Novel nine-month regimens for rifampicin-resistant tuberculosis: results of the endTB trial

RESIST-TB Series Webinar 30 May 2024

Dr Kunda Kwabisha Mikanda, MBChB, Dip HIV Man (SA)

MDR-TB Senior Medical Officer and Lesotho Site principal investigator for endTB trial

Tuberculosis: Background & (Lack of) Innovation

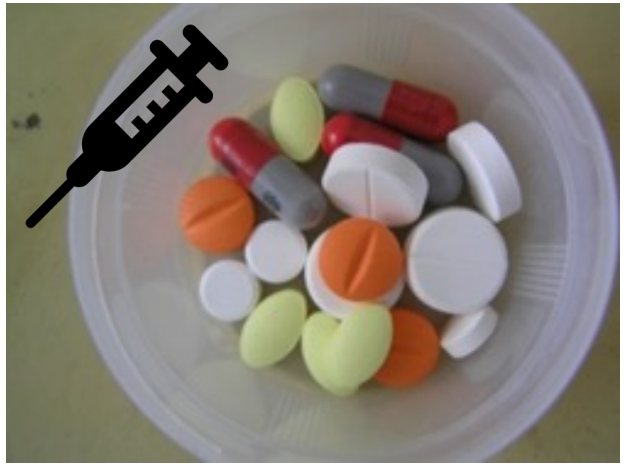
- Airborne infectious disease, disproportionately affecting impoverished populations
- Caused by *Mycobacterium tuberculosis*
- Kills 1.3 million/year: greatest infectious killer
- Newly affects 10 million annually, 60-70% are treated
  - 4-drug regimens for 6 months or 4 months
- 500,000 each year fall sick with multidrug-resistant or rifampin-resistant TB
- Main diagnostic ~140 years old
- Only vaccine 120 years old
- Main treatment is 75 years old
- Annual research funding shortfall >$1.4B

endTB Clinical Trial: Background & Design

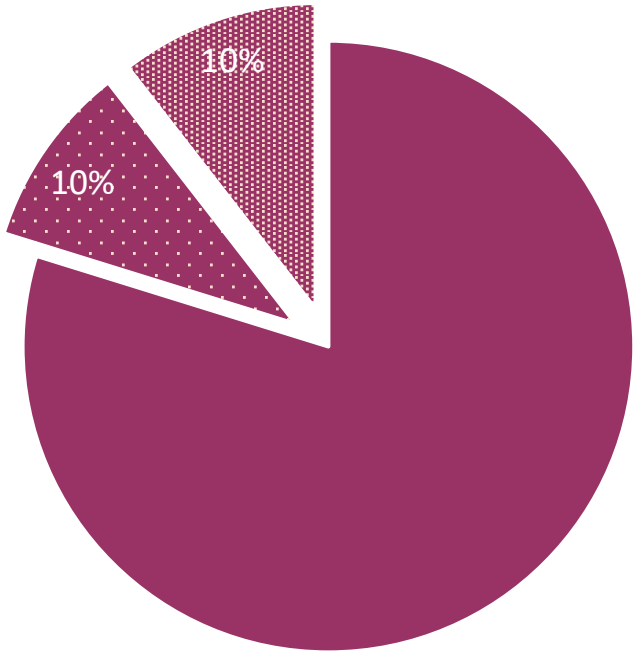
State of Treatment for multidrug/rifampin-resistant TB c. 2013[1]

MDR-TB/RR-TB treatment:

- Long
- Complex
- Toxic
- High pill burden
- Expensive
- Largely based on expert opinion and very low-quality of evidence



Success reported in 52% of patients treated.[3]



500K new cases/year

[1] Brigden et al. Bull WHO, 2013; [2] WHO. Global TB report, 2014; [3]WHO. Global TB report, 2016.

Background c. 2013

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The Diarylquinoline TMC207 for Multidrug-Resistant Tuberculosis

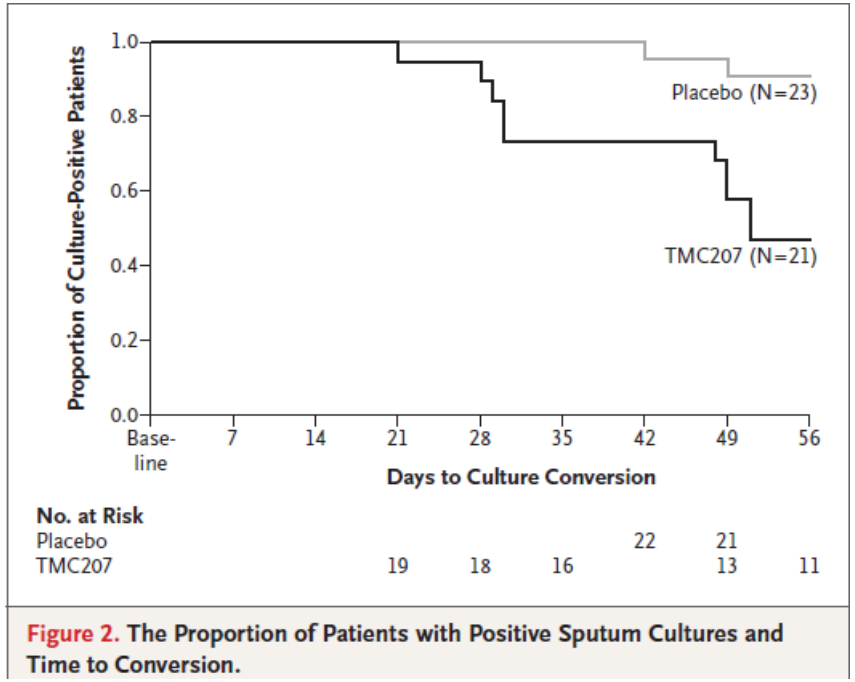

Figure 2. The Proportion of Patients with Positive Sputum Cultures and Time to Conversion.

Bedaquiline (US FDA Dec 2012)

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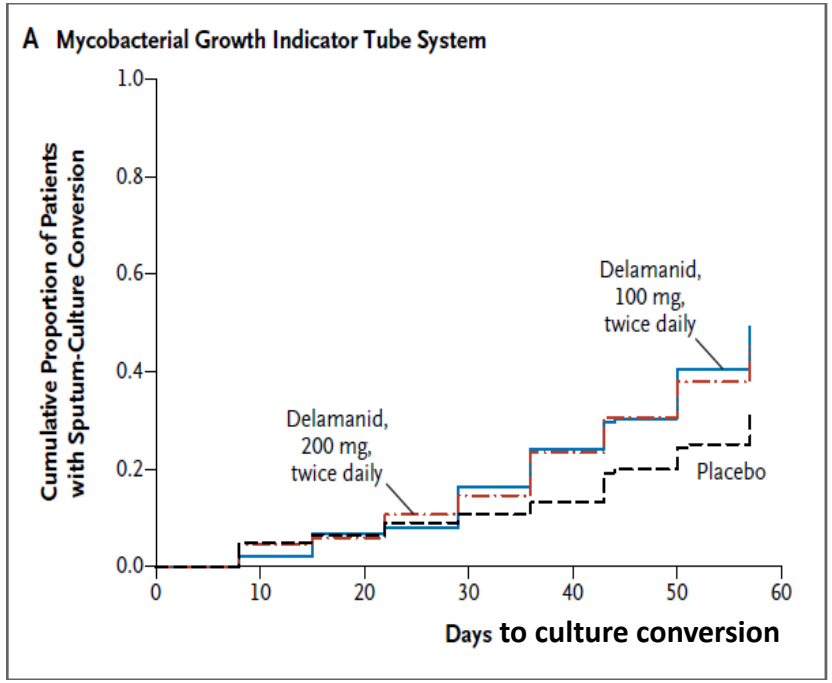
Delamanid for Multidrug-Resistant Pulmonary Tuberculosis



Delamanid (EMA Nov 2013)

Goals of the endTB project

- Expand access to new/repurposed TB drugs
- Find better, shorter, less toxic regimens
- Generate & disseminate evidence

Components of the endTB project

endTB observational study (complete)
17 Countries, > 2800 patients

endTB clinical trial (complete) 7 Countries, 750 participants
Rifampicin-resistant and FQ-susceptible pulmonary TB (FQ-S)
9 months

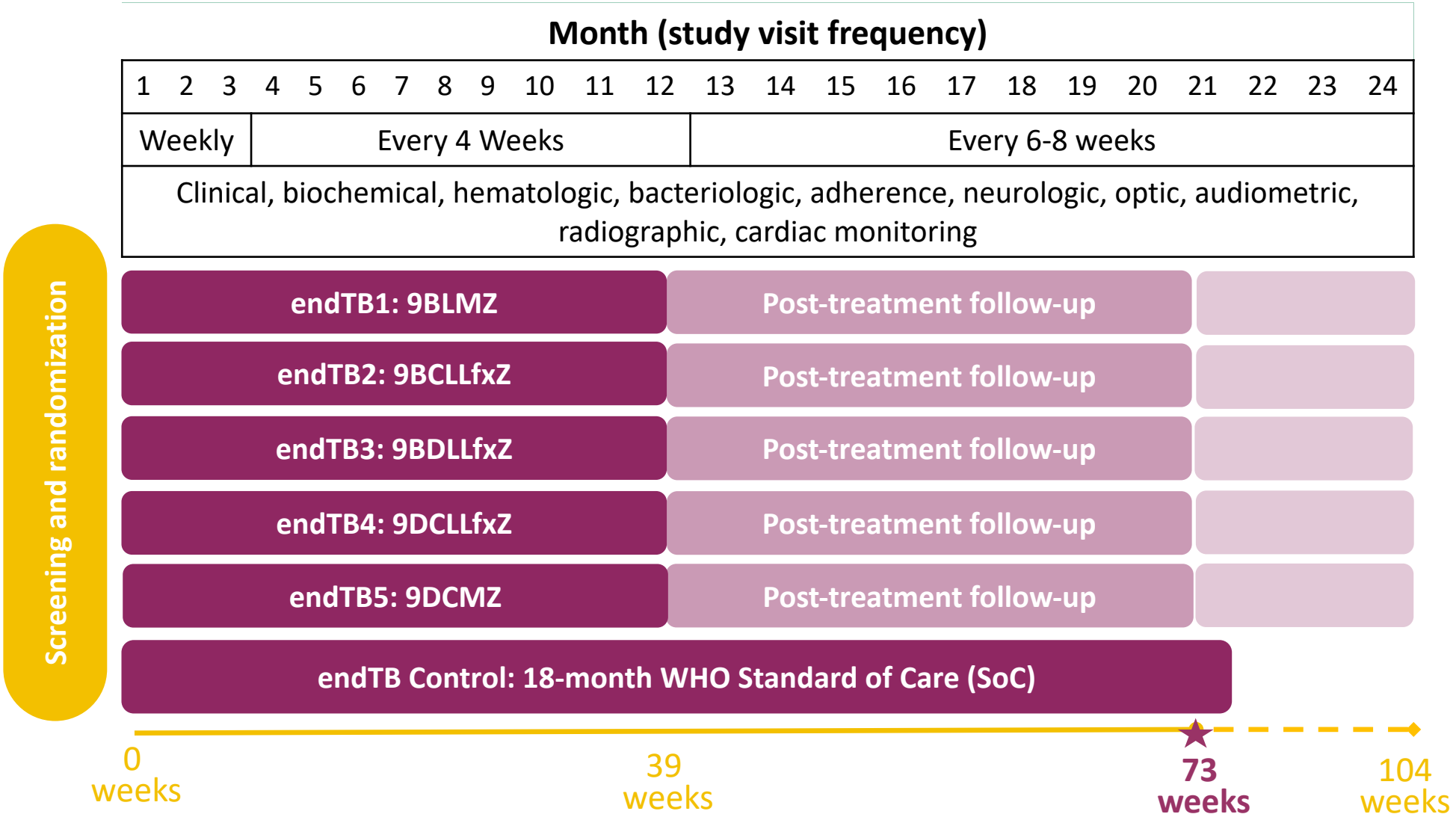
endTB-Q trial (follow-up) 6 Countries, 324 participants
Rifampicin- and FQ-resistant pulmonary TB (FQ-R)
6 to 9 months

endTB Trial Design[1]

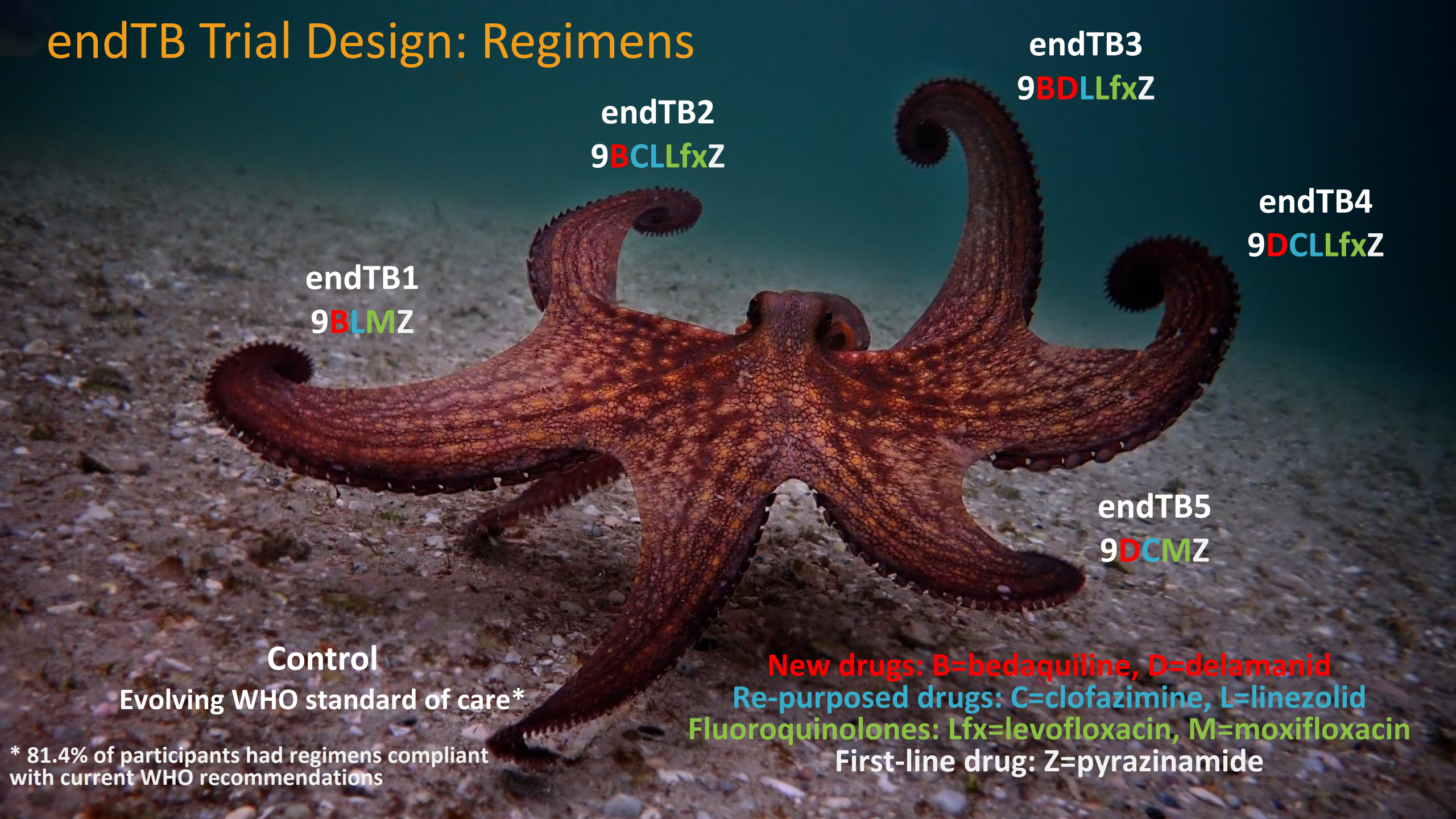
- Randomized, controlled, open-label, non-inferiority, Phase III trial
- Compares each of 5 experimental regimens to control
  - Efficacy
  - Safety
- Bayesian adaptive randomization[2,3]:
  - Fixed 1:1:1:1:1:1 for first 180 patients, then
  - Adjusted randomization probabilities according to non-inferior performance of experimental vs control on week 8 culture negativity and week 39 favorable outcome
- Detect as many non-inferior regimens as possible

[1] Guglielmetti et al, *Trials,* 2021;[2] Cellamare et al, *Clinical Trials*, 2017; [3]Cellamare et al, *Int J Tuberc Lung Dis*, 2016.

endTB Trial Design: Study Schema



endTB Trial Design: Regimens



endTB1
9BLMZ

endTB2
9BCLLfxZ

endTB3
9BDLLfxZ

endTB4
9DCLLfxZ

endTB5
9DCMZ

Control
Evolving WHO standard of care*

* 81.4% of participants had regimens compliant with current WHO recommendations

New drugs: B=bedaquiline, D=delamanid
Re-purposed drugs: C=clofazimine, L=linezolid
Fluoroquinolones: Lfx=levofloxacin, M=moxifloxacin
First-line drug: Z=pyrazinamide

endTB Trial Design: Main Inclusion & Exclusion Criteria

Inclusion

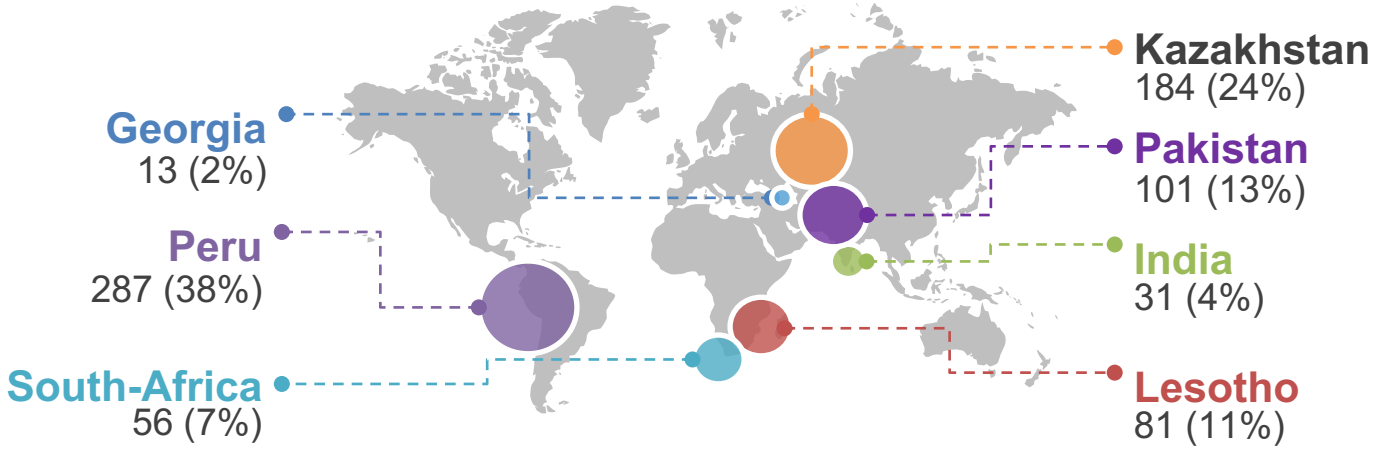
- **Pulmonary TB, RIF-resistant, FQ-susceptible**
- **≥ 15 years of age**
- Negative pregnancy test
- Informed consent

Exclusion

- Allergy or hypersensitivity to study drugs
- Exposure, resistance: Bdq, Dlm, Lzd, Cfz
- Pregnancy, breastfeeding
- Severe lab abnormalities
  - K+ disorders Grade 2 or higher*
  - Other electrolytes disorders*, hemoglobin, creatinine, liver enzymes Grade 3 or higher
  - Other tests Grade 4 or higher
- Cardiac risk factors
  - QTcF≥ 450 ms
  - Other factors predisposing to cardiac arrhythmia

* Uncorrectable

The endTB clinical trial



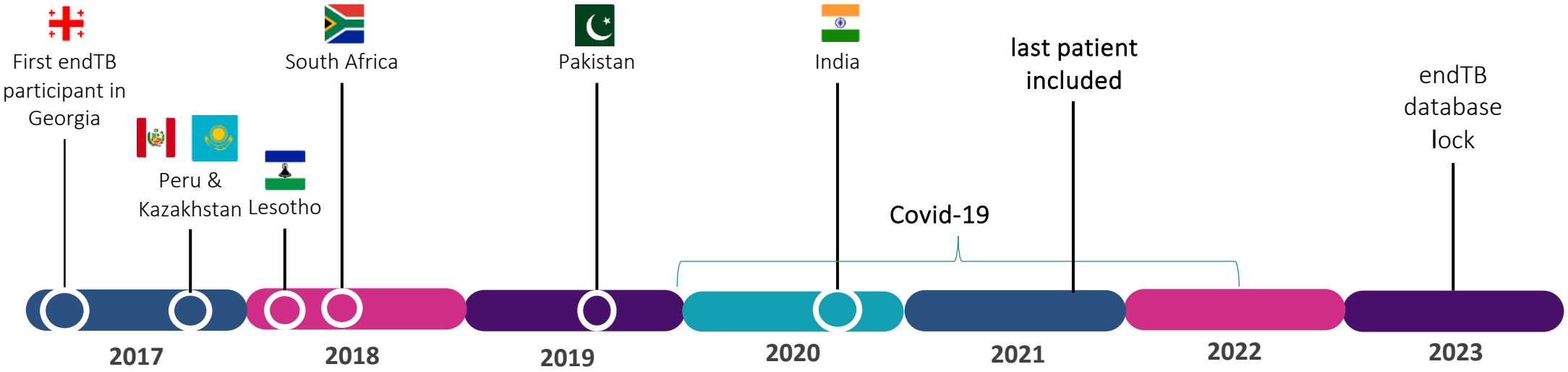
7 countries

12 sites

1539 screened

754 randomized

More than 18,000 visits



endTB trial-Design: Main Analysis Populations

Safety population

- All randomized participants who **received ≥1 dose of study treatment**.

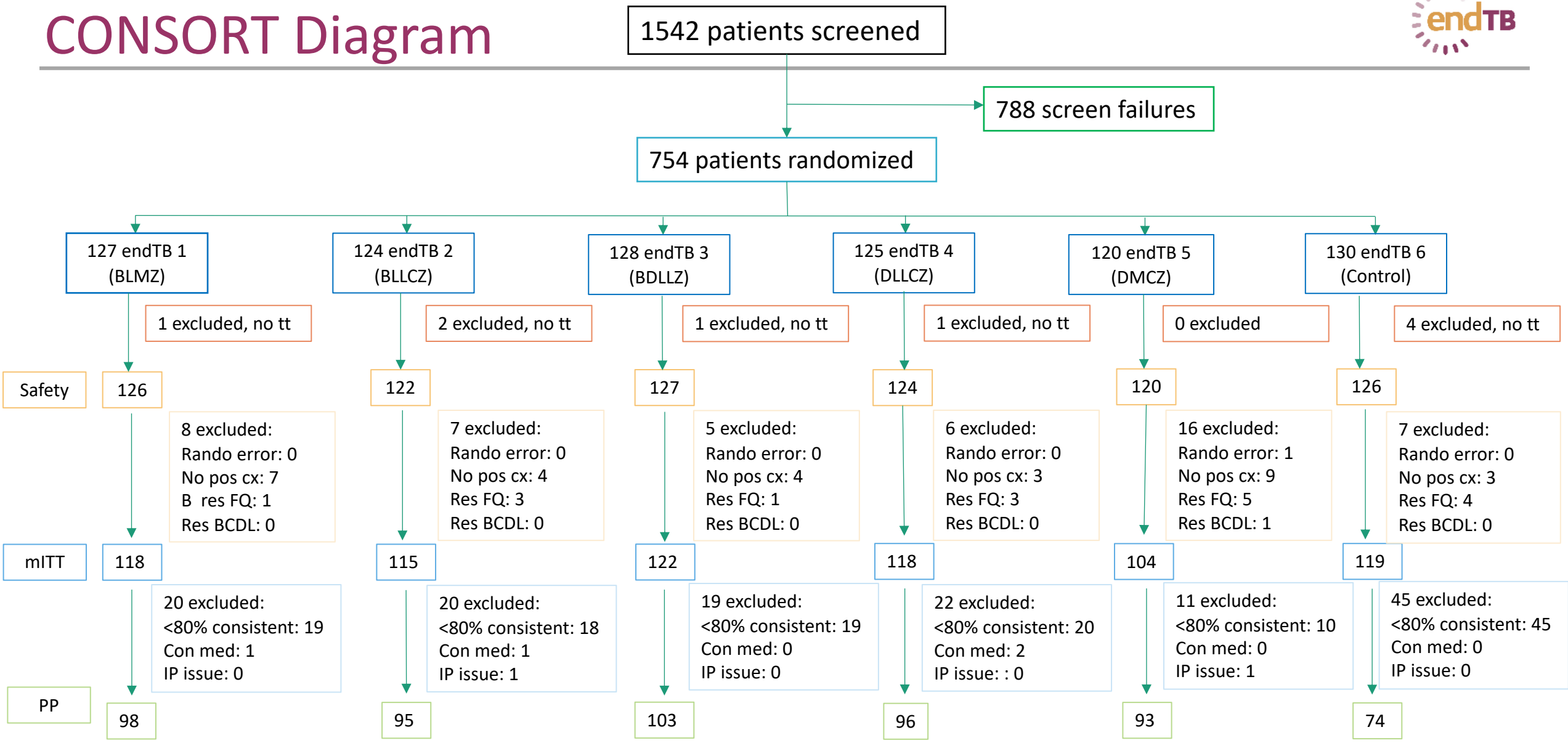
Modified intent to treat (mITT) population (co-primary)

- **Safety population with culture-positive, RIF-resistant TB**; with any post-baseline data; and **without resistance to Bdq, Cfz, Dlm, FQ, and/or Lzd**.

Per Protocol (PP) population (co-primary)

- mITT population who:
  - **Completed a protocol-consistent course of treatment** (or didn't because of treatment failure or death). Protocol-consistent course of treatment comprises 80% of expected doses within 120% of the regimen duration.
  - Were **not exposed to >7 days of** either a **prohibited concomitant medication** or an anti-TB drug not prescribed according to protocol.

CONSORT Diagram



No tt: No study treatment received| Rando error: Randomized by error | No pos cx: No positive culture before randomization | Res FQ: baseline resistance to fluoroquinolone (moxifloxacin and/or levofloxacin) on phenotypic DST| Res BCDL: baseline resistance to bedaquiline, delamanid, linezolid, or clofazimine on phenotypic DST | <80% consistent: <80% protocol-consistent treatment*|Con med: >7 days of prohibited concomitant medication*| IP issue: >7 days of IP not prescribed according to protocol* (*other than death and treatment failure)

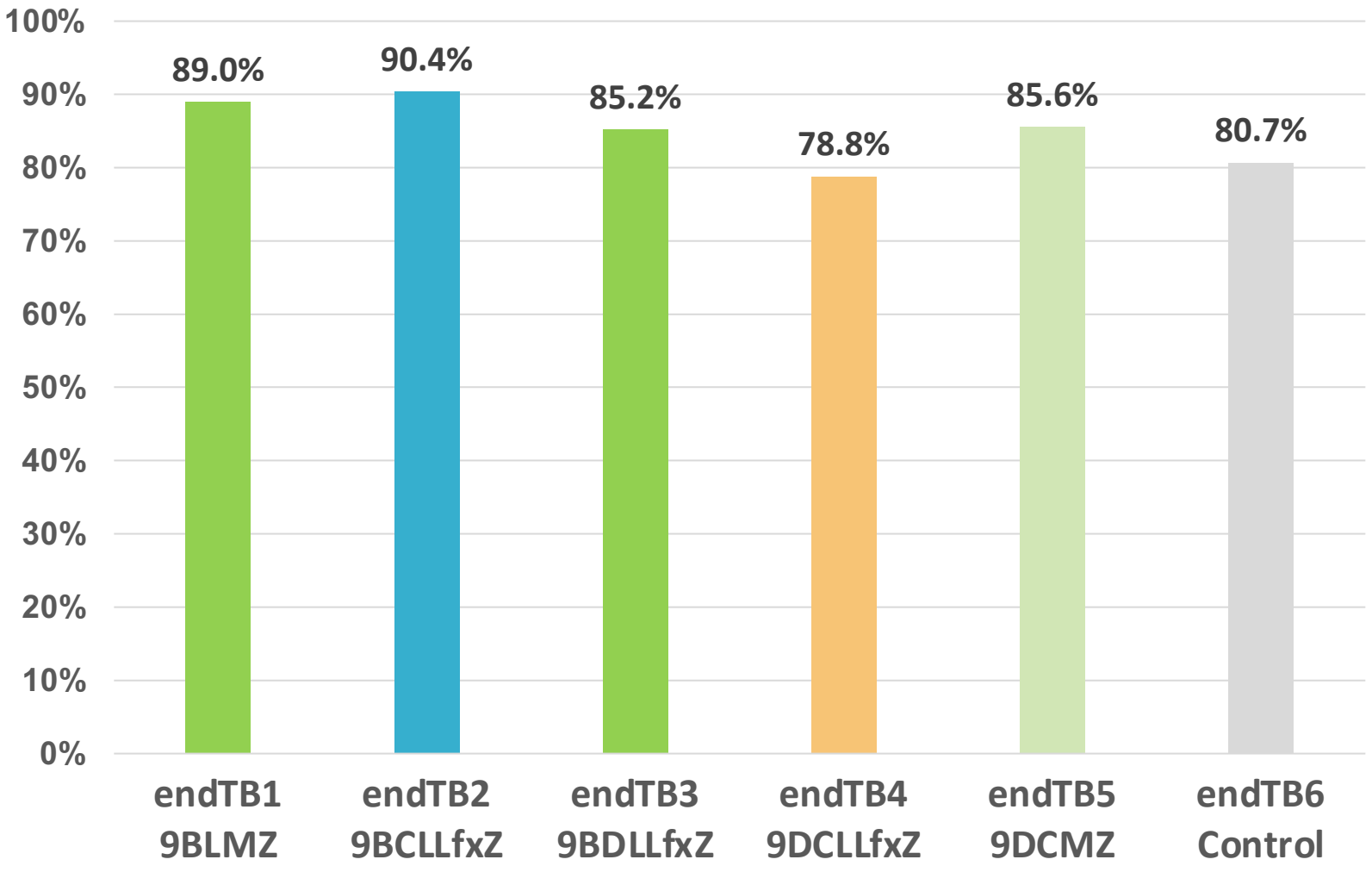
Selected baseline characteristics

Baseline characteristic	Total (N = 696)
Age (years), median (range)	32.0 [15.0;71.0]
Sex, female	264 (37.9%)
BMI (kg/m^2), median (IQR)	20.4 [18.0;22.8]
Pyrazinamide resistance	374 (**53.7%**)
HIV positive*	98 (**14.1%**)
Hepatitis B*	17 (2.4%)
Hepatitis C*	26 (3.7%)
Diabetes	104 (**14.9%**)
Sputum smear positive	565 (**81.2%**)
Lung cavitation	396 (**56.9%**)
Prior exposure to other 2nd line drugs	78 (11.2%)

* Prior history, new diagnosis during trial screening/baseline visits, new diagnosis while in trial

endTB Clinical Trial: Efficacy results

Efficacy results at 73 weeks, mITT (N=696)



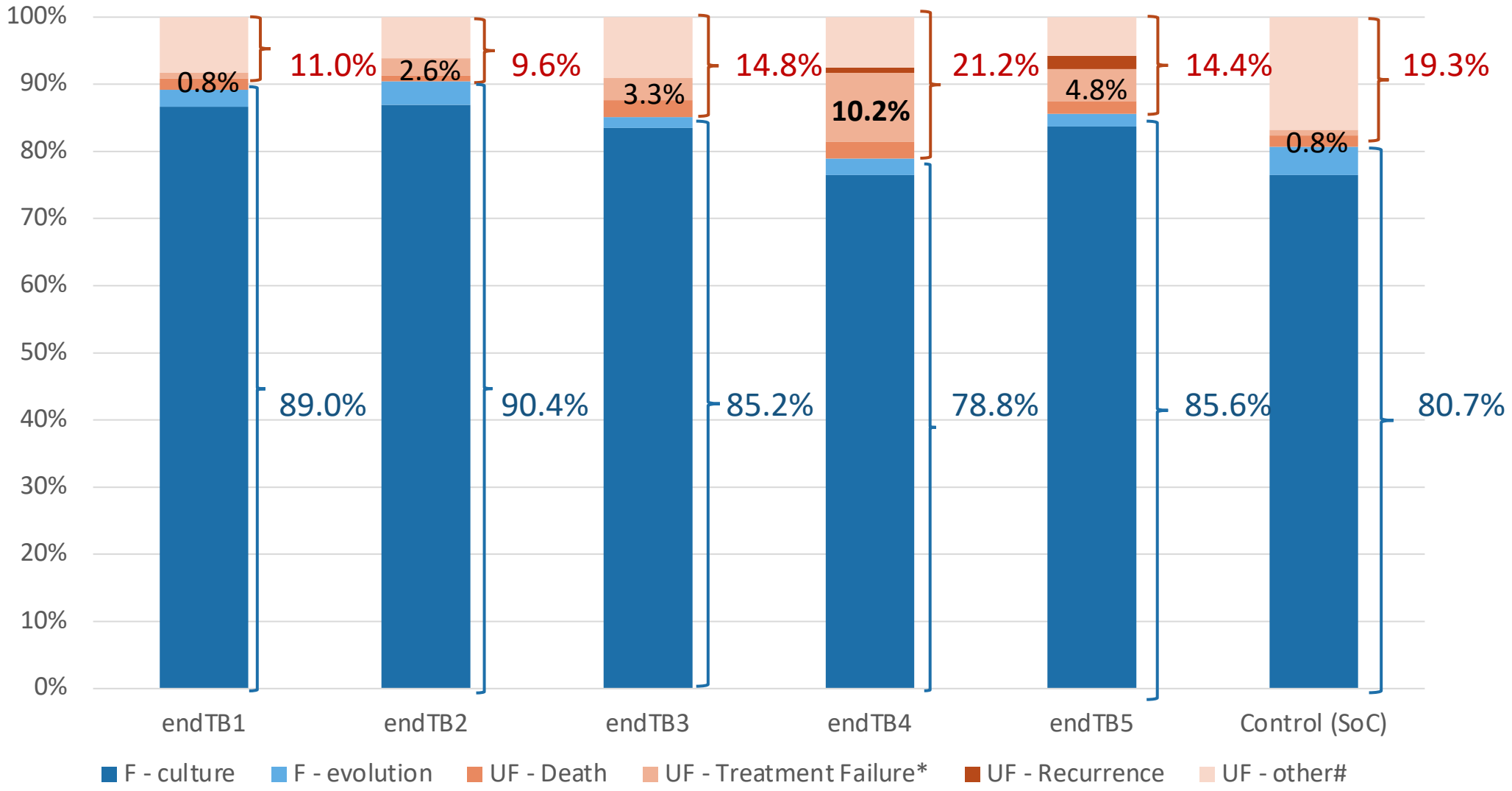
Efficacy compared to control

- Superior
- Non-inferior (all analyses)
- Non-inferior (only in mITT)
- Not non-inferior

Results consistent across analysis populations, endpoints, adjusted, & sensitivity

Detailed W73 treatment outcomes, mITT

Recurrence: 0.4%



F=Favorable;
UF=Unfavorable

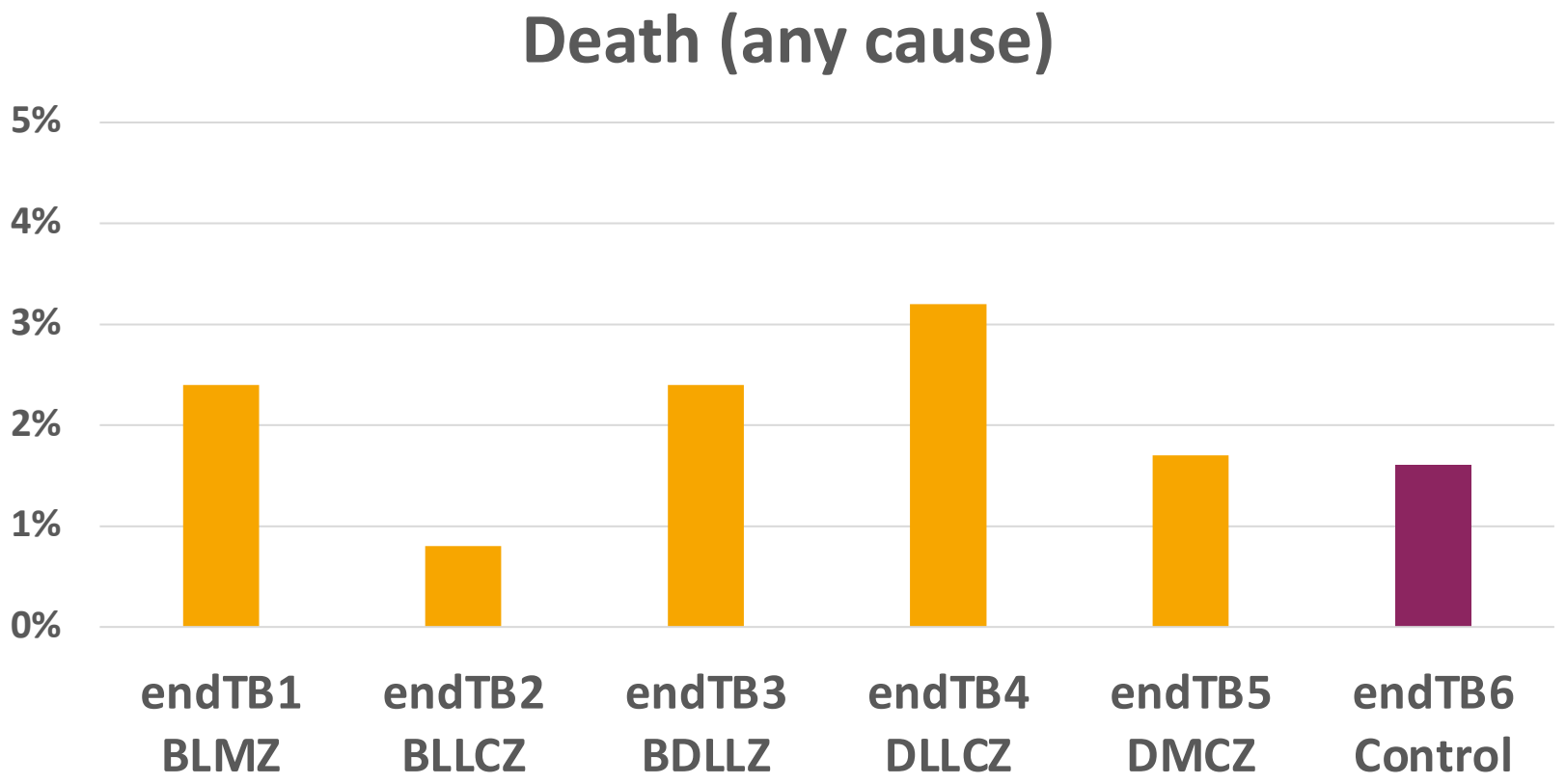
* Treatment failure = poor evolution (incl. Missing culture from Week 65 to Week 73) (7); positive culture (19)
# Poor adherence/LTFU (23); AE-related drug discontinuation (11); consent withdrawal (16); Not assessable post treatment (6), Investigator's judgement (4), Pregnancy/breastfeeding (2), Use of prohibited concomitant medication (1)

Efficacy Conclusions

- Provides robust evidence for 3 regimens that are NI to a contemporaneous, modern, control regimen (endTB1=BLMZ, endTB2=BLLCZ, endTB3=BDLLZ)
  - Offers **patient-centered treatment options** for all age groups: adults, adolescents, children (all drugs in the regimens have pediatric formulations, endorsements for use in kids), and pregnant people
  - Excellent results in population with **severe disease, comorbidities** (HIV, DM, Hepatitis B/C)
- In addition, endTB5 (DMCZ) offers possible, shortened, all-oral alternative for patients unable to take linezolid or bedaquiline
- Importance of well-performing control arm
  - **High threshold for non-inferiority** (compared to other trials)
  - Could result in **higher certainty of evidence**, strong recommendation

endTB Clinical Trial: Safety results

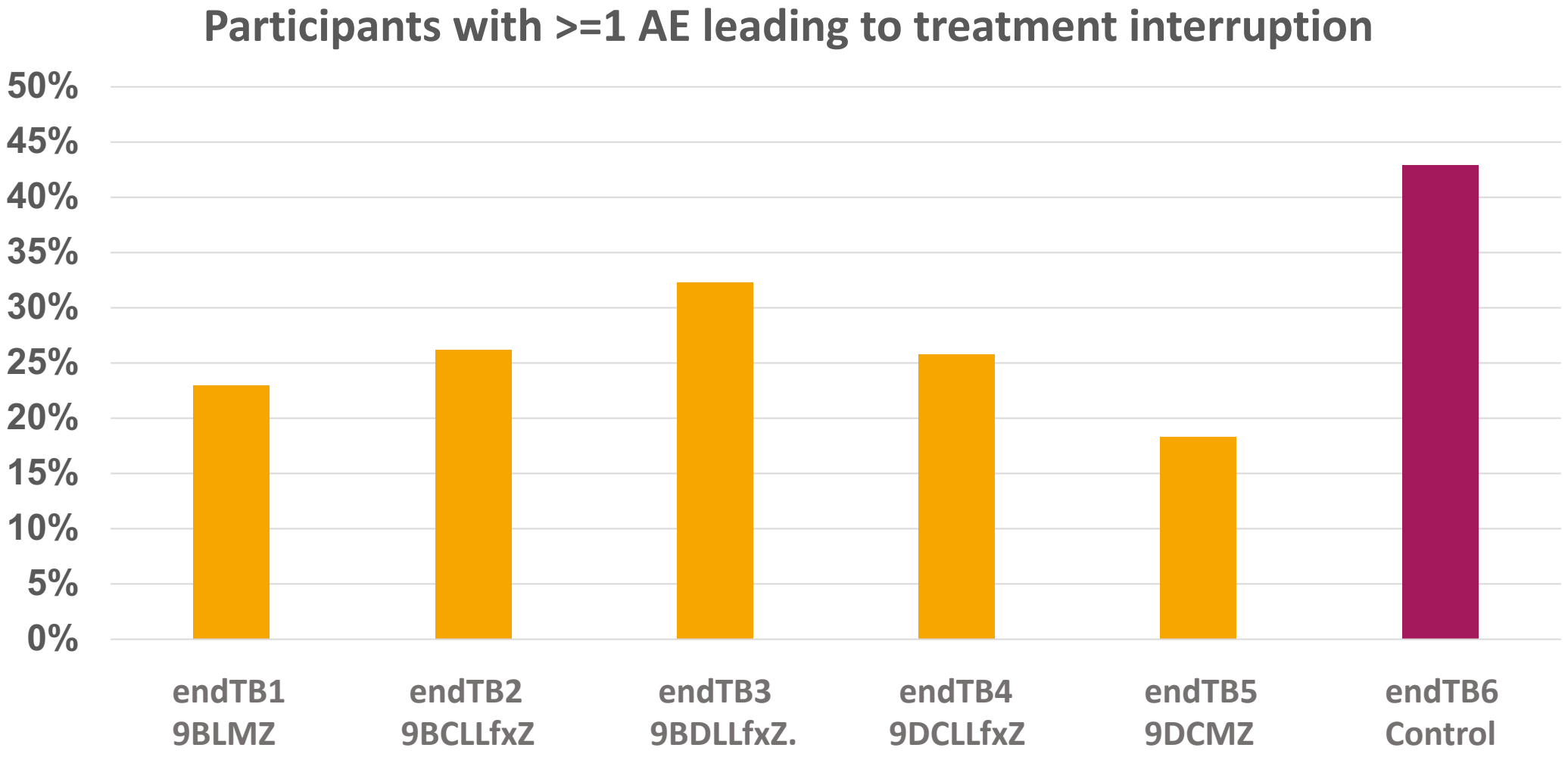
Deaths - Week 73 (Safety population, N=745)



Total N= 15.

No death was considered to be related to study drugs.

Safety endTB-Week 73

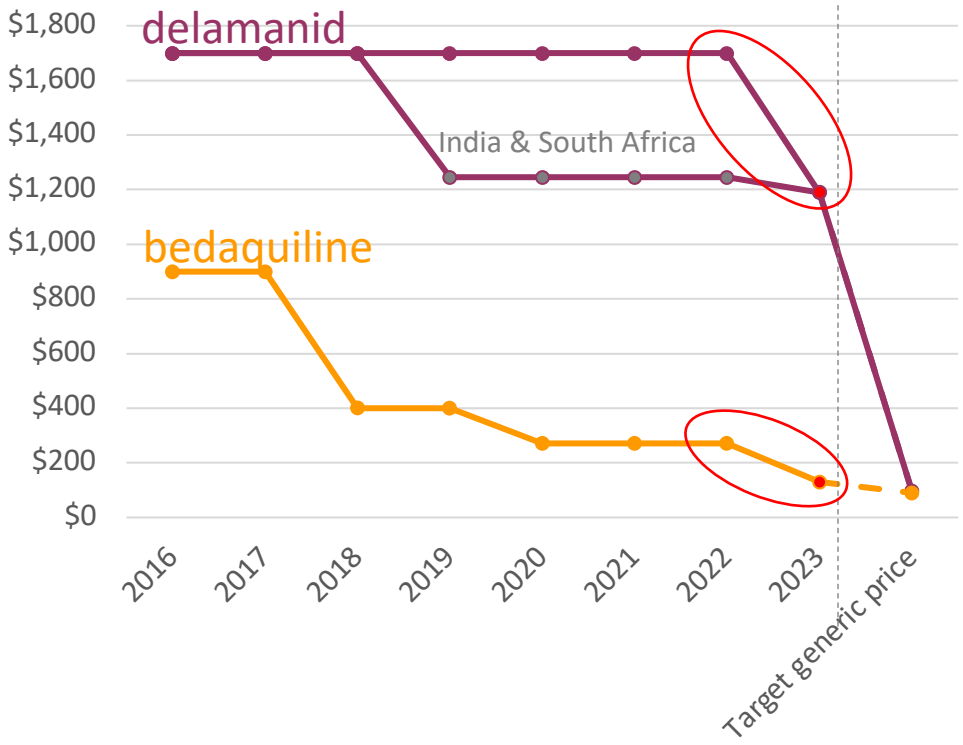


endTB trial – Safety Conclusions

- Low mortality (experimental and control)
- Permanent drug stoppage due to AEs more frequent in the control arm
- Comparable frequency of important AEs in experimental and control arms
    - Higher than expected in all arms: reflects comprehensive pharmacovigilance in the trial, includes many unrelated events
    - Linezolid-related toxicity common in control & experimental, QT prolongation not a major issue, more hepatic toxicity in experimental arms (none fatal)
- Confirms importance of appropriate, risk-based AE monitoring and prompt management

Cost and pill burden consideration

Price decrease on drugs



Cost & pill burden#

Regimen	Current regimen cost, US$*	Potential regimen cost with optimal generic competition, US$**	Pill burden, Daily
9BLMZ	**290**	189-262	**7**
9BCLLfxZ	**341**	264-337	**8**
9BDLLfxZ	2,023	183-352	11
9DCMZ	1,977	262-358	**9**
6BPaLM	**416**	189-386	**5**
Long treatment (18)	5,008	~3,000	20

*Based on lowest GDF prices (Oct 2023)
** Based on lowest GDF prices (Oct 2023), except estimated cost-based generic prices for Bdq, Dlm & Pa
#For people of 35-50kg

Courtesy of Christophe Perrin, MSF Access Campaign

endTB Resources

https://endtb.org/

PowerPoint slides of the endTB trial results presentations at the Union World Conference

You can download the PowerPoint slides of our endTB trial results presentations at the Union World Conference, 15-18 November 2023.

More details on the endTB clinical trial results at this link: https://endtb.org/endtb-clinical-trial-results

Download the leaflet on the endTB clinical trial results here:

Leaflet on the endTB Clinical Trial results (4.28 MB)

FAQs

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Nine-month, all-oral regimens for rifampin-resistant tuberculosis

Lorenzo Guglielmetti, Uzma Khan, Gustavo E.Velásquez, Maelenn Gouillou, Amanzhan Abubakirov, Elisabeth Baudin, Elmira Berikova, Catherine Berry, Maryline Bonnet, Matteo Cellamare, Vijay Chavan, Vivian Cox, Zhanna Dakenova, Bouke Catherine de Jong, Gabriella Ferlazzo, Aydarkhan Karabayev, Ohanna Kirakosyan, Nana Kiria, Mikanda Kunda, Nathalie Lachenal, Leonid Lecca, Helen McIlleron, Ilaria Motta, Sergio Mucching-Toscano, Hebah Mushtaque, Payam Nahid, Lawrence Oyewusi, Samiran Panda, Sandip Patil, Patrick Phillips, Jimena Ruiz, Naseem Salahuddin, Epifanio Sanchez-Garavito, Kwonjune J. Seung, Eduardo Ticona, Lorenzo Trippa, Dante Vargas, Sean Wasserman, Michael L. Rich, Francis Varaine, Carole D. Mitnick

doi: https://doi.org/10.1101/2024.01.29.24301679

Are you interested in further learning from the endTB project data?

The endTB data sharing initiative (eDSI) aims to give ethical, equitable and transparent access to endTB data for a range of users who share the common goal of increasing knowledge and disseminating information to improve care for MDR-TB patients.

The endTB data is a unique set of data on MDR-TB:

- **more than 3,700 participants** across our **3 prospective studies**
- **18 countries across 4 continents**, all WHO Regions
- **standardized patient monitoring and outcome assignment**; standardized procedures, data collection, and reporting
- **longitudinal recording of participant characteristics**, regimen composition, adverse events, and treatment response
- **quality control/assurance** including internal & external monitoring for the clinical trials

Please scan this QR code to sign up and be notified when new endTB data becomes available

Global Health Innovations in endTB

Consortium

- Direct service, human-rights/social-justice organizations
- Participant support
- Community engagement
- Access warriors
- Pharmacovigilance

Funder

- New to (TB) trials

Design

- Bayesian, response-adaptive randomization
- Hybrid follow-up
- Control changed w/SoC

Population

- Inclusive
- Adolescents
- Pregnancy

Special thanks to the people and organizations who have made the endTB clinical trial a reality…

The 754 trial participants, and the other 785 patients screened

All the team members, investigators and sites which implemented the trial during 7 years
National TB Programs and all local partners in Georgia, India, Kazakhstan, Lesotho, Pakistan, Peru and South Africa

The Sponsor and research partners:

MEDECINS SANS FRONTIERES · Partners In Health · IRD Interactive Research & Development · Institute of Tropical Medicine Antwerp · Harvard Medical School · epicentre Épidémiologie • Epidemiology

The PIs, the central endTB team, all contributing expert teams (Protocol Writing Committee, Scientific Advisory Committee, MSF Logistique, unblinded statisticians, the Clinical Advisory Committee, the Pharmacovigilance unit, Data and Safety Monitoring Board, MSF Access Campaign, Global Tuberculosis Community Advisory Board and WHO) and all other support teams

Our funder and long-term partner:

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We are grateful to all endTB trial participants and endTB teams!








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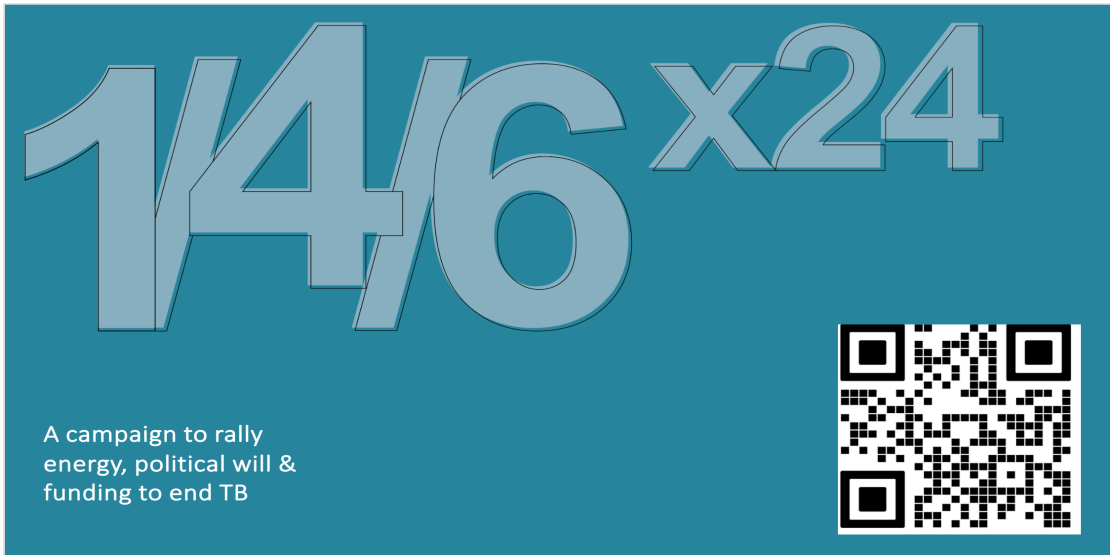

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