

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

WHO EURO Virtual Medical TB Consilium, 26th webinar

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endTB Clinical Trial: Background & Design

The endTB project and clinical trials

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 (over)
17 Countries, > 2600 patients

endTB clinical trial (completed) 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

- 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 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
- Secondary randomization to linezolid dose reduction strategy at Week 16, from 600 mg daily to:
 - 600 mg 3 x week
 - 300 mg daily

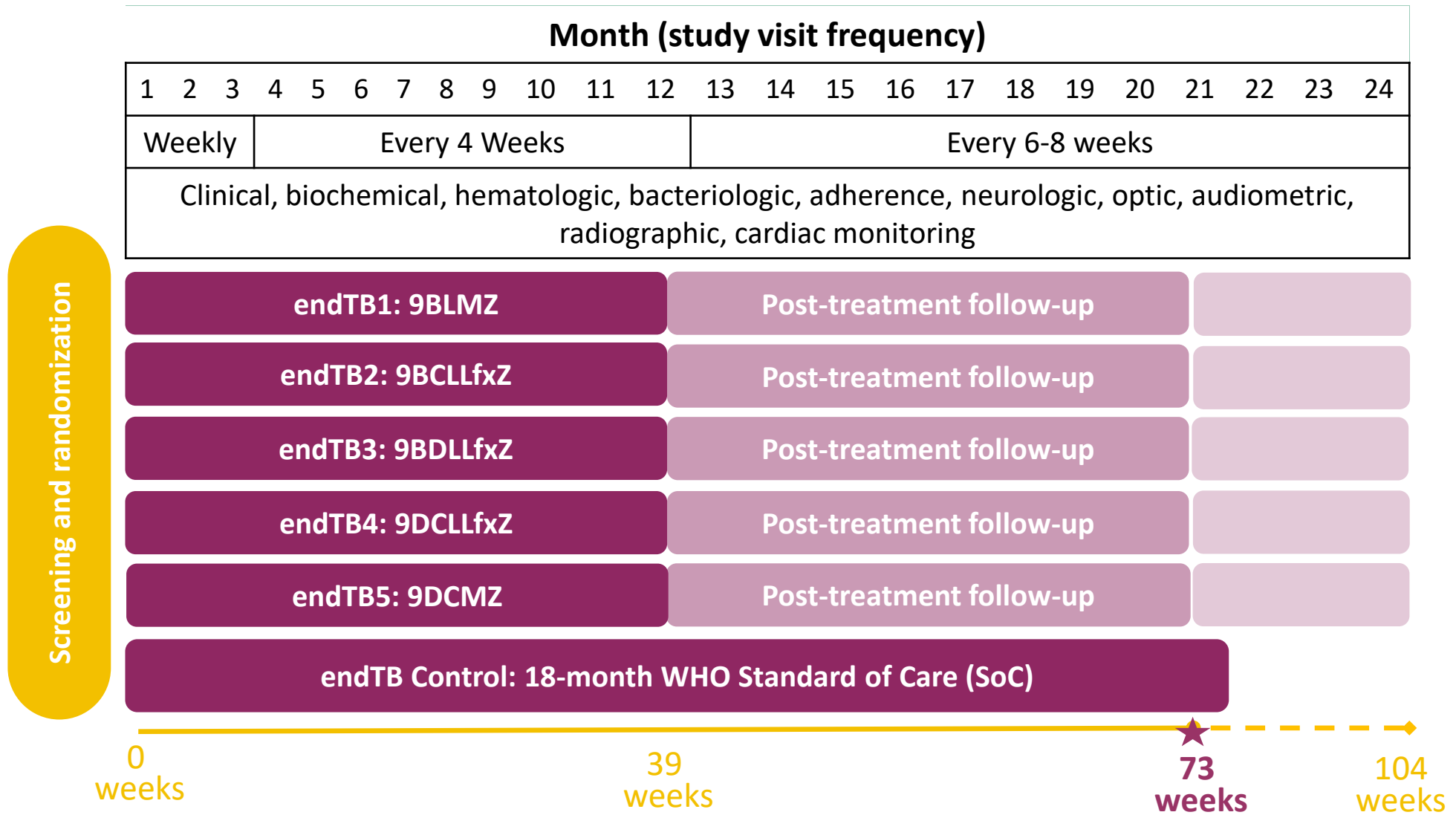
¹Guglielmetti et al, *Trials*, 2021;² Cellamare et al, *Clinical Trials*, 2017; ³Cellamare et al, *Int J Tuberc Lung Dis*, 2016.

endTB Trial Design



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

endTB Trial Design: Study Schema



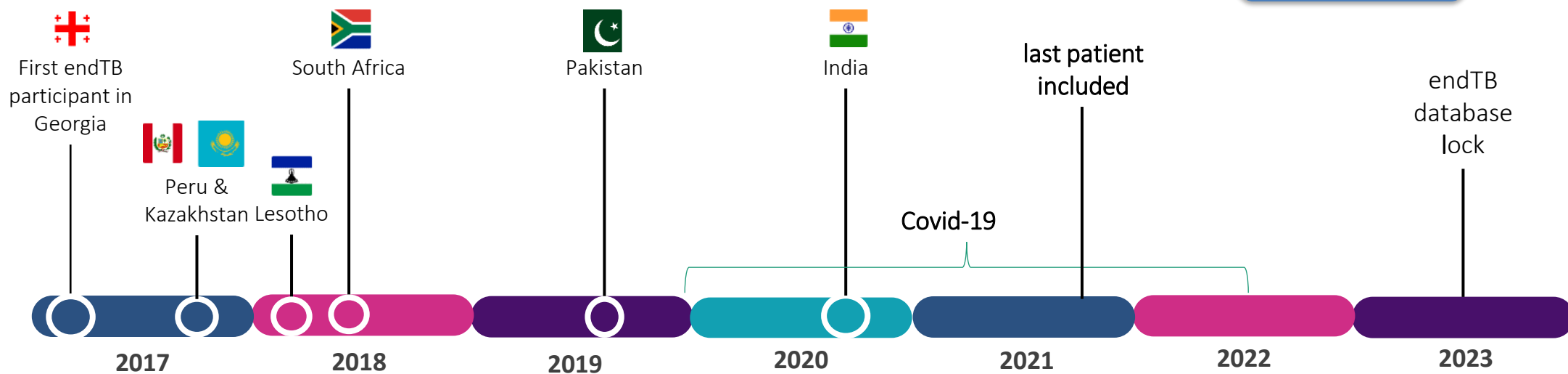
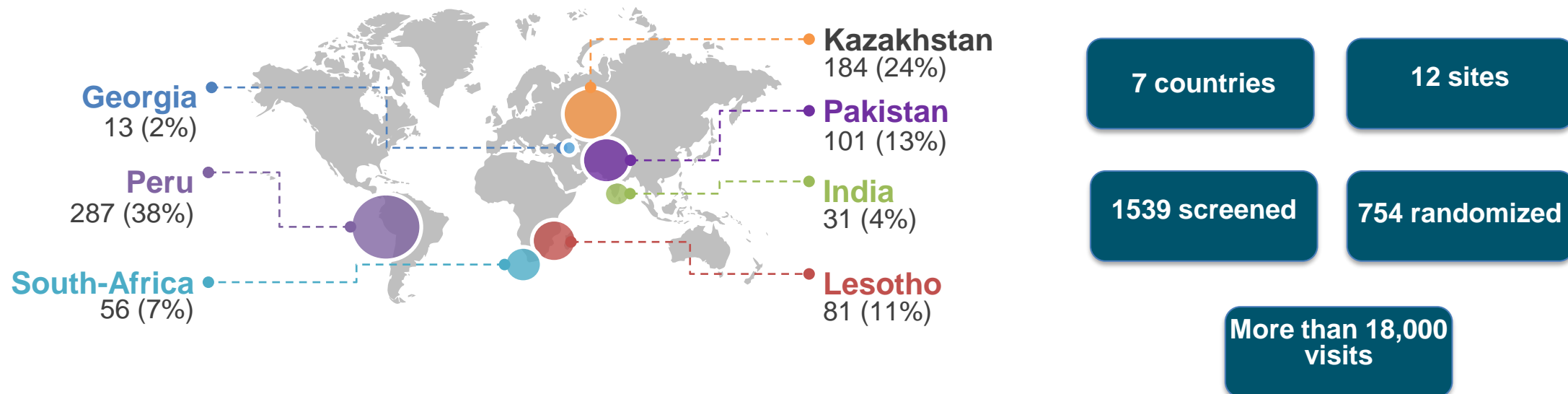
Inclusion

- **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

The endTB clinical trial



Safety population

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

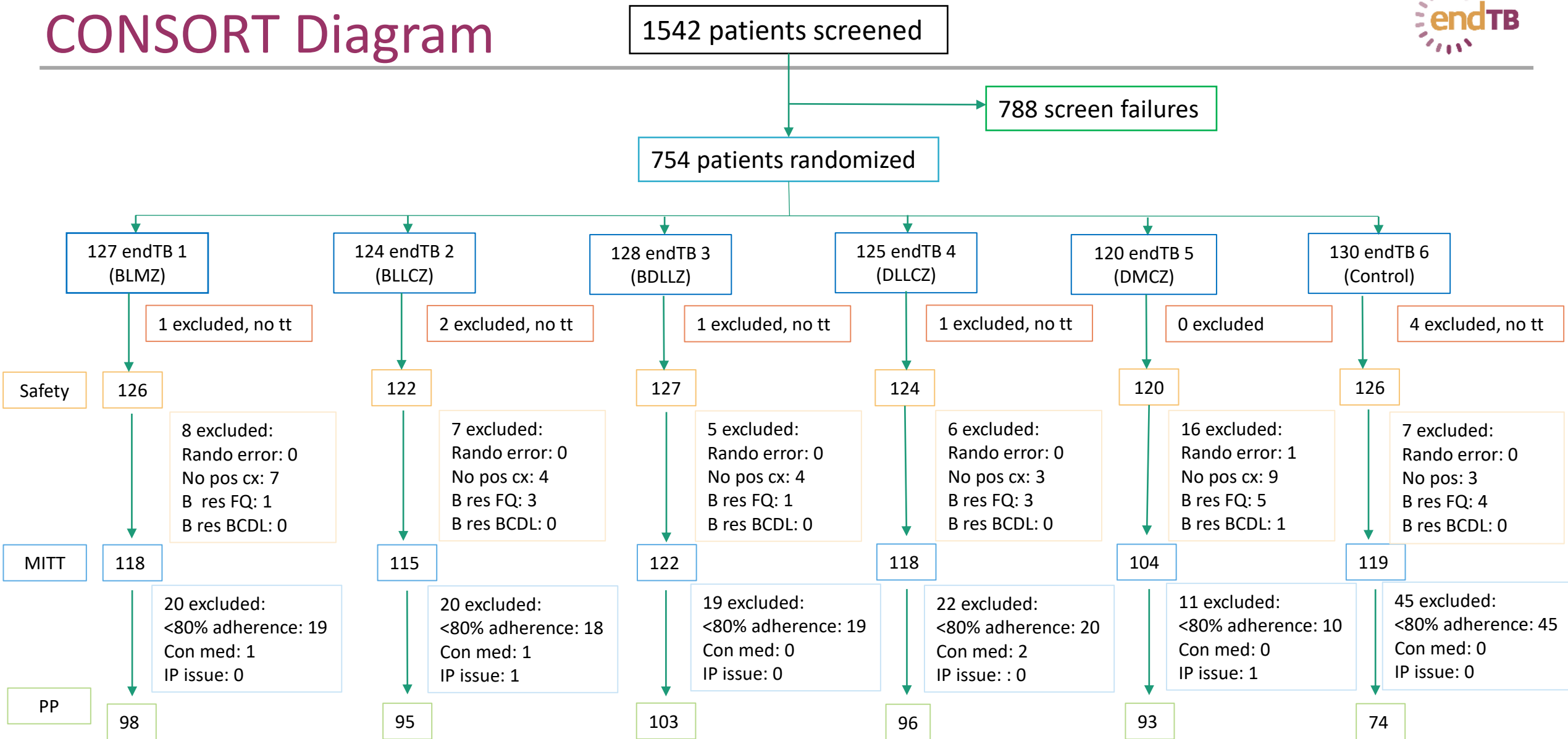
Modified intent to treat (mITT) population (co-primary)

- **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-adherent course of treatment** (or didn't because of treatment failure or death). Protocol-adherent 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 | B res FQ: baseline resistance to fluoroquinolone (moxifloxacin and/or levofloxacin) on phenotypic DST | B res BCDL: baseline resistance to bedaquiline, delamanid, linezolid, or clofazimine on phenotypic DST | <80% adherence: <80% protocol-adherent 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)

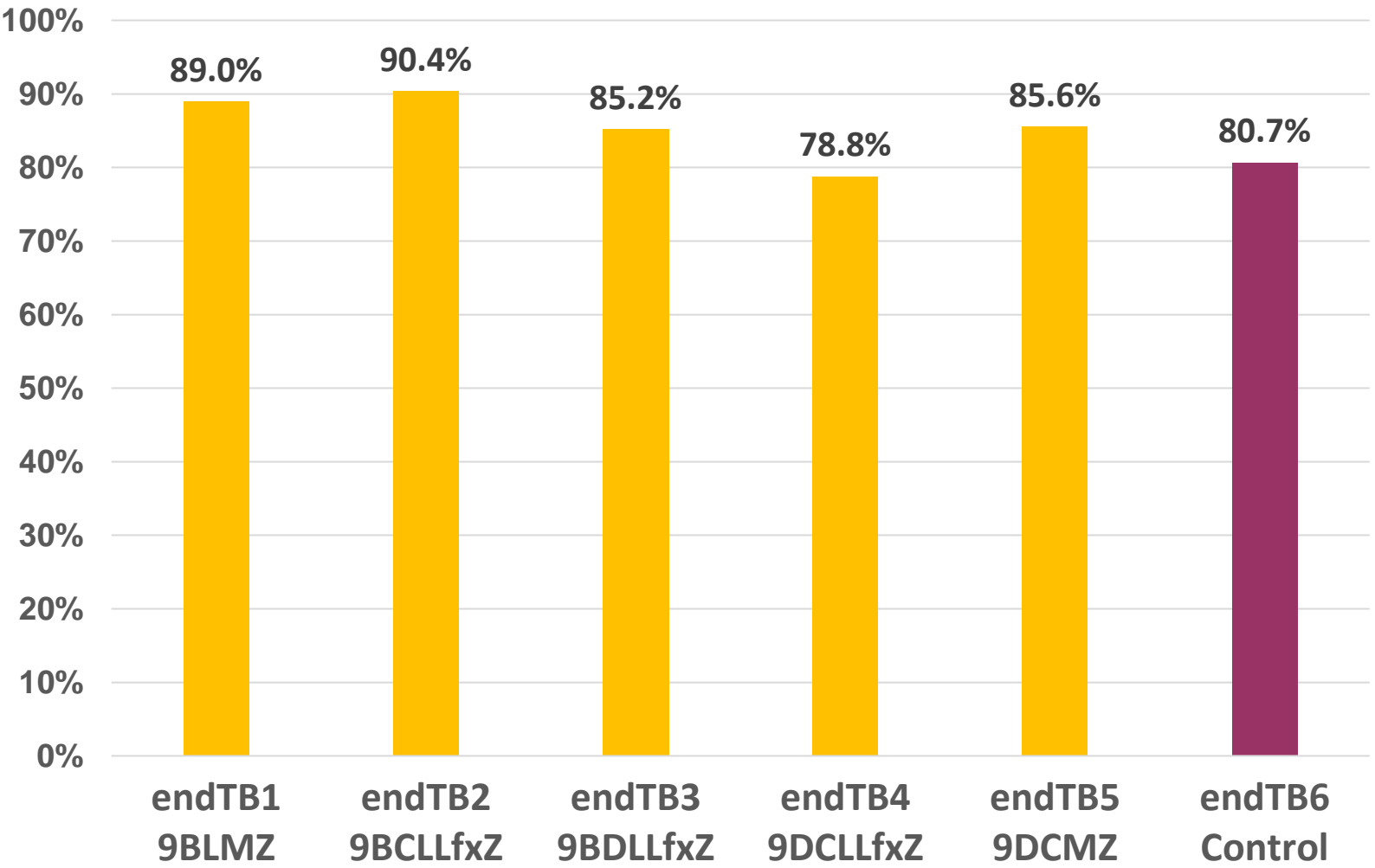
Selected baseline characteristics

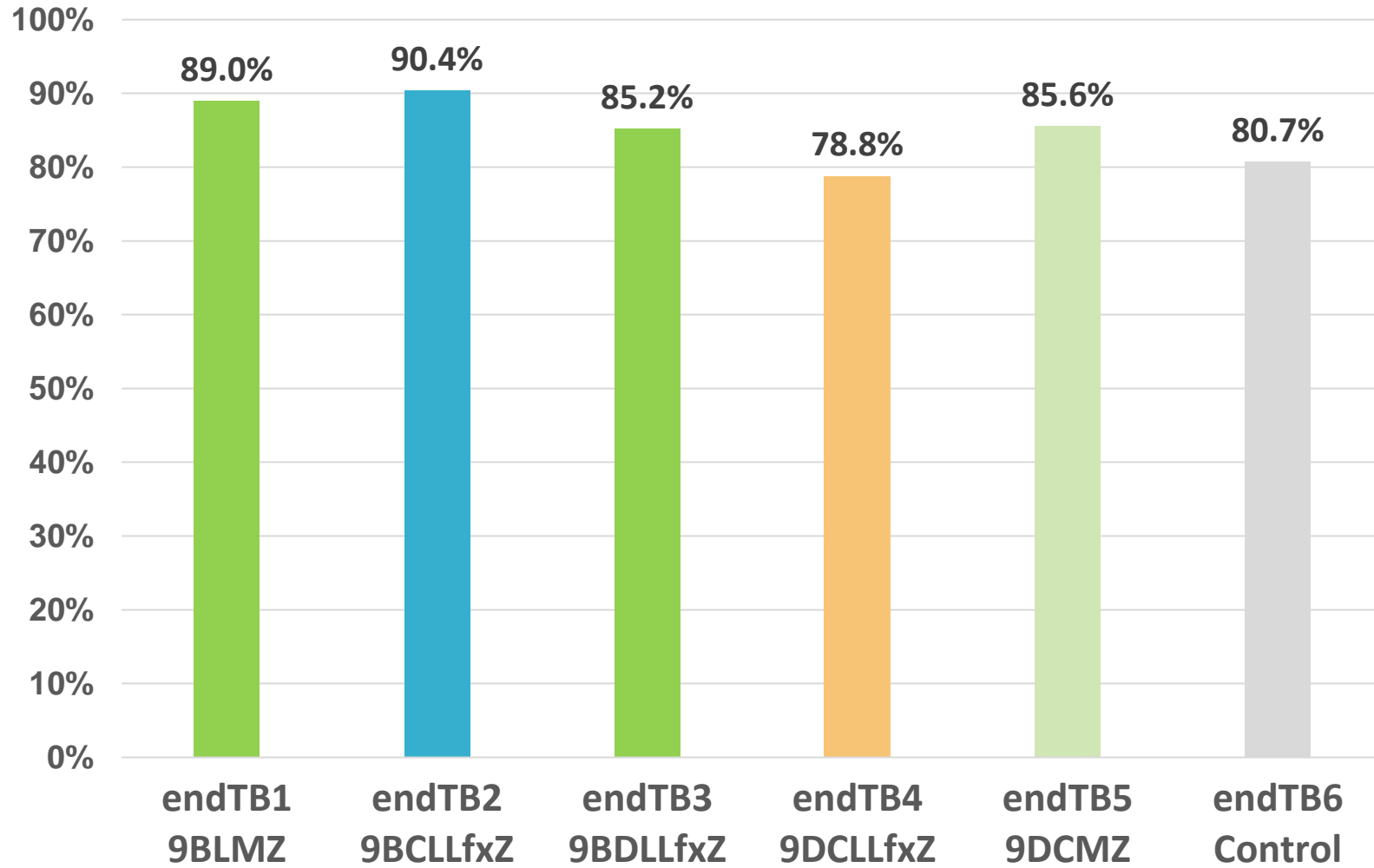
Baseline characteristic	Total (N = 696)
Age (years), median (range)	32.0 [15.0;71.0]
Sex, female	264 (37.9%)
BMI (kg/m ²), median (IQR)	20.4 [18.0;22.8]
Pyrazinamide resistance	374 (53.7%)
HIV positive*	98 (14.1%)
Hepatitis B*	17 (2.4%)
Hepatitis C*	26 (3.7%)
Diabetes	104 (14.9%)
Sputum smear positive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

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

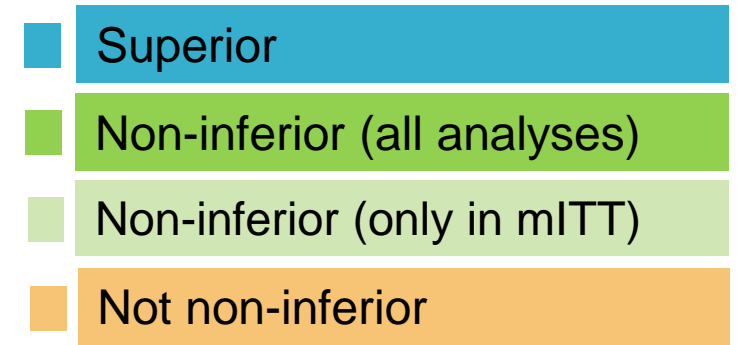
endTB Clinical Trial: Efficacy results

endTB Regimens | Efficacy results and comparison with control, mITT (N=696)





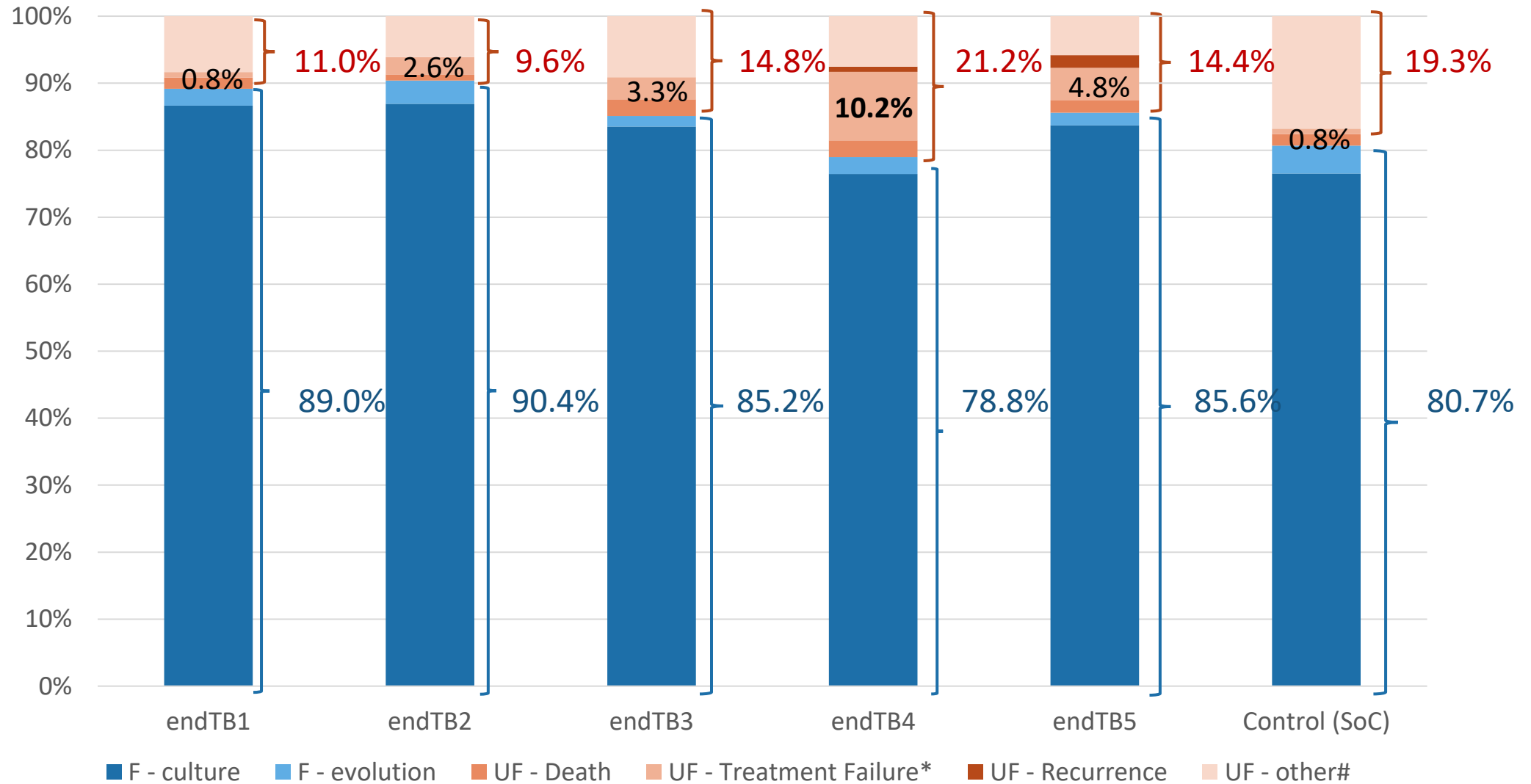
Efficacy compared to control



Detailed W73 treatment outcomes, mITT



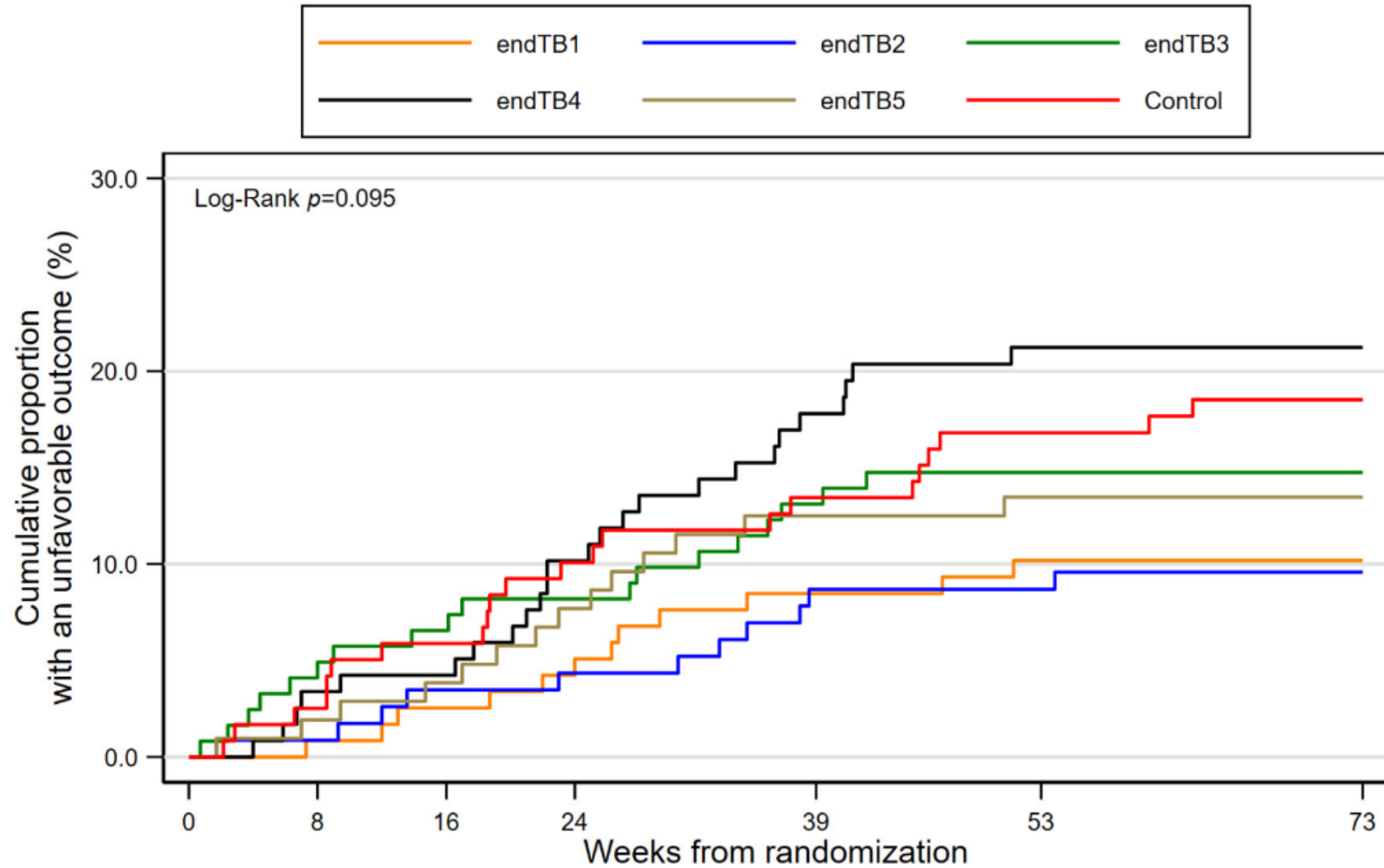
**Recurrence:
0.4%**



* 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)

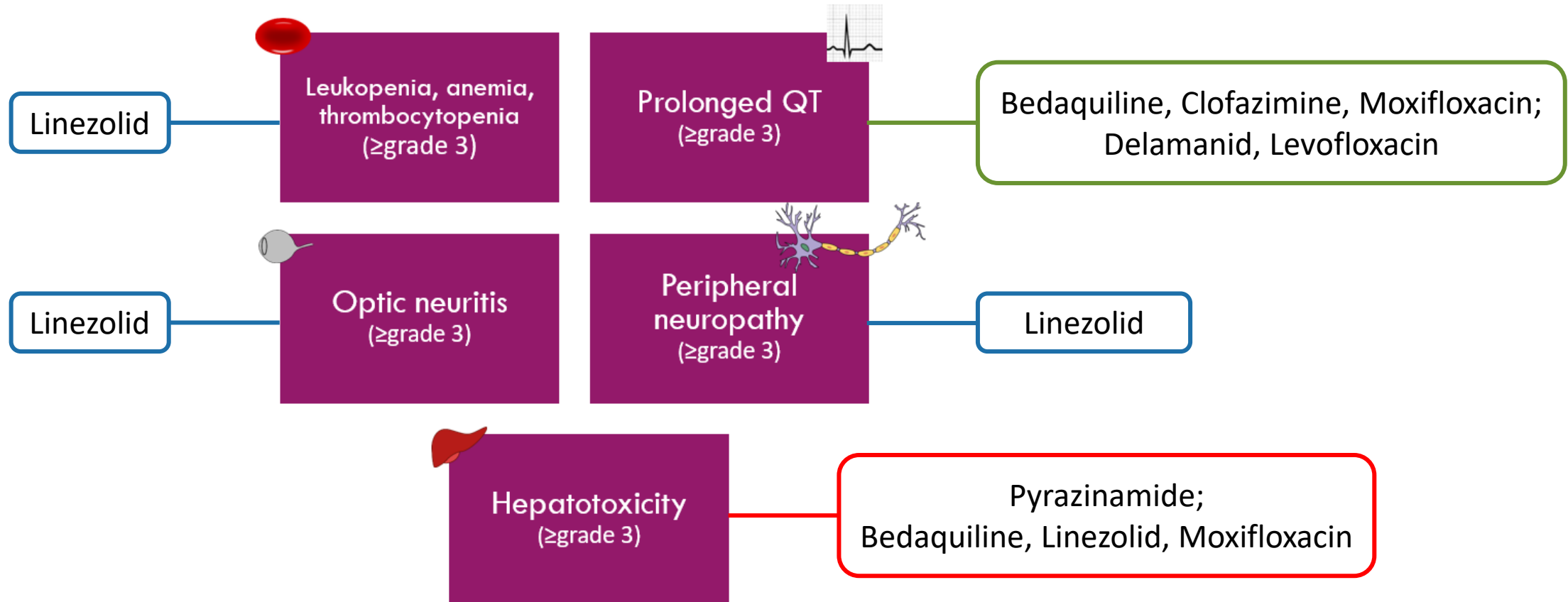
Survival analysis – time to W73 unfavourable outcome, mITT



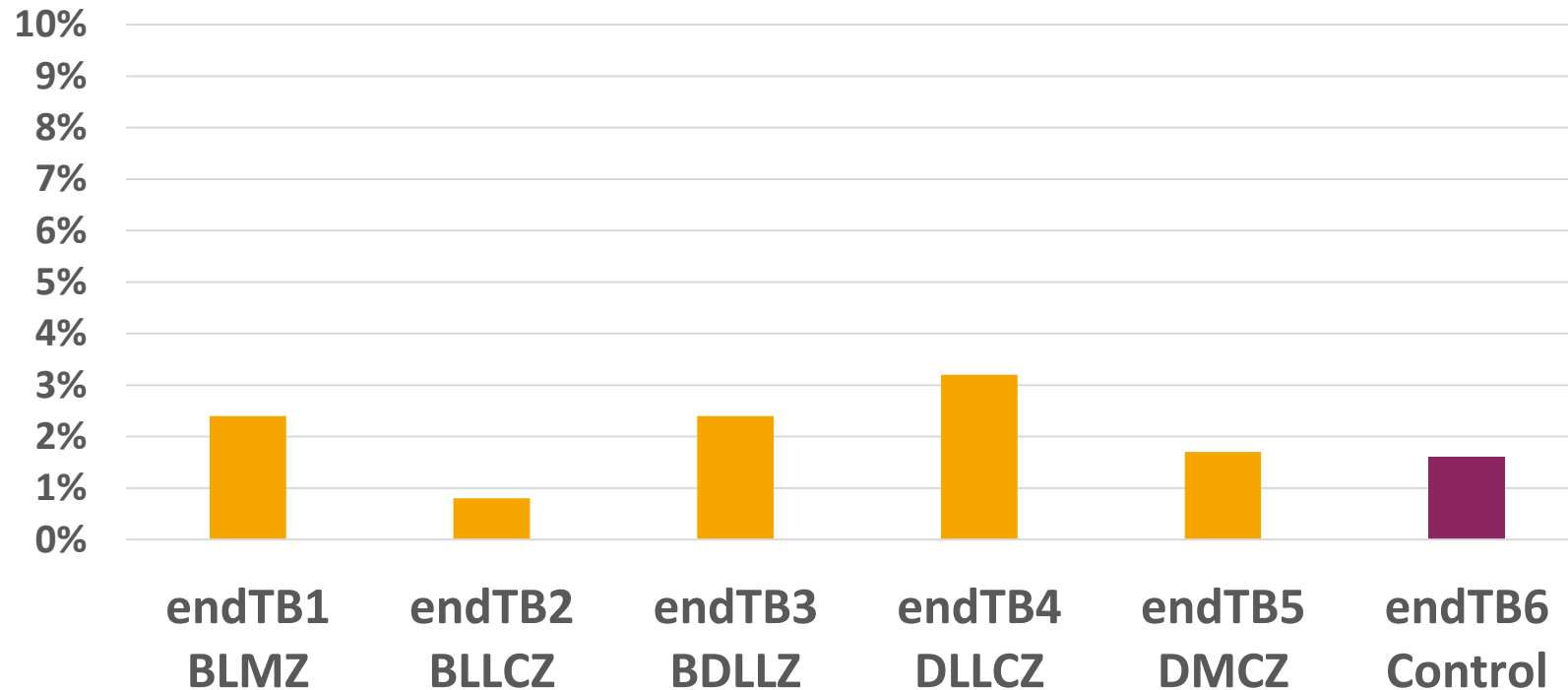
- Provides robust evidence for 3 regimens that are NI to a contemporaneous, modern, control regimen (endTB1=BLMZ, endTB2=BLLCZ, endTB3=BDLLZ)
 - Offers **patient-centered treatment options** for all age groups: adults, adolescents, children (all drugs in the regimens have pediatric formulations, endorsements 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
 - Sets a **high bar for non-inferiority** (compared to other trials)
 - Could result in **higher certainty of evidence**, strong recommendation

endTB Clinical Trial: Safety results

Adverse events of special interest (AESIs)



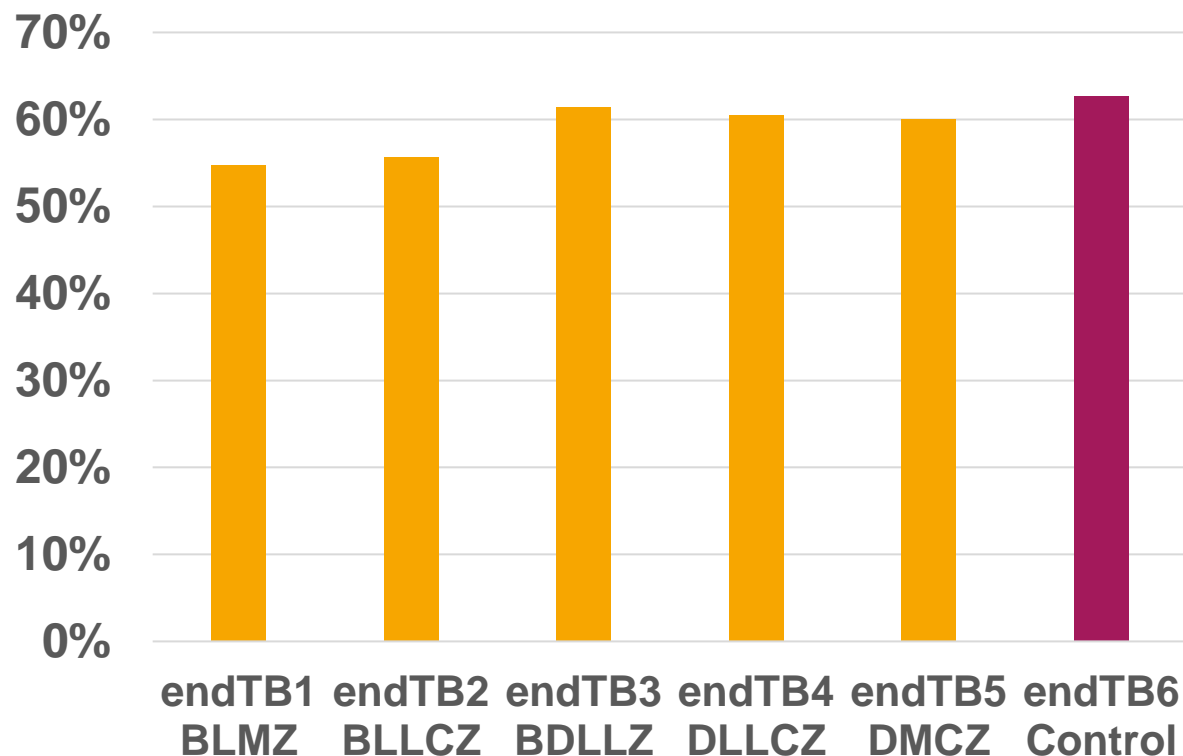
Death (any cause)



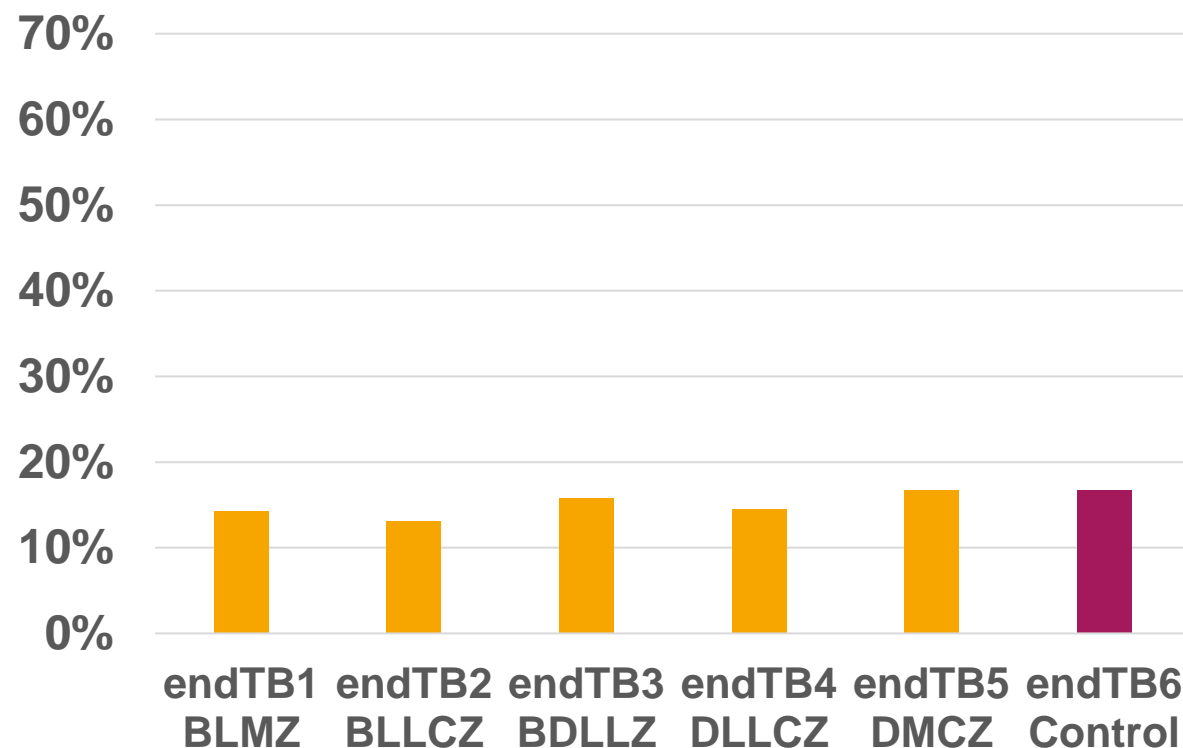
Total N= 15.

No death was considered to be related to study drugs.

Participants with at least one Grade ≥ 3 adverse event*



Participants with at least one serious adverse event**



* Graded according to MSF Severity Scale; ** Serious adverse event = leading to death or life threatening; or leading to hospitalization, permanent disability or congenital defect; or otherwise medically important.

AE of Special Interest (AESIs) by arm by Week 73 – Safety population

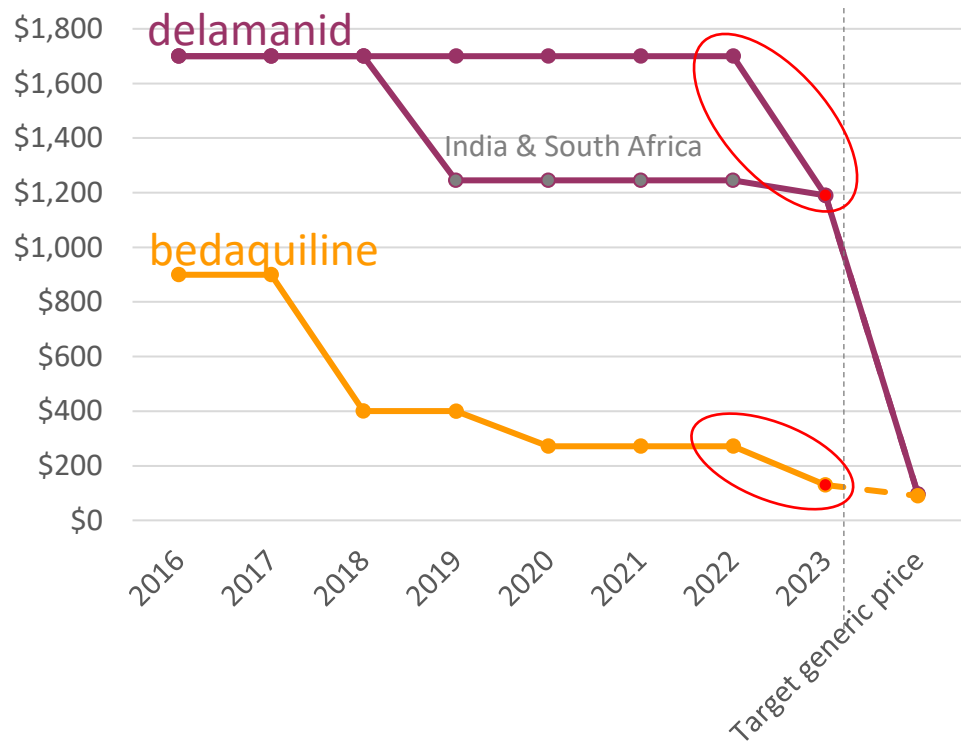
Adverse events	endTB1 (BLMZ) (n = 126)	endTB2 (BLLCZ) (n = 122)	endTB3 (BLLDZ) (n = 127)	endTB4 (DLLCZ) (n = 124)	endTB5 (DMCZ) (n = 120)	endTB6 (Control) (n = 126)	Total (n = 745)
Participants with ≥1 AESI	35 (27.8%)	33 (27.1%)	25 (19.7%)	33 (26.6%)	26 (21.7%)	26 (20.6%)	178 (23.9%)
Grade ≥ 3 hematologic toxicity	11 (8.7%)	9 (7.4%)	10 (7.9%)	13 (10.5%)	9 (7.5%)	13 (10.3%)	65 (8.7%)
Grade ≥ 3 peripheral neuropathy	4 (3.2%)	5 (4.1%)	9 (7.1%)	3 (2.4%)	3 (2.5%)	6 (4.8%)	30 (4.0%)
Grade ≥ 3 optic neuropathy	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	2 (1.6%)	4 (0.5%)
Grade ≥ 3 QT prolongation	0 (0.0%)	4 (3.3%)	0 (0.0%)	0 (0.0%)	5 (4.2%)	0 (0.0%)	9 (1.2%)
Grade ≥ 3 hepatotoxicity	23 (18.3%)	17 (13.9%)	8 (6.3%)	18 (14.5%)	12 (10.0%)	9 (7.1%)	87 (11.7%)

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



Costs estimates and pill burden

Regimen (number of months)	Current regimen cost, US\$*	Potential regimen cost with optimal generic competition, US\$**	Pill burden, Daily
<u>endTB1</u> Bdq-Lzd-Mfx-Z (9)	290	189-262	7
<u>endTB2</u> Bdq-Cfz-Lfx-Lzd-Z (9)	341	264-337	8
<u>endTB3</u> Bdq-Dlm-Lfx-Lzd-Z (9)	2,023	183-352	11
<u>endTB5</u> Dlm-Cfz-Mfx-Z (9)	1,977	262-358	9
BPaLM (6)	416	189-386	5
Long treatment (18)	5,008	~3,000	20

*Based on lowest GDF prices (Oct 2023) - For people of 35-50kg

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

<https://endtb.org/>



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

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



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](#)

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:



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:





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



Thank you. Questions?

Extra resources:

<https://endtb.org/endtb-clinical-trial-results>

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

IT'S TIME FOR \$5!
XDR-TB TEST NEXT!

A price drop to \$7.97 for only the Xpert MTB/RIF test is not enough.

We need Danaher & Cepheid to also drop the price of the Xpert MTB/XDR test which is still priced at \$14.90!

TIME FOR

Join the campaign!