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Tuberculosis Treatment

2026 Tuberculosis Treatment Pipeline Report

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Introduction

The tuberculosis (TB) treatment pipeline is bustling with activity. Trials are addressing unfinished business for short-course rifamycin- and bedaquiline-based regimens and new drugs are zipping through phase II studies with several already in or very soon to enter phase III. The speed with which new drugs are moving through middle development can be attributed to improved collaboration, new approaches that combine different elements of phase I and II studies, and platform trial designs. Phase II studies also avail smaller sample sizes powered to detect differences in interim endpoints (e.g., rates of sputum culture conversion) that are an important indicator of treatment efficacy but have a mixed record in terms of their ability to predict how regimens perform against long term clinical endpoints like relapse-free cure. Finally, selected study populations are also helping drugs move through phase II trials with greater speed. Drug sponsors are studying new drugs and regimens first among people with drug-sensitive TB – a population that’s easier to find and quicker to enroll – but phase III registrational trials and regulatory strategies remain focused on drug-resistant TB.

United States Government (USG) policies are a major source of concern and uncertainty for TB research, but the executive order that banned U.S. foreign aid and assistance to South Africa that threw South African research institutions and their collaborators around the world into a panic last year is no longer being applied to NIH funding.¹ Funding will flow through new, cumbersome mechanisms the National Institutes of Health (NIH) set up for funding collaborative international research projects (PF5).² The damage done to TB research in the 18 months the executive order was in effect has yet to be fully accounted for. Research interruptions and delays are expensive but the loss of site staff, expertise, and community trust following retrenchments is incalculable.

The 2026 Tuberculosis Treatment Pipeline Report covers a selection of results from recent studies and provides an overview of the state of the clinical TB treatment research pipeline in five tables. Table 1 reminds readers how studies with recent results were designed. Table 2 covers ongoing and planned trials of regimens composed of existing drugs. This year, the studies in Table 2 are organized not just by indication (drug-sensitive or -resistant TB), but also according to strategy and objective. For example, rifamycin-selection and -dose optimization studies are grouped together, as are studies to fill knowledge gaps in treating children. Studies are otherwise listed in the chronological order in which they are expected to be completed. A new addition, Table 3, covers host-directed therapies (HDTs) in phase II development or later. Table 4 lists new drugs in clinical development for TB and Table 5 covers trials of investigational regimens that advance these new drugs.

Highlights include results from two phase III studies (**SURE** and **INSPIRE-CODA**) and two phase II studies (**DECISION** and **NC-009**), and eight new drugs already in or soon to enter phase III (already in: quabodepistat, contezolid, sudapyridine, sitafloxacin; soon to enter: sorfequiline, ganfeborole, BTZ-043, delpazolid). This year's report also features a section describing how TB treatment trials are evolving to address person-centered outcome measures (PCOMs). The research and development of long-acting formulations of TB medicines is covered separately in the inaugural *Tuberculosis Long-Acting Technologies Pipeline Report*, available [here](#).

Figure 1. Global Pipeline of Medicines in Clinical Development for TB

Phase 1	Phase 2	Phase 3	Regulatory Market Approvals
Bedaquiline (long acting) TBD11 (CLB073) AKG-100 (long acting)	Sorfequiline (TBAJ-876) TBAJ-587 JDB0131 TBD09 (MK-7762) TBI-223 Delpazolid Tedizolid Sutezolid BTZ-043 Macozinone (PBTZ-169) TBA-7371 Pyrifazimine (TBI-166) Ganfeborole (GSK-656) Telacebec (Q203) Alpibectir (BVL-GSK098) SQ-109	Sudapyridine (WX-081) Sitafloxacin Contezolid Quabodepistat (OPC-167832)	Bedaquiline Delamanid Pretomanid Linezolid Clofazimine* Moxifloxacin* Levofloxacin*

Figure adapted from Stop TB Partnership Working Group on New Drugs.

Diarylquinoline; Oxazolidinone; DprE1 inhibitor; Riminophenazine Nitroimidazole; Fluroquinolone.

Drugs that appear in black font are from classes and/or with mechanisms of action not otherwise represented by the other colors.

* Approved for other indications and used off-label for TB

Results of Recent Studies

SURE was a phase III trial of a short, intensive regimen for the treatment of TB meningitis (TBM) in children. The trial compared a six-month regimen of isoniazid, rifampicin, pyrazinamide, and levofloxacin, all given at higher doses, to the 12-month standard of care regimen recommended by the World Health Organization (WHO) for treating TBM in children (2HRZE/10HR). The trial also evaluated the effect of high dose aspirin vs. placebo given as an adjunctive therapy for the first two months of treatment. Corticosteroids were given to children in both arms as part of usual care. Both regimens performed well: 86% of 369 children enrolled in the trial survived with 80% free from disability, but the shorter intensive regimen failed to demonstrate non-inferiority to the longer standard of care (the non-inferiority margin was 10%).³ By 48 weeks of follow-up, 16% (29) of the children who received the shorter, intensive regimen had died compared to 12%

(21) who received the standard treatment (aRD=5.1% [95% CI: -1.7 to 12.0%, p=0.14]).⁴ Aspirin also failed to demonstrate any benefit in terms of mortality or neurological disability, instead showing a quantitatively but non-statistically significant increased risk of harm. By 48 weeks of follow-up, 22% (38/176) of children in the aspirin group had severe disability or died compared to 15% (25/170) in the placebo group (aOR=1.80 [95% CI: 0.95 to 3.41, p=0.07]).⁵

On overall safety, children that received the shorter, intensive regimen had more side-effects: 54% (100/186) of children treated with the intensive regimen experienced at least one Grade 3 or 4 adverse event compared to 43% (79/183) of children treated with the standard of care (p=0.04).⁶ The difference in safety was driven by liver toxicity that required treatment interruption or changes.⁷ Similarly, children given aspirin experienced more side effects with 56% (103/185) experiencing at least one Grade 3 or 4 adverse event compared to 41% (76/184) of children given placebo (p=0.006).⁸

These findings call into question a six-month, intensive regimen that's conditionally recommended by the WHO as an alternative to the 12-month standard of care for treating TBM in children.⁹ The only differences between the six-month intensive regimen evaluated in the SURE trial (6H₂₀R₃₀Z₄₀L₂₀) and the one conditionally recommended by the WHO (6H₂₀R₂₀Z₄₀Eto₂₀) is that the latter includes ethionamide instead of levofloxacin and doses rifampicin at 20 mg/kg instead of 30 mg/kg used in the trial. The conditionally recommended shorter, intensive regimen has long been the standard of care in South Africa but has never been evaluated in a randomized controlled trial (RCT). The conditional WHO recommendation was made based on a systematic review and meta-analysis of data from observational studies (hence the “very low certainty of evidence” categorization that accompanies the recommendation). Though the results are disappointing, SURE is the first large, phase III RCT to offer high-quality evidence on the treatment of TBM in children. The results mirror a similar negative finding in a RCT of a high dose rifampicin-based regimen administered to adults with TBM from the HARVEST trial published in 2025.¹⁰ We urgently need more research to optimize regimens and improve outcomes for this difficult to treat and difficult to study form of TB in both children and adults (see Table 2), and to evaluate whether any of the new drugs have good cerebrospinal fluid penetration.

INSPIRE-CODA is a phase III trial comparing a 6-month contezolid-containing regimen to an 18-month standard of care regimen containing linezolid for the treatment of rifampicin-resistant TB in China (see Table 1). Based on an interim analysis of 212 participants, the study team reported favorable outcomes among 85.6% (77/90) of participants given the contezolid-containing regimen at the end of treatment.¹¹ Rates of **sputum culture conversion (SCC)** at eight weeks were similar between arms (83.3%

Sputum culture conversion (SCC) is a way to measure the efficacy of a drug against TB. SCC measures how many cultures “convert” from positive to negative by 8 weeks of treatment. SCC is an interim, bacteriologic measure of efficacy, it doesn't perfectly predict clinical outcome, i.e., if a drug or regimen will result in relapse free cure.

vs. 81.7%, $p=0.93$). The big difference reported was in terms of safety. Participants in the contezolid-containing arm reported fewer adverse events overall (38.9% vs. 67.7%) and fewer linezolid related toxicities compared to participants in the control arm (peripheral neuropathy: 2.8% vs. 17.2%, myelosuppression: 5.6% vs. 28.0%). The most common adverse events in the contezolid-containing arm were gastrointestinal events (13.5%) and transaminase elevations (9.0%). These interim results suggest contezolid may be a viable, safer alternative to linezolid, but this needs to be confirmed by the final outcome analysis.

DECISION/ UNITE4TB-02 was a phase IIb dose-ranging study of a novel DprE1 inhibitor, BTZ-043. Ninety-two participants were randomized among four arms: bedaquiline and delamanid given with BTZ-043 at 500mg, 1,000mg, or 1,500mg, or with moxifloxacin. The arms in which BTZ-043 was dosed at 1,000mg and 1,500mg performed similarly to the bedaquiline-delamanid-moxifloxacin arm (based on **time to positivity [TTP]**).¹² Three participants—one in each BTZ-043 arm—experienced serious adverse events (two of these were liver toxicity). Nine participants experienced Grade 3 adverse events. These findings informed dose selection for the trials listed in Table 5.

NC-009 was a phase IIb dose-ranging study of sorfequiline (formerly TBAJ-876), a second generation diarylquinoline, given in combination with pretomanid and linezolid. Three hundred and nine participants were randomized to five treatment arms including three doses of sorfequiline: 25mg, 50mg, and 100mg (see Table 1). The proportion of participants with SCC by week eight were 31%, 48%, and 59% for the 25mg, 50mg, and 100mg sorfequiline arms, respectively compared to 45% for both the BPaL and HRZE arms.¹³ By week 15 the proportion of participants with SCC were 76%, 86%, and 93% for the 25mg, 50mg, and 100mg sorfequiline arms, respectively compared to 89% and 88% for the BPaL and HRZE arms.¹⁴ The investigators reported fewer Grade 3 or higher treatment-emergent adverse events in the sorfequiline and BPaL arms compared to the HRZE arm. These findings suggest that sorfequiline has dose-dependent efficacy and comparable safety across doses and to existing standard of care regimens up to the first eight weeks of treatment. An ongoing phase IIb study (**NC-010**) will provide additional safety data (with sorfequiline given for four months) and determine if the dose of sorfequiline can be further optimized before phase III (see Table 5).

Time to positivity (TTP)

is another way to measure the efficacy of a drug against TB. Sputum samples are taken and cultured on a weekly basis. The TB bacterial load is then measured by how long it takes the culture to become positive. The longer the TTP the lower the bacterial load. TTP is an interim, bacteriologic measure of efficacy, it doesn't perfectly predict clinical outcome, i.e., if a drug or regimen will result in relapse free cure.

Table 1. Studies with Recent Results

Study Name	Experimental Arms [Control]	Indication	Number of Participants	Phase	Primary Endpoints
SURE ISRCTN40829906	6HR _{Hd} ZLx ± aspirin [2HRZE/10HR ± aspirin]	TBM (children)	369	III	Mortality Disability
INSPIRE-CODA NCT06081361	6BDCzd (Fq or Cz) [6BLzCsCzFq/12CsCzFq] ^α ^α For FQ-R, Lx will be replaced by Pto, Z, PAS, or E.	MDR-TB, pre-XDR- TB	212	III	SCC* Safety*
DECISION/ UNITE4TB-02 NCT05926466	4BDT ₅₀₀ /2HR 4BDT ₁₀₀₀ /2HR 4BDT ₁₅₀₀ /2HR [4BDM/2HR]	DS-TB	92	IIb	TTP SCC
NC-009 NCT06058299	2S ₂₅ PaL/2-4HR 2S ₅₀ PaL/2-4HR 2S ₁₀₀ PaL/2-4HR 6BPaL [2HRZE/4HR]	DS-TB	309	IIb	SCC

* These are the endpoints that were presented in the interim analysis shared during the 2025 Union Conference. The primary efficacy endpoints for the trial are favorable outcome at treatment completion and after 24 months of follow up.

- DS-TB = drug-sensitive TB; MDR-TB = multidrug-resistant TB (resistant to rifampicin and isoniazid); pre-XDR-TB = pre-extensively drug-resistant TB (resistant to rifampicin, isoniazid, and fluoroquinolones); TBM = TB meningitis; SCC = sputum culture conversion; TTP = time to positivity
- 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
- Letters indicate TB drugs: B = bedaquiline, Cz = clofazimine, Czd = contezolid, Cs = cycloserine, D = delamanid, E = ethambutol, Fq = fluoroquinolone (M or Lx), H = isoniazid, Lx = levofloxacin, L, Lz = linezolid, M = moxifloxacin, Pa = pretomanid, PAS = para-aminosalicylic acid, Pto = prothionamide, R = rifampicin, S = sorfequiline, T = BTZ-043, Z = pyrazinamide

Ongoing and Planned Trials that Fill Data Gaps for Existing Regimens

Researchers are chipping away at remaining data gaps for the short-course TB treatment regimens introduced since 2020. The four-month rifapentine- and moxifloxacin-containing regimen can be safely given to people living with HIV (PLHIV) on dolutegravir-based antiretroviral therapy. **A5406** ([NCT05630872](#)) determined that twice-daily dolutegravir is safe and effective at maintaining target concentrations and viral suppression during four months of treatment with HPMZ.¹⁵ Data gaps keeping children and pregnant women from accessing HPMZ will be addressed by **SMILE-TB** and **IMPAACT study 2047** (see Table 2). **Radiant-Kids** has not yet been funded.

Fixed-dose-combinations (FDCs) of HPM/Z submitted to the WHO Pre-Qualification Program (PQ) are expected to address the four-month regimen's high pill burden, bringing it down to just four tablets per day, the same as HR/ZE. However, cost and tolerability

remain key concerns.¹⁶ As such, several ongoing and planned studies are examining whether treatment duration, rifamycin selection, and dosing can be further optimized (see Table 2). Two such studies, **STEP2C-01** and **OptiRiMoxTB** will report results at the 2026 Union Conference in Rio. Short-course, rifamycin-sparing regimens are also under investigation for the treatment of drug-sensitive TB. For example, **TBTC Study 38/CRUSH-TB** is evaluating four-month regimens built on a bedaquiline, moxifloxacin, pyrazinamide backbone — results from wave I of the study will be presented at the Union Conference in Rio.

Ongoing and planned drug-resistant TB treatment studies are evaluating different durations of bedaquiline- and pretomanid- or delamanid-containing regimens (**PRISM-TB**, **DRAMATIC**), and how to modify BPAL-based regimens when there is additional bedaquiline resistance (**BacTR**) — see Table 2 for additional details.

Data from **A5356** (NCT05007821) presented earlier this year confirmed the linezolid dosing strategy currently recommended by the WHO in the context of a pretomanid-sparing regimen (6BDLC). The study found that both linezolid dosing strategies (600mg daily and 1,200mg daily for four weeks and then thrice weekly) had high rates of culture conversion by the end of treatment (95%). However, the 1,200mg dose did not improve efficacy or safety over the 600mg dose recommended by the WHO. The higher dose was associated with less rapid time to culture conversion and less favorable treatment outcomes (16% vs. 8%), driven by more premature treatment discontinuations.¹⁷ How the two dosing strategies compare based on outcomes at 72 weeks (10 months after treatment completion) is still under evaluation.

BDLC is also the regimen that was evaluated for people with RR-/MDR-TB with additional fluoroquinolone resistance (pre-XDR-TB) in the endTB-Q trial. The results of the endTB-Q trial (covered in the *2025 TB Treatment Pipeline Report*) prompted a review of the WHO guidelines for treating pre-XDR-TB earlier this year. Based on data from **endTB-Q**, **BEAT Tuberculosis**, and **TB-PRACTECAL**,* the WHO recently recommended a stratified medicine approach to treating pre-XDR-TB.¹⁸ The updated treatment guidelines recommend that people with non-severe disease receive BPAL (or BDLC) and people with severe disease receive BPALC (or a longer individualized regimen). A stratified medicine approach to using BPAL/C has not been formally studied but a prospective cohort study in Belarus and Uzbekistan offers some reassurance. Successful treatment outcomes were documented in 90.4% (207/229) of people with pre-XDR-TB treated with BPALC.¹⁹ Follow up of the cohort, including to ascertain recurrences, is ongoing.

BDLC (for non-severe disease) and a longer individualized regimen (for severe disease) are recommended by WHO for people with pre-XDR-TB who are ineligible to receive pretomanid-based regimens. For pregnant women and children under age 14, pretomanid ineligibility is due to safety data gaps. Encouragingly, the single-dose pediatric study of pretomanid has been completed (**P2034**; NCT05586230). Results were presented during the 2025 Union Conference; a single dose of pretomanid was safe and well tolerated.²⁰ The protocol for a multi-dose study is being developed by the IMPAACT network (**P2051**). The TB Alliance has compiled and published all available pre-clinical and clinical data relevant to the use of pretomanid during pregnancy, establishing an important evidence-base for formally studying pretomanid during pregnancy.²¹ Of note, pregnant women in their second or third trimester are eligible to enroll in **PRISM-TB**, which is evaluating a stratified medicine approach to RR-/MDR-TB treatment using BPALM.

* For more information about these trials see TAG's TB Treatment Pipeline Reports published in 2022 and 2025.

Table 2. Trials of Regimens Composed of Existing Drugs

Study Name	Experimental Arms [Control]	Indication	Number of Participants	Phase	Status [Est. Completion Date]
Drug-Sensitive TB					
STEP2C-01 NCT05807399	4R _{Hd} HZM ₆₀₀ 3R _{Hd} HZ _{Hd} M ₆₀₀ [2HRZE/4HR]	DS-TB	270	IIb/c	Results forthcoming at Union 2026
OptiRiMoxTB NCT05575518	4HR _{Hd} ZE 4HR _{Hd} MZ [2HRZE/4HR]	DS-TB	414	III	Results forthcoming at Union 2026
2021010 NCT05047055	2HRZEM/2HREM [none]	DS-TB	550	III	Completed in Apr 2026
PORT NCT06057519	2HR _{Hd} ZE/4HR _{Hd} [2HRZE/4HR]	DS-TB	164	III	Recruiting [Dec 2026]
ORIENT NCT05401071	2HP ₆₀₀ MZ/2HP ₆₀₀ M* 2HP ₉₀₀ MZ/2HP ₉₀₀ M 2HP ₁₂₀₀ MZ/2HP ₁₂₀₀ M [2HRZE/4HR] *P ₆₀₀ dosing strategy dropped after stage 1	DS-TB	2,442	II/III	Stage 1 results published Aug 2026 ²² Stage 2 recruiting [Nov 2027]
PRaCTISe-HR CT026/02/102698	2HR ₂₅ ZE/4HR ₁₀ E 2HR ₂₅ ZE/4HR ₂₅ E 2HR ₂₅ ZELx/2HR ₂₅ ELx [SOC]	DS-TB	2,500	III	Recruiting [Dec 2029]
A5414 / SPECTRA-TB NCT07595042	10wkHP ₁₅₀₀ MZ 12wkHP ₁₅₀₀ MZ 14wkHP ₁₅₀₀ MZ 16wkHP ₁₅₀₀ MZ 18wkHP ₁₅₀₀ MZ 26wkHP ₁₅₀₀ MZ [2HRZE/4HR] Duration assigned depending on risk score (lower risk: 10-18wk; higher risk: 26wk).	DS-TB	900	IIc	Not yet recruiting [Oct 2029]

Study Name	Experimental Arms [Control]	Indication	Number of Participants	Phase	Status [Est. Completion Date]
RIFastrat NCT07118696	2HR _{Hd} ZE/2HR _{Hd} [2HRZE/4HR]	DS-TB nonsevere	1,400	III	Not yet recruiting [Jan 2030]
SMILE-TB NCT06253715	2HPMZ [SOC]	DS-TB (children)	860	III	Recruiting [Sept 2027]
REDUCE TB NCT07656012	2HRZE 2HRZE/3wksHR 2HRZE/6wksHR 2HRZE/9wksHR [SOC]	DS-TB (children)	230	IIc	Not yet recruiting
Radiant-Kids	Pediatric PK and safety study of 4HPMZ	DS-TB (children)	60	I/II	Protocol in development – seeking funding
IMPAACT 2047 / RADIANT-MOMS	2HPMZ/2HPM [2HRZE/4HR]	DS-TB (pregnant women)	TBD	II	Protocol in development
RADIO-TB NCT07163143	2HRZE 2HRZE/1HR 2HRZE/2HR 2HRZE/3HR [2HRZE/4HR – immediate] [2HRZE/4HR – deferred]	aTB	784	III	Not yet recruiting [Apr 2029]
<i>Rifamycin-sparing regimens for treatment shortening</i>					
TBTC Study 38 / CRUSH-TB NCT05766267	2BMZRb/2BMRb 2BMZD/2BMD [2HRZE/4HR]	DS-TB	292	IIc	Results forthcoming at Union 2026
PRESCIENT NCT05556746	3BDZC [2HRZE/4HR]	DS-TB	94	IIc	Active, not recruiting [Jan 2027]
<i>Treatment optimization for TB meningitis</i>					
INTENSE-TBM NCT04145258	2HR _{Hd} ZEL/7HR ± aspirin [2HRZE/7HR ± aspirin]	TBM	768	III	Recruiting [Sept 2026]
A5384 / IMAGINE- TBM NCT05383742	2HR _{Hd} ZL/4HR _{Hd} [2HRZE/7HR]	TBM	330	II	Recruiting [Sept 2029]

Study Name	Experimental Arms [Control]	Indication	Number of Participants	Phase	Status [Est. Completion Date]
INSHORT NCT05917340	2HR _{Hd} ZM/4HRZ + aspirin, steroid 2HR _{Hd} ZM/4HRZ + steroid [2HRZE/7HR]	TBM	372	III	Recruiting [Sept 2028]
STUDY00024610 NCT07227779	1BP _a LMZ/5BP _a M [HRZE]* *The phase IIa is a single arm safety study; phase IIb will be an RCT.	TBM	IIa: 40 IIb: 272	IIa/b	Recruiting [IIa: Dec 2027] [IIb: Sept 2030]
Drug-Resistant TB					
PROSPECT NCT05306223	6B*LLxCsCz/4LxCsCz 9LLxCsCzZPto** *B extended to 9 months if cultures remained positive at week 16 **Pto given for first 4 months only	MDR-TB	217	IV	Interim results published in 2026 ²³ Final results forthcoming in 2027 ²⁴
PA-824-401 Study	6-9BP _a L/M [none]	MDR-TB, pre-XDR-TB	110	IV	Active, not recruiting [Jan 2027]
BDL Study	6-9BDL [none]	MDR-TB	45	III	Active, not recruiting [2027]
DRAMATIC NCT03828201	16wkBDCLxL _{8wk} 24wkBDCLxL _{8wk} 32wkBDCLxL _{8wk} 40wkBDCLxL _{8wk} [none]	MDR-TB	271	IIc	Active, not recruiting [May 2027]
INSPIRE-TB NCT05081401	9BLFqCsC 9BLFqCsZ 9BLFqCsZ* 9BFqCsCZ 9FqCsCZ 9BLCsCZ [Chinese SOC] *L given for first 2 months only	MDR-TB, pre-XDR-TB	1,050	III	Recruiting [Dec 2027]

Study Name	Experimental Arms [Control]	Indication	Number of Participants	Phase	Status [Est. Completion Date]
BacTR DOH-27-052026-6539	6-18B _{Hd} PaL + AmCpmLx _{Hd} Cs* [none – historical 9-18mo SOC] *Referred to as “BPaLLplus” – depending on resistance, other group B and C drugs swapped in until at five-drug regimen.	At risk of or confirmed BDQ-R TB	125	III	Recruiting [Dec 2029]
PRISM-TB NCT06441006	3BPaLM* 6BPaLM* 4BPaLM [SOC] *Duration assigned depending on risk score.	MDR-TB	400	II/III	Recruiting [Aug 2031]
TMC207-C211 NCT02354014	Pediatric PK and safety study of bedaquiline	MDR-TB (children)	60	II	Recruiting [Nov 2028]
IMPAACT 2051	Pediatric PK and safety study of pretomanid given as BPaL/M	MDR-TB, pre-XDR-TB (children)	50	II	Protocol in development
■ aTB = asymptomatic TB, defined in the RADIO-TB trial as radiographically apparent but bacteriologically unconfirmed TB; BDQ-R = bedaquiline-resistant; DDI = drug-drug interaction; DTG = dolutegravir; DS-TB = drug-sensitive TB; MDR-TB = multidrug-resistant TB; PK = pharmacokinetics; pre-XDR-TB = pre-extensively drug-resistant TB; RR-TB = rifampicin-resistant TB; SOC = standard of care; TBD = to be determined; TBM = tuberculous meningitis; XDR-TB = extensively drug-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 (i.e., wk = weeks, mo = months); 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: Am = amikacin, B = bedaquiline, C, Cz = clofazimine, Cpm = carbapenem, Cs = cycloserine, D = delamanid, E = ethambutol, Fq = fluoroquinolone (M or Lx), H = isoniazid, Lx = levofloxacin, L = linezolid, M = moxifloxacin, P = rifapentine, Pa = pretomanid, Pto = prothionamide, R = rifampicin, Rb = rifabutin, Z = pyrazinamide					

Person-Centered Outcome Measures

TB treatment trials typically evaluate how regimens perform based on microbiological and clinical endpoints, (e.g., sputum culture conversion, cure, relapse, death, and safety measured by Grade 3+ and severe adverse events). These endpoints don't capture treatment or recovery experiences or answer questions about how regimens perform against other indicators that are important to people on TB treatment or with lived experience with TB, referred to as “person-centered outcome measures,” or PCOMs. “PCOMs” is sometimes incorrectly used interchangeably with

“patient reported outcomes (PROs)”. PROs come directly from the patient and primarily reflect health status in terms of patient-reported feeling and/or function — these are often captured using quality of life (QoL) questionnaires. PCOMs are a broader category of health metrics that patients identify as meaningful or important to them. PROs can be PCOMs, but PCOMs are not limited to PROs.

PCOMs might include measures like “home time”— the number of days spent at home without in-person healthcare interactions.²⁵ They might also include outcomes designed to better capture tolerability, like completion of an assigned study regimen within a specific time frame, or measuring the overall burden of treatment side-effects over time (not just the highest degree experienced as is traditionally reported on). PCOMs could include measures of post-TB respiratory symptoms and lung function.

The adoption of PCOMs will help to ensure that research reflects community priorities and will facilitate adoption. Demonstrating non-inferiority against traditional endpoints provides incomplete information needed to write policy and change practice. A community-informed, prioritized list of PCOMs is urgently needed to inform future study designs and research to policy translation. In the meantime, there is growing interest among research and product sponsors in better capturing how regimens are experienced by people with TB. Some of this interest is starting to show up in trial designs, but mostly as PROs captured via standard quality of life questionnaires:

- An amendment to **CRUSH-TB** to enrich the enrollment of priority populations (i.e., PLHIV, people 55 years and older) in wave 1A of the study also introduced an acceptability assessment and a physical, mental, and social health-related quality of life questionnaire (PROMIS-29).
- **PRISM-TB** includes an acceptability sub-study and the primary outcome for stage I of the trial will be analyzed using a Desirability of Outcome Ranking (DOOR) endpoint that incorporates efficacy, safety (Grade 3 or higher adverse events), and tolerability (treatment changes).²⁶
- **PARADIGM4TB** includes a quality-of-life questionnaire to capture information across five domains: physical, social, emotional, spiritual, functional wellbeing (FACIT-TB).
- In **QUANTUM-TB**, Otsuka is incorporating a variety of patient reported outcomes and functional assessments, including a mental and physical health survey (SF-36), a respiratory questionnaire and function test, and patient reported assessments of the severity and impact of adverse events related to treatment (PRO-CTCAE).²⁷

Researchers are also paying more attention to lung health after TB cure by identifying risk factors, designing trials to better capture longer term outcomes, and studying interventions to protect people from “post-TB lung disease” or PTLT.^{28,29} One such intervention, HDT, is offered during TB treatment to modify the immune response to TB to make treatment more effective and protect against damage caused by inflammation (see Table 3).

Table 3. Trials of Host-Directed Therapies

Study Name	Experimental Arms [Control]	Indication	Number of Participants	Phase	Status [Est. Completion Date]
ATORTUB NCT06199921	Astin ₂₀ Astin ₄₀ Astin ₆₀ [2HRZE/4HR]	DS-TB	440	II	Recruiting [Sept 2026]
DIRECT NCT06446245	8wkDoxy [SOC]	TBM	200	II	Recruiting [Dec 2027]
TIMPANI NCT05590455	ADA* [SOC] *Given by injection once every two weeks for the first 10 weeks of treatment	TBM	130	II	Recruiting [Dec 2027]
Gates MRI TBD15-201 NCT07517445	2NAM ₁₅₀₀ 2NAM ₂₅₀₀ [2BPAL*] *After 2 months, participants complete treatment with the SOC.	DS-TB	165	II	Temporarily suspended
AHA-PLUS NCT07393438	AHA ₅₀₀ AHA ₇₅₀ AHA ₁₀₀₀ [6-9BDLLfxC or 6-9BDCZ]	MDR-TB	120	II	Not yet recruiting
panTB-HM NCT05686356	4BPau ₁₂₀₀ 4BPau ₁₆₀₀ 4BPau ₁₆₀₀ + NAC ₁₈₀₀ BID [2HRZE/4HR]	DS-TB	352	II/III	Results forthcoming at Union 2026
AIPH-TB-RCT-P2 NCT07467252	HCQ [2HRZE/4HR]	DS-TB	200	II	Not yet recruiting
NAC-PTLD NCT06909799	NAC [2HRZE/4HR]	DS-TB	242	III	Recruiting [Dec 2027]

Study Name	Experimental Arms [Control]	Indication	Number of Participants	Phase	Status [Est. Completion Date]
Doxy-TB NCT05473520	2Doxy [2HRZE/4HR]	DS-TB	150	III	Recruiting [Jan 2030]
TB-MET-NAC NCT07136987	Metformin NAC [2HRZE/4HR]	DS-TB	1,104	III	Not yet recruiting

- Unless otherwise indicated, HDTs are added to the same regimen as the control arm.
- 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, mo = months); 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; SOC = standard of care
- ADA = Adalimumab, AHA = Acetohydroxamic Acid, Astin = atorvastatin, B = bedaquiline, Doxy = Doxycycline, E = ethambutol, H = isoniazid, HCQ = Hydroxychloroquine, NAC = N-Acetylcysteine, NAM = Nicotinamide (vitamin B3), Pa = pretomanid, R = rifampicin, U = sutezolid, Z = pyrazinamide

Updates on New Drugs in Clinical Development for TB

The pipeline contains a total of 22 new or repurposed drugs in clinical development for TB. The latest entries are JDB0131, a next generation nitroimidazole sponsored by WestVac Biopharma, and AKG-100, a long-acting, intravenous oxazolidinone sponsored by Akagera Medicines.^{30,31} More information on long-acting formulations of TB drugs that are getting closer to entering the clinical pipeline are reported separately (see TAG's inaugural *Tuberculosis Long-Acting Technologies Pipeline Report*). One compound fell out of the pipeline in 2026: GSK is no longer pursuing the development of sanfetrinem cilexetil for TB.^{32,33}

In the last year, several compounds have advanced to the next stage of development, and results from the first phase III studies of the next generation diarylquinolines (sudapyridine) and oxazolidinones (sutezolid, contezolid) are expected later this year. These and other updates are summarized in the bullet points below, organized by drug class. More information about each compound and the trials advancing them through clinical development can be found in Tables 4 and 5.

Oxazolidinones (possible advantaged alternatives to linezolid)[†]

- TBD09 sponsored by the Gates Medical Research Institute entered phase IIa ([NCT07525427](#)).
- Delpazolid sponsored by LigaChem will soon enter phase III (**MDR-END Plus**).
- Results from **panTB-HM**, a phase IIc trial to evaluate whether sutezolid given with bedaquiline and pretomanid can shorten treatment for DS-TB to four months will be presented at the Union Conference in Rio.

[†] Next generation oxazolidinones are expected to have similar efficacy to linezolid but with less toxicity.

- Final results from **INSPIRE-CODA**, a phase III trial of contezolid given in place of linezolid in the BEAT Tuberculosis regimen (6BDLLC) for MDR-TB and pre-XDR-TB will be presented at the Union Conference in Rio. Interim results of another phase III trial of contezolid (**C-STAR**) will also be presented there.

Diarylquinolines (possible advantaged alternatives to bedaquiline)[‡]

- Sorfequiline, sponsored by the TB Alliance, will soon enter phase III. It will be evaluated in combination with PaL/M for four months and compared to six months of BPaL/M for a drug-resistant TB indication (basically a 1:1 swap of sorfequiline for bedaquiline in the BPaL/M regimen with a shorter duration of treatment). A second phase IIb study (**NC-010**) is being conducted to collect additional safety data and optimize the dose of sorfequiline taken into phase III. The phase III study is projected to open in 2027.³⁴
- TBAJ-587, also sponsored by the TB Alliance, entered phase IIa (**SYNERGY**).
- Results from **WISH**, a phase III trial of sudapyridine given for six months on top of an optimized background regimen for MDR-TB will be presented at the Union Conference in Rio.

Fluoroquinolones (possible advantaged alternatives to moxifloxacin and levofloxacin)[§]

- Sitafloracin, sponsored by Daiichi Sankyo, entered phase III (**PAN-USR TB**).

New drugs with novel mechanisms of action:

- TBD11 (inhibits cholesterol metabolism), sponsored by the Gates Medical Research Institute, completed phase I (**NCT06707142**). Results will be presented at the 2026 Union Conference in Rio.
- Alpibectir, an ethionamide booster sponsored by GSK (pulmonary TB) and BioVersys (TBM) entered phase IIb (**STEP2C-03**). Results from the phase IIa study for pulmonary TB (**ENABLE-TB**) will be presented at the 2026 Union Conference in Rio.
- Ganfeborole (inhibits protein synthesis [LeuRS]), sponsored by GSK, and BTZ-043 (a DprE1 inhibitor), sponsored by University of Munich, completed phase IIb. Results from wave I of the **PARADIGM4TB** trial will be presented at the 2026 Union Conference in Rio.
- Quabodepistat (a DprE1 inhibitor), sponsored by Otsuka, entered phase III (**QUANTUM-TB**).

[‡] Next generation diarylquinolines are expected to be more potent than bedaquiline and to have an improved safety profile, including less effect on the QT interval. Preclinical studies also suggest they might work against bedaquiline-resistant strains of TB.

[§] Preclinical studies suggest that sitafloracin may have more durability against the development of resistance compared to levofloxacin and moxifloxacin, and that it might work against some fluoroquinolone-resistant strains of TB.

Table 4. New (and Repurposed) Drugs in Clinical Development for TB

Drug	Class	Mechanism of Action	Sponsor	Phase	Clinical Trial(s)	
Energy Production						
TBD11 (CLB073)	Not available	Inhibits cholesterol metabolism (adenyl cyclase activation)	GMRI	Ia/Ib	NCT06707142	
pyrifazimine (TBI-166)	Riminophenazine	Inhibits ion transport and bacterial respiration	IMM/CAMS/ PUMC	IIa	ChiCTR1800018780 NCT04670120	
sudapyridine (WX-081)	Diarylquinoline	Inhibits ATP synthase	Shanghai Jiatan Pharmatech Co.	III	NCT06117514 NCT06701110 NCT06701136 NCT04608955 NCT05824871	
TBAJ-587	Diarylquinoline	Inhibits ATP synthase	TB Alliance/ ERA4TB	IIa+	NCT04890535 NCT07773610	← NEW
sorfequiline (TBAJ-876)	Diarylquinoline	Inhibits ATP synthase and bacterial respiration	TB Alliance	IIb	NCT04493671 NCT05526911 NCT06058299 NCT07672405	← NEW
telacebec (Q203)	Imidazopyridine	Inhibits ATP synthesis (QcrB) and bacterial respiration	Qurient/ TB Alliance/ Infectex	IIa	NCT02530710 NCT02858973 NCT03563599	
Cell Wall Synthesis						
BTZ-043	Benzothiazinone	Inhibits cell wall synthesis (DprE1)	LMU/DZIF	IIb/c	NCT03590600 NCT04044001 NCT04874948 NCT05382312 NCT05926466 NCT06114628 NCT05807399	
alpipectir (BVL-GSK098)	Amido-piperidine	Inhibits cell wall synthesis via boosting ethionamide	BioVersys/GSK	IIb/c	NCT04654143 NCT05473195 NCT06748937 NCT07350174 NCT05807399	← NEW ← NEW

	Drug	Class	Mechanism of Action	Sponsor	Phase	Clinical Trial(s)	
NEW →	JDB0131	Nitroimidazole	Inhibits cell wall synthesis	WestVac Biopharma	IIb	ChiCTR2500112822 NCT06224036 NCT07170800	
	macozinone (PBTZ169)	Benzothiazinone	Inhibits cell wall synthesis (DprE1)	iM4TB/ Medincell	Ib/IIa	NCT03036163 NCT03423030 NCT04150224 NCT03776500 NCT03334734	
	quabodepistat (OPC-167832)	Carbostyryl	Inhibits cell wall synthesis (DprE1)	Otsuka	III	NCT03678688 NCT05221502 NCT05971602 NCT06114628 NCT07209761	← 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	IIa	NCT03199339 NCT04176250	
Protein Synthesis							
NEW →	AKG-100	Oxazolidinone	Inhibits protein synthesis	Akagera Medicines	Ia/Ib	DOH-27-102024-7819	
	contezolid	Oxazolidinone	Inhibits protein synthesis (23S ribosome)	MicuRx	III	NCT03033342 NCT03033329 NCT03747497 NCT06811012 NCT06811025 NCT06081361	

Drug	Class	Mechanism of Action	Sponsor	Phase	Clinical Trial(s)	
delpazolid (LCB01-0371)	Oxazolidinone	Inhibits protein synthesis (50S ribosomal subunit)	LigaChem Biosciences	IIb/c	NCT01554995 NCT01842516 NCT02540460 NCT02836483 NCT04550832 NCT06114628 NCT05807399 NCT07675954	← NEW ← NEW
sutezolid (PNU-100480)	Oxazolidinone	Inhibits protein synthesis (50S ribosomal subunit)	Sequella/TB Alliance	IIc	NCT00871949 NCT00990990 NCT01225640 NCT03199313 NCT03959566 NCT06192160 NCT05971602 NCT05686356 NCT06192160	
tedizolid*	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	IIa+	NCT03758612 NCT04865536 NCT06192160	
TBD09 (MK-7762)	Oxazolidinone	Inhibits protein synthesis (50S ribosomal subunit)	GMRI/Merck	IIa	NCT05824091 NCT07094932 NCT07525427	← NEW ← NEW
ganfeborole (GSK-656)	Oxaborole	Inhibits protein synthesis (LeuRS)	GSK	IIb/c	NCT03075410 NCT03557281 NCT05382312 NCT06114628 NCT06354257 NCT05807399	← NEW

Drug	Class	Mechanism of Action	Sponsor	Phase	Clinical Trial(s)
DNA Synthesis					
sitafloxacin*	Fluoroquinolone	Inhibit bacterial DNA synthesis	Daiichi Sankyo/ Zhejiang University	III	NCT05454345 NCT06905522 NCT07076225
*Repurposed Phase listed represents the most advanced trial that is ongoing/completed. ATP = adenosine triphosphate CAMS = Chinese Academy of Medical Sciences DprE1 = decaprenylphosphoryl-β-d-ribose 2'-epimerase, an enzyme involved in cell wall synthesis DZIF = German Center for Infection Research GMRI = Bill & Melinda Gates Medical Research Institute GSK = GlaxoSmithKline GyrB = DNA gyrase subunit B, an enzyme involved in DNA synthesis iM4TB = Innovative Medicines for Tuberculosis IMM = Institute of Materia Medica, China LeuRS = leucyl-tRNA synthetase, an enzyme involved in protein synthesis LMU = Ludwig Maximilian University of Munich MmpL3 = mycobacterial membrane protein large 3, mycolic acid and lipid transporter required for cell growth and viability PUMC = Peking Union Medical College, China QcrB = cytochrome b subunit of the cytochrome bc1 complex, an essential component of the respiratory electron transport chain required for ATP synthesis					

Table 5. Trials of Investigational Regimens That Advance New Drugs

Study Name	Experimental Arms [Control]	Indication	Number of Participants	Phase	Status [Est. Completion]
A5409/RAD-TB NCT06192160	2BP <u>U</u> ₈₀₀ /4HR 2BP <u>U</u> ₁₆₀₀ /4HR 2BP <u>TBI-223</u> ₁₂₀₀ /4HR 2BP <u>TBI-223</u> ₂₄₀₀ /4HR 2BP <u>PaL</u> /4HR [2HRZE/4HR]	DS-TB	315	Ila+	Recruiting [Aug 2027]
SYNERGY NCT07773610	Part A: 2 <u>TBAJ-587</u> ₁₀₀ PaL/4HR 2 <u>TBAJ-587</u> ₂₀₀ PaL/4HR Part B: 2 <u>TBAJ-587</u> Pa <u>T</u> /4HR 2 <u>TBAJ-587</u> Pa <u>Q</u> /4HR 2 <u>TBAJ-587</u> Pa <u>GL</u> /4HR	DS-TB	Part A: 60 Part B: 75	Ila+	Recruiting [May 2028]
JD-RISE NCT07170800	2 <u>J</u> ₁₀₀ BLLx/Cfz* 2 <u>J</u> ₂₀₀ BLLx/Cfz* [2DBLLx/Cfz]* *Regimens will include Lx or Mx for FQ-S and Cfz for FQ-R	MDR-TB, pre-XDR-TB	60	Iib	Recruiting [Sept 2026]
NC-010 NCT07672405	1 <u>S</u> ₂₀₀ PaL/3 <u>S</u> ₁₀₀ PaL 4 <u>S</u> ₁₀₀ PaL [none]	DS-TB	100	Iib	Recruiting [June 2028]

Study Name	Experimental Arms [Control]	Indication	Number of Participants	Phase	Status [Est. Completion]
PARADIGM4TB / UNITE4TB-01 NCT06114628	Wave 1 4BDM 4BDGM 4BPaGM 4BDGZ 4BDGL* 4BD ~~T~~ M 4BPa ~~T~~ M 4BD ~~T~~ Z 4BD ~~T~~ L* 4BDG ~~T~~ 4BM ~~T~~ Z Wave 2 4BD ~~Q~~ M 4BPa ~~Q~~ M 4BDG ~~Q~~ 4BPa ~~G~~ Q [2HRZE/4HR] *L for the first 8 weeks only.	DS-TB	1,100	IIb/c	Phase IIb, Wave 1: results forthcoming at Union 2026 Phase IIb, Wave 2: active, not recruiting [Mar 2027] Phase IIc: Recruiting* [Nov 2028] *Regimens to be announced at Union 2026
STEP2C-02 NCT05807399	4RHZ ~~T~~ /2HR [2HRZE/4HR]	DS-TB	270	IIb/c	Active, not recruiting [Dec 2026]
STEP2C-03 NCT05807399	6PaG ~~T~~ Dzd 2RZEEto-Alp/4HR 6BPaG ~~T~~ [2HRZE/4HR]	DS-TB	150	IIb/c	Recruiting [Mar 2028]
panTB-HM NCT05686356	4BPa ~~U~~ ₁₂₀₀ 4BPa ~~U~~ ₁₆₀₀ 4BPa ~~U~~ ₁₆₀₀ + NAC _{1800 BID} [2HRZE/4HR]	DS-TB	352	IIc	Results forthcoming at Union 2026
C-STAR	6FqB ~~Czd~~ Cfz/12Fq ~~Czd~~ Cfz [6FqBLCfz/12FqLCfz] 6B ~~Czd~~ CsCfz/14 ~~Czd~~ CsCfz [6BLCsCfz/14LCsCfz]	MDR-TB pre-XDR-TB	165	III	Active, not recruiting [Oct 2026]

Study Name	Experimental Arms [Control]	Indication	Number of Participants	Phase	Status [Est. Completion]
INSPIRE-CODA NCT06081361	6BD Czd (Lx or Cz) [6BLzCsCzLx/12CsCzLx]* *For FQ-R, Lx will be replaced by Pto, Z, PAS, or E.	MDR-TB, pre-XDR-TB	212	III	Results forthcoming at Union 2026
WISH NCT05824871	6W + OBR [6B + OBR] OBR given for up to 18 months.	MDR-TB	450	III	Results forthcoming at Union 2026
QUANTUM-TB NCT07209761	4BPa QM 6BPa Q [6BPaL/M]	MDR-TB, pre-XDR-TB	532	III	Recruiting [Sept 2028]
PAN-USR TB NCT06905522	2-3B Sx LZ [2HRZE/4HR] [6BPaLM]	DS-TB, MDR-TB	610	III	Recruiting [Dec 2029]
Elderly-USR NCT07076225	2-3B Sx LZ [2HRZE/4HR]	DS-TB	300	III	Not yet recruiting
MDR-END Plus NCT07675954	6BDLxZ Dzd [South African SOC]	MDR-TB	294	III	Not yet recruiting
CLOBBER-TB	6-9Pa SQU [18- to 20-month individualized regimen]	XDR-TB	120	III	Protocol in development – seeking funding
EX-DR	9Pa GTDzd 6Pa GTDzd + TBAJ-587 [SOC]	BDQ-R TB	400	III	Protocol in development

- BDQ-R = bedaquiline-resistant TB; DS-TB = drug-sensitive TB; FQ-R = fluoroquinolone-resistant TB; MDR-TB = multidrug-resistant TB; RR-TB = rifampicin-resistant TB; XDR-TB = extensively drug-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; TIW = thrice weekly
- NAC = N-acetyl cysteine (a repurposed host-directed therapy)
- OBR = optimized background regimen
- Letters indicate TB drugs: B = bedaquiline, Cs = cycloserine, Cfz = clofazimine, Czd = contezolid, D = delamanid, Dz = delpazolid, E = ethambutol, Eto-Alp = ethionamide + alipsectir, Fq = fluoroquinolone (either moxifloxacin or levofloxacin), G = ganfemorole, H = isoniazid, J = JDB0131, S = sorfequiline (TBAJ-876), TBAJ-587 = TBAJ-587, TBD09 = TBD09, TBD11 = TBD11, L = linezolid, Lx = levofloxacin, M, Mx = moxifloxacin, Pa = pretomanid, PAS = para-aminosalicylic acid, Pto = prothionamide, Q = quabodepistat, R = rifampicin, U = sutezolid, SMZ/TMP = sulfamethoxazole/ trimethoprim, Sx = sitafloxacin, T = BTZ-043, TBI-223 = TBI-223, W = WX-081, Z = pyrazinamide

Pediatric Investigations of New Drugs

While bedaquiline and delamanid are already recommended by the WHO for the treatment of children of all ages, pharmacokinetic (PK) and safety studies are still ongoing to optimize their dosing for children under two years old.^{¶,35,36} Janssen's pediatric study (**C211**; NCT02354014) opened in 2016 but a decade later has not yet been completed. At the time of writing, the study was listed as suspended on clinicaltrials.gov pending a protocol-specified interim PK analysis that identified lower-than-anticipated bedaquiline exposures. A PK and safety study of delamanid (**P2005**; NCT01859923) sponsored by the NIH-funded IMPAACT network has been completed. Results will be presented during the Union Conference in Rio. As mentioned earlier in this report, the single-dose study of pretomanid sponsored by the IMPAACT network has been completed (**P2034**; NCT05586230) and the protocol for a multidose study is under development (**P2051**). It's been seven years since pretomanid was approved for use in adults, maintaining long and worrisome delays between when new TB drugs are approved in adults and when children can benefit from access to them.

Planning is underway for pediatric investigations of several new drugs. Most sponsors still need to conduct juvenile animal toxicity studies and develop pediatric formulations before pediatric PK and safety studies can begin, but they are in discussions with regulators and actively working on their pediatric investigational plans (PIPs).

- **Contezolid:** a pediatric study of contezolid is ongoing in adolescents and children 6-17 years old in China but is focused on its use for treating complicated skin and soft tissue infections.^{37,38}
- **Quabodepistat:** Adolescents down to 14 years old are included in the phase III trial of quabodepistat. The PIP for younger adolescents and children was being negotiated with regulators at the time of writing. Otsuka hopes to open its pediatric study of quabodepistat before the phase III study completes enrollment.³⁹
- **Ganfeborole:** GSK submitted its PIP for ganfeborole to the pediatric committee (PDCO) of the European Medicines Agency (EMA).⁴⁰
- **BTZ-043:** Ludwig Maximilian University of Munich (LMU) has initiated discussions and fundraising efforts to start pediatric investigational plan development and regulatory engagement. They hope to initiate a pediatric PK and safety study of BTZ-043 by the time the drug completes phase 3.⁴¹

CHEETA (CHasing Expedited and Equitable Treatment Access for Children), a global consortium comprised of pediatric TB treatment research experts, is engaging sponsors as they develop their PIPs with the goal of optimizing their design to close the current 8-13-year gap between when new TB medicines are indicated for use in adults and children.^{42,43}

¶ WHO recommendations for the use of bedaquiline in younger children are currently based on data from the pediatric PK and safety study of bedaquiline conducted by the IMPAACT network (P1108, NCT02906007). WHO recommendations for the use of delamanid in children are currently based on data from the pediatric PK and safety study of delamanid conducted by Otsuka (232, NCT01856634; 233; NCT01859923).

Conclusions

The TB treatment pipeline is fuller than it has been in the past and there's a lot to pay attention to, especially in phase II. The details of individual studies are important, but they shouldn't overshadow the broader themes. Looking across the pipeline, several issues stand out as priorities for the coming years:

- Recent WHO guidelines updates highlight important evidence gaps and the urgent need to develop and execute a multidisciplinary research agenda focused on pre-XDR-TB and additional resistance to bedaquiline and/or linezolid (XDR-TB).
- Non-inferiority is no longer enough to write policy and change practice, especially as standards of care for TB treatment have been dramatically upgraded in recent years with the introduction of new and repurposed TB medicines. A prioritized list of community-informed PCOMs and tools for measuring them is urgently needed.
- The lack of evidence to support the co-administration of bedaquiline and delamanid presented a major barrier to the introduction of both drugs and took years to resolve. Evidence gaps for using new drugs together that are currently at a similar stage of development are predictable based on the current roster of ongoing and planned studies covered in this year's Pipeline Report:
 1. Regimens that combine ganfeborole and BTZ-043 are under evaluation in PARADIGM4TB wave I and STEP2C-03;
 2. Regimens that combine ganfeborole and quabodepistat are included in PARADIGM4TB wave II; and
 3. TBAJ-587 will be evaluated in combination with ganfeborole, BTZ-043, and quabodepistat (each separately) in SYNERGY.

But no one is evaluating ganfeborole, BTZ-043 or quabodepistat in combination with sarefiquiline, and drugs in the same class aren't being compared head-to-head. Additionally, accelerated TB drug development pathways that combine elements of phase I and phase II studies, and in doing so evaluate new drugs in novel combinations sooner, may present challenges for determining the individual contributions of each drug in the regimen. Knowing what each component contributes is important for determining how new TB drugs may work outside of the regimens they are being trialed in. Research and product sponsors should avoid repeating mistakes made in the mid-2000s. New drugs that are already in or soon to enter phase III trials need to be studied together and with comparators that provide relevant and meaningful information if we hope to introduce them without delay and within a paradigm that improves treatment for drug-resistant TB.

Results to look out for at the 2026 Union Conference in Rio de Janeiro:

1. **STEP2C-01 and OptiRiMoxTB** on whether we can replace rifapentine with high-dose rifampicin in shorter regimens for drug-sensitive TB.
2. **CRUSH-TB** will reveal whether short-course regimens for drug-sensitive TB can be built on a bedaquiline, moxifloxacin, pyrazinamide backbone, and what regimen(s) we might expect to be tested in the next wave of combinations that enter the trial.
3. **PARADIGM4TB** for what regimens from wave I will advance to stage IIc, and what combinations we might expect to see ganfeborole and BTZ-043 evaluated in in phase III.
4. **PanTB-HM, INSPIRE-CODA, and C-STAR** on whether next generation oxazolidinones, contezolid and sutezolid can replace linezolid; and
5. **P2005** on whether we need to adjust the dose of delamanid recommended for children under two years old.

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