Pipeline Report » 2022

Tuberculosis Treatment

TAG
Treatment Action Group

Tuberculosis Treatment Pipeline Report

By Lindsay McKenna

Introduction

In the last three years, decades of investments in tuberculosis (TB) drug and regimen development have been translated to successfully shorten treatment to just four months for drug-sensitive TB and six months for drug-resistant TB.[1] The World Health Organization (WHO) recommends the four-month regimens from the SHINE and Tuberculosis Trials Consortium (TBTC) Study 31/ AIDS Clinical Trials Group (ACTG) A5349 studies and the six-month regimens from the ZeNix and TB-PRACTECAL studies covered in the 2020 and 2021 Pipeline Reports.[2,3,4,5] In 2022, results from six other phase III drug-sensitive and drug-resistant TB treatment shortening trials were presented or published, and several new compounds have already moved or are poised to move forward, including through long-standing research consortia and more newly established public-private collaborations.

The 2022 Tuberculosis Treatment Pipeline Report reviews recent results and puts them in context and provides an overview of the state of the clinical TB treatment research pipeline in four tables: Table 1 covers recently completed trials; Table 2 covers trials of regimens composed of existing drugs; Table 3 covers new drugs in clinical development for TB; and Table 4 covers trials of investigational regimens that advance new drugs.

Figure 1. 2022 Pipeline of New TB Drugs in Clinical Development

Phase 1	Phase 2	Phase 3 Results expected in 2023	Regulatory Market Approvals
TBAJ-587 TBAJ-876 TBI-223 GSK.286 SPR720	Sudapyridine (WX-081) Delpazolid Sutezolid Tedizolid BTZ-043 Macozinone (PBTZ-169) TBA-7371 OPC-167832 Pyrifazimine (TBI-166) GSK-656 Telacebec BVL-GSK098 Sanfetrinem SQ-109	Simplici TB (4-month regimen, DS-TB) endTB (9-month regimen, DR-TB) BEAT-Tuberculosis (6-month regimen, DR-TB)	Bedaquiline Delamanid Pretomanid Linezolid* Clofazimine* Moxifloxacin* Levofloxacin*

Figure adapted from Stop TB Partnership Working Group on New Drugs. * Approved by Stringent Regulatory Authority and used to treat TB, but label does not include TB among approved indications. Diarylquinoline; Oxazolidinone; DprE1 inhibitor; Riminophenazine; Nitroimidazole; Fluroquinolone. DS-TB = drug-sensitive TB; DR-TB = drug-resistant TB.

Results from Recently Completed Treatment Trials

Recent approaches to shorten treatment for TB have relied on two primary strategies – optimizing the dose and combination of existing drugs and/or replacing or supplementing them with new or repurposed drugs. Several late-stage TB treatment-shortening trials reported results in 2022 (see Table 1).

Table 1. Key Findings from Recently Completed Treatment-Shortening Trials

<table>
<tr><th>Study Name
(Type of TB; Sample Size)</th><th>Study Arms
Experimental Regimens
[Control Regimen]</th><th>Key Findings</th></tr>
<tr><td rowspan="6">RIFASHORT
NCT02581527
(DS-TB; 672)</td><td rowspan="6">(a)2HR$_{1200}$ZE/2HR$_{1200}$
(b) 2HR$_{1800}$ZE/2HR$_{1800}$
(c) [2HRZE/4HR]</td><td>Primary Efficacy Outcome:
The four-month high-dose rifampicin regimens failed to demonstrate non-inferiority to the standard of care (mITT). The NI margin was 8%.
<table><tr><td>Unfavorable outcomes:</td><td></td><td>Risk difference, experimental-control (95% confidence interval)</td></tr><tr><td>(a)</td><td>19/186 (10.2%)</td><td>3.1 (-1.6 to 7.9)</td></tr><tr><td>(b)</td><td>25/186 (13.4%)</td><td>6.3 (1.1 to 11.5)</td></tr><tr><td>(c)</td><td>13/187 (7%)</td><td>NA</td></tr></table></td></tr>
<tr><td>Primary Safety Outcome:
The four-month high dose rifampicin regimens were safe.
<table><tr><td></td><td>Any grade 3 or 4 AEs</td><td>Any serious AEs</td><td>Deaths</td></tr><tr><td>(a)</td><td>10 (4.5%)</td><td>3 (1.3%)</td><td>8 (3.6%)</td></tr><tr><td>(b)</td><td>10 (4.4%)</td><td>3 (1.3%)</td><td>3 (1.3%)</td></tr><tr><td>(c)</td><td>9 (4.0%)</td><td>3 (1.3%)</td><td>5 (2.2%)</td></tr></table></td></tr>
<tr><td colspan="3">Jindani A. RIFASHORT. Presented at the Union World Conference on Lung Health during Researchers sharing with communities (part 1): shorter regimens for drug-sensitive TB [Community Connect, Track 4]. 2022 November 11. https://theunion.floq.live/event/worldconf2022/dailyprogramme?objectClass=timeslot&objectId=630f46a2c933270a967dd2d0&type=detail.</td></tr>
<tr><td rowspan="6">TRUNCATE-TB
NCT03474198
(DS-TB; 675; PLHIV not included)</td><td rowspan="6">(a) 2HR$_{Hd}$ZELz$_{600}$
(b) 2HR$_{Hd}$ZEC
(c) 2HP$_{1200}$ZLz$_{600}$Lx
(d) 2HZELz$_{600}$B
(e) [2HRZE/4HR]
Regimens (b) and (c) were stopped early for practical reasons.</td><td>Primary Efficacy Outcome:
The two-month bedaquiline- and linezolid-containing regimen (d) demonstrated non-inferiority to the standard of care (ITT). The NI margin was 12%.
<table><tr><td>Unfavorable outcomes:</td><td></td><td>Risk difference, experimental - control (95% confidence interval)</td></tr><tr><td>(a)</td><td>21/184 (11.4%)</td><td>7.2 (1.4 to 13.0)</td></tr><tr><td>(b)</td><td>NA</td><td>NA</td></tr><tr><td>(c)</td><td>NA</td><td>NA</td></tr><tr><td>(d)</td><td>11/189 (5.8%)</td><td>0.8 (-3.4 to 5.0)</td></tr><tr><td>(e)</td><td>7/181 (3.9%)</td><td>NA</td></tr></table></td></tr>
<tr><td>Primary Safety Outcome:
No statistically significant differences in safety were detected between arms.
<table><tr><td></td><td>Any grade 3 or 4 AEs</td><td>Any serious AEs</td><td>Deaths</td></tr><tr><td>(a)</td><td>30 (16.3%)</td><td>18 (9.8%)</td><td>5 (2.7%)</td></tr><tr><td>(d)</td><td>30 (16.2%)</td><td>14 (7.4%)</td><td>1 (0.5%)</td></tr><tr><td>(e)</td><td>27 (14.9%)</td><td>11 (6.1%)</td><td>3 (1.7%)</td></tr></table></td></tr>
<tr><td colspan="3">Paton N. Efficacy and safety results from the treatment strategy. Presented at the Union World Conference on Lung Health during SP-10 Two-month Regimens Using Novel Combinations to Augment Treatment Effectiveness for Drug-sensitive Tuberculosis (TRUNCATE-TB Trial). 2022 November 9. https://theunion.floq.live/event/worldconf2022/dailyprogramme?objectClass=timeslot&objectId=62d1102d56523d8cb086eed0&type=detail.</td></tr>
</table>

<table>
<tr><th>Study Name
(Type of TB; Sample Size)</th><th>Study Arms
Experimental Regimens
[Control Regimen]</th><th>Key Findings</th></tr>
<tr><td>SimpliciTB
NCT03338621
(DS-TB, RR-/MDR-TB; 455)</td><td>(a) 4BPaMZ
(b) [2HRZE/4HR]
(c) 6BPaMZ</td><td>Results forthcoming, CROI 2023</td></tr>
<tr><td>STREAM II
NCT02409290
(RR-/MDR-TB; 588)</td><td>(a) 4BCLxEZH$_{Hd}$Pto/5BCLxEZ
(b) 2BCLxZH$_{Hd}$K/4BCLxZ
(c) [4CLxEZH$_{Hd}$KPto/5CLxZE]</td><td>Primary Efficacy Outcome:
Both bedaquiline-containing regimens demonstrated non-inferiority and superior efficacy to the nine-month injectable-containing regimen (mITT). The NI margin was 10%.
<table><tr><th colspan="2">Unfavorable outcomes:</th><th>Risk difference, control-experimental (95% confidence interval)</th></tr><tr><td>(a)</td><td>34 (17%)</td><td>a-c1: 11 (2.9 to 19.0)</td></tr><tr><td>(b)</td><td>12 (9%)</td><td>b-c2: 22.2 (13.1 to 31.2)</td></tr><tr><td>(c1)</td><td>54 (29%)</td><td>NA</td></tr><tr><td>(c2)</td><td>40 (31%)</td><td>NA</td></tr></table>Primary Safety Outcome:
No significant differences in safety were detected between arms, except hearing loss observed at significantly higher rates in the nine-month injectable-containing control (c1) compared to the nine-month all-oral regimen (a).
<table><tr><th></th><th>Any grade 3 or 4 AEs</th><th>Any serious AEs</th><th>Deaths</th><th>Hearing loss</th></tr><tr><td>(a)</td><td>106 (50%)</td><td>38 (18%)</td><td>7 (3%)</td><td>4 (2%)</td></tr><tr><td>(b)</td><td>70 (55%)</td><td>27 (19%)</td><td>2 (1%)</td><td>6 (4%)</td></tr><tr><td>(c1)</td><td>108 (53%)</td><td>35 (17%)</td><td>5 (2%)</td><td>18 (9%)</td></tr><tr><td>(c2)</td><td>74 (54%)</td><td>26 (19%)</td><td>2 (1%)</td><td>11 (8%)</td></tr></table></td></tr>
<tr><td colspan="3">Goodall RL, Meredith SK, Nunn AJ, et al. Evaluation of two short standardised regimens for the treatment of rifampicin-resistant tuberculosis (STREAM stage 2): an open-label, multicentre, randomised, non-inferiority trial. Lancet. 2022 Nov 26;400(10366):1858–1868. doi: https://doi.org/10.1016/S0140-6736(22)02078-5.</td></tr>
</table>

<table>
<tr><th>Study Name
(Type of TB; Sample Size)</th><th>Study Arms
Experimental Regimens
[Control Regimen]</th><th colspan="4">Key Findings</th></tr>
<tr><td rowspan="11">TB-PRACTECAL
NCT02589782
(RR-/MDR-TB
Pre-XDR-TB; 552)</td><td rowspan="11">(a) 6BPaLzM
(b) 6BPaLzC
(c) 6BPaLz
(d) [9–20mo local SOC]</td><td colspan="4">Primary Efficacy Outcome:
All three bedaquiline- and pretomanid-based regimens demonstrated non-inferiority and an improved safety profile compared with the standard-of-care group (mITT). The NI margin was 12%.</td></tr>
<tr><td colspan="2">Unfavorable outcomes:</td><td colspan="2">Risk difference, experimental - control (95% confidence interval)</td></tr>
<tr><td>(a)</td><td>7 (11%)</td><td colspan="2">-37 (-53 to -22)</td></tr>
<tr><td>(b)</td><td>12 (19%)</td><td colspan="2">-30 (-45 to -14)</td></tr>
<tr><td>(c)</td><td>14 (23%)</td><td colspan="2">-25 (-41 to -9)</td></tr>
<tr><td>(d)</td><td>32 (48%)</td><td colspan="2">NA</td></tr>
<tr><td colspan="4">Primary Safety Outcome:
The incidence of AEs was lower in the groups receiving bedaquiline- and pretomanid-based regimens.</td></tr>
<tr><td></td><td>Any serious or grade 3+ AEs</td><td colspan="2">Deaths</td></tr>
<tr><td>(a)</td><td>14 (19%)</td><td colspan="2">0 (0%)</td></tr>
<tr><td>(b)</td><td>23 (32%)</td><td colspan="2">1 (2%)</td></tr>
<tr><td>(c)</td><td>15 (22%)</td><td colspan="2">0 (0%)</td></tr>
<tr><td>(d)</td><td>43 (59%)</td><td colspan="2">2 (3%)</td></tr>
<tr><td colspan="6">Nyang'wa BT, Berry C, Kazounis E, et al. A 24-week, all-oral regimen for rifampin-resistant tuberculosis. 2022 December 22. N Engl J Med;387:2331–2343. doi: 10.1056/NEJMoa2117166.</td></tr>
<tr><td rowspan="8">BEAT-TB India
CTRI/2019/01/017310
(Pre-XDR-TB; 165; PLHIV not included)</td><td rowspan="8">(a) 6BDLzC
(b) [none]</td><td colspan="4">Primary Efficacy Outcome:
The six-month bedaquiline- and delamanid-containing regimen was efficacious, producing a favorable outcome among 91% of participants at treatment completion and 86% of participants six months later (mITT).</td></tr>
<tr><td colspan="2">Unfavorable outcomes:</td><td colspan="2">Risk difference, experimental-control (95% confidence interval)</td></tr>
<tr><td>(a)</td><td>14 (9%)</td><td colspan="2">NA</td></tr>
<tr><td>(b)</td><td>NA</td><td colspan="2">NA</td></tr>
<tr><td colspan="4">Primary Safety Outcome:
The six-month bedaquiline- and delamanid-containing regimen was generally safe with most AEs easily identified and managed (e.g., anemia, neuropathy, skin hyperpigmentation).</td></tr>
<tr><td></td><td>Any grade 3 or 4 AEs</td><td>Any serious AEs</td><td>Deaths</td></tr>
<tr><td>(a)</td><td>47 events</td><td>33 events</td><td>4 deaths</td></tr>
<tr><td>(b)</td><td>NA</td><td>NA</td><td>NA</td></tr>
<tr><td colspan="6">Padmapriyadarsini C, Vohra V, Bhatnagar A, et al. Bedaquiline, delamanid, linezolid and clofazimine for treatment of pre-extensively drug-resistant tuberculosis. Clin Infect Dis. 2022 Jun 29:ciac528. doi: 10.1093/cid/ciac528.</td></tr>
</table>

<table>
<tr><th>Study Name
(Type of TB; Sample Size)</th><th>Study Arms
Experimental Regimens
[Control Regimen]</th><th colspan="4">Key Findings</th></tr>
<tr><td rowspan="6">BEAT Tuberculosis
NCT04062201
(RR-/MDR-TB, Pre-XDR; 374 enrolled, 199 included in interim analysis)</td><td rowspan="6">(a) 6BDLz (Lx, C, or both)
(b) [9–12mo SOC]</td><td colspan="4">Primary Efficacy Outcome:
The six-month bedaquiline- and delamanid-based regimen had similar efficacy to the standard-of-care regimen (ITT). The NI margin was 10%.</td></tr>
<tr><td colspan="2">Unfavorable outcomes:</td><td colspan="2">Risk difference, experimental-control (95% confidence interval)</td></tr>
<tr><td>(a)</td><td>13 (13%)</td><td colspan="2">-1.4 (-10.9 to 8.1)</td></tr>
<tr><td>(b)</td><td>14 (14%)</td><td colspan="2">NA</td></tr>
<tr><td colspan="4">Primary Safety Outcome:
The six-month bedaquiline- and delamanid-based regimen had similar safety to the standard-of-care regimen.</td></tr>
<tr><td></td><td>Any grade 3 or 4 AEs</td><td>Any serious AEs</td><td>Deaths</td></tr>
<tr><td>(a)</td><td>49 (25.7%)</td><td>33 (17.3%)</td><td>7 (3.7%)</td></tr>
<tr><td>(b)</td><td>51 (27.9%)</td><td>31 (16.9%)</td><td>6 (3.3%)</td></tr>
<tr><td colspan="6">Conradie F, Phillips P, Badet T, et al. High rate of successful outcomes treating RR-TB with a delamanid-bedaquiline regimen in BEAT Tuberculosis: an interim analysis. Presented at the Union World Conference on Lung health during LBTB The Union/CDC late-breaker session on TB. 2022 November 11. https://theunion.floq.live/event/worldconf2022/dailyprogramme?objectClass=timeslot&objectId=62fb512decb44417ab3bf64b&type=detail.</td></tr>
<tr><td rowspan="6">MDR-END
NCT02619994
(MDR-TB; 214; PLHIV not included)</td><td rowspan="6">(a) 9DLzLxZ
(b) [20mo IA-containing regimen]</td><td colspan="4">Primary Efficacy Outcome:
The nine-month delamanid-based regimen demonstrated non-inferiority to a 20-month injectable-containing regimen–the standard of care in 2014 (mITT). The NI margin was -10%.</td></tr>
<tr><td colspan="2">Unfavorable outcomes:</td><td colspan="2">Risk difference, experimental-control (95% confidence interval)</td></tr>
<tr><td>(a)</td><td>25 (29.4%)</td><td colspan="2">4.4 (-9.5 to ∞)</td></tr>
<tr><td>(b)</td><td>18 (25%)</td><td colspan="2">NA</td></tr>
<tr><td colspan="4">Primary Safety Outcome:
No statistically significant differences in safety were detected between arms.</td></tr>
<tr><td></td><td>Any grade 3 or 4 AEs</td><td>Any serious AEs</td><td>Deaths</td></tr>
<tr><td>(a)</td><td>29 (36.7%)</td><td>20 (25.3%)</td><td>5 (6%)</td></tr>
<tr><td>(b)</td><td>26 (29.2%)</td><td>19 (21.3%)</td><td>2 (2%)</td></tr>
<tr><td colspan="6">Mok J, Lee M, Kim DK, et al. 9 months of delamanid, linezolid, levofloxacin, and pyrazinamide versus conventional therapy for treatment of fluoroquinolone-sensitive multidrug-resistant tuberculosis (MDR-END): a multicentre, randomised, open-label phase 2/3 non-inferiority trial in South Korea. Lancet. 2022 Oct 29;400(10362):1522–1530. doi: 10.1016/S0140-6736(22)01883-9.</td></tr>
</table>

- Post-2021 definitions for pre-extensively drug-resistant TB (pre-XDR-TB) and extensively drug-resistant TB (XDR-TB) are used in Table 1, i.e., pre-XDR-TB: multidrug-resistant TB (MDR-TB) with additional resistance to the fluoroquinolones; XDR-TB: MDR-TB with additional resistance to the fluoroquinolones and other group A drugs (bedaquiline or linezolid).
- AEs = adverse events; CROI = Conference on Retroviruses and Opportunistic Infections, DS-TB = drug-sensitive TB; mITT = modified intention to treat, NI = non-inferiority margin; PLHIV = people living with HIV, RR-TB = rifampicin-resistant TB, SOC = standard of care
- 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; letters represent the individual drugs comprising each regimen.
- Subscripts indicate dosing in mg; Hd = high dose

Letters indicate TB drugs: B = bedaquiline, C = clofazimine, D = delamanid, E = ethambutol, H = isoniazid, IA = injectable agent, K = kanamycin, Lx = levofloxacin, Lz = linezolid, M = moxifloxacin, P = rifapentine, Pa = pretomanid, Pto = prothionamide, R = rifampicin, Z = pyrazinamide.

A joint statement published by TAG and the Global TB Community Advisory Board (TB CAB) summarized which of these results answer longstanding questions and validate existing policies.[6] The following paragraphs discuss which of these results should inform new policies and future research.

Results from **STREAM 2** validated the nine-month all-oral regimen (with bedaquiline given in place of the injectable agent) recommended by the WHO since 2020 for drug-resistant TB. The nine-month all-oral regimen – most recently recommended by WHO with two months of linezolid given in place of ethionamide – still plays an important role among populations with drug-resistant TB not eligible to receive the six-month pretomanid-based regimens validated in the **TB-PRACTECAL** and ZeNix trials (e.g., children, pregnant people). However, the relevance of the nine-month regimen may shift when results from **BEAT-TB** India and **BEAT Tuberculosis** (South Africa) undergo WHO policy review (especially given that the BEAT regimens are taken for just six months and are composed of four or five drugs, whereas the nine-month regimen is composed of up to seven drugs). BEAT Tuberculosis allowed for the enrollment of pregnant people and children 6 years of age and older.

The **MDR-END** trial is the first to evaluate a short regimen that contains delamanid without bedaquiline. The trial compared the investigational regimen to a 20-month regimen recommended by the WHO as the standard of care in 2014. This limits the MDR-END trial's relevance to the current drug-resistant TB treatment landscape, but these and other relevant delamanid data,[7] including those still expected from endTB in 2023, offer important new information and warrant a WHO policy review to re-examine the role of delamanid in the treatment of drug-resistant TB (last evaluated in 2018).

The four-month high-dose rifampicin-containing regimens evaluated in **RIFASHORT** ultimately failed to demonstrate non-inferiority to the six-month standard of care for drug-sensitive TB. Still, participants did well, and there were no safety issues. RIFASHORT and other rifampicin dose-optimization work conducted by the PanACEA network and published between 2015 and 2021 have set the stage for an iterative investigation to evaluate a four-month high-dose rifampicin-containing regimen given with and without moxifloxacin (OptiRiMoxTB; NCT05575518) – this and other ongoing and planned treatment-shortening trials of regimens composed of existing drugs are summarized in Table 2. If proven, a four-month high-dose rifampicin-based regimen might be more readily accessible than the current WHO-recommended four-month rifapentine-based regimen from TBTC S31/ACTG A5349, given rifapentine drug-supply and pricing issues that have hampered programmatic uptake.

Finally, the **TRUNCATE-TB** trial pushed treatment shortening for drug-sensitive TB beyond the four-month benchmark, demonstrating the ability of a bedaquiline- and linezolid-containing regimen to shorten treatment to just two months. However, the results of this proof-of-concept strategy trial should not be translated directly into policy, as further research is still required to optimize the regimen deployed within the TRUNCATE-TB strategy and to test the strategy itself in program settings and a broader population, including people living with HIV.

Table 2. Trials of Treatment-Shortening Regimens Composed of Existing Drugs

Study Name	Experimental Arms [Control]	For Treatment of	Number of Participants	Phase	Status [Est. Completion Date]
Drug-Sensitive TB					
A5362 / CLO-FAST NCT04311502	2CHPZE/1CHPZ [2HRZE/4HR]	DS-TB	185	IIc	Recruiting [Oct 2024]
HIGHSHORT-RP NCT04694586	$2HR_{Hd}ZE/2HR_{Hd}$ [2HRZE/4HR]	DS-TB	40	II	Recruiting [May 2026]
STEP2C	$3R_{Hd}HZM_{600}$ $3R_{Hd}HZHdM_{600}$ [2HRZE/4HR]	DS-TB	90 per arm	IIb/c	Not yet recruiting
ORIENT NCT05401071	$2HP_{600}MZ/2HP_{600}M$ $2HP_{900}MZ/2HP_{900}M$ $2HP_{1200}MZ/2HP_{1200}M$ [2HRZE/4HR]	DS-TB	2,904	III	Not yet recruiting
OptiRiMoxTB NCT05575518	$4HR_{Hd}ZE$ $4HR_{Hd}MZ$ [2HRZE/4HR]	DS-TB	414	III	Not yet recruiting
Hi-DoRi-3 NCT04485156	$1\text{-}2HR_{Hd}Z/3HR_{Hd}$ [2HRZE/4HR]	DS-TB	926	III	Not yet recruiting
PRESCIENT NCT05556746	2BDZCz [2HRZE/4HR]	DS-TB	156	IIc	Not yet recruiting
TBTC Study 38 / CRUSH TB	4BMZRb 4BMZD [2HRZE/4HR]	DS-TB	228	IIc	Not yet recruiting
ACTG A5414 / SPECTRA	Stratified medicine approach to shortening HPMZ	DS-TB	900	IIc	Protocol in development

Study Name	Experimental Arms [Control]	For Treatment of	Number of Participants	Phase	Status [Est. Completion Date]
Drug-Resistant TB					
endTB NCT02754765	9BLzMZ 9BLzLxCZ 9BLzLxDZ 9DLzLxCZ 9DMCZ [9–20mo SOC]	MDR-TB	754	III	Fully enrolled [Sept 2023]
BEAT-Tuberculosis NCT04062201	6BDLz (Lx, C, or both) [9–12mo SOC]	RR-TB, MDR-TB, Pre-XDR-TB	402	III	Fully enrolled [Jun 2023]
mBPaL NCT05040126	$2BPaLz_{600}/4BPaLz_{300}$ $3BPaLz_{600}/3BPaLz_{300}$ [$6BPaLz_{600}$]	Pre-XDR-TB, TI-NR-MDR-TB	400	III	Recruiting [Mar 2024]
endTB-Q NCT03896685	6BDLzC 9BDLzC [9–20mo SOC]	Pre-XDR-TB	324	III	Recruiting [Feb 2024]
DRAMATIC NCT03828201	$16wkBDCLxLz_{8wk}$ $24wkBDCLxLz_{8wk}$ $32wkBDCLxLz_{8wk}$ $40wkBDCLxLz_{8wk}$ [none]	MDR-TB	220	IIc	Recruiting [July 2025]
PROSPECT NCT05306223	9BLxCsCzLz 6LxCsCzZPtoLz	MDR-TB	212	IV	Recruiting [Aug 2025]
ACTG A5356 NCT05007821	$1BDCLz_{1200\ QD}/5BDCLz_{1200\ TIW}$ $6BDCLz_{600\ QD}$ [none]	RR-TB, MDR-TB, pre-XDR-TB	132	II	Recruiting [Sept 2025]

Post-2021 definitions for pre-extensively drug-resistant TB (pre-XDR-TB) and extensively drug-resistant TB (XDR-TB) are used in Table 2, i.e., pre-XDR-TB: multidrug-resistant TB (MDR-TB) with additional resistance to the fluoroquinolones; XDR-TB: MDR-TB with additional resistance to the fluoroquinolones and other group A drugs (bedaquiline or linezolid).

DS-TB = drug-sensitive TB, RR-TB = rifampicin-resistant TB, SOC = standard of care, TI-NR-MDR-TB = treatment-intolerant or non-responsive MDR-TB.

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, QD = once daily, TIW = thrice weekly.

Letters indicate TB drugs: B = bedaquiline, C = clofazimine, Cs = cycloserine, Cz = clofazimine, D = delamanid, E = ethambutol, H = isoniazid, IA = injectable agent, K = kanamycin, Lx = levofloxacin, Lz = linezolid, M = moxifloxacin, P = rifapentine, Pa = pretomanid, Pto = prothionamide, R = rifampicin, Z = pyrazinamide.

Pediatric Investigations of TB Drugs

Previously reported pediatric investigations of bedaquiline (Janssen C211, NCT02354014; IMPAACT 1108, NCT02906007) and delamanid (IMPAACT 2005; NCT03141060) are still ongoing. And the planned single-dose pediatric study of pretomanid is getting closer to opening (IMPAACT 2034; NCT05586230) – these data, and data from the multidose pretomanid study that will need to follow, are critical to ensuring children are able to benefit from the scientific progress that has enabled treatment shortening for drug-resistant TB to six months in adults.

Another critical gap standing between children and the shorter regimens currently recommended by the WHO for adults is the lack of a pediatric formulation of rifapentine, despite its position on the PADO-TB (Pediatric Antituberculosis Drug Optimization) priority list and both the Global Fund Expert Review Panel and WHO Pre-Qualification Program Expression of Interest lists for several years. Pediatric investigations of rifapentine for TB preventive treatment (TPT) are ongoing and planned (TBTC Study 35, NCT03730181; IMPAACT 2024), and in the last year there has been meaningful progress by the TBTC to plan a phase I/II pediatric pharmacokinetic, safety, and tolerability study of the four-month rifapentine- and moxifloxacin-containing regimen proven in TBTC Study 31/ACTG A5349 – the TBTC study is called Radiant Kids.

Finally, there are currently five compounds in phase IIb (see Table 3) – this is the stage at which pediatric investigational planning should begin, especially if we hope to close the seven- to thirteen-year gap that currently exists between when new TB medicines are approved for use in adults versus in children. A new group has recently formed, called the CHEETA Task Force (CHEETA stands for **Ch**asing **E**xpedited and **E**quitable **T**reatment **A**ccess for children), to engage industry, regulators, and other stakeholders regarding the status of pediatric investigational plans for new TB drugs in clinical development in adults and approaches to accelerating their initiation and completion.

Updates on New Drugs in Clinical Development for TB

Nineteen new or repurposed compounds are currently in clinical development for TB (see Table 3). This includes ten compounds from a new class or with a new mechanism of action and eight potentially advantaged alternatives to existing TB drugs, including one approved for other indications and now under investigation for TB.

In 2022, several phase IIa study results were published or presented, including for GSK-656 and BTZ-043.[8,9,10] Results from a phase IIb study of sutezolid (SUDOCU) will be presented at CROI 2023. With the opening of Otsuka's Trial 323-201-00006 in April 2022, OPC-167832 entered phase IIb/c, the first DprE1 inhibitor to do so. U.S. government-funded research networks – ACTG and TBTC – and newer public-private collaborations – PAN-TB (Project to Accelerate New Treatments for Tuberculosis) and UNITE4TB (academia and industry united innovation and treatment for tuberculosis) – have begun to publicly share their planned approaches to advancing new compounds and combinations through phase II (see Table 4). All the experimental regimens that will be evaluated in the first wave of trials advanced by these initiatives include a bedaquiline and delamanid or pretomanid backbone and will be measured against the six-month standard of care for drug-sensitive TB.

Table 3. New (and Repurposed) 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	IV	see Tables 2, 4	
pyrifazimine (TBI-166)	Riminophenazine	Inhibits ion transport and bacterial respiration	IMM/CAMS/ PUMC	IIa	ChiCTR1800018780 NCT04670120	
NEW → sudapyridine (WX-081)	Diarylquinoline	Inhibits ATP synthase	Shanghai Jiatan Pharmatech Co.	IIa/IIb	NCT04608955	
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 NCT05526911	
telacebec (Q203)	Imidazopyridine	Inhibits ATP synthesis (QcrB) and bacterial respiration	Qurient/ Infectex	IIa	NCT02530710 NCT02858973 NCT03563599	
Cell Wall Synthesis						
BTZ-043	Benzothiazinone	Inhibits cell wall synthesis (DprE1)	University of Munich/DZIF	Ib/IIa	NCT03590600 NCT04044001 NCT04874948	
BVL-GSK098	Amido-piperidine	Inhibits cell wall synthesis via boosting ethionamide	BioVersys/GSK	IIa	NCT04654143 NCT05473195	← NEW
delamanid	Nitroimidazole	Inhibits cell wall synthesis and bacterial respiration	Otsuka	IV	see Tables 2, 4	
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	IIb/c	NCT03678688 NCT05221502	← NEW
pretomanid	Nitroimidazole	Inhibits cell wall synthesis and bacterial respiration	TB Alliance	IV	see Tables 2, 4	
sanfetrinem	Carbapenem	Inhibits cell wall synthesis	GSK/GMRI	IIa	NCT05388448	← NEW
SQ109	Ethylenediamine	Inhibits cell wall synthesis (MmpL3)	Sequella	IIb	NCT01585636 NCT00866190 NCT01358162 NCT01218217 NCT01785186	
TBA-7371	Azaindole	Inhibits cell wall synthesis (DprE1)	TB Alliance/ GMRI/FNDR	IIa	NCT03199339 NCT04176250	

Drug	Class	Mechanism of Action	Sponsor	Phase	Clinical Trial(s)
Protein Synthesis					
delpazolid (LCB01-0371)	Oxazolidinone	Inhibits protein synthesis (50S ribosomal subunit)	LegoChem Biosciences	IIb	NCT01554995 NCT01842516 NCT02540460 NCT02836483 NCT04550832
sutezolid (PNU-100480)	Oxazolidinone	Inhibits protein synthesis (50S ribosomal subunit)	Sequella/TB Alliance	IIb/c	NCT00871949 NCT00990990 NCT01225640 NCT03199313 NCT03959566
NEW → tedizolid *repurposed	Oxazolidinone	Inhibits protein synthesis (50S ribosomal subunit)	Assistance Publique – Hôpitaux de Paris	IIa	NCT05534750
TBI-223	Oxazolidinone	Inhibits protein synthesis (50S ribosomal subunit)	TB Alliance/IMM	Ib	NCT03758612 NCT04865536
GSK3036656 (GSK-656)	Oxaborole	Inhibits protein synthesis (LeuRS)	GSK	IIa	NCT03075410 NCT03557281 NCT05382312 ← NEW
DNA Synthesis					
SPR720	Benzimidazole	Inhibits bacterial DNA synthesis (GyrB)	Spero Therapeutics/ GMRI	Ia/Ib	NCT03796910
Cholesterol Catabolism					
GSK2556286 (GSK-286)	Pyrimidine	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
FNDR: Foundation for Neglected Disease Research, Korea
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

Table 4. Trials of Investigational Regimens that Advance New Drugs

Study Name	Experimental Arms [Control]	For Treatment of	Number of Participants	Phase	Status [Est. Completion Date]
SUDOCU NCT03959566	$3BDMS_{600}$/3HR $3BDMS_{1200}$/3HR $3BDMS_{600\ BID}$/3HR $3BDMS_{800\ BID}$/3HR [3BDM/3HR]	DS-TB	75	IIb	*Results forthcoming, CROI 2023
DECODE NCT04550832	$4BDMDzd_{400}$ $4BDMDzd_{800}$ $4BDMDzd_{1200}$ $4BDMDzd_{800\ BID}$ [4BDM]	DS-TB	76	IIb	Fully enrolled [Mar 2024]
Trial 323-201-00006 NCT05221502	$4O_{10}BD$ $4O_{30}BD$ $4O_{90}BD$ [2HRZE/4HR]	DS-TB	120	IIb/c	Recruiting [Feb 2024]
A5409 / RAD-TB	2BPaL/4HR 2BPaS/4HR 2BPaTBI-223/4HR [2HRZE/4HR]	DS-TB	45 per arm	II	Protocol in development
Gates MRI-TBD06-201	2–4PaBOS 2–4DBOS [2HRZE/4HR]	DS-TB MDR-TB	43 per arm / 70 per arm	IIb/c	Protocol in development
UNITE4TB	2–4BDGM 2–4BDGZ 2–4BDGL 2–4BDTM 2–4BDTZ 2–4BDTL 2–4BDM [2HRZE/4HR]	DS-TB	33 per arm / 44 per arm	IIb/c	Protocol in development

CROI = Conference on Retroviruses and Opportunistic Infections, DS-TB = drug-sensitive TB, MDR-TB = multidrug-resistant TB

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; letters represent the individual drugs comprising each regimen.

Subscripts indicate dosing in mg; BID = twice daily.

Letters indicate TB drugs: B = bedaquiline, D = delamanid, E = ethambutol, Dzd = delpazolid, G = GSK-656, H = isoniazid, L = linezolid, M = moxifloxacin, O = OPC-167832, Pa = pretomanid, R = rifampicin, S = sutezolid, T = BTZ-043, TBI-223 = TBI-223, Z = pyrazinamide.

Conclusion

There has been substantial progress to improve TB treatment in recent years and to replenish the pipeline with new candidates. The four- and six-month regimens recommended by the WHO in 2021 and 2022, potentially with some modifications depending on recently completed, ongoing, and planned research, will likely be "it" for at least the next few years. As such, national governments should move quickly to update TB treatment policies and programs to provide access to these shorter, safer, and more effective regimens. A more ambitious, accelerated approach to translating research and global policy at the national level is urgently required to make up for ground lost in the global fight against TB in recent years. For the next generation of TB drugs and regimens making their way through the pipeline – as they progress from phase II to phase III, product and research sponsors need to prioritize a more inclusive research agenda and to accelerate pediatric investigations, to enable equitable access sooner. Finally, research and product sponsors urgently need to consider how to address the unmet needs of people with XDR-TB (people with multidrug-resistant TB with additional resistance to fluoroquinolones and at least one other group A drug, e.g., bedaquiline, linezolid). The approach to addressing the needs of people with XDR-TB should be two pronged, including both research and pre-approval access to new drugs. Without urgent action, people with XDR-TB will continue to be relegated to treatment regimens not recommended or used since the early 2000s, when a drug-resistant TB diagnosis was considered by many to be a death sentence.

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