Pipeline Report » 2021

Tuberculosis Treatment

TAG
Treatment Action Group

The 2021 Tuberculosis Treatment Pipeline Report

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Introduction

The past year was one of forward momentum for regimens and drugs in clinical development for tuberculosis (TB). Three phase III trials of six-month regimens for drug-resistant TB produced results (TB-PRACTECAL, ZeNix, NEXT) and six new drugs advanced to the next phase of development (pyrifazimine, TBAJ-587, BVL-GSK098, OPC-167832, sutezolid, TBI-223).

Treatment Action Group's *2021 Tuberculosis Treatment Pipeline Report* provides an overview of the state of the clinical pipeline in three tables presented in order of proximity to reaching TB-affected communities. Table 1 covers recently completed trials, Table 2 covers ongoing and planned trials, and Table 3 provides a snapshot of the new drugs organized by the way they target the TB bacteria—for example, by attacking its ability to make energy, to build its cell wall, or to make critical proteins.

Results from Recently Completed Treatment Trials

Last year's *Pipeline Report* covered results from two landmark phase III trials (TBTC Study 31/ ACTG A5349 and SHINE) that successfully shortened treatment for drug-sensitive TB to just four months, offering an alternative to the six-month standard of care in place for the last 40 years.[1,2,3] The gains made in 2021 and covered here are focused on drug-resistant TB—improving the safety and tolerability of the BPaL regimen and expanding the options available and opportunity to benefit from a six-month regimen to people with rifampicin-resistant and multidrug-resistant TB (RR-/MDR-TB).

TBTC Study 31/ACTG A5349 (S31/A5349) is a phase III randomized controlled study conducted by Tuberculosis Trials Consortium (TBTC) and AIDS Clinical Trials Group (ACTG), which found a four-month regimen with rifapentine given in place of rifampicin and moxifloxacin given in place of ethambutol (2HPMZ/2HPM) noninferior to the six-month standard of care for adults and adolescents with drug-sensitive TB.

SHINE is a phase III randomized controlled study sponsored by University College London, which determined that the continuation phase of the standard six-month treatment regimen for drug-sensitive TB could be shortened from four to two months for children with non-severe TB (2HRZ[E]/2HR).

For more detailed information about S31/A5349 and SHINE, see TAG's *2020 TB Treatment Pipeline Report* and *An Activist's Guide to Shorter Regimens for Drug-Sensitive TB*, references 1 and 3.

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

Table 1. Recently Completed Trials

Study Name	Experimental Arms [Control]	For Treatment of	Number of Participants	Phase	Status
ZeNix NCT03086486	$6BPaLz_{1200}$ $2BPaLz_{1200}/4BPa$ $6BPaLz_{600}$ $2BPaLz_{600}/4BPa$ [none] *B_{200} daily for 8 weeks then B_{100} daily	TI/NR MDR-TB Pre-XDR-TB XDR-TB	181	III	Estimated to complete Dec 2021; Results at IAS
TB-PRACTECAL NCT02589782	6BPaMLz 6BPaLzC 6BPaLz [9–20mo local SOC] *Lz_{600} for first 4 months then Lz_{300}	MDR-TB Pre-XDR-TB XDR-TB	630	II/III	Estimated to complete Sept 2022; Preliminary results at Union
NEXT NCT02454205	6–9BLzLxTzdZ (Eto or H_{Hd}) [9–20mo IA-containing regimen]	MDR-TB	154	III	Completed Dec 2020 Results at SA TB Conference

- Pre-2021 definitions for pre-XDR-TB and XDR-TB are used in Table 1, i.e., pre-XDR-TB: MDR-TB with additional resistance to the fluoroquinolones or the injectable agents; XDR-TB: MDR-TB with additional resistance to the fluoroquinolones and the injectable agents; TI/NR = treatment-intolerant or non-responsive.
- Numbers at the beginning of each regimen or after the forward slash (for regimens with intensive and continuation phases) represent the duration of treatment in months; letters represent the individual drugs comprising each regimen.
- Subscripts indicate dosing in mg; Hd = high dose.

B = bedaquiline, Pa = pretomanid, Lz = linezolid, Lx = levofloxacin, M = moxifloxacin, Z = pyrazinamide, Eto = ethionamide, H = isoniazid, Tzd = terizidone (cycloserine), C = clofazimine, IA = injectable agent, IAS = International AIDS Society Conference on HIV Science (held July 2021), Union = Union World Conference on Lung Health (held Oct 2021), SA TB Conference = South African TB Conference (held June 2021)

ZeNix

In July 2021, at the 11th International AIDS Society (IAS) Conference on HIV Science, the TB Alliance presented results from ZeNix, a phase III study designed to improve the safety and tolerability of the BPaL regimen by optimizing the dose and duration of linezolid. ZeNix builds on the earlier Nix-TB study (covered in detail in the *2020 TB Treatment Pipeline Report*). In Nix-TB, 90% (98/109) of participants had a favorable outcome six months after the end of treatment. In terms of safety, 57% of participants treated with the

BPaL regimen in Nix-TB experienced adverse events of grade three or higher, with peripheral neuropathy reported among 81% and myelosuppression reported among 48% of participants; only 34% of participants were able to complete six months of linezolid (at any dose) without interruption.[4,5] Limitations of the Nix-TB study, including the lack of a randomized control group, are well described elsewhere.[6,7] Because of these limitations and the frequency and severity of adverse events in the Nix-TB trial, the BPaL regimen is currently recommended by the World Health Organization (WHO) for a limited population and under conditions of operational research.[8]

The ZeNix study included four arms with linezolid given at 600 mg or 1,200 mg daily for two or six months. In all four arms, bedaquiline was administered using a simplified dosing schedule (200 mg daily for eight weeks followed by 100 mg daily; bedaquiline is normally given at 400 mg daily for two weeks followed by 200 mg thrice weekly). ZeNix enrolled 181 participants from 11 sites across South Africa, Georgia, Moldova, and Russia. The study population included 36 (19.9%) people living with HIV, 112 (61.9%) people with cavities present on chest X-ray, and 85 (47%) and 75 (41.4%) people with pre-extensively drug-resistant TB (pre-XDR-TB) and extensively drug-resistant TB (XDR-TB), respectively, defined according to the pre-2021 definitions.

Overall, six months after the end of treatment 89.3% (158/181) of participants had a favorable outcome in the modified intention to treat (mITT) population. In the mITT population, 93.2% (41/44), 88.9% (40/45), 90.9% (40/44), and 84.1% (37/44) of participants who received linezolid at 1,200 mg for six months, 1,200 mg for two months, 600 mg for six months, and 600 mg for two months, respectively, had a favorable outcome six months after the end of treatment (similar to what was observed in Nix-TB). Among the unfavorable outcomes there was one treatment failure (in the linezolid 600 mg, two-month arm) and four confirmed relapses (two in the linezolid 1,200 mg two-month arm, one in the linezolid 600 mg six-month arm, and one in the linezolid 600 mg two-month arm). And four participants required re-treatment (two in the linezolid 1,200 mg six-month arm, one in the linezolid 600 mg six-month arm, and one in the linezolid 600 mg two-month arm) based on standard of care radiological tests in Russia; all four participants were sputum negative for TB at the time of re-treatment.[9]

In terms of safety, 24.9% (45/181) of participants overall experienced any grade 3 or higher adverse event. These were most pronounced in the linezolid 1,200 mg six-month arm, in which 37.8% (17/45) of participants experienced at least one adverse event of peripheral neuropathy and 22.2% (10/45) of participants experienced at least one event of myelosuppression. There were also four

In clinical trials, adverse events (AEs) are often "graded" using standard scales so they can be compared among sites and studies. The scale usually ranges from 1 to 5, with 1 being a mild event and 5 being death. In ZeNix, AEs were graded from 1 to 4 (1 = mild, 2 = moderate, 3 = severe, 4 = potentially life threatening).

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

Cavities are abnormal, thick-walled, air-filled spaces within the lung caused by infection or trauma, the presence of which is an indicator of increased TB disease severity.

The modified intention to treat analysis includes all participants randomized to the study except those whose outcomes were not assessable because they were lost to follow up (2 participants), died – from non-TB related cause (1 participant due to accidental overdose of methadone), or withdrew from the trial (1 participant during follow up due to incarceration).

cases of optic neuropathy, all in the linezolid 1,200 mg six-month arm. In the linezolid 1,200 mg two-month, 600 mg six-month, and 600 mg two-month arms, respectively, at least one adverse event of peripheral neuropathy was reported among 23.9% (11/46), 24.4% (11/45), and 13.3% (6/45) of participants, and at least one adverse event of myelosuppression among 15.2% (7/46), 2.2% (1/45), and 6.7% (3/45) of participants. Of the participants in the 1,200 mg six-month arm, 51% required linezolid dose reduction, interruption, or discontinuation compared to 28%, 13%, and 13% in the 1,200 mg two-month, 600 mg six-month, and 600 mg two-month arms.[10]

Optic neuropathy refers to damage to the optic nerve in your eye, which can cause sudden vision loss.

ZeNix was not powered to directly compare the four different linezolid dosing strategies evaluated in the study; however, the findings suggest a better safety profile can be achieved with reduced doses and/or shorter durations of linezolid with limited effect on the efficacy of the BPaL regimen. Full results will be published in 2022.[11]

TB-PRACTECAL

In October 2021, at the 52nd Union World Conference on Lung Health, Médecins Sans Frontières (MSF) presented preliminary results from TB-PRACTECAL, a phase II/III randomized, controlled, open-label study to evaluate six-month bedaquiline-, pretomanid-, and linezolid-based regimens for the treatment of MDR-TB with and without additional fluoroquinolone resistance. TB-PRACTECAL was conducted in two stages and enrolled a total of 552 participants from seven sites across Belarus, South Africa, and Uzbekistan. During the first stage of the study, participants were randomized to one of three experimental regimens (BPaL + moxifloxacin, BPaL + clofazimine, BPaL alone) or to the control arm, the duration and composition of which varied by country and changed over the course of the study. Different from the simplified bedaquiline dosing approach used in ZeNix and in line with how its currently prescribed by programs, bedaquiline was administered at 400 mg daily for two weeks followed by 200 mg thrice weekly. All three experimental regimens were eligible to advance from stage one to stage two of the trial based on pre-specified eight-week efficacy and safety criteria: 77.1% (37/48), 67.3% (33/49), and 45.7% (21/46) of people randomized to receive BPaLM, BPaLC, and BPaL, respectively, culture converted by eight weeks, and 7.7% (4/52), 5.8% (3/52), and 9.8% (5/51) discontinued treatment for any reason or died.[12] Of note, among participants randomized to receive the BPaL regimen in TB-PRACTECAL, culture conversion occurred less frequently than in other cohorts treated with the Nix-TB regimen (in Nix-TB, 79% of participants culture positive at baseline converted at eight weeks and ZeNix data showed similar conversion rates at this timepoint).[13] Further investigations into these differences are required. The TB-PRACTECAL Trial Scientific Committee recommended that two of the three experimental regimens (BPaLM and

Prespecified efficacy and safety criteria: To advance to stage two of the trial, each experimental regimen had to demonstrate equal to or greater than 40% culture conversion at eight weeks and less than 45% treatment discontinuation for any cause.

BPaLC) move forward; however, due to recruitment challenges and the ongoing COVID-19 pandemic, only one experimental regimen advanced to stage two of the trial: BPaLM.

In March 2021, just four months after opening, randomization to stage two of the TB-PRACTECAL trial was discontinued. This decision followed an unplanned interim analysis conducted at the request of the trial Data Safety Monitoring Board (DSMB) that determined "more data was extremely unlikely to change the results of the trial."[14] A pre-defined threshold for a statistically significant difference in the primary endpoint (unfavorable outcome 72 weeks after randomization) had been met, favoring BPaLM compared to the control.[15] The results of stage two of the TB-PRACTECAL trial presented during the 52nd Union Conference compared outcomes among those with week 72 outcomes (primary endpoint) data available: 73 of 152 people randomized to receive treatment with the standard of care and 72 of 151 people randomized to receive treatment with BPaLM. This included people with MDR-TB with additional fluoroquinolone resistance (25%), people living with HIV (22.7%), and people with cavities present on chest X-ray (62.5%).

In the **modified intention to treat (mITT) analysis**, 48.5% (32/66) of participants randomized to the control arm had an unfavorable treatment outcome compared to 11.3% (7/62) of participants randomized to the BPaLM regimen, representing a **risk difference** of -37.2% (-∞ to -21.6%).[16] Treatment discontinuation was more common in the control arm compared to BPaLM (28/66 [42.4%] vs. 5/62 [8.1%]). Reasons for treatment discontinuation in the control vs. BPaLM arm included adherence issues (3 vs. 0), adverse events (16 vs. 5), investigator discretion (3 vs. 0), and withdrawal of consent (6 vs. 0). No treatment failures or recurrences were reported in either arm, loss to follow-up was limited to just two participants per arm (3%), and two participants (3%) died in the control arm vs. none in the BPaLM arm. In the **per protocol analysis**, which excluded participants who discontinued treatment for any reason other than failure or death, 12.1% (4/33) of participants randomized to the control arm had an unfavorable treatment outcome compared to 3.5% (2/57) of participants randomized to the BPaLM regimen, representing a risk difference of -8.6% (-∞ to -4.5%). In both the mITT and per protocol analyses, the six-month BPaLM regimen was found **noninferior** to the control (the noninferiority margin was 12%). **Superiority** was demonstrated only in the mITT population. The investigators conducted subgroup analyses based on age, sex, country, HIV status, smear status, presence of cavitation, and fluoroquinolone resistance. Differences between subgroups were not statistically significant but suggest that people living with HIV and people with fluoroquinolone resistance might be at an increased risk of an unfavorable outcome and may need to be monitored more closely.

The modified intention to treat analysis included all participants randomized to the study with week 72 outcomes data available except those who were sputum culture negative and/or rifampicin sensitive at inclusion.

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.

The per protocol analysis included the mITT population, excluding participants who did not complete a protocol-adherent course of treatment (80% of doses within 120% of the prescribed duration) for any reason other than treatment failure or death.

In the case of TB-PRACTECAL, **noninferior** means that the intervention (BPaLM) is *no worse than* the control (9- or 20-month, injectable-containing or injectable-sparing standard of care regimens for RR/-MDR-TB). Said differently, the difference between the experimental treatment intervention (BPaLM) and the control falls within a prespecified acceptable range (called the noninferiority margin).

In the case of TB-PRACTECAL, **superior** means that the intervention (BPaLM) *is better than* the control (9- or 20-month, injectable-containing or injectable-sparing standard of care regimens for RR/-MDR-TB).

In terms of safety, in the **intention to treat (ITT)** population, 58.6% (43/73) of participants randomized to the control arm experienced any grade 3 or higher adverse event or **serious adverse event** compared to 19.5% (14/72) of participants randomized to receive the BPaLM regimen, representing a risk difference of -39.5% (-∞ to -23.7%).[17] Said differently, 80% of participants avoided any major side effects in the BPaLM arm compared to 40% in the control group.[18] Adverse events of special interest included liver dysfunction (10 in control vs. 2 in BPaLM) and **QTc interval prolongation** (7 in control vs. 0 in BPaLM). QTc interval prolongation was significantly lower at 24 weeks in the BPaLM arm compared to the control with a mean difference of 27 vs. 44.9 milliseconds, respectively. There were no grade 3 or higher peripheral neuropathy or optic nerve events (14 people in the control vs. 3 people in the BPaLM arms experienced any grade peripheral neuropathy).

The intention to treat population includes all participants randomized to the study in time to have week 72 outcomes data available at the time of analysis.

Serious adverse events were defined as events that were fatal or immediately life threatening, required hospitalization, caused disability or incapacity, or that were otherwise medically important.

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

The last patient's last follow-up visit is not until August 2022. As such, we currently only have 72-week outcomes data available for 73/152 and 72/151 participants randomized to the control and BPaLM arms, respectively. Additionally, as noted, there was heterogeneity in the control arm: some participants received longer, injectable-containing or injectable-sparing regimens; others received shortened injectable-containing or all-oral regimens. Specifically, the number of participants in the control arm who received a nine-month, bedaquiline-based, all-oral regimen and who are in the provisional mITT analysis population (13/66 [19.7%]) is too small to draw any definitive conclusions regarding how the BPaLM regimen might compare to the most current standard of care for MDR-TB globally, especially under program conditions where criteria for treatment discontinuation might be less conservative than they were in the trial. Moreover, important heterogeneity in results by HIV status, fluoroquinolone resistance pattern, and geography (the difference between the control and BPaLM was more pronounced in Belarus and Uzbekistan than in South Africa) reinforces the importance of full follow-up and further study of this regimen compared to the current standard. Still, TB-PRACTECAL has demonstrated that the six-month BPaLM regimen is better than the collection of standard of care regimens. Overall, the standard of care resulted in more treatment discontinuations and deaths compared with the BPaLM regimen. The BPaLM regimen also appeared to be safer. Taking into account the aforementioned limitations, the results are promising and represent an important step forward, enabling for the first time an extension of the benefits of a six-month regimen to people with MDR-TB.[19]

NEXT

The NEXT trial, conducted in South Africa with funding from the South African Medical Research Council, examined another 6–9-month regimen for MDR-TB. In June 2021, at the 6th South African TB Conference, researchers from the

University of Cape Town reported results from NEXT, a phase III randomized controlled trial to evaluate a 6–9-month regimen consisting of bedaquiline, linezolid, levofloxacin, terizidone (very similar to cycloserine), ethionamide or high dose isoniazid, and pyrazinamide for MDR-TB. NEXT enrolled 111 of 240 planned participants from five sites in South Africa, including 51 (55%) people living with HIV with a median CD4 cell count of 158 cells/mL and 48 (51.6%) people with cavitary disease. The trial was terminated early when the guidelines in South Africa changed to include bedaquiline as the standard of care for MDR-TB (from 2014–2016, participants randomized to the control arm received a 18–20-month, injectable-containing regimen; from 2016–2018, participants randomized to the control arm received a 9–11-month, injectable-containing regimen). Even though the trial was terminated early, a significant difference in outcomes was detected between participants randomized to receive the experimental 6–9-month NEXT regimen compared to the longer, injectable-containing regimens in the control arm.

At 24-months posttreatment initiation (6–18 months after the completion of treatment depending on the study arm/duration of the regimen), the **modified intention to treat analysis** found that a favorable outcome was more than twice as likely among participants randomized to receive the experimental 6–9-month NEXT regimen (51% [25/49]) compared to the control (22.7% [10/44]), with a relative risk of 2.2 (1.2, 4.1) and a risk difference of 28.3 (9.6–47.0, p=0.006).[20] They also observed quicker time to culture conversion in the experimental arm. The findings of the **per protocol analysis** were consistent, with 56.8% (25/44) vs. 27.9% (12/43) of participants achieving a favorable outcome with the 6–9-month NEXT regimen compared to the control, representing a relative risk of 2.4 (1.3, 4.5) and risk difference of 33.6 (14.2–52.9, p=0.002). The investigators remarked on the low percentage of successful treatment outcomes in the study relative to what might be expected, attributing this to "toxicity-related drug substitutions," a consequence of the WHO defined outcome measure used in the trial. If two drugs or one key drug that would disrupt the assigned regimen (i.e., bedaquiline, linezolid or levofloxacin, or the injectable in the control arm) were stopped because of toxicity, the outcome was classified as treatment failure, even if participants were well at the end of treatment. In the control arm, 65.9% (29/44) of participants experienced an adverse event requiring the discontinuation of at least one drug compared to 36.7% (18/49) of participants in the 6–9-month experimental arm. Most toxicity-related drug substitutions were due to kanamycin-induced hearing loss in the control arm (52.3% [23/44]) and linezolid-induced anemia in the 6–9-month experimental arm (30.6% [15/49]). In terms of other safety outcomes, 27.3% (12/44) of participants randomized to the control arm experienced any grade 3 or higher adverse event and 22.7% (10/44) experienced any serious adverse event compared to 30.6% (14/49) and 28.6% (14/49) of participants randomized to receive the 6–9-month NEXT regimen.

The modified intention to treat analysis excluded people who received regimens outside the scope of the protocol or were randomized in error (e.g., people with baseline hearing loss or renal impairment) and people found to have non-rifampicin- or multidrug-resistant TB (i.e., people with rifampicin-sensitive TB and people with resistance to fluoroquinolones and/or second line injectable medicines).

The per protocol analysis included the mITT population minus people who were lost to follow up or withdrew consent.

Adverse events of special interest included high frequency hearing loss (43.2% in the control arm vs. 2% in the experimental arm), anemia (2.3% vs. 20.4%), and peripheral neuropathy (13.6% vs. 24.5%). There were eight deaths in the trial, four in each arm.

The NEXT trial further supports that shortening treatment for MDR-TB to six months is feasible using an all-oral regimen, this one without pretomanid. The 6–9-month all-oral NEXT regimen performed better than the 9–20-month, injectable-containing standard of care regimens. In the primary analysis, however, 49% of participants treated with the 6–9-month all-oral NEXT regimen experienced unfavorable outcomes, many due to adverse events leading to regimen changes. This leaves plenty of room for further improvements to six-month, all-oral regimens for MDR-TB. And, like the situation for TB-PRACTECAL, we don't know how the 6–9-month NEXT regimen compares to the most current standard of care for MDR-TB globally, i.e., the nine-month, bedaquiline-based, all-oral regimen. Dynamic treatment guidelines for MDR-TB, regularly updated in response to emerging data from both clinical trials and TB programs, have necessitated the adoption of control arms in clinical trials that change with the standard of care. Dynamic control arms are ethically necessary but make interpretation of results more difficult, especially for policymakers and other stakeholders charged with deciding whether the standard of care should again change in response to findings from clinical trials. Expanding resources to accelerate the pace at which TB treatment trials enroll (and/or identifying and validating biomarkers available earlier that reliably correlate with relapse free cure) could help ensure that study findings better retain their relevance for policy and other decision making.

Overview of Ongoing and Planned Treatment Shortening Trials

Ongoing trials to shorten treatment for TB continue to evaluate different approaches to optimizing drug selection, dosing, and duration of treatment. Clinical trials of regimens for drug-sensitive TB are focused on shortening treatment to two-to-four months by optimizing rifamycin selection (i.e., rifampicin or rifapentine) and dosing and/or by introducing new and repurposed medicines to first-line regimens. Clinical trials of regimens for drug-resistant TB are focused on shortening treatment to six-to-nine months and improving outcomes and tolerability by optimizing oxazolidinone selection (i.e., linezolid or sutezolid), dose, and duration, and/or by evaluating different combinations of new and repurposed medicines. Table 2 provides an overview of ongoing and planned phase IIa+, IIb/c, and III TB treatment shortening trials.

Table 2. Trials to Shorten Treatment for TB

Study Name	Experimental Arms [Control]	For Treatment of	Number of Participants	Phase	Status [Est. Completion Date]
Active; Drug-Sensitive TB					
SimpliciTB NCT03338621	4BPaMZ [2HRZE/4HR] 6BPaMZ [none] *B_{200} daily for first 8 weeks then B_{100} daily	DS-TB MDR-TB	455	IIc	Fully enrolled [Feb 2022]
TRUNCATE-TB NCT03474198	$2HR_{Hd}ZELz_{600}$ $2HR_{Hd}ZEC$ $2HP_{1200}ZLz_{600}Lx$ $2HZELz_{600}B$ [2HRZE/4HR]	DS-TB	900	II/III	Fully enrolled [Mar 2022]
RIFASHORT NCT02581527	$2HR_{1200}ZE/2HR_{1200}$ $2HR_{1800}ZE/2HR_{1800}$ [2HRZE/4HR]	DS-TB	654	III	Fully enrolled [Apr 2022]
APT NCT02256696	2PaRbHZ/1PaRbH 2PaRHZ/1PaRH [2HRZE/1HR]	DS-TB	150	IIb	Fully enrolled [Apr 2022] *Preliminary results at Union 2021[21]
A5362 / CLO-FAST NCT04311502	2CHPZE/1CHPZ [2HRZE/4HR] *C_{300} daily for first 2 weeks then C_{100} daily	DS-TB	185	IIc	Recruiting [Nov 2022]
SUDOCU NCT03959566	$3BDMStz_{600}/3HR$ $3BDMStz_{1200}/3HR$ $3BDMStz_{600\ BID}/3HR$ $3BDMStz_{800\ BID}/3HR$ [3BDM//3HR]	DS-TB	75	IIb	Recruiting [May 2022]
DECODE NCT04550832	$4BDMDzd_{400}$ $4BDMDzd_{800}$ $4BDMDzd_{1200}$ $4BDMDzd_{800\ BID}$ [4BDM]	DS-TB	75	IIb	Recruiting [Jan 2023]

Study Name	Experimental Arms [Control]	For Treatment of	Number of Participants	Phase	Status [Est. Completion Date]
Planned; Drug-Sensitive TB					
A5409 / RAD-TB	6–8-week experimental combinations NA at time of publication	DS-TB	35 per arm	IIa+	Protocol in development
Trial 323-201-00006 (Otsuka IIb/c of OPC-167832)	4OBD [2HRZE/4HR]	DS-TB	NA	IIb/c	Protocol in development
Study name NA GMRI PAN-TB	2–4-month experimental regimens NA at time of publication	DS-TB MDR-TB	70 per arm	IIb/c	Protocol in development
TBTC Study 38 / CRUSH TB	4BMZRb 4BMZD [2HRZE/4HR]	DS-TB	90 per arm	IIc	Protocol in development
PanACEA STEP2C	$3R_{Hd}HZM_{600}$ $3R_{Hd}HZ_{Hd}M_{600}$ 4BDMStz [2HRZE/4HR]	DS-TB	90 per arm	IIc	Protocol in development
CORTAIL CTRI/2019/03/018102	$2RHZC_{100}/2RHC_{100}$ [2HRZE/4HR]	DS-TB	320	III	Not yet recruiting
Hi-DoRi-3 NCT04485156	$1\text{-}2HR_{Hd}Z^{*}/3HR_{Hd}$ [2HRZE/4HR] *discontinue Z after culture conversion	DS-TB	926	III	Not yet recruiting
Active; Drug-Resistant TB					
MDR-END NCT02619994	9–12DLzLxZ [20mo IA-containing regimen]	MDR-TB	238	II/III	Fully enrolled [May 2021] *Results to be published in 2022
BEAT TB CTRI/2019/01/017310	6–9BDLzC [none]	Pre-XDR-TB XDR-TB	165	III	Fully enrolled [Jul 2022] *Preliminary results at Union 2021[22]
STREAM II NCT02409290	$4BCLxEZH_{Hd}Pto/5BCLxEZ$ $2BCLxZH_{Hd}K/4BCLxZ$ $[4CLxEZH_{Hd}KPto/5CLxZE]$	MDR-TB	588	III	Fully enrolled [Aug 2022]
endTB NCT02754765	9BLzMZ 9BLzLxCZ 9BLzLxDZ 9DLzLxCZ 9DMCZ [9–20mo SOC]	MDR-TB	750	III	Fully enrolled [Feb 2023]

Study Name	Experimental Arms [Control]	For Treatment of	Number of Participants	Phase	Status [Est. Completion Date]
Active; Drug-Resistant TB					
BEAT-Tuberculosis NCT04062201	6BDLz (Lx, C or both) [9–12mo SOC]	RR-TB MDR-TB FQ-R-MDR-TB	400	III	Recruiting [Mar 2023]
endTB-Q NCT03896685	6BDLzC 9BDLzC [9–20mo SOC]	FQ-R-MDR-TB	324	III	Recruiting [Jun 2024]
Planned; Drug-Resistant TB					
DRAMATIC NCT03828201	16wkBDCLxLz$_{8wk}$ 24wkBDCLxLz$_{8wk}$ 32wkBDCLxLz$_{8wk}$ 40wkBDCLxLz$_{8wk}$ [none]	MDR-TB	220	IIc	Not yet recruiting
ACTG A5356	1BDCLz$_{1200\ QD}$/ 5BDCLz$_{1200\ TIW}$ 6BDCLz$_{600}$ [none] *B_{200} for first 8 weeks followed by B_{100} daily; D_{200} daily throughout; C_{300} for first 2 weeks followed by C_{100} daily	RR-TB, MDR-TB, pre-XDR-TB, XDR-TB	132	II	Protocol in development
ACTG 5373/ FIRST	2RZELx/4RLx [6H$_{Hd}$RZE]	HR-TB	556	III	Protocol in development

- Pre-2021 definitions for pre-XDR-TB and XDR-TB are used in Table 2, i.e., pre-XDR-TB: MDR-TB with additional resistance to the fluoroquinolones or the injectable agents; XDR-TB: MDR-TB with additional resistance to the fluoroquinolones and the injectable agents; TI/NR = treatment-intolerant or non-responsive.
- Numbers at the beginning of each regimen or after the forward slash (for regimens with intensive and continuation phases) represent the duration of treatment in months, unless otherwise specified (i.e., wk = weeks); letters represent the individual drugs comprising each regimen.
- Subscripts indicate dosing in mg; Hd = high dose, BID = twice daily.

P = rifapentine, Rb = rifabutin, O = OPC167832, Stz = sutezolid, Dzd = delpazolid, B = bedaquiline, D = delamanid, Pa = pretomanid, Lz = linezolid, Lx = levofloxacin, M = moxifloxacin, Z = pyrazinamide, Eto = ethionamide, H = isoniazid, Tzd = terizidone (cycloserine), C = clofazimine, IA = injectable agent.

Pediatric Investigations of TB Drugs

There are two ongoing pharmacokinetic (PK) and safety studies of **bedaquiline** in children: C211 (NCT02354014) is currently recruiting children to the third of four cohorts (2 ≤ 5 years old) in clinical sites in Russia, South Africa, Uganda, the Philippines, and Mozambique;[23] and IMPAACT P1108 (NCT02906007) is currently enrolling its final two cohorts in parallel, children aged 2 < 6 years old and 0 < 2 years old, from sites in Haiti, India, and South Africa. In August 2021, based on data from C211 and P1108, the WHO recommended bedaquiline for use in children of all ages (previously this recommendation was limited to children six years and older).[24] Janssen's 20 mg bedaquiline dispersible tablet is approved by stringent regulatory authorities for children 5 < 12 years old weighing at least 15 kg and is available via the Stop TB Partnership Global Drug Facility.[25]

Otsuka completed its pediatric PK and safety study of **delamanid** in children (Otsuka 232/233; NCT01856634/NCT01859923) in 2020. Based on these data, in August 2021, the WHO recommended delamanid for use in children of all ages (previously this recommendation was limited to children three years and older). Otsuka's 25 mg delamanid dispersible tablet is approved by the European Medicines Agency for children and infants weighing at least 10 kg and is soon to be available via the Stop TB Partnership Global Drug Facility.[26] The IMPAACT network is currently enrolling P2005 (NCT03141060), a PK 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.

As reported in last year's *Pipeline Report*, the IMPAACT network is working with the TB Alliance to develop a protocol to evaluate the PK and safety of a single dose of **pretomanid** in children receiving treatment for drug-resistant TB (IMPAACT P2034). 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; opened September 2021; expected to complete by April 2023).

Pediatric investigations of **rifapentine** administered alongside isoniazid as part of the TB preventive treatment regimens, 3HP and 1HP, are ongoing and planned (TBTC Study 35, NCT03730181; IMPAACT P2024)—see TAG's *2021 Pipeline Report on Tuberculosis Preventive Treatment* for more information. A separate pediatric PK and safety study of rifapentine administered in the four-month regimen from TBTC Study 31/ACTG A5349, in which rifapentine is dosed daily at 1,200 mg (rather than 900 mg once weekly for 3HP or 600 mg daily for 1HP), is an urgent unmet need.

The dose and administration schedule for several existing and newer TB medicines that have already undergone pediatric investigations are being optimized only in adults, creating new PK and safety data gaps for "old" drugs in children. Gaps for rifampicin are being addressed (OptiRif[27]; HighRif-C, NCT04437836), but pediatric investigations of newer approaches to dosing bedaquiline and linezolid (via ZeNix), for example, have not been discussed.

There is currently no clearly delineated funding mechanism or pathway (or responsible party) for implementing the pediatric investigations required to extend to children the benefits of ongoing dose optimization work in adults.

Finally, several new TB drugs are already or soon to be in phase IIb, including telacebec, OPC-167832, sutezolid, and delpazolid (see Table 3)—this is the point at which experts recommend pediatric investigational planning begin. It's important to start planning pediatric investigations for these new TB drugs soon and to design these investigations in a way that supports their expeditious completion, e.g., by adopting parallel enrollment (rather than using a sequential, age de-escalation approach) and cutting-edge population pharmacokinetic modeling techniques that enable an evidence-based approach to formulation and dose selection and optimization, especially for the youngest and smallest children. Without earlier planning, better pediatric study designs, and increased pediatric TB research capacity, the years-long delay between when a new TB drug is approved for adults vs. children observed with rifapentine, bedaquiline, delamanid, and pretomanid will be repeated for new TB drugs.

Updates on New Drugs in Clinical Development for TB

There are currently 15 new compounds in clinical development for TB, nine from a new class or with a new mechanism of action and six potentially advantaged alternatives to existing TB medicines (see Table 3).

Table 3. New Drugs in Clinical 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)	Riminophenazine	Inhibits ion transport and bacterial respiration	IMM/CAMS/ PUMC	IIa	ChiCTR1800018780 NCT04670120 ← NEW
NEW → TBAJ-587	Diarylquinoline	Inhibits ATP synthase	TB Alliance/ ERA4TB	Ia/Ib	NCT04890535
TBAJ-876	Diarylquinoline	Inhibits ATP synthase and bacterial respiration	TB Alliance	Ia/Ib	NCT04493671
telacebec (Q203)	Imidazopyridine	Inhibits ATP synthesis (QcrB) and bacterial respiration	Qurient/ Infectex	IIa	NCT02530710 NCT02858973 NCT03563599

Drug	Class	Mechanism of Action	Sponsor	Phase	Clinical Trial(s)
Cell Wall Synthesis					
BTZ-043	Benzothiazinone	Inhibits cell wall synthesis (DprE1)	University of Munich/DZIF	Ib/IIa	NCT03590600 NCT04044001 NCT04874948
NEW → BVL-GSK098	Amido piperidine	Inhibits cell wall synthesis via boosting ethionamide	BioVersys/ GSK	Ia/Ib	NCT04654143
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/ IIa	NCT03036163 NCT03423030 NCT03776500 NCT03334734
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/ GMRI	IIa	NCT03199339 NCT04176250
Protein Synthesis					
delpazolid (LCB01-0371)	Oxazolidinone	Inhibits protein synthesis (23S ribosome)	LegoChem Biosciences	IIb	NCT01554995 NCT01842516 NCT02540460 NCT02836483 NCT04550832
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	Ib	NCT03758612 NCT04865536 ← NEW
GSK3036656 (GSK-656)	Oxaborole	Inhibits protein synthesis (LeuRS)	GSK	IIa	NCT03075410 NCT03557281

Drug	Class	Mechanism of Action	Sponsor	Phase	Clinical Trial(s)
DNA Synthesis					
SPR720	Benzimidazole	Inhibits bacterial DNA synthesis (GyrB)	Spero Therapeutics/ GMRI	Ia/Ib	NCT03796910
Cholesterol Catabolism					
GSK2556286 (GSK-286)		Inhibits cholesterol catabolism (target to be determined)	GSK	Ia/Ib	NCT04472897

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

CAMS: Chinese Academy of Medical Sciences

DZIF: German Center for Infection Research

GMRI: 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

Of the 15 new compounds in clinical development for TB, five have advanced to a new phase in the last year. These updates are summarized below by compound in the order in which they appear in Table 3:

- Pyrifazimine, a member of the riminophenazine class, like clofazimine, entered phase IIa in March 2021.[28] The study will recruit 56 participants in China to explore the early bactericidal activity (EBA) of pyrifazimine when dosed between 100 mg and 300 mg and is expected to complete before the end of the year.
- TBAJ-587, a bedaquiline analogue, is the third member of the diarylquinoline class to enter clinical trials. The phase I trial, which opened December 2020[29] and is expected to complete in March 2023, will recruit 100 participants in the Netherlands to evaluate single and multiple ascending doses of TBAJ-587 in healthy volunteers.
- BVL-GSK098, an ethionamide booster developed by BioVersys and GSK under the IMI AMR Accelerator program (see Highlight Box 2 for more information), entered phase I in January 2021. BVL-GSK098 works by acting on the pathway through which ethionamide is converted to its active form, increasing ethionamide's potency, which in turn may overcome resistance and support lowering of doses to improve its gastrointestinal tolerability profile.[30]
- In August 2021, the Bill and Melinda Gates Foundation awarded Otsuka a grant up to $17.8 million for a phase IIb/c treatment shortening trial combining OPC-167832 with delamanid and bedaquiline.[31] This investigational four-month regimen will be compared to the six-month standard of care for the treatment of drug-sensitive TB. The study is expected to begin in 2022. OPC-167832 will be the first of the DprE1 inhibitors to enter phase IIb. Results from earlier clinical studies of OPC-167832, including interim results from the phase Ib/IIa study were presented at the 52nd Union World Conference on Lung Health.[32,33]
- In May 2021, SUDOCU, a phase IIb dose-finding study of sutezolid in combination with bedaquiline, delamanid, and moxifloxacin finally began enrolling participants in South Africa and Tanzania.[34] Led by the

Pan-African Consortium for the Evaluation of Antituberculosis Antibiotics (PanACEA), this trial will advance the clinical development of sutezolid (a member of the oxazolidinone class, like linezolid), stalled since Pfizer licensed the rights to Sequella in 2011.

- TBI-223, another oxazolidinone, advanced to phase Ib in February 2021.[35] The study, which is sponsored by the TB Alliance and currently enrolling healthy volunteers in the United States, will evaluate multiple ascending doses of TBI-223 up to 3,000 mg.
- In February 2021, Spero Therapeutics' phase IIa trial of SPR720 for Mycobacterium Avium Complex (MAC) was put on clinical hold by the U.S. Food and Drug Administration. According to the company, the hold is a precautionary measure taken following "mortalities with inconclusive causality to treatment" observed in an adult non-human primate study conducted to assess the potential toxicity of SPR720 over a four-month period.[36] Spero Therapeutics licensed the rights to SPR720 for TB to the Gates Medical Research Institute in 2019.[37] Since receiving these rights, the Gates Medical Research Institute has been working to fill preclinical data gaps before moving forward with a phase IIa trial of SPR720 for TB.

The top half of Figure 1 groups new TB drugs by class and target to help demonstrate where new TB drugs that share a common class and/or target are in the clinical development pathway with respect to each other. The six alternatives to existing TB medicines are grouped in red, orange, blue, and yellow, and the nine compounds from a new class or with a new mechanism of action are grouped in green. The bottom half of Figure 1 shows where different stakeholders and initiatives sit within the clinical drug and regimen development landscape for TB.

Figure 1. The TB Drug and Regimen Development Landscape

	Phase IA	Phase IB	Phase IIA	Phase IIB or IIB/C	Phase III	Phase IV
Diarylquinolines					bedaquiline	
	TBAJ-587					
	TBAJ-876					
Nitroimidazoles						delamanid
					pretomanid	
Oxazolidinones (like linezolid)				delpazolid		
				sutezolid		
		TBI-223				
Riminophenazine (like clofazimine)			pyrifazimine (TBI-166)			
DprE1 Inhibitors		BTZ-043				
		macozinone (PBTZ169)				
				OPC-167832		
			TBA-7371			
QcrB Inhibitor			telacebec (Q203)			
MmpL3 Inhibitor				SQ109		
GyrB Inhibitor	SPR720					
Cholesterol Catabolism Inhibitor	GSK-286					
LeuRS Inhibitor			GSK-656			

<table>
<tr><th>Phase IA</th><th>Phase IB</th><th>Phase IIA</th><th>Phase IIB or IIB/C</th><th>Phase III</th><th>Phase IV</th></tr>
<tr><td colspan="3">IMI ERA4TB</td><td colspan="2">IMI UNITE4TB</td><td></td></tr>
<tr><td colspan="3">GMRI</td><td>PAN-TB</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td colspan="3">CDC TBTC</td></tr>
<tr><td></td><td></td><td colspan="4">NIH ACTG, IMPAACT</td></tr>
<tr><td></td><td></td><td colspan="4">EDCTP PanACEA</td></tr>
<tr><td colspan="6">Pharmaceutical Companies
(e.g., Otsuka, Janssen, TB Alliance, GlaxoSmithKline, Qurient, LegoChem)</td></tr>
</table>

CDC TBTC: US 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

IMPAACT: International Maternal Pediatric Adolescent AIDS Clinical Trials Network

NIH ACTG: US National Institutes of Health AIDS Clinical Trials Group

PAN-TB: Project to Accelerate New Treatments for Tuberculosis

The advancement of new TB drugs from phase II combination studies and beyond looks like it will increasingly depend on publicly and philanthropically funded research consortia. Newer initiatives such as the Project to Accelerate New Treatments for TB (PAN-TB) and the latest Innovative Medicines Initiative (IMI) Antimicrobial Resistance (AMR) Accelerator project, UNITE4TB, are expected to begin phase IIb/c studies in the next year. At the time of publication, neither initiative had announced what experimental combinations would be taken forward; however, other aspects of their respective study plans were tentatively presented during the annual meeting of the Stop TB Partnership Working Group on New Drugs and during TB Science sessions at the 52nd Union World Conference on Lung Health.

The PAN-TB collaboration is aligned on a two-stage phase IIb/c study design for future regimen testing. The first stage, designed to "de-risk" the subsequent phase IIb/c trial, will evaluate two four-month regimens against the six-month standard of care regimen for drug-sensitive TB. Prespecified assessment criteria, including time to TB detection in liquid culture (TTD) and proportion of unfavorable outcomes at the end of treatment, will determine which regimen(s) advance to stage two.[38] Stage two will evaluate whether the regimen(s) that passed stage one can be further shortened to two months using a duration randomization approach (i.e., randomizing participants in the experimental arms to receive 2, 2.5, 3, 3.5, or 4 months of treatment to identify the optimal duration for each experimental regimen).[39] The proportion of participants with an unfavorable outcome 12 months post randomization (6–10 months after treatment completion) will determine which regimen(s) and duration(s) should be taken forward for evaluation in a future phase III trial. Stage two of the IIb/c will include an observational cohort of people with MDR-TB treated with the four-month regimen(s) that pass stage one. Outcomes among participants in the stage two observational cohort will inform whether the phase III trial will include a randomized comparison of the four-month regimen(s) to a standard of care control arm for MDR-TB.[40]

UNITE4TB is planning a platform for a series of trials that they liken to a racetrack, whereby regimens (racecars) can be modified or replaced entirely at planned interim analysis points (pitstops) over the course of the phase IIb/c trials.[41] UNITE4TB is also planning to use a two-stage approach for introducing regimens to its phase IIb/c trials. The first stage will be a phase IIb safety lead-in study comparing experimental regimens taken for 16 weeks to the six-month standard of care regimen for drug-sensitive TB. The most promising and safe regimens will advance to phase IIb/c and be evaluated using a duration randomization approach to identify the optimal duration(s) for each experimental regimen for further evaluation in a future phase III trial. UNITE4TB is still determining what tools will inform initial regimen prioritization and selection and the endpoints that will determine which regimens move forward for duration randomization.[42]

IMI AMR Accelerator TB Projects

The AMR Accelerator is an Innovative Medicines Initiative (IMI) program set up to advance the development of medicines to treat or prevent infections caused by TB, nontuberculous mycobacteria, and Gram-negative bacteria. Funding for the AMR Accelerator comes from the European Union's Horizon 2020 research and innovation program and the European Federation of Pharmaceutical Industries and Associations (EFPIA). The TB-focused projects established under the AMR Accelerator—UNITE4TB, ERA4TB, RespiriTB, and TRIC-TB—are described below.

UNITE4TB is a seven-year, €185M project, co-funded by the German Federal Ministry of Research and Education. The project, which started in June 2021, is a collaborative effort between twenty-two European academic institutions, three research institutions from the United States and South Africa, three EFPIA members, and two Associated Partners (APs) from Germany. By the end of the project, the consortium expects to deliver innovative phase 2 clinical trials that speed the passage of new TB drugs and regimens to definitive phase 3 trials and regulatory approval.

ERA4TB is a six-year, €207M project that brings together a multidisciplinary team of thirty organizations, including seven academic institutions, four nonprofit organizations, eight public research organizations, five small-medium enterprises, three EFPIA members, and three APs. The project, which started in January 2020, has already brought two new drugs into clinical development (TBAJ-587 and GSK-286). By the end of the project, the consortium expects to have developed at least two new combination regimens with treatment-shortening potential ready for phase II clinical evaluation via UNITE4TB.

RespiriTB is a six-year, €9.9M project focused on discovering and developing new drugs that interfere with the TB bacteria's ability to make energy (like bedaquiline). The project, which started in May 2019 and brings together nine partners, including six European academic institutions, two small-medium enterprises, and one EFPIA member, is expected to advance novel drugs that target the respiratory pathway and other essential proteins, and that may work synergistically with bedaquiline. The project is also exploring host-directed therapies to support the development of novel treatment regimens that are shorter and less prone to drug resistance.

TRIC-TB is a four-year, €8.3M project that started in 2019. Under the project, BioVersys, GSK, and the University of Lille are developing transcription related inhibitory compounds (TRICs), including BVL-GSK098, a drug designed to boost ethionamide's activity against TB. Ethionamide is included in certain regimens used to treat TB meningitis (TBM) and the 9–11-month all-oral regimen recommended by WHO for rifampicin- and multidrug-resistant TB. It's also a group C drug, used in longer regimens for the treatment of drug-resistant TB when an effective four-to-five drug regimen can't otherwise be composed of medicines from groups A and B. Ethionamide is categorized as a group C drug because of dose-related gastrointestinal intolerance and cross-resistance with isoniazid (via mutations in the *inhA* promoter region). Ethionamide is converted into its active form inside the TB bacteria by a specific enzyme. Some TB bacteria (including those with mutations in the *inhA* promoter region) have evolved to block this enzyme, preventing ethionamide from converting to its active form, inhibiting its ability to kill TB bacteria. TRICs, like BVL-GSK098, increase the level of alternative bacterial enzymes that can activate ethionamide and do so more efficiently, overcoming resistance (*in vitro* and *in vivo*) and supporting administration of ethionamide at lower doses, which may improve its gastrointestinal tolerability profile.[43] A phase I single and multiple ascending dose (SAD/MAD) study of BVL-GSK098 in healthy volunteers opened in January 2021, and a phase II early bactericidal activity (EBA) study is planned with TASK in South Africa in 2022 with funding support from the EDCTP.[44,45]

More information on these TB projects is available here: **https://amr-accelerator.eu/**.

Conclusion

TB treatment researchers and drug developers are trying to do several things at once— shorten treatment; make it all-oral; optimize drug doses, combinations, and duration; minimize toxicities; and expand treatment indications. Some of these we've accomplished or made significant progress toward, others are still in flux. This next phase of TB drug and regimen development—what some have coined the "third wave"—offers a chance to take care of unfinished business. Don't look away—2022 is expected to bring additional results from several late-stage TB treatment shortening trials, including SimpliciTB, TRUNCATE-TB, RIFASHORT, BEAT TB, and STREAM II, and to kick off a series of phase II trials that will advance next generation oxazolidinones and diarylquinonlines, as well as DprE1 inhibitors, the first new class of TB drugs with a new mechanism of action since bedaquiline and delamanid.

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