Overview of Novel TB Compounds and Practices of Pre-Access

Ilaria Motta

Medecins Sans Frontieres- APH

Agenda

Novel TB Compounds:

- Pipeline
- Quabodepistat
- BTZ-043
- Ganfeborole
- Telacebec
- New oxazolidinones
- TBAJ-587, TBAJ-876

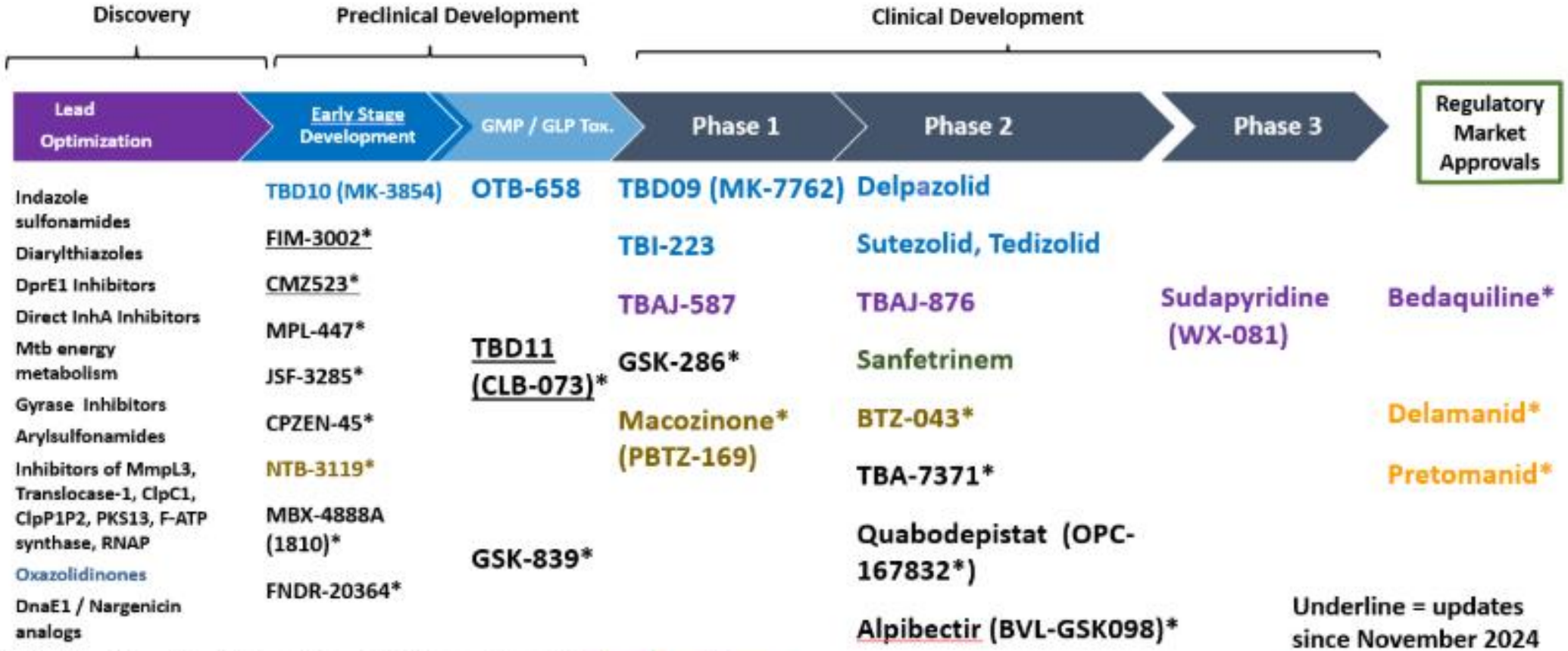
Practices of Pre-Access

MEDECINS SANS FRONTIERES

Novel TB Compounds

MEDECINS SANS FRONTIERES

2024 Global New TB Drug Pipeline[1]



*New chemical class. Known chemical classes for any indication are color coded: rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound identified: http://www.newtbdrugs.org/pipeline/discovery

Underline = updates since November 2024

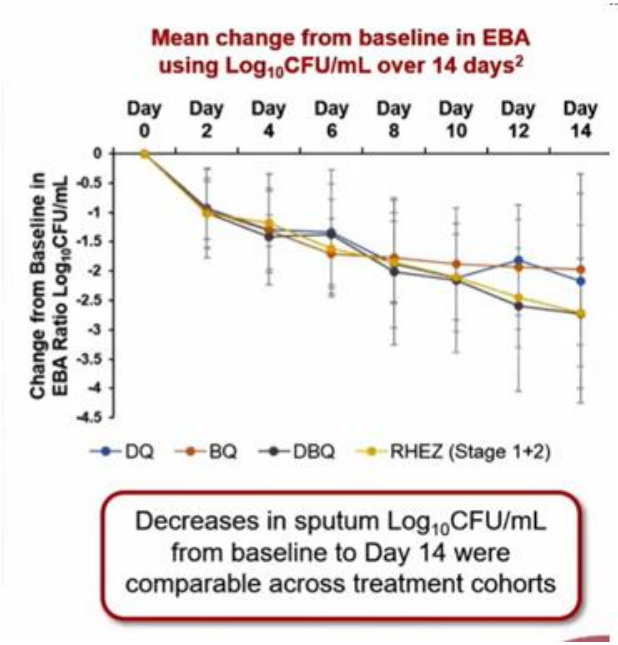
WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: November 2024

Quabodepistat

- DprE1 inhibitor of cell wall biosynthesis;
- Has completed phase 2 testing;
- Found to be relatively safe in 4-month regimens, although the PAN-TB trial did not meet its efficacy endpoint.



Safety, pharmacokinetics, and early bactericidal activity of quabodepistat in combination with delamanid, bedaquiline, or both in adults with pulmonary tuberculosis: a randomised, active-controlled, open-label trial

Rodney Dawson, Andreas H Diacon, Veronique De Jager, Kim Narunsky, V Mischka Moodley, Kelly W Stinson, Yongge Liu, Bo Zheng, Jeffrey Hafkin

Summary

Background Quabodepistat (formerly OPC-167832) showed potent activity in preclinical studies and in the first stage of an early bactericidal activity study in adults with smear-positive, drug-susceptible pulmonary tuberculosis. Stage 2 of this study was designed to evaluate the safety, tolerability, pharmacokinetics, and early bactericidal activity of quabodepistat in combination with delamanid, bedaquiline, or both versus rifampicin, isoniazid, ethambutol, and pyrazinamide combination therapy for 14 days.

Methods Stage 2 of this open-label, active-controlled, randomised, parallel-group study was conducted at two research sites in South Africa in adults (aged 18–64 years) with drug-susceptible pulmonary tuberculosis. Eligible participants had a BMI of 16–32 kg/m² and the ability to produce an adequate volume of sputum (≥10 mL overnight) and were excluded if they had drug-resistant tuberculosis or previous treatment for *Mycobacterium tuberculosis* within the past 3 years. Participants were centrally randomly assigned via interactive web response technology system, with no stratification, into four treatment groups in a ratio of 14:14:14:4 (quabodepistat 30 mg plus delamanid 300 mg, quabodepistat 30 mg plus bedaquiline 400 mg, or quabodepistat 30 mg plus delamanid 300 mg plus bedaquiline 400 mg orally once daily for 14 days, or rifampicin, isoniazid, ethambutol, and pyrazinamide combination therapy [control] according to local standard of care for 20 days). The primary outcomes were safety and tolerability during and after 14 days of treatment in all participants who received any study medication and pharmacokinetics at day 1 and day 14 in participants in the quabodepistat groups with adequate data for deriving pharmacokinetics parameters. The main secondary outcome was bactericidal activity from baseline to day 14 in all eligible participants who were quantitatively culture-positive at baseline. The study was not powered for formal statistical hypothesis testing; therefore, data were summarised by treatment group with descriptive statistics. This study is registered with ClinicalTrials.gov (NCT03678688) and is closed to new participants.

Findings 98 participants were screened for entry into stage 2 of the trial between Feb 1, 2021, and Jan 27, 2022, of whom 46 were randomly assigned (14 to each quabodepistat group, 4 to the control group) and 44 received at least one dose of study medication (one patient excluded from the quabodepistat plus delamanid and quabodepistat plus bedaquiline groups). 32 (73%) of 44 participants had at least one treatment-emergent adverse event. Most events (30/32 [94%]) were mild or moderate; the most common treatment-emergent adverse events (≥2 participants; not related to study drugs) were headache (4/44 [9%]), dizziness (3/44 [7%]), abdominal pain (2/44 [5%]), pruritus (2/44 [5%]), and nausea (2/44 [5%]). Two serious adverse events were reported in two participants in the quabodepistat and bedaquiline cohort (anal abscess [n=1], pneumothorax [n=1]); both were deemed not related to study drug. Quabodepistat exposure was minimally affected by coadministration of delamanid or bedaquiline, with lower exposure in the quabodepistat and bedaquiline cohorts (maximum plasma concentration for quabodepistat plus delamanid 208 ng/mL [SD 61; n=11]; quabodepistat plus bedaquiline 175 ng/mL [31; n=10]; quabodepistat plus delamanid plus bedaquiline 183 ng/mL [52; n=11]). Maximum quabodepistat concentrations were achieved approximately 3 h after administration in all combinations. Mean elimination half-life was shorter in combinations with bedaquiline than without bedaquiline (12·3–14·5 h *vs* 15·2 h).

Lancet Infect Dis 2024

Published Online November 26, 2024 https://doi.org/10.1016/S1473-3099(24)00601-7

See Online/Comment https://doi.org/10.1016/S1473-3099(24)00653-4

Division of Pulmonology, Department of Medicine, University of Cape Town Lung Institute, Cape Town, South Africa (Prof R Dawson PhD); **TASK Applied Science, Cape Town, South Africa** (A H Diacon MD, V De Jager MD); **University of Cape Town, Lung Institute, Cape Town, South Africa** (K Narunsky MBChB); **Otsuka Novel Products, Munich, Germany** (V M Moodley PhD); **Cultura, Decatur, GA, USA** (K W Stinson MPH); **Otsuka Pharmaceutical Development & Commercialization, Rockville, MD, USA** (Y Liu PhD, B Zheng PhD, J Hafkin MD)

Correspondence to: Jeffrey Hafkin, Otsuka Pharmaceutical Development & Commercialization, Rockville, MD 20850, USA **jeffrey.hafkin@otsuka-us.com**

Lancet Inf Dis, 2024 Nov

PanTB trial – interim results

PAN-TB Collaboration

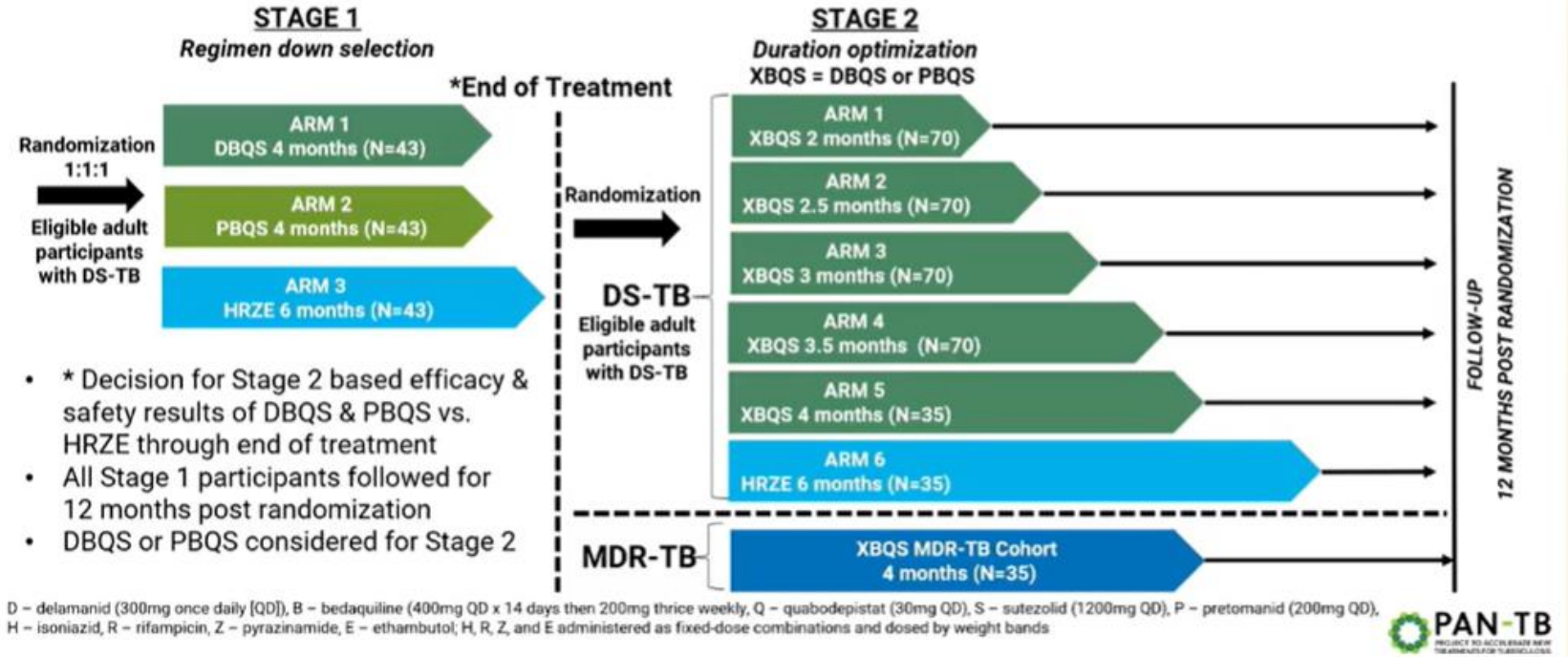
Project to Accelerate New Treatments for TuBerculosis

evotec · gsk · janssen · GF · Otsuka · TB Alliance

GATES MRI Funded by BMGF and clinical studies to be conducted by Gates MRI

PAN-TB / TBD06-201 Trial to Evaluate DBQS and PBQS

2-Stage, Phase 2b/c Design to Identify 3-Month Regimen



Enrolment started in June 2023
ceased 14 July 2024
94 randomized
57 completed study treatment

From Union 2024

DBQS = Dlm, Bdq, **quabodepistat (OPC-167832)** and sutezolid
PBQS = Ptm, Bdq, **quabodepistat** and sutezolid

Summary and Conclusions on Pathway to 3-Month Regimen Within PAN-TB Trial

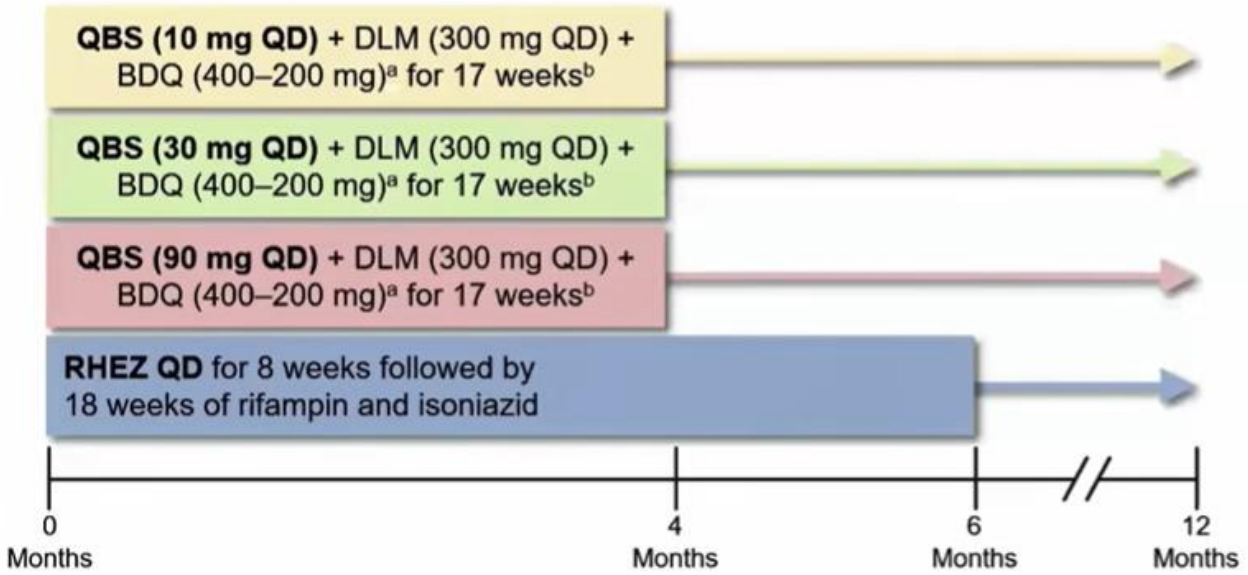
- Staged trial design and patient population with greater disease severity were strategic for answering key research question
- No safety concerns identified for either investigational regimen
- DBQS & PBQS sputum culture conversion rates at 2 and 3 months do not support the trial objective of identifying a ≤3-month regimen
- Number of Investigator-assessed TB treatment re-initiation or extension of TB treatment with HRZE during follow-up period do not support identifying a potential ≤3-month regimen for Stage 2 of the trial
- Whole genome sequencing, MIC, and PK data forthcoming to help interpret findings
- Potential limitations: small sample size; more severe patient population; open-label design → possible bias against XBQS arms;
  6 cultures per timepoint → possible ↓ comparability to other trials

From Union 2024

2024 Jan 19;25(1):70.

Methodology: A phase 2b/c randomized trial

Objective: Evaluate the safety, efficacy, PK, and optimal dose of QBS in combination with DLM and BDQ for 4 months in participants with DS-TB compared to 6-month RHEZ treatment[1]



- Participants were randomized 1:2:2:1
- Randomization: Stratified by presence of bilateral cavitation on screening CXR
- ***Primary endpoints*: Safety and the proportion of participants achieving SCC in liquid MGIT by the end of the treatment period**
- *Exploratory endpoints*: Long term follow-up efficacy outcomes
- Analyses presented here are in the modified intention-to-treat population

Protocol published in *Trials 2024 Jan 19;25(1):70.*

From Union 2024

High SCC rates were achieved in the DBQ arms at the end of treatment

Primary endpoint

	Overall		With Bilateral Cavitation		Without Bilateral Cavitation	
	n/N	% with SCC (95% CI)	n/N	% with SCC (95% CI)	n/N	% with SCC (95% CI)
Pooled DBQ	96/100	**96.0** (90.1, 98.9)	13/13	100.0 (75.3, 100.0)	83/87	95.4 (88.6, 98.7)
DBQ10	20/20	**100.0** (83.2, 100.0)	2/2	100.0	18/18	100.0 (81.5, 100.0)
DBQ30	39/42	**92.9** (80.5, 98.5)	6/6	100.0 (54.1, 100.0)	33/36	91.7 (77.5, 98.2)
DBQ90	37/38	**97.4** (86.2, 99.9)	5/5	100.0	32/33	97.0 (84.2, 99.9)
RHEZ	21/21	**100.0** (83.9, 100.0)	4/4	100.0	17/17	100.0 (80.5, 100.0)

Difference in proportion of SCC between the pooled DBQ and RHEZ arm was:
–4.0% (80% CI, –7.4%, 3.4%)

- Non-inferiority was established (NI margin: -12%). **Thus, the study achieved its primary objective**
- The proportion of SCC at the end of treatment did not vary by bilateral cavitation status

From Union 2024

Favorable outcome and relapse

Exploratory endpoints

Exploratory endpoints

- Proportion of participants with a **favorable outcome** at 12 months post-randomization and 6 months post end-of-treatment
- Proportion of participants with **relapse** at 12 months post-randomization

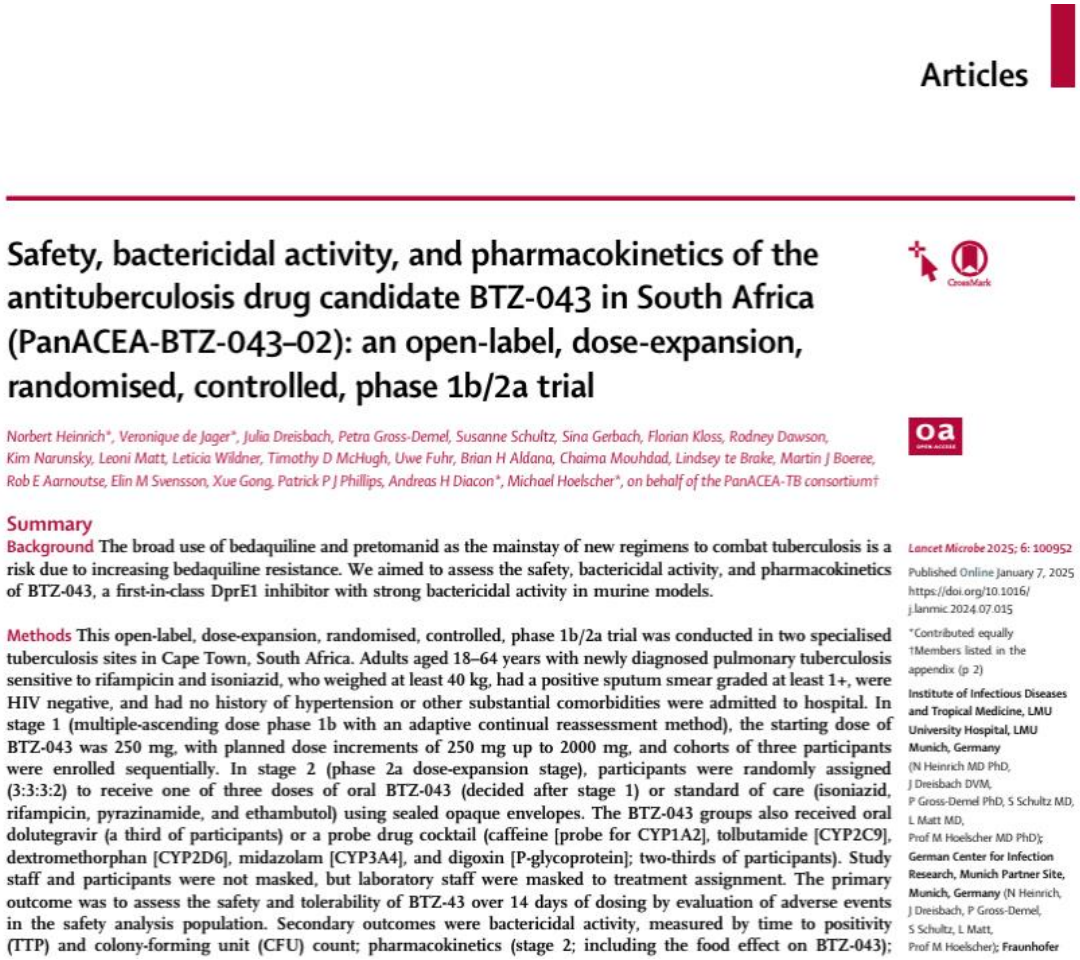
Follow-up outcomes n/N (%)	**DBQ10**	**DBQ30**	**DBQ90**	**Pooled DBQ**	**RHEZ**
12 months post-randomization					
Favorable outcome	17/20 (85.0)	34/42 (81.0)	32/38 (84.2)	**83/100 (83.0)**	**20/21 (95.2)**
Relapse	2/20 (10.0)	5/42 (11.9)	5/38 (13.2)	**12/100 (12.0)**	**1/21 (4.8)**

At 12 months post-randomization [8 months follow-up for DBQ arms and 6 months follow-up for RHEZ arm]

- The RHEZ arm had numerically more favorable outcomes and fewer relapses than the DBQ arm

From Union 2024

BTZ-043



Articles

Safety, bactericidal activity, and pharmacokinetics of the antituberculosis drug candidate BTZ-043 in South Africa (PanACEA-BTZ-043–02): an open-label, dose-expansion, randomised, controlled, phase 1b/2a trial

Norbert Heinrich*, Veronique de Jager*, Julia Dreisbach, Petra Gross-Demel, Susanne Schultz, Sina Gerbach, Florian Kloss, Rodney Dawson, Kim Narunsky, Leoni Matt, Leticia Wildner, Timothy D McHugh, Uwe Fuhr, Brian H Aldana, Chaima Mouhdad, Lindsey te Brake, Martin J Boeree, Rob E Aarnoutse, Elin M Svensson, Xue Gong, Patrick P J Phillips, Andreas H Diacon*, Michael Hoelscher*, on behalf of the PanACEA-TB consortium†

Summary

Background The broad use of bedaquiline and pretomanid as the mainstay of new regimens to combat tuberculosis is a risk due to increasing bedaquiline resistance. We aimed to assess the safety, bactericidal activity, and pharmacokinetics of BTZ-043, a first-in-class DprE1 inhibitor with strong bactericidal activity in murine models.

Methods This open-label, dose-expansion, randomised, controlled, phase 1b/2a trial was conducted in two specialised tuberculosis sites in Cape Town, South Africa. Adults aged 18–64 years with newly diagnosed pulmonary tuberculosis sensitive to rifampicin and isoniazid, who weighed at least 40 kg, had a positive sputum smear graded at least 1+, were HIV negative, and had no history of hypertension or other substantial comorbidities were admitted to hospital. In stage 1 (multiple-ascending dose phase 1b with an adaptive continual reassessment method), the starting dose of BTZ-043 was 250 mg, with planned dose increments of 250 mg up to 2000 mg, and cohorts of three participants were enrolled sequentially. In stage 2 (phase 2a dose-expansion stage), participants were randomly assigned (3:3:3:2) to receive one of three doses of oral BTZ-043 (decided after stage 1) or standard of care (isoniazid, rifampicin, pyrazinamide, and ethambutol) using sealed opaque envelopes. The BTZ-043 groups also received oral dolutegravir (a third of participants) or a probe drug cocktail (caffeine [probe for CYP1A2], tolbutamide [CYP2C9], dextromethorphan [CYP2D6], midazolam [CYP3A4], and digoxin [P-glycoprotein]; two-thirds of participants). Study staff and participants were not masked, but laboratory staff were masked to treatment assignment. The primary outcome was to assess the safety and tolerability of BTZ-43 over 14 days of dosing by evaluation of adverse events in the safety analysis population. Secondary outcomes were bactericidal activity, measured by time to positivity (TTP) and colony-forming unit (CFU) count; pharmacokinetics (stage 2; including the food effect on BTZ-043);

Lancet Microbe 2025; 6: 100952
Published Online January 7, 2025
https://doi.org/10.1016/j.lanmic.2024.07.015

*Contributed equally
†Members listed in the appendix (p 2)

Institute of Infectious Diseases and Tropical Medicine, LMU University Hospital, LMU Munich, Germany (N Heinrich MD PhD, J Dreisbach DVM, P Gross-Demel PhD, S Schultz MD, L Matt MD, Prof M Hoelscher MD PhD); **German Center for Infection Research, Munich Partner Site, Munich, Germany** (N Heinrich, J Dreisbach, P Gross-Demel, S Schultz, L Matt, Prof M Hoelscher); **Fraunhofer**

Lancet Microbe 2025; 6:100952

- DprE1 inhibitor of cell wall biosynthesis;
- Appears to be safe in shorter trials (EBA), with signs of adaptation of hepatic metabolism;
- Also being assessed in 4-month trial (2b/c) for DS-TB (UNITE4TB consortium).

MEDECINS SANS FRONTIERES

Cross resistance to DprE1 inhibitors

New class:	
Quabodepistat	*DprE1 enzyme involved in the synthesis of arabinogalactan*
BTZ-043	
Macozinone	
TBA-7371	

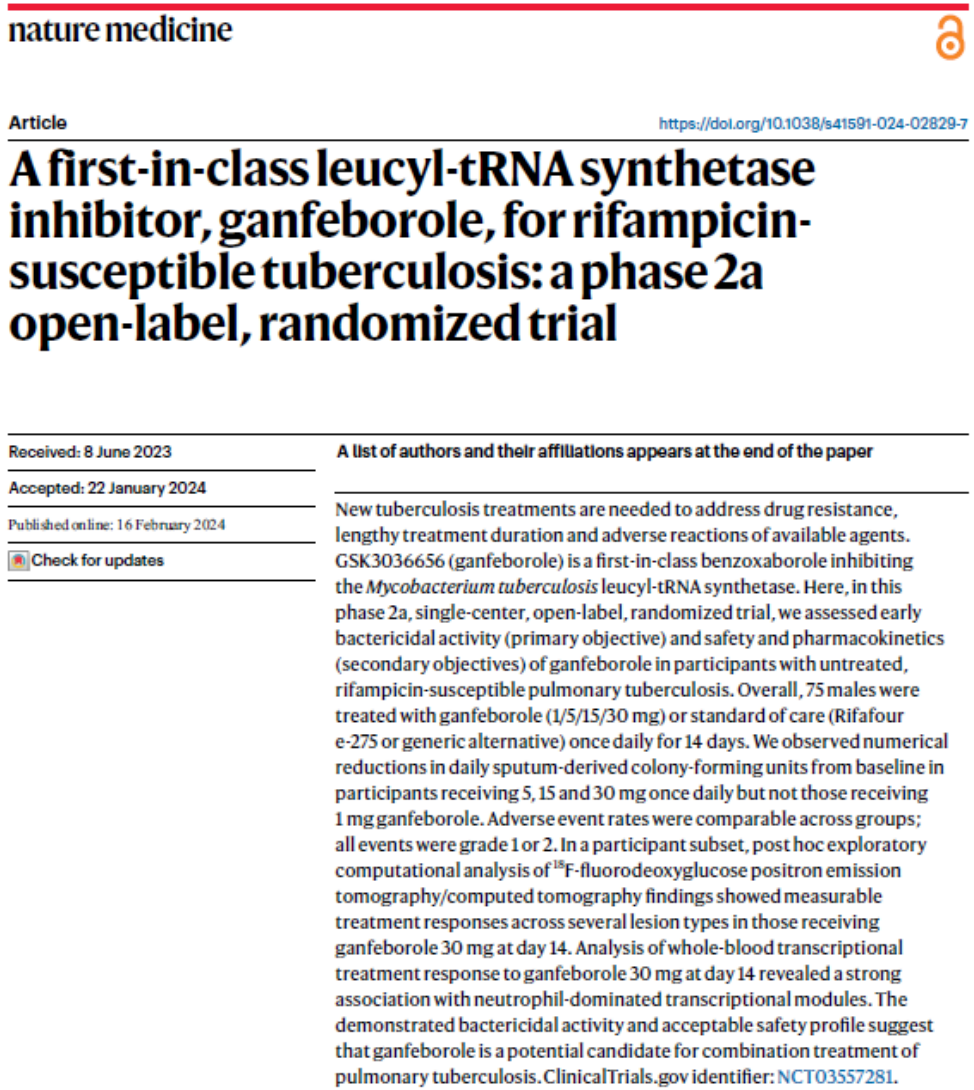
- Clinically prevalent mutations in *rv0678* confer **low level cross-resistance to DprE1 inhibitors;**
- While it is yet unclear whether rv0678 mutations would render them ineffective in treating TB.

Poulton NC, AAC 2022;
Almeida DV, AAC 2023

MEDECINS SANS FRONTIERES

Ganfeborole

- Protein synthesis inhibitor;
- GSK is sponsor;
- teratogenic effects based in animal studies in 2 species;
- EBA study with Bdq and/or Dlm. other arms ongoing
- Also being assessed in 4-month trial (2b/c) for DS-TB (UNITE4TB consortium)



nature medicine

Article

https://doi.org/10.1038/s41591-024-02829-7

A first-in-class leucyl-tRNA synthetase inhibitor, ganfeborole, for rifampicin-susceptible tuberculosis: a phase 2a open-label, randomized trial

Received: 8 June 2023

Accepted: 22 January 2024

Published online: 16 February 2024

Check for updates

A list of authors and their affiliations appears at the end of the paper

New tuberculosis treatments are needed to address drug resistance, lengthy treatment duration and adverse reactions of available agents. GSK3036656 (ganfeborole) is a first-in-class benzoxaborole inhibiting the *Mycobacterium tuberculosis* leucyl-tRNA synthetase. Here, in this phase 2a, single-center, open-label, randomized trial, we assessed early bactericidal activity (primary objective) and safety and pharmacokinetics (secondary objectives) of ganfeborole in participants with untreated, rifampicin-susceptible pulmonary tuberculosis. Overall, 75 males were treated with ganfeborole (1/5/15/30 mg) or standard of care (Rifafour e-275 or generic alternative) once daily for 14 days. We observed numerical reductions in daily sputum-derived colony-forming units from baseline in participants receiving 5, 15 and 30 mg once daily but not those receiving 1 mg ganfeborole. Adverse event rates were comparable across groups; all events were grade 1 or 2. In a participant subset, post hoc exploratory computational analysis of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography findings showed measurable treatment responses across several lesion types in those receiving ganfeborole 30 mg at day 14. Analysis of whole-blood transcriptional treatment response to ganfeborole 30 mg at day 14 revealed a strong association with neutrophil-dominated transcriptional modules. The demonstrated bactericidal activity and acceptable safety profile suggest that ganfeborole is a potential candidate for combination treatment of pulmonary tuberculosis. ClinicalTrials.gov identifier: NCT03557281.

Nat Med 2024 Mar;30(3):896-904.

MEDECINS SANS FRONTIERES

Telacebec

Telacebec (Q203), a New Antituberculosis Agent

TO THE EDITOR: Shortly after the discovery of streptomycin in 1943, it became clear that successful treatment of tuberculosis and prevention of drug resistance required a combination of at least three effective drugs. What followed in the 1950s was the introduction of triple therapy with streptomycin, aminosalicylic acid, and isoniazid, the so-called 100% effective regimen and a major milestone on the path to modern antimicrobial therapy.[1,2]

After the stepwise introduction of more potent agents and massive efforts toward tuberculosis control, the disease that once killed one in four persons became a seemingly distant threat in many countries. However, an increasing prevalence of drug resistance has made the goal of global elimination of tuberculosis a far-removed prospect once more. New drugs and regimens are needed to ensure continued progress toward this goal.

Telacebec (Q203) is a novel first-in-class antituberculosis drug that targets *Mycobacterium tuberculosis* cellular energy production through inhibition of the mycobacterial cytochrome bc1 complex. In vitro, depletion of ATP synthesis resulted in cell death regardless of the replication status of the bacteria.[3] For proof of concept in humans, we conducted a phase 2, prospective, randomized, open-label trial involving 61 patients with newly diagnosed, rifampin- and isoniazid-susceptible pulmonary tuberculosis (ClinicalTrials.gov number, NCT03563599). Patients were assigned to receive 14 days of oral telacebec at a dose of 100 mg, 200 mg, or 300 mg once daily or combination therapy with rifampin, isoniazid, pyrazinamide, and ethambutol (RHZE). Serial (16-hour) sputum samples were collected daily, and time to positivity for microbial growth in liquid culture was measured in hours (BACTEC MGIT 960 System, Becton Dickinson). We created a linear mixed-effects model of the daily change in $\log_{10}$ time to positivity to determine bactericidal activity. (The protocol is available with the full text of this letter at NEJM.org.)

N Engl J Med. 2020 Mar 26;382(13)1280-81.

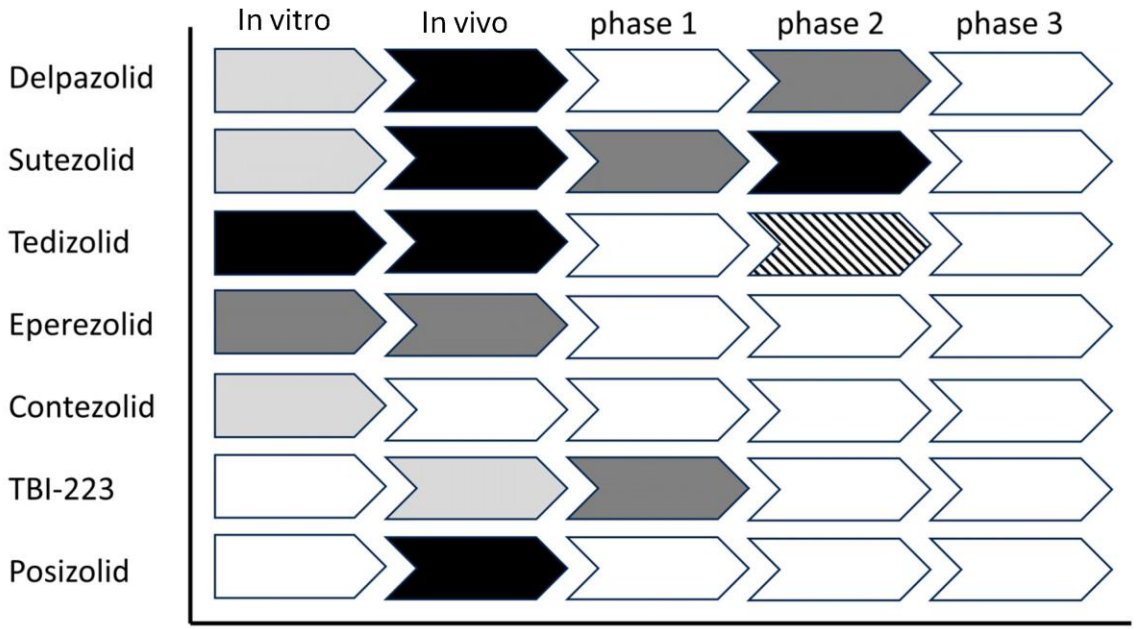
- Inhibits ATP synthesis; new class
- Developed by Qurient, now held by TBA;
- Seems to be stalled in development.

MEDECINS SANS FRONTIERES

New oxazolidinones

- inhibit bacterial protein synthesis
- TBI-223 (Phase I)
- Delpazolid (better safety)
- Sutezolid (pan-TB) better safety
- Tedizolid

Safety
Efficacy
DDI



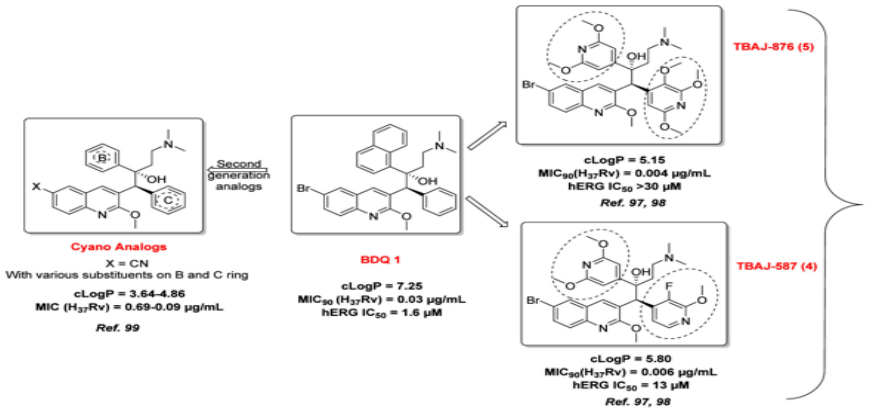
white = no data available, light grey = data available from 1 single study, dark grey = data available from 2-3 studies, black data = available from > 3 studies, stripes = studies planned

TBAJ-587

Diarylquinoline similar to BD; Greater in vitro potency (potential to reduce duration);
Reduced cardiovascular liability;
Maintains higher activity against Rv0678 mutants compared to Bdq;
In Phase 1

TBAJ-876

Shorter half life than Bdq;
Reduced cardiovascular liability;
MIC Rv0678 0.25 Bdq vs 0.025;
In Phase 2 (NC-009, 3 doses with PaL vs RHZE vs BPaL)



New-generation analogs of BDQ **1** with improved profile: cyano analogs TBAJ-587 (**4**) and TBAJ-876 (**5**

Holt E, Lancet Microbe 2024

MEDECINS SANS FRONTIERES

"Enough storyboarding. Let's shoot something."

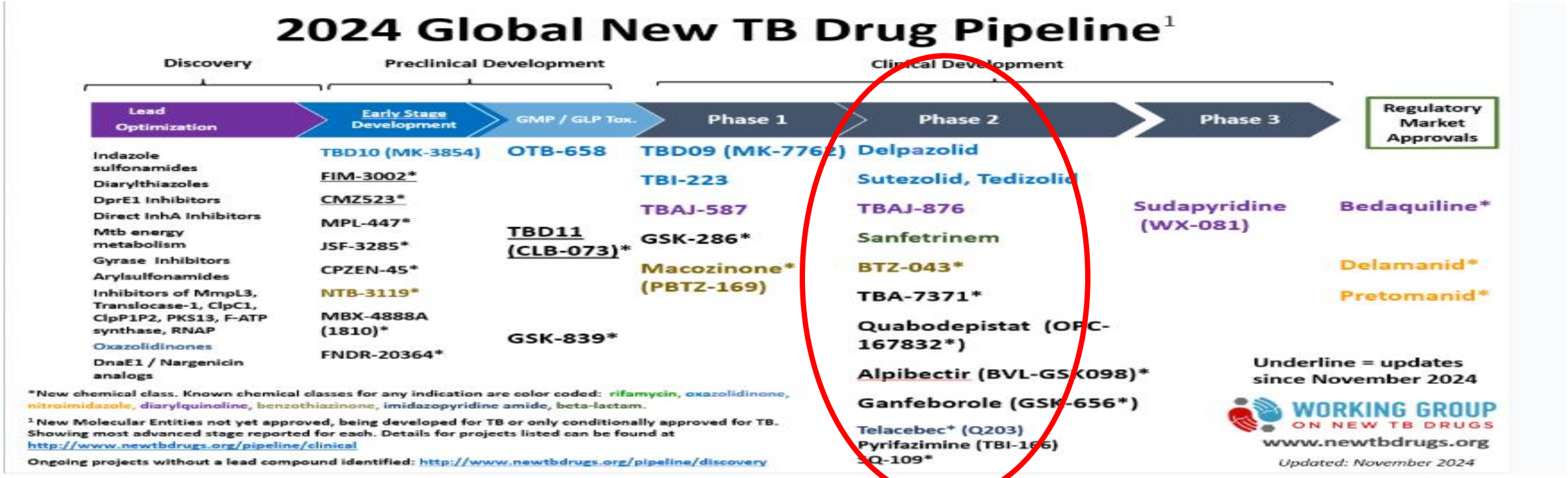
Practices of Pre-Access

Why considering CU now for TB ?

- **People currently with strains of TB with expanded drug resistance**
- **Lessons learnt from past CU programs with Bdq, Dlm and Pa**

- Pros: lives saved, earlier programmatic uptake of new medicines once WHO recommended, etc...
- Cons from sponsors: challenges regarding drug combinations, varying minimum data necessary to move ahead with a CU program, challenging exclusion criteria in CU protocols, etc...

- **New compounds under clinical development with phase II data published**



MSF *modus operandi* (as a proxy)

- **Patient**
  - Be well-informed about the experimental compound (intended efficacy, potential AEs)
  - Understand that there is no guarantee of benefit from the experimental compound
  - Consent in writing before CU treatment initiation
- **Practitioner**
  - Responsible for filling a request form on behalf of the patient (key medical history data)
  - Agree to follow the CU protocol from sponsors and to report within 48 hours any SAE
  - Covered by the physician agreement signed by MSF with sponsors
- **Medical committee for CU**
  - Review CU requests from practitioners of MSF and PIH projects
  - Formulate recommendations for individual patients based on indications and requirements
  - Report to MSF Ethical Review Board
  - Composed of MDR-TB experts (from MSF and outside)
- **MSF Pharmacovigilance unit**
  - Training of in-country trainers to PV best practices (note: compulsory requirement from Otsuka for CU with Dlm)

-> Modus operandi approved by MSF Ethical Review Board

MEDECINS SANS FRONTIERES

Pre-requisites to fulfil in country before doing CU

- Consultation of the National TB Programme level regarding the medical added value of doing CU in TB with defined compounds

-> At least Phase II clinical data for each new compound which is a CU candidate

- As per international standards for CU:

  - evaluation of CU protocols by an Ethics Review Board (often in each hospital where CU for TB could be implemented)

  - availability of an informed consent procedure for patients

  - review of the pharmaceutical quality documents for each new compound which is a CU candidate (National Regulatory Authority)

  - requirements set for the importation of drugs under CU

MEDECINS SANS FRONTIERES

Sponsor/drug developer/innovator

- Provide the full CU treatment for a new compound
- Provide information on pharmaceutical quality of the new compound with local regulatory authorities (Good Manufacturing Practices certificate, certificate of analysis, etc…)
- Provide all relevant information to practitioners and patients
- Provide feedback on SAE with reference regulatory authorities

-> Has the final say on whether its new compound(s) will be provided under CU or not, and to which patients (see CU protocols, CU request approval procedures)

-> More common rule is for the CU compound to be provided for free including freight costs by sponsors

-> Asks practitioners (or their institutions) to sign a physician agreement including a confidentiality clause

-> Can make PV training pre-requisites to practitioners

-> Proposes their own informed consent form

MEDECINS SANS FRONTIERES

Funders

- Medical committee for CU = key element based on Bdq and Dlm CU past projects

  - to support physicians identifying CU needs with all necessary clinical expertise

  - to enhance trust at sponsors

  - to engage with sponsors to streamline CU processes

-> “one-stop-shop” for sponsors and physicians (with support from CSOs)

- Interest expressed by several innovators to consider developing a CU regimen combining several new compounds

-> if confirmed, StopTB Global Drug Facility (GDF)* would consider supporting the consolidated supply of all needed compounds (if available funds)

- Challenges for some innovators like PDPs (*e.g.*, TB Alliance) to cover for freight costs

-> GDF expressed interest to explore potential supply support (if available funds)

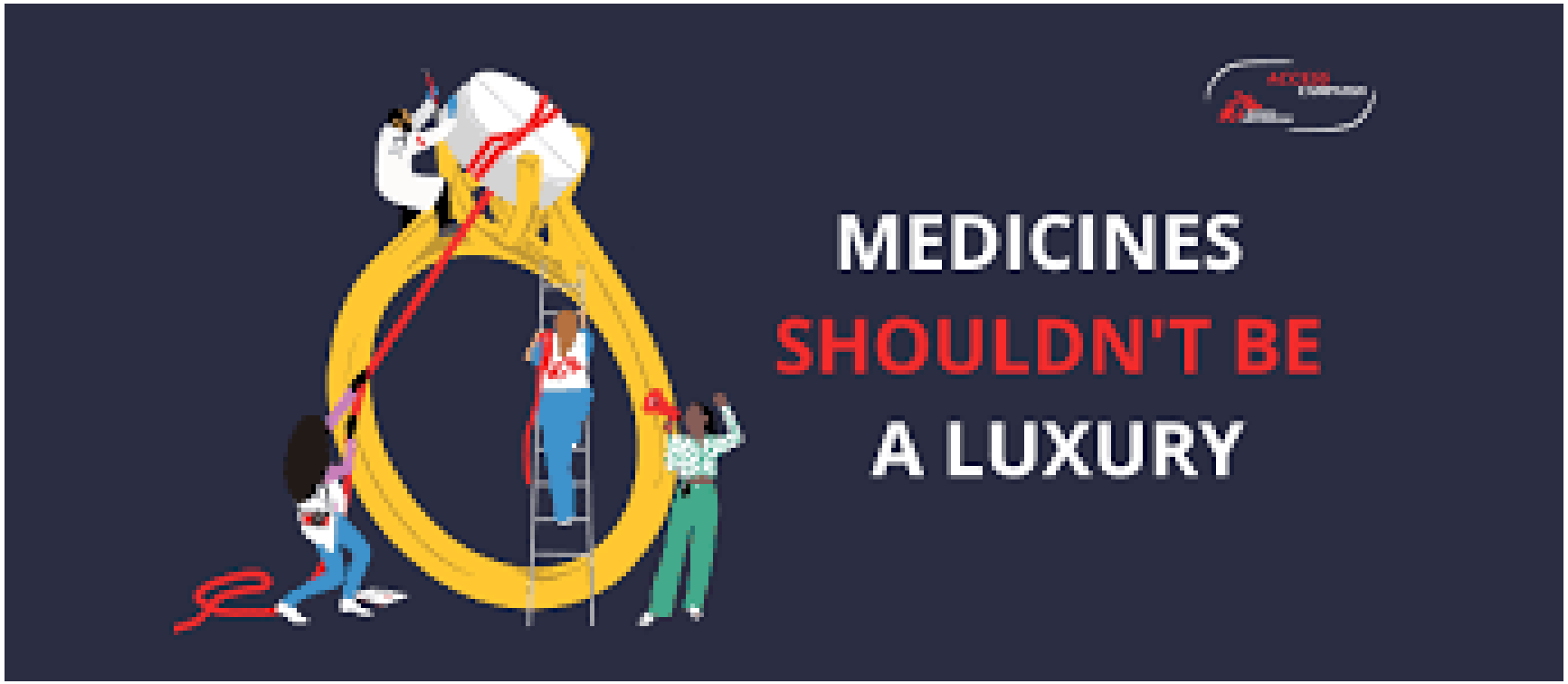
- If more frequent requests from sponsors of PV training pre-requisites, financial support might be needed for experts to deliver these trainings at country level

- Academic institutions with new TB compounds (*e.g.*, Ludwig-Maximilians-University in Germany for BTZ-043): no fund to provide CU treatments for free or cover freight costs to countries and insurance costs linked CU program

https://www.stoptb.org/facilitate-access-to-tb-drugs-diagnostics/global-drug-facility-gdf

MEDECINS SANS FRONTIERES

Thank you for your attention



llaria.motta@msf.org