [2HRZE/4HR]	DS-TB	2,516	III	Results presented 2020
<b>NEXT</b> <a href="#">NCT02454205</a>	6-9JLzLxZ (Eto or H <sub>Hd</sub> or Tzd) [12-24mo IA-containing regimen]	MDR-TB	154	III	Dec 2020 [fully enrolled]
<b>endTB</b> <a href="#">NCT02754765</a>	9JLzMZ 9JLzLxCZ 9JLzLxDZ 9DLzLxCZ 9DMCZ [9-20mo SOC]	MDR-TB	750	III	Apr 2021
<b>MDR-END</b> <a href="#">NCT02619994</a>	9-12DLzLxZ [20mo IA-containing regimen]	MDR-TB	238	II/III	Jun 2021
<b>SUDOCU</b> <a href="#">NCT03959566</a>	3JDMStz <sub>600</sub> 3JDMStz <sub>1200</sub> 3JDMStz <sub>600</sub> BID 3JDMStz <sub>800</sub> BID [3JDM]	DS-TB	75	IIb	Oct 2021
<b>RIFASHORT</b> <a href="#">NCT02581527</a>	2HR <sub>1200</sub> ZE/2HR <sub>1200</sub> 2HR <sub>1800</sub> ZE/2HR <sub>1800</sub> [2HRZE/4HR]	DS-TB	654	III	Dec 2021
<b>ZeNix</b> <a href="#">NCT03086486</a>	6JPaLz <sub>1200</sub> 2JPaLz <sub>1200</sub> /4JPa 6JPaLz <sub>600</sub> 2JPaLz <sub>600</sub> /4JPa [none]	TI/NR MDR-TB Pre-XDR-TB XDR-TB	180	III	Dec 2021 [fully enrolled]
<b>TRUNCATE-TB</b> <a href="#">NCT03474198</a>	2HR <sub>Hd</sub> ZELz 2HR <sub>Hd</sub> ZEC 2HPZLzLx 2HZELzJ [2HRZE/4HR]	DS-TB	675	II/III	Dec 2021 [fully enrolled]
<b>SimpliciTB</b> <a href="#">NCT03338621</a>	4JPamZ [2HRZE/4HR]	DS-TB MDR-TB	455	IIc	Feb 2022 [fully enrolled]
<b>DECODE</b> <a href="#">NCT04550832</a>	4JDMdZd <sub>400</sub> 4JDMdZd <sub>800</sub> 4JDMdZd <sub>1200</sub> 4JDMdZd <sub>800</sub> BID [4JDM]	DS-TB	75	IIb	May 2022

Study Name	Experimental Arms [Control]	For Treatment of	Number of Participants	Phase	Estimated Completion Date
<b>STREAM II</b> <u>NCT02409290</u>	4JCLxEZH <sub>Hd</sub> Pto/5JCLxEZ 2JCLxZH <sub>Hd</sub> K/4JCLxZ [4CLxEZH <sub>Hd</sub> KPto/5CLxZE]	MDR-TB	588	III	Jul 2022 [fully enrolled]
<b>APT</b> <u>NCT02256696</u>	2PaBHZ/1PaBH 2PaRHZ/1PaRH [2HRZE/1HR]	DS-TB	183	II	Sep 2022
<b>endTB-Q</b> <u>NCT03896685</u>	6JDLzC 9JDLzC [9-20mo SOC]	FQ-R-MDR-TB	324	III	Dec 2022
<b>BEAT TB</b> <u>CTRI/2019/01/017310</u>	6-9JDLzC [none]	Pre-XDR-TB XDR-TB	165	III	Jan 2023
<b>TB PRACTECAL</b> <u>NCT02589782</u>	6JPaMLz 6JPaLzC 6JPaLz (Lz <sub>600</sub> for first 4 months followed by Lz <sub>300</sub> ) [9-20mo local SOC]	MDR-TB Pre-XDR-TB XDR-TB	630	II/III	Feb 2023
<b>BEAT-Tuberculosis</b> <u>NCT04062201</u>	6JDLz (Lx, C or both) [9-12mo SOC]	RR-TB MDR-TB FQ-R-MDR-TB	400	III	Mar 2023
<b>ACTG A5356</b>	1JDCLz <sub>1,200 QD</sub> / 5JDCLz <sub>1,200 T1W</sub> JDCLz <sub>600</sub> (J <sub>200</sub> for first 8 weeks followed by J <sub>100</sub> ; D <sub>200</sub> daily throughout; C <sub>300</sub> for first 2 weeks followed by C <sub>100</sub> ) [none]	RR-TB, MDR-TB, pre-XDR-TB, XDR-TB	132	II	Protocol in development
<b>ACTG A5362/ CLO-Fast</b>	2CHPZE/1CHPZ (C <sub>300</sub> for first 2 weeks followed by C <sub>100</sub> ) [2HRZE/4HR]	DS-TB	185	IIc	Protocol in development
<b>ACTG 5373/ FIRST</b>	6H <sub>Hd</sub> RZE [2RZELx/4RLx]	HR-TB	556	III	Protocol in development
<b>ACTG A5384/ IMAGINE-TB</b>	6R <sub>Hd</sub> H <sub>Hd</sub> Lz [2HRZE/7HR]	TBM	300	II	Protocol in development
<b>DRAMATIC</b>	4JDCLxLz <sub>Bwk</sub> 6JDCLxLz <sub>Bwk</sub> 8JDCLxLz <sub>Bwk</sub> 10JDCLxLz <sub>Bwk</sub>	MDR-TB	180	II	Protocol in development
<b>PRET-TBZ-3001</b>	6JPaMZ 6JPaLz <sub>600</sub> [9-12mo SOC]	RR-TB MDR-TB	351	III	Protocol in development

Study Name	Experimental Arms [Control]	For Treatment of	Number of Participants	Phase	Estimated Completion Date
<b>TBTC CRUSH TB</b>	2JMZB/2JMB 2JMZD/2JMD [2HRZE/4HR]	DS-TB	270	IIc	Protocol in development
<b>TBTC SPECTRA TB</b>	2HPZE 2HPZE/2HP 2HPZE/4HP [2HRZE/4HR]	DS-TB	1,800	III	Protocol in development
*Unless otherwise indicated (i.e., experimental dosing indicated by numbers in subscript), numbers represent the duration of treatment in months (mo). Letters represent the individual drugs comprising each regimen (see Table 1). Slashes are used to separate intensive and continuation phases of treatment.					
BID: twice daily dosing DS-TB: drug-sensitive TB FQ-R: fluoroquinolone-resistant HR-TB: isoniazid mono-resistant TB MDR-TB: multidrug-resistant TB		Pre-XDR-TB: pre-extensively drug-resistant TB QD: once daily dosing RR-TB: rifampicin-resistant TB RSA: South Africa SOC: standard of care		TBM: tuberculous meningitis TI/NR: treatment-intolerant or non-responsive TIW: thrice weekly dosing XDR-TB: extensively drug-resistant TB	

## UPDATES ON NEW DRUGS IN CLINICAL DEVELOPMENT

With the entry of TBAJ-876 and GSK-286 into phase I studies in June and October 2020, respectively, there are now 14 compounds in clinical development for TB (see Table 3). Eight of these compounds pursue five novel targets:

1. **QcrB** (cytochrome bc complex), an essential component of the respiratory electron transport chain required for ATP synthesis;
2. **DprE1** (decaprenylphosphoryl-  $\beta$ -D-ribose 2-epimerase), an enzyme important for cell wall synthesis;
3. **LeuRS** (leucyl-tRNA synthetase), an enzyme important for protein synthesis;
4. **GyrB** (DNA gyrase subunit B), which plays an essential role in DNA replication; and
5. Target not yet fully determined, necessary for cholesterol catabolism.

Compounds that have new targets and/or mechanisms of action are important for constructing effective regimens and staying ahead of drug resistance. The pipeline of compounds in clinical development also includes three oxazolidinones, one riminophenazine, and one diarylquinoline, of interest as potential advantaged alternatives to the existing TB medicines, linezolid, clofazimine, and bedaquiline, respectively. Table 3 and the text that follows provide updates on each drug organized by mechanism of action.

Table 3. Drugs in Clinical Development for TB

Drug	Class	Mechanism of Action	Sponsor	Phase	Clinical Trial(s)
<b>ENERGY PRODUCTION</b>					
bedaquiline	Diarylquinoline	Inhibits ATP synthase and bacterial respiration	Janssen	III	see Table 2
pyrifazimine (TBI-166)	Riminophenazine	Inhibits ion transport and bacterial respiration	IMM/CAMS/PUMC	I	<a href="#">ChiCTR1800018780</a>
<b>NEW ▶</b> TBAJ-876	Diarylquinoline	Inhibits ATP synthase and bacterial respiration	TB Alliance	Ia/Ib	<a href="#">NCT04493671</a>
telacebec (Q203)	Imidazopyridine	Inhibits ATP synthesis (QcrB) and bacterial respiration	Qurient/ Infectex	Ila	<a href="#">NCT02530710</a> <a href="#">NCT02858973</a> <a href="#">NCT03563599</a>
<b>CELL WALL SYNTHESIS</b>					
BTZ-043	Benzothiazinone	Inhibits cell wall synthesis (DprE1)	University of Munich/DZIF	Ib/Ila	<a href="#">NCT03590600</a> <a href="#">NCT04044001</a>
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/ Ila	<a href="#">NCT03036163</a> <a href="#">NCT03423030</a> <a href="#">NCT03776500</a> <a href="#">NCT03334734</a>
OPC-167832	Carbostyryl	Inhibits cell wall synthesis (DprE1)	Otsuka	Ib/Ila	<a href="#">NCT03678688</a>
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	<a href="#">NCT01585636</a> <a href="#">NCT00866190</a> <a href="#">NCT01358162</a> <a href="#">NCT01218217</a> <a href="#">NCT01785186</a>
TBA-7371	Azaindole	Inhibits cell wall synthesis (DprE1)	TB Alliance/ GMRI	Ila	<a href="#">NCT03199339</a> <a href="#">NCT04176250</a>

◀ NEW

Drug	Class	Mechanism of Action	Sponsor	Phase	Clinical Trial(s)
<b>PROTEIN SYNTHESIS</b>					
delpazolid (LCB01-0371)	Oxazolidinone	Inhibits protein synthesis (23S ribosome)	LegoChem Biosciences	IIb	<a href="#">NCT01554995</a> <a href="#">NCT01842516</a> <a href="#">NCT02540460</a> <a href="#">NCT02836483</a> <a href="#">NCT04550832</a>
sutezolid (PNU-100480)	Oxazolidinone	Inhibits protein synthesis (23S ribosome)	Sequella/TB Alliance	IIb	<a href="#">NCT00871949</a> <a href="#">NCT00990990</a> <a href="#">NCT01225640</a> <a href="#">NCT03199313</a> <a href="#">NCT03959566</a>
TBI-223	Oxazolidinone	Inhibits protein synthesis (23S ribosome)	TB Alliance/ IMM	Ia	<a href="#">NCT03758612</a>
GSK3036656 (GSK-656)	Oxaborole	Inhibits protein synthesis (LeuRS)	GSK	IIa	<a href="#">NCT03075410</a> <a href="#">NCT03557281</a>
<b>DNA SYNTHESIS</b>					
SPR720	Benzimidazole	Inhibits bacterial DNA synthesis (GyrB)	Spero Therapeutics/ GMRI	Ia/Ib	<a href="#">NCT03796910</a>
<b>CHOLESTEROL CATABOLISM</b>					
<b>NEW ▶</b> <a href="#">GSK2556286 (GSK-286)</a>		Inhibits cholesterol catabolism (target to be determined)	GSK	Ia/Ib	<a href="#">NCT04472897</a>
<p>*Phase listed represents the most advanced trial that is ongoing/completed.</p> <p>CAMS: Chinese Academy of Medical Sciences  DZIF: German Center for Infection Research  GMRI: Bill &amp; Melinda Gates Medical Research Institute  GSK: GlaxoSmithKline  iM4TB: Innovative Medicines for Tuberculosis  IMM: Institute of Materia Medica, China  PUMC: Peking Union Medical College, China</p>					

◀ NEW

## Energy Production

### Pyrifazimine (TBI-166)

No new developments to report—a phase I study of pyrifazimine opened in China in January 2018. The study sponsors have not responded to requests for additional information, including regarding the current status of the phase I study or future plans.

### Telacebec (Q203)

In March 2020, results from Qurient's 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 were published in a letter to the editor of the New England Journal of Medicine. The investigators determined that telacebec demonstrated good dose-dependent EBA, with increasing doses of telacebec associated with greater reductions in viable TB bacteria measured in sputum, and reported acceptable adverse-event rates equally distributed among all groups.<sup>58</sup> A phase IIb treatment shortening study to evaluate telacebec, given in combination with respiratory chain modulators such as bedaquiline and clofazimine, to people with drug-resistant TB is being planned.<sup>59</sup>

**Early bactericidal activity studies** are typically conducted over the course of 7-14 days in people with TB disease, and used to evaluate a drug's ability to kill TB when administered alone or in combination with other TB drugs.

### TBAJ-876

In June 2020, TBAJ-876, a bedaquiline analogue, became the second member of the diarylquinoline class to enter clinical trials. In pre-clinical studies, TBAJ-876 demonstrated higher potency, less lipophilicity (fat-solubility), and less inhibition of a key cardiac potassium channel protein than bedaquiline.<sup>60</sup> These characteristics may reduce drug accumulation in the tissues and the risk of QT prolongation—a safety concern that has hampered the introduction and broader use of bedaquiline. The TB Alliance is conducting a combined phase Ia single ascending dose (SAD) with food-effect and phase Ib multiple ascending dose (MAD) study to evaluate the safety, tolerability, and pharmacokinetics of TBAJ-876 administered at different doses (10–400 mg) for 28 days to healthy volunteers in the United States. The phase Ia portion of the study is in progress with phase Ib expected to start in March 2021.<sup>61</sup> Results are expected after January 2022.

## Cell Wall Synthesis

### BTZ-043

A phase Ib/IIa 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 opened in South Africa in November 2019. Recruitment was slowed down by COVID-19, and results are now expected by mid-2021.<sup>62</sup>

### Macozinone (PBTZ169)

A phase IIa EBA study conducted by Nearmedic in Russia was completed in 2018 after enrolling 16 participants with drug-sensitive TB. Macozinone was administered at different doses (160–640 mg) once daily for 14 days and compared to a 600 mg dose of isoniazid. The study revealed statistically significant

early bactericidal activity in the group administered 640 mg macozinone per day, and no cases of death or severe adverse events related to the study drug.<sup>63</sup> The phase Ib MAD study conducted by Innovative Medicines for Tuberculosis (iM4TB) in Lausanne was closed in April 2020 before enrolling the final cohort due to the rapidly evolving COVID-19 pandemic situation. Analysis is ongoing (participants were dosed up to 600 mg daily) and iM4TB reports that the results of the MAD trial show good tolerability and an acceptable absorption profile.<sup>64</sup> iM4TB is now in the early stages of planning a phase IIa EBA study to be conducted in Tanzania.

### OPC-167832

Stage one of the ongoing phase Ib/IIa MAD/EBA study to evaluate the safety, tolerability, and pharmacokinetics of OPC-167832 administered at 3 mg, 10 mg, 30 mg, and 90 mg once daily was completed in 2020. Stage two, to evaluate the safety, tolerability, pharmacokinetics, and early bactericidal activity of OPC-167832 administered at 30 mg once daily in combination with 300 mg delamanid or bedaquiline (dosed daily at 700 mg on day one, 500 mg on day two, and 400 mg on days three to 14), and both 300 mg delamanid and bedaquiline (dosed according to the aforementioned schedule) for 14 days to participants with drug-sensitive TB, is expected to open in January 2021.<sup>65</sup> Results are expected by the end of 2021.

### TBA-7371

Under a non-exclusive license from the TB Alliance to develop TBA-7371, the GMRI opened a phase IIa EBA study in South Africa in January 2020. The phase IIa study to evaluate the safety, pharmacokinetics, and early bactericidal activity of TBA-7371 administered as an oral suspension at different doses (up to 400 mg daily) for 14 days to participants with drug-sensitive TB was temporarily paused due to COVID-19, but re-opened to enrollment in August 2020. Results are expected in 2021.

## Protein Synthesis

### Delpazolid (LCB01-0371)

The phase IIa EBA study that opened in South Korea in 2016 to evaluate the safety, pharmacokinetics, and bactericidal activity of delpazolid over the course of 14 days in people with drug-sensitive TB produced final results in 2020. LegoChem Biosciences found the EBA achieved with delpazolid in the 800 mg QD, 400 mg BID, 800 mg BID, and 1200 mg QD groups to be 22.8%, 26.4%, 22.8%, and 10.4%, respectively, of the EBA achieved with isoniazid, rifampicin, pyrazinamide, and ethambutol combined (HRZE).<sup>66</sup>

**QD** is short for “*quaque die*” which is Latin for “once a day” and is used as short form to indicate when a medicine is given once daily.

**BID** is short for “*bis in die*” which is Latin for “two times a day” and is used as short form to indicate when a medicine is given twice daily.

To gauge how the EBA of delpazolid might compare to the EBA of other oxazolidinones in use or in development for TB, we calculated the percent of the EBA of HRZE achieved by linezolid and sutezolid in 14-day EBA studies conducted previously in South Africa. The EBA achieved with linezolid ranged from 14% to 62% of the EBA achieved with HRZE, and the EBA achieved with sutezolid ranged from 35% to 45% of the EBA achieved with HRZE.<sup>67,68</sup> Delpazolid is cleared from plasma more rapidly than linezolid,<sup>69</sup> which may lower the risk of mitochondrial toxicity, the symptoms of which include peripheral neuropathy, given that the toxicity has been associated with the trough levels of the oxazolidinone.<sup>70</sup>

LegoChem Biosciences is working with the PanACEA consortium to conduct a phase IIb study of delpazolid at four different doses (400 mg QD, 800 mg QD, 1,200 mg QD, 800 mg BID) given for four months in combination with a backbone regimen of bedaquiline, delamanid, and moxifloxacin, and compared to four months of bedaquiline, delamanid, and moxifloxacin alone (DECODE; NCT04550832). DECODE is scheduled to open in South Africa and Tanzania by the end of 2020 and will enroll people with uncomplicated drug-sensitive pulmonary TB. Participants who achieve sputum culture conversion by eight weeks and remain sputum culture negative at week 16 will discontinue TB therapy and be followed for relapse up to 12 months post randomization. Participants who do not achieve sputum culture conversion by eight weeks or do not remain sputum culture negative until the end of therapy will be referred to the National TB Program for further treatment. Interim efficacy results are expected after August 2022 and will inform the safety, optimal dose, and efficacy of delpazolid administered in combination with bedaquiline, delamanid, and moxifloxacin for four months, and the approach to future evaluations of delpazolid-containing regimens in subsequent phase IIc and III trials for drug-sensitive and drug-resistant TB.<sup>71</sup>

### Sutezolid (PNU-100480)

The phase IIb dose-finding study, SUDOCU (NCT03959566), planned by the PanACEA network in collaboration with Sequella to evaluate the safety, pharmacokinetics, and exposure-response relationship of different doses of sutezolid (600 mg QD, 1,200 mg QD, 600 mg BID, 800 mg BID) administered for three months in combination with bedaquiline, delamanid, and moxifloxacin to participants with drug-sensitive TB was expected to open in South Africa and Tanzania in 2019. After some delays, the study is now expected to open in late 2020. The results are expected in October 2021 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.<sup>72</sup>

## TBI-223

The TB Alliance completed a phase Ia SAD study of the safety, tolerability, and pharmacokinetics of TBI-223 in March 2020, investigating doses up to 2,600 mg delivered using orally administered capsules, as well as immediate and sustained release tablets in healthy volunteers. A phase Ib MAD study, expected to open in the first quarter of 2021, will investigate three dose escalations in healthy volunteers.<sup>73</sup>

## GSK3036656 (GSK-656)

No new developments to report—the 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 is recruiting. Results are expected in mid-2021.

## DNA Synthesis

### SPR720

Spero Therapeutics completed a phase Ia/Ib SAD/MAD study of SPR720 in late 2019, finding doses up to 1,000 mg administered for 14 days safe and well tolerated among healthy volunteers. The GMRI—which received an exclusive license in 2019 to develop, manufacture, and commercialize SPR720 for TB in low- and middle- income countries<sup>74</sup>—is currently working to fill pre-clinical data gaps for SPR720 against TB, while Spero Therapeutics pursues development of the compound for the treatment of non-tuberculous mycobacterial (NTM) infections. The GMRI is hoping to initiate a phase IIa EBA study to evaluate the safety, tolerability, pharmacokinetics, and early bactericidal activity of SPR720 within the next two years.<sup>75</sup>

**Cholesterol catabolism:** the process through which cholesterol is broken down into more simple metabolites that are used by *Mycobacterium tuberculosis* to regulate metabolic pathways such as those that generate energy and cell wall lipids.

## Cholesterol Catabolism

### GSK2556286 (GSK-286)

In the fourth quarter of 2020, GSK opened a first time in human (FTIH) study (a phase Ia/Ib SAD/MAD study) to evaluate the safety, tolerability, and pharmacokinetics of single and repeat ascending doses of GSK2556286 in healthy adults. GSK2556286 is a first-in-class compound with a novel mechanism of action related to **cholesterol catabolism**, that in pre-clinical studies demonstrated ability to penetrate **TB lesions** and to reduce relapse rates in mice.<sup>76</sup> Results from the FTIH study are expected in November 2021.

**TB lesions** develop as a result of the body's immune response to surround and wall off TB bacteria in the lungs.

## THE FUTURE OF TB DRUG AND REGIMEN DEVELOPMENT

A number of factors need to be considered when designing a treatment regimen for TB, including to inform the optimal dose, duration, and combination of medicines. Primary among these considerations are drug safety, mechanism of action, synergistic activity and/or absence of interaction with other TB medicines, and ability to reach and kill subpopulations of TB bacteria that differ in metabolic state (based on the microenvironment and presence of antibacterial metabolites in the tissues and lesions where TB bacteria reside in the body).<sup>77</sup> Innovations in pre-clinical research and translational models for TB (informed and continuously refined by pre-clinical and clinical data) have resulted in a variety of tools increasingly capable of accelerating and de-risking clinical trials by predicting the combined effects of these considerations earlier in the development pathway.

Examples of pre-clinical tools include in vitro assays (e.g., growth inhibitory and time kill assays, the hollow fiber system [HFS]) and in vivo models (e.g., mouse, rabbit, non-human primate). Examples of clinical and translational tools that can be used to integrate relevant physiological and pharmacological relationships between host, drug(s), and bacteria to enable prediction of clinical outcomes include: plasma pharmacokinetic studies, to determine plasma concentration, tissue distribution, and to inform dosing; lesion PK studies, to determine whether a new drug is likely to reach site(s) of disease; immune system quantification/ bacterial growth dynamics, to model the impact of host adaptive immune responses on the treatment effect; monotherapy and combination pharmacokinetics-pharmacodynamics models, to link drug concentration to drug effect and define optimal drug combinations; and resistance models, to incorporate mechanisms related to the emergence of resistance to treatment overtime.<sup>78</sup>

Additionally, innovations that are being proposed and trialed in the clinic, especially in phase II studies, are expected to generate more robust data capable of better informing the selection of regimens for further evaluation in phase III trials by addressing what has been coined the “trilemma”—dose, combination, duration—of TB regimen development.<sup>79</sup> Examples of innovative clinical trial designs and elements, include: phase IIa 14+14 studies, to measure the EBA of a drug at different doses alone and in combination with other drugs; phase IIb studies with intensive sputum sampling and longitudinal modeling of quantitative bacteriology, to assess time to culture conversion and/or positivity (rather than a static/ binary eight-week culture conversion endpoint); multi-arm multi-stage (MAMS) designs, which allow testing of a broad range of combinations, dose levels, and durations without requiring a large sample size; and “selection trial with extended post-treatment follow-up” or STEP (phase IIc) designs, wherein follow up data on relapse are collected in addition to data on culture conversion.<sup>80,81</sup> Innovative approaches to phase IIb and IIc trials in particular, attempt to correct for the existing lack of direct measures of TB treatment response and adequate and reliable surrogate markers of long-term clinical outcomes of interest (i.e., relapse free cure). TB biomarker studies are increasingly being embedded in clinical trials, with some promising assays for measuring treatment response in development (see *The Tuberculosis Diagnostics Pipeline Report: Advancing the Next Generation of Tools*, October 2020).

Initiatives like the GMRI PAN-TB Collaboration and IMI European Regimen Accelerator for Tuberculosis (ERA4TB)<sup>82</sup> and Academia and Industry United Innovation and Treatment for Tuberculosis (UNITE4TB)<sup>83</sup> are actively or soon to undertake pre-clinical evaluations and modeling exercises to determine which compounds will be taken forward, at what doses, in which combinations, for what durations, and using which phase II designs. Publicly funded research networks, such as: the AIDS Clinical Trials Group (ACTG),

with its proposed RAD-TB phase IIa+ adaptive, dose-ranging, six-week platform trial;<sup>84</sup> the Tuberculosis Trials Consortium (TBTC), with its CRUSH-TB phase IIb platform trial in protocol development; and the Pan-African Consortium for the Evaluation of Anti-tuberculosis Antibiotics (PanACEA), with its ongoing use of MAMS and STEP (phase IIb/c) designs, are also advancing innovative approaches to phase II development.

The TB drug pipeline is increasingly dynamic, both in terms of drug candidates and stakeholders involved in conducting pre-clinical and clinical research. Moving forward, it's critically important that the multitude of efforts and approaches to TB drug and regimen development be complementary and collaborative in nature, and work to fill earlier the data gaps that plagued the development and introduction of the first new TB drugs in the last 40 years—bedaquiline, delamanid, and pretomanid. Data on drug-drug interactions and the earlier inclusion of special populations (e.g., children, pregnant women, people trying to avoid pregnancy, people who use drugs or alcohol or who are on opioid substitution therapy [OST], people with diabetes, and people with underlying liver and kidney issues) are critical to addressing access and equity, and to informing policy and clinical guidance. Efforts to accelerate clinical trials should not come at the expense of scientific rigor, and for novel chemical entities with new mechanisms of action, robust safety data will be of critical importance. Finally, community engagement, especially by new TB research initiatives and product sponsors, will be required to ensure ongoing and planned research efforts reflect and address the priorities and needs of TB-affected communities, and to continue to build TB research literacy among the TB-affected communities from which these new and innovative TB clinical trials will seek participation.

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