endTB Clinical Trial: Design, Efficacy, Safety & Linezolid Dose-Reduction Randomization Results

15 November 2023
Union World Conference, Paris

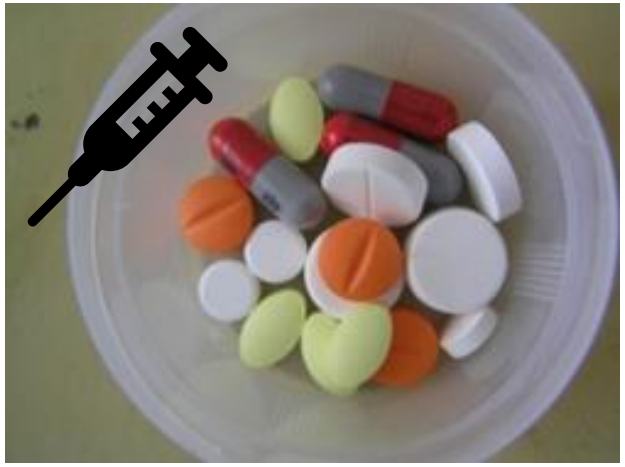
endTB Clinical Trial: Background, Design & Baseline Characteristics

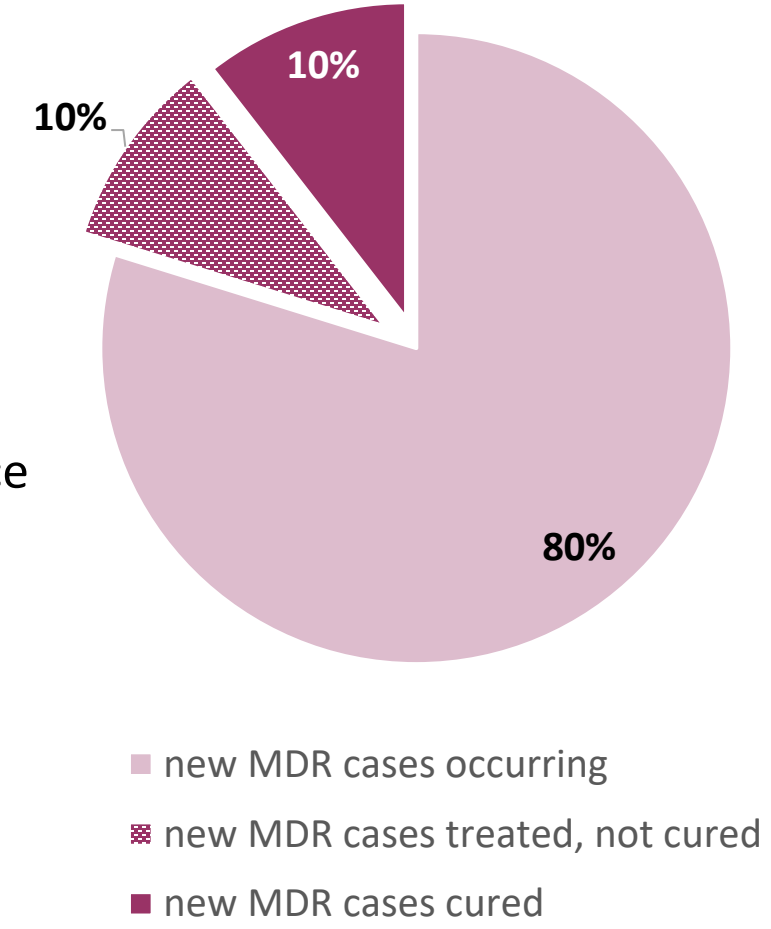
Background

State of MDR/RR-TB c. 2013

MDR-TB treatment:[1]

- Long
- Toxic
- Complex
- High pill burden
- Expensive
- Impossible to scale-up
- Largely based on expert opinion and very low quality of evidence
- Poorly effective





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

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

Background c. 2013

The NEW ENGLAND JOURNAL of MEDICINE

The Diarylquinoline TMC207 for Multidrug-Resistant Tuberculosis

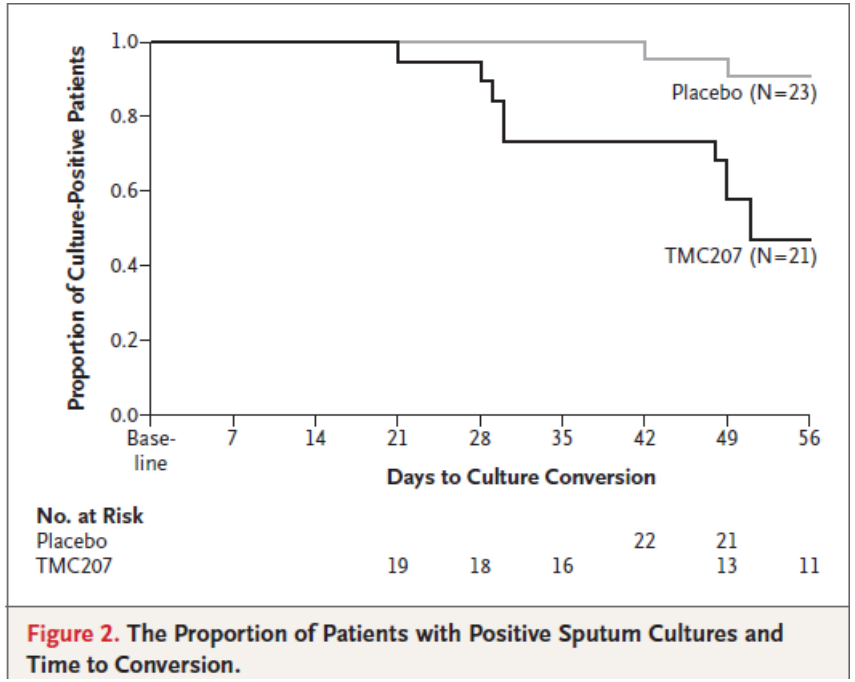
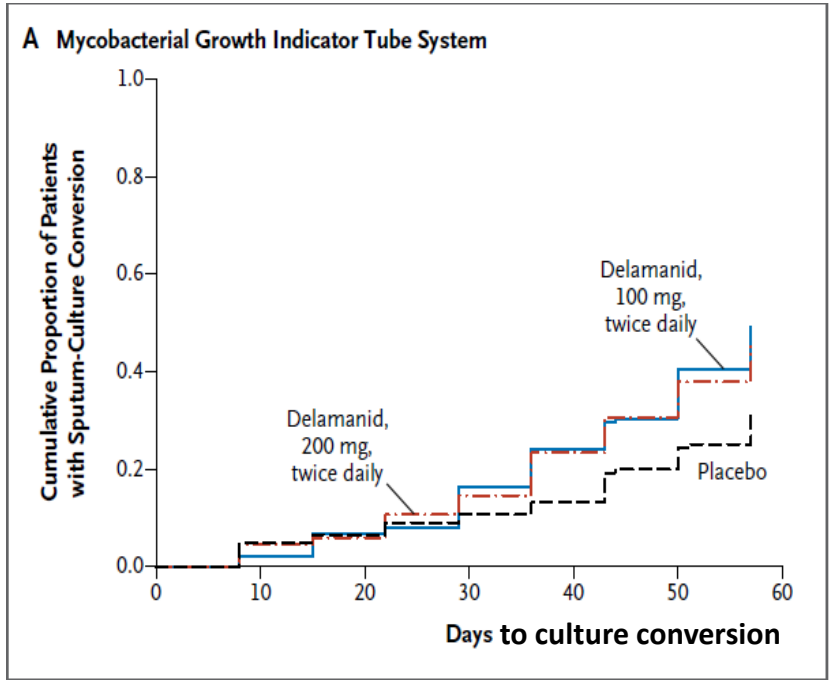


Figure 2. The Proportion of Patients with Positive Sputum Cultures and Time to Conversion.

Bedaquiline (US FDA Dec 2012)

The NEW ENGLAND JOURNAL of MEDICINE

Delamanid for Multidrug-Resistant Pulmonary Tuberculosis



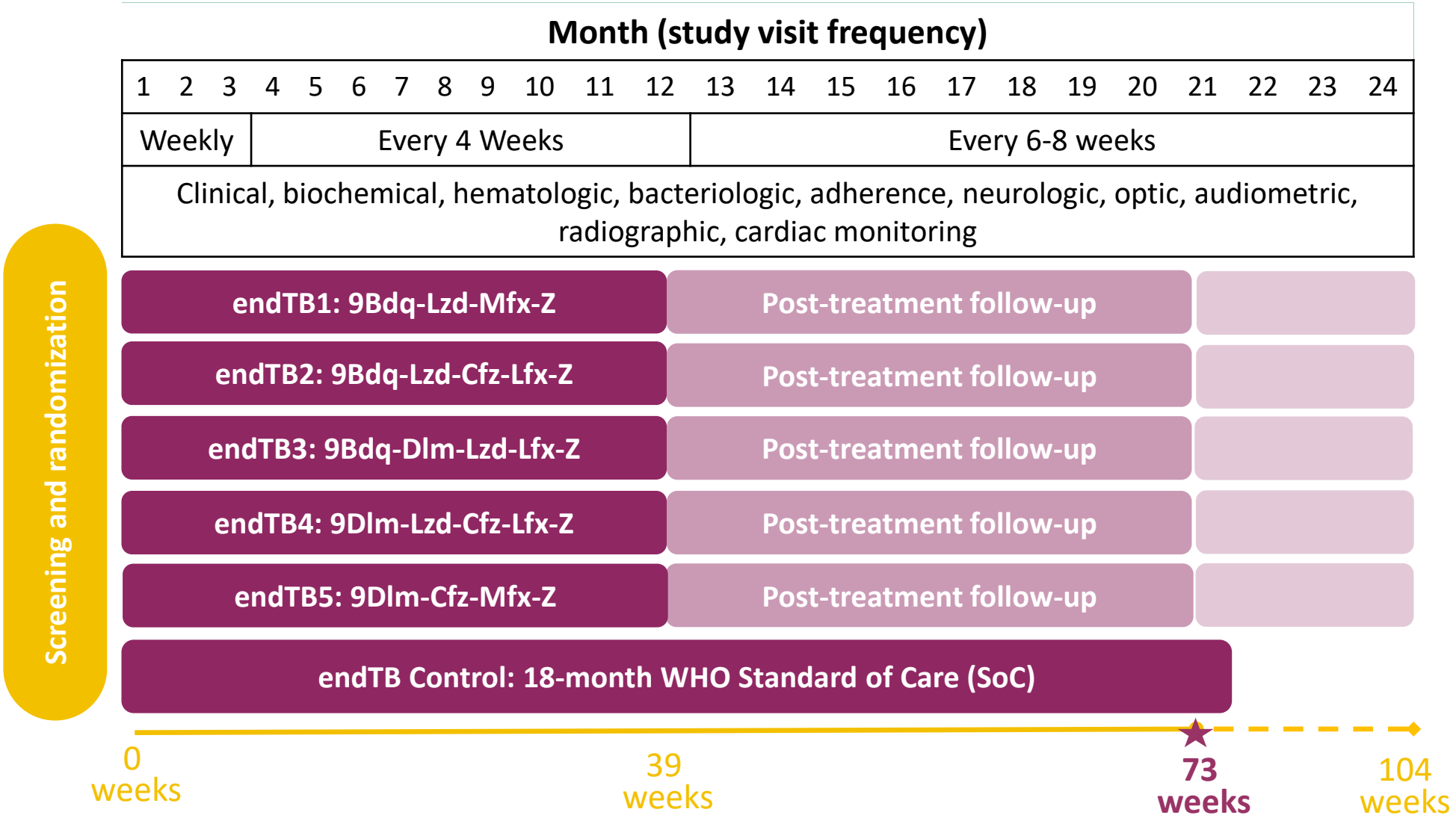
Delamanid (EMA Nov 2013)

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: Objectives

- **Primary:** to assess whether the efficacy of experimental regimens at Week 73 is non-inferior to that of the control
- **Secondary efficacy:** compare to control
  - Early treatment response (8 weeks)
  - Favorable outcomes at 39 weeks
  - Favorable outcomes at 104 weeks
- **Secondary safety:** compare to control at 73 and 104 weeks (death, grade 3 or higher AEs, SAEs, AESIs)
- **Exploratory (selected):**
  - Subgroup analyses (demographics, comorbidities, TB disease risk factors)
  - Compare efficacy & safety across select experimental arms
  - Nested substudy: Compare efficacy and linezolid-related toxicity between linezolid dose-reduction strategies

endTB Trial Design: Sample Size Estimation

- Favorable outcome at W73:
  - 75% in experimental arms
  - 70% in control
- Alpha: 2.5%
- Non-inferiority margin: -12%
- Power: 80% to detect non-inferiority of ≥ 3 experimental regimens in the modified intention-to-treat and up ≥ 2 in the per-protocol populations.
- Not powered for formal comparison of safety endpoints or for comparison between arms.
- Sample size: 750

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

endTB trial-Design: Main Analysis Populations

Safety population

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

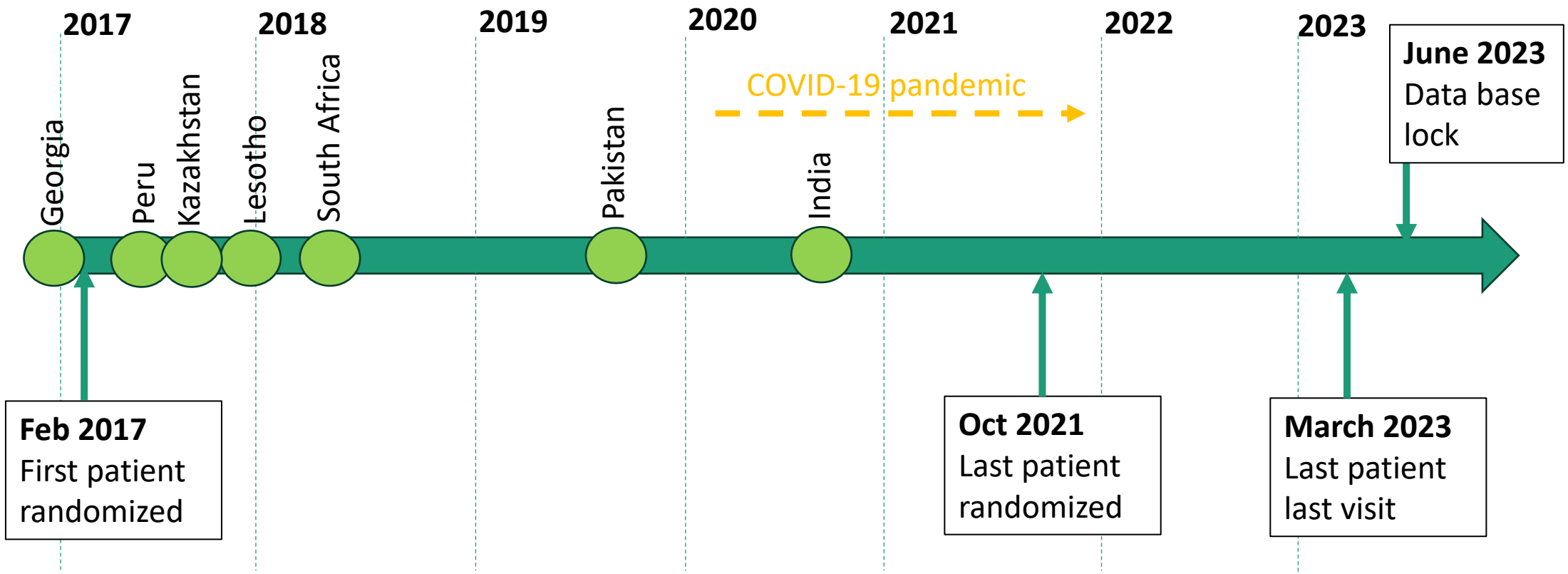
Modified intent to treat (mITT) population (co-primary)

- 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-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.

endTB Trial Timeline



12 sites in 7 countries

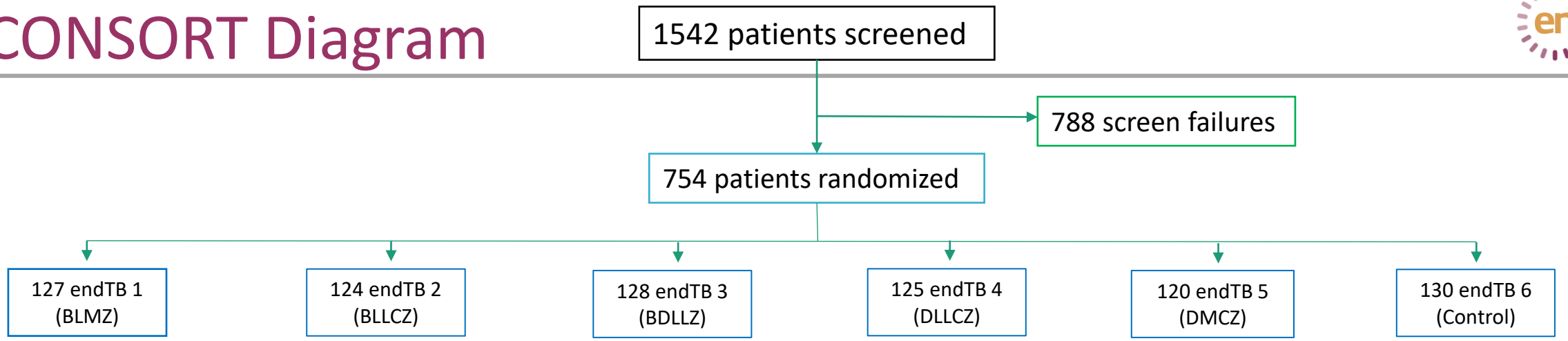
4 continents

Results: Populations & Baseline Characteristics

Screening & Enrollment

Patient disposition - screened	n (%) of patients
Screened	1542 (100%)
Randomized	754 (48.9%)
Excluded	788 (51.1%)
Primary reason for study exclusion	**n (%) of excluded**
MTB detection, RIF resistance, FQ susceptibility not established	619 (78.7%)
- MTB not detected in molecular test	168 (21.3%)
- RIF susceptible or indeterminate	189 (24.0%)
- FQ resistant or indeterminate	236 (29.9%)
- Molecular tests incomplete in screening window	26 (3.3%)
Laboratory values outside acceptable range	58 (7.4%)
Cardiac risk factors present	35 (4.4%)
Investigator discretion	31 (3.9%)
Other	45 (5.7%)

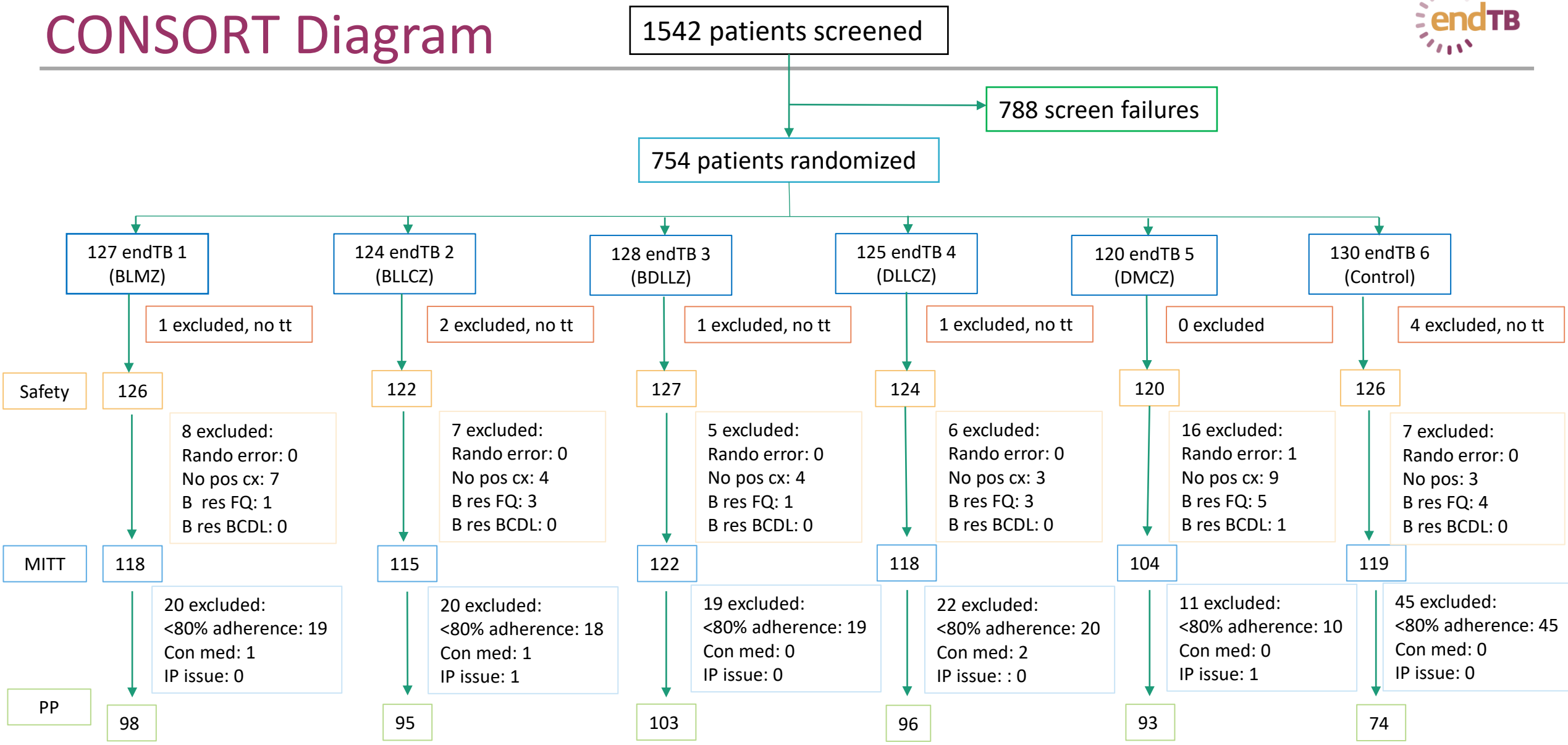
CONSORT Diagram



Randomized patients by country

Country	endTB1 (BLMZ) (n = 127)	endTB2 (BLLCZ) (n = 124)	endTB3 (BDLLZ) (n = 128)	endTB4 (DLLCZ) (n = 125)	endTB5 (DMCZ) (n = 120)	endTB6 (Control) (n = 130)	Total (N = 754)
Georgia	2 (1.6%)	3 (2.4%)	1 (0.8%)	3 (2.40%)	1 (0.8%)	3 (2.3%)	13 (1.7%)
India	10 (7.9%)	4 (3.2%)	4 (3.1%)	5 (4.0%)	3 (2.5%)	5 (3.9%)	31 (4.11%)
Kazakhstan	31 (24.4%)	37 (29.8%)	34 (26.6%)	23 (18.4%)	30 (25.0%)	29 (22.3%)	184 (24.4%)
Lesotho	14 (11.0%)	13 (10.5%)	16 (12.5%)	11 (8.8%)	14 (11.7%)	13 (10.0%)	81 (10.7%)
Peru	40 (31.5%)	41 (33.1%)	51 (39.8%)	55 (44.0%)	47 (39.2%)	53 (40.8%)	287 (38.1%)
Pakistan	20 (15.7%)	17 (13.7%)	14 (10.9%)	14 (11.2%)	19 (15.8%)	18 (13.8%)	102 (13.5%)
South-Africa	10 (7.9%)	9 (7.3%)	8 (6.3%)	14 (11.2%)	6 (5.0%)	9 (6.9%)	56 (7.4%)

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-mITT Population

Baseline characteristic	endTB1 (BLMZ) (n = 118)	endTB2 (BLLCZ) (n = 115)	endTB3 (BDLLZ) (n = 122)	endTB4 (DLLCZ) (n = 118)	endTB5 (DMCZ) (n = 104)	endTB6 (Control) (n = 119)	Total (N = 696)
Age (years), median [IQR]	31.0 [25.0;41.0]	38.0 [26.0;50.0]	32.0 [22.0;45.0]	30.5 [22.0;41.0]	32.0 [23.5;46.0]	31.0 [22.0;42.0]	32.0 [23.0;44.0]
Female	41 (34.7%)	37 (32.2%)	55 (45.1%)	38 (32.2%)	45 (43.3%)	48 (40.3%)	264 (37.9%)
BMI (kg/m^2), median [IQR]	19.9 [17.5;22.1]	20.0 [18.4;23.6]	20.9 [18.8;22.8]	20.6 [18.1;23.6]	19.9 [17.9;22.4]	20.8 [17.6;23.0]	20.4 [18.0;22.8]
PZA resistance	57 (48.3%)	63 (54.8%)	66 (54.1%)	66 (55.9%)	63 (60.6%)	59 (49.6%)	374 (53.7%)
HIV positive	15 (12.7%)	14 (12.2%)	17 (13.9%)	18 (15.3%)	15 (14.4%)	19 (16.0%)	98 (14.1%)
Hepatitis B*	3 (2.5%)	3 (2.6%)	0 (0.0%)	2 (1.7%)	4 (3.8%)	4 (3.4%)	16 (2.3%)
Hepatitis C	5 (4.2%)	5 (4.3%)	3 (2.5%)	4 (3.4%)	3 (2.9%)	6 (5.0%)	26 (3.7%)
Diabetes	19 (16.1%)	18 (15.7%)	20 (16.4%)	16 (13.6%)	16 (15.4%)	15 (12.6%)	104 (14.9%)
SARS-Cov-2 infection**	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.84%)	3 (0.3%)

* HbsAg+; ** positive antibody, antigen, or PCR test.

Selected baseline characteristics - mITT Population

Baseline characteristic	endTB1 (BLMZ) (n = 118)	endTB2 (BLLCZ) (n = 115)	endTB3 (BDLLZ) (n = 122)	endTB4 (DLLCZ) (n = 118)	endTB5 (DMCZ) (n = 104)	endTB6 (Control) (n = 119)	Total (N = 696)
Smear result							
Negative/Scanty	20 (16.9%)	19 (16.5%)	31 (25.4%)	24 (20.3%)	18 (17.3%)	19 (16.0%)	131 (18.8%)
1-2+	57 (48.3%)	59 (51.3%)	58 (47.5%)	49 (41.5%)	43 (41.3%)	52 (43.7%)	318 (45.7%)
3+	41 (34.7%)	37 (32.2%)	33 (27.0%)	45 (38.1%)	43 (41.3%)	48 (40.3%)	247 (35.5%)
Cavitation*	68 (57.6%)	69 (60.0%)	73 (59.8%)	53 (44.9%)	58 (55.8%)	75 (63.0%)	396 (56.9%)
Prior exposure to 2nd line drugs*	15 (12.7%)	19 (16.5%)	15 (12.3%)	7 (5.9%)	11 (10.6%)	11 (9.2%)	78 (11.2%)

*cavitation: unknown for 3 participants; prior exposure: unknown for 25 participants.

Control Arm Regimens: Drug No. & Composition at Initiation (mITT)

Number of drugs in control arm regimen	Total
N (%)	119 (100.0%)
4	1 (0.8%)
5	87 (73.1%)
6	24 (20.2%)
7	7 (5.9%)

Drugs	Total
N (%)	119 (100.0%)
Levofloxacin	113 (95.0%)
Moxifloxacin	6 (5.0%)
Bedaquiline	96 (80.7%)
Linezolid	86 (72.3%)
Clofazimine	94 (79.0%)
Cycloserine or terizidone	81 (68.1%)
Pyrazinamide	55 (46.2%)
Ethionamide/Prothionamide	30 (25.2%)
Ethambutol	21 (17.6%)
Capreomycin	13 (10.9%)
Delamanid	12 (10.1%)
Kanamycin	9 (7.6%)
PAS	6 (5.0%)
Isoniazid	6 (5.0%)

Regimens conforming to **2022** WHO Guidelines: **77.3%** long regimen, **4.2%** shortened, all-oral, total of **81.5%**

endTB Clinical Trial: Efficacy Results

Methods | Key Efficacy Endpoints

Week 73 efficacy endpoint (primary)

Favorable Outcome: MUST have no previous unfavorable result AND at least one of the following:

- 2 consecutive negative cultures (latest between Week 65 & 73)
- < 2 consecutive negative culture between Weeks 65 & 73 and favorable clinical, radiological, & bacteriological findings

Unfavorable Outcome

- Death
- Change in drugs[1] or starting a new treatment
- One of two final cultures are positive
- Poor Evolution: No interpretable culture result, and unfavorable clinical, radiological, & bacteriological findings
- Previously classified as unfavorable
- Outcome unassessable

Week 104 efficacy endpoint (secondary)

- **Favorable:** Similar to Week 73, key evaluations between Weeks 97 & 104
- **Unfavorable:** Similar to Week 73 and lost to follow up

[1]>=1 in experimental arm or short control; >=2 in conventional control arm

Methods | Key Efficacy Analysis (1/2)

Primary, unadjusted efficacy analysis (Week 73) in mITT & PP populations

- Compare % of favorable outcomes in each experimental regimen vs. control
  - Risk difference: % favorable$_{experimental}$ - % favorable$_{control,}$ estimate 95% CI
  - Compare lower bound of 95% CI to NI margin (-12%)
  - Control type 1 error: order sequence of comparisons, from highest % favorable outcome; stop if NI is not established
  - If non-inferiority is demonstrated, test for superiority in mITT (5% level of significance)

Secondary, unadjusted efficacy analysis (Weeks 39, 104) in mITT & PP populations

- Similar to analysis of primary endpoint

Methods | Key Efficacy Analysis (2/2)

Adjusted analysis

- Adjusted **estimate of risk difference with corresponding 95% CI** using a binomial regression model. **Pre-specified covariates** that were considered significant ($p<0.05$) were retained in the final model

Exploratory Analysis

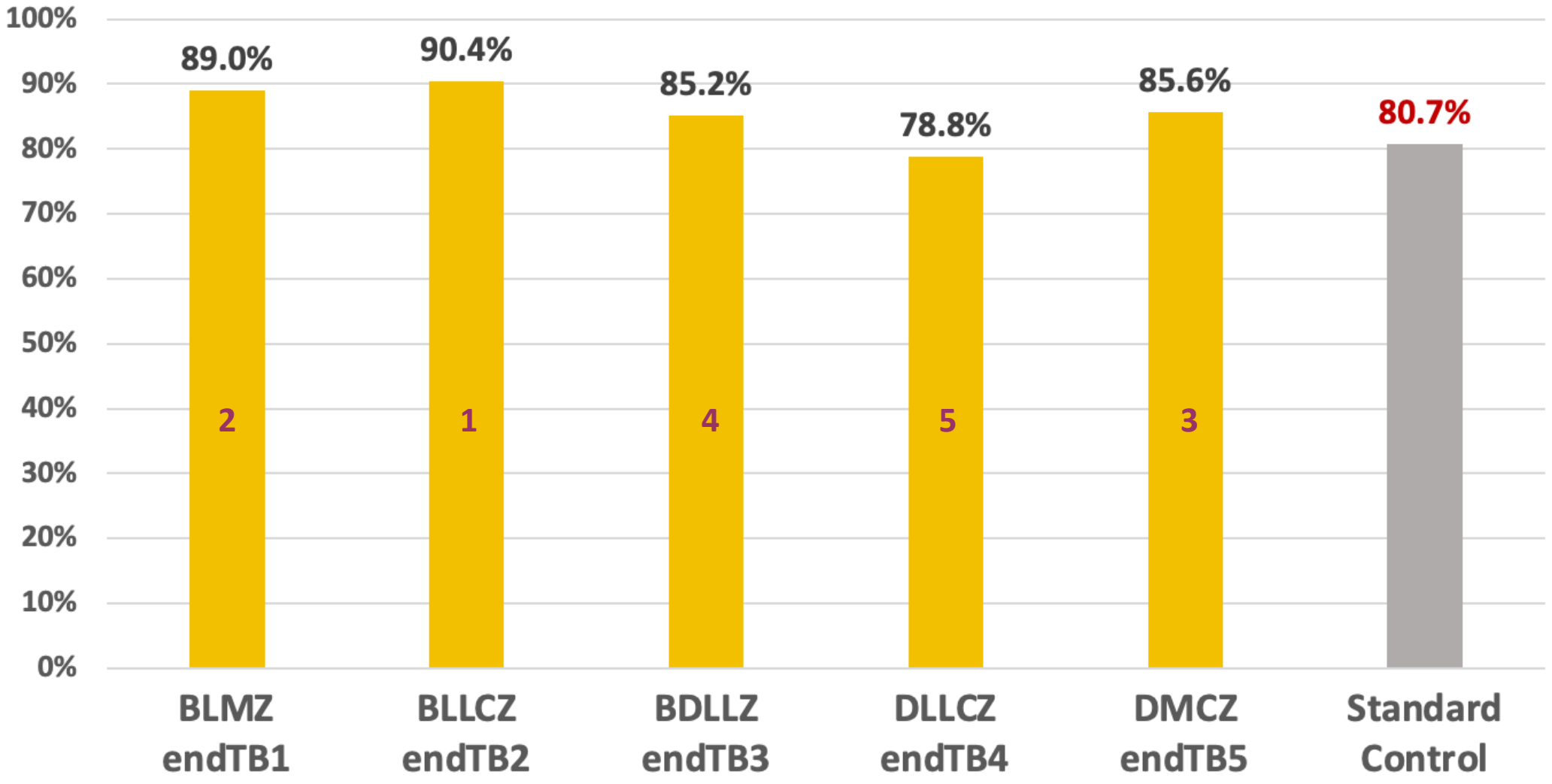
- **Comparison** between select **experimental regimens**:
  - Bdq vs Dlm | Cfz-Lfx vs Mfx | Cfz vs Dlm | Cfz vs Bdq

Sensitivity analyses at 73-week and 104-week efficacy in:

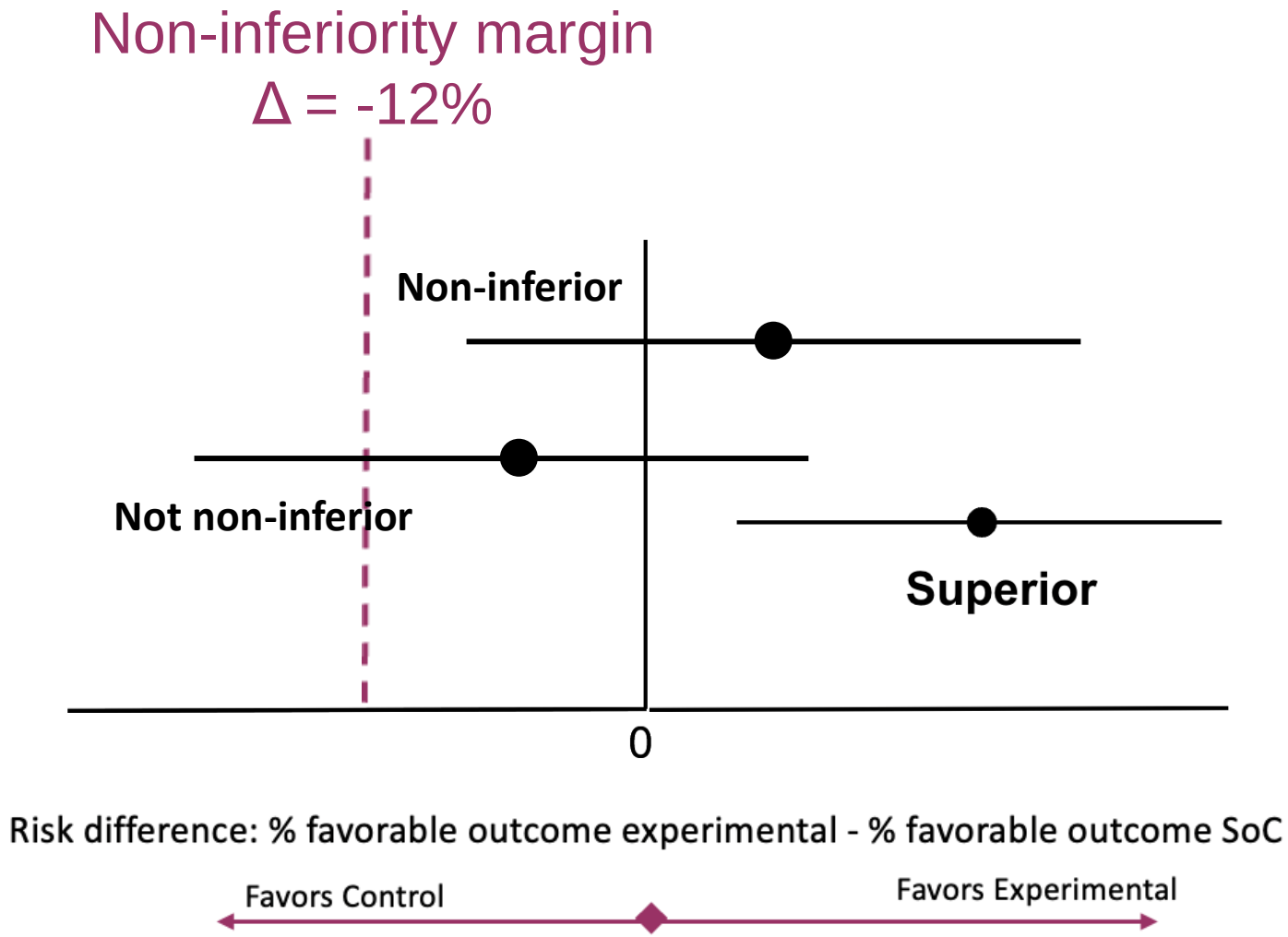
- All culture mITT: includes mITT **+ culture negative** at baseline.
- All DST mITT: includes mITT + **DST to Bdq, Cfz, Dlm, and/or Lzd** at baseline
- Assessable PP: excludes unassessable, voluntary withdrawal, LTFU

[1]Country, BMI, pyrazinamide resistance, injectable resistance, age, sex, comorbidity (HIV, Hepatitis B and C, diabetes, SARS-Cov-2 infection/COVID-19), smear result, cavitation, prior TB treatment, extent of disease on X-ray; [2]HIV co-infection, lung cavitation, sputum smear grade, and pyrazinamide resistance.

endTB Regimens | Primary Efficacy Endpoint, mITT (W73)

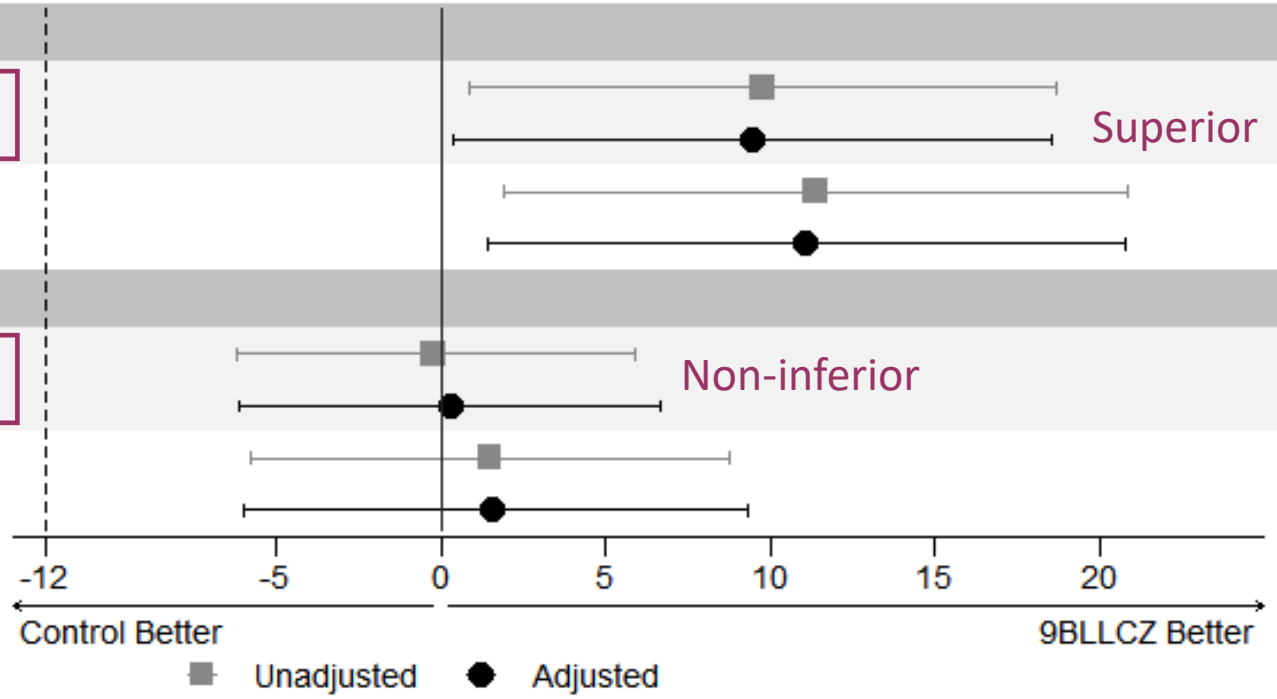


Assessing non-inferiority



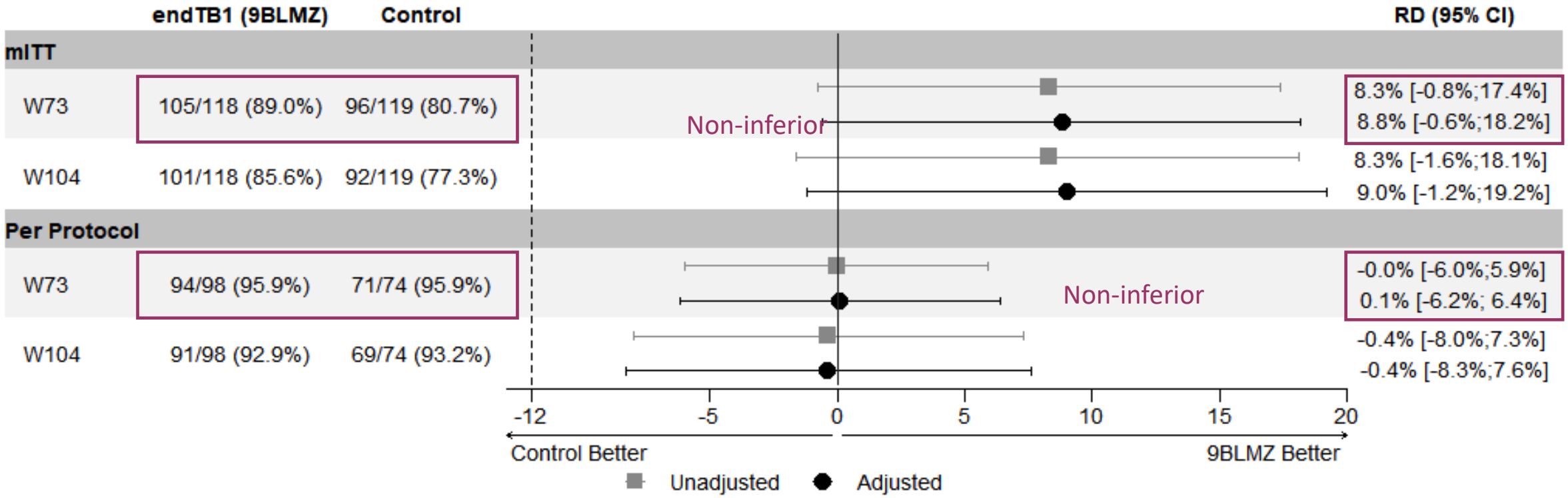
Efficacy of endTB2 (BLLCZ) vs. SoC

	endTB2 (9BLLCZ)	Control	RD (95% CI)
mITT			
W73	104/115 (90.4%)	96/119 (80.7%)	9.8% [0.9%;18.7%] 9.5% [0.4%;18.6%]
W104	102/115 (88.7%)	92/119 (77.3%)	11.4% [1.9%;20.9%] 11.1% [1.4%;20.8%]
Per Protocol			
W73	91/95 (95.8%)	71/74 (95.9%)	-0.2% [-6.2%;5.9%] 0.3% [-6.1%; 6.7%]
W104	90/95 (94.7%)	69/74 (93.2%)	1.5% [-5.8%;8.8%] 1.6% [-6.0%;9.3%]



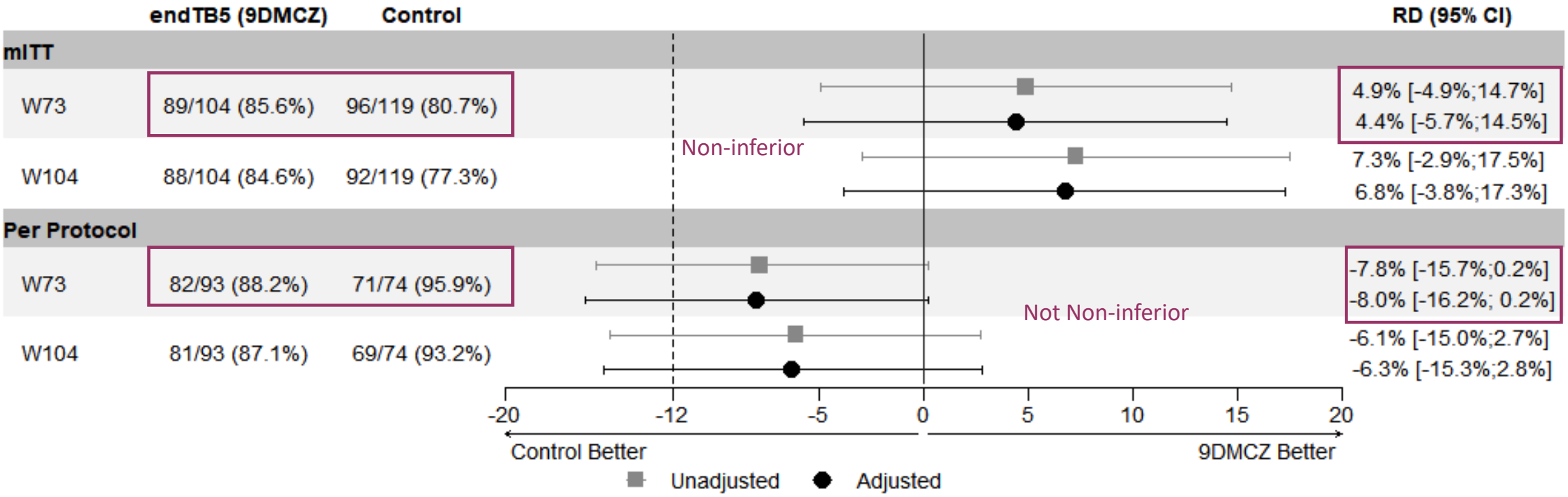
All adjusted analyses yield similar results

Efficacy of endTB1 (BLMZ) vs. SoC



All adjusted analyses yield similar results

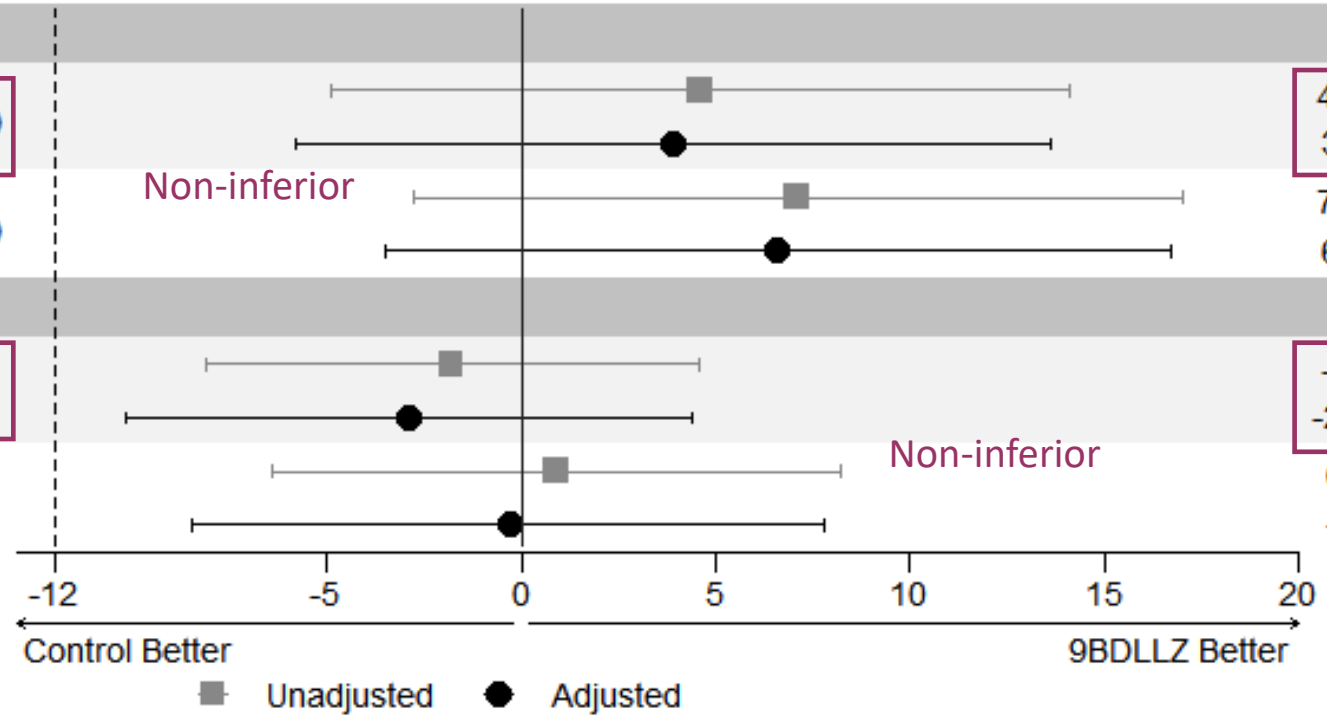
Efficacy of endTB5 (DMCZ) vs. SoC



All adjusted analyses yield similar results

Efficacy of endTB3 (BDLLZ) vs. SoC

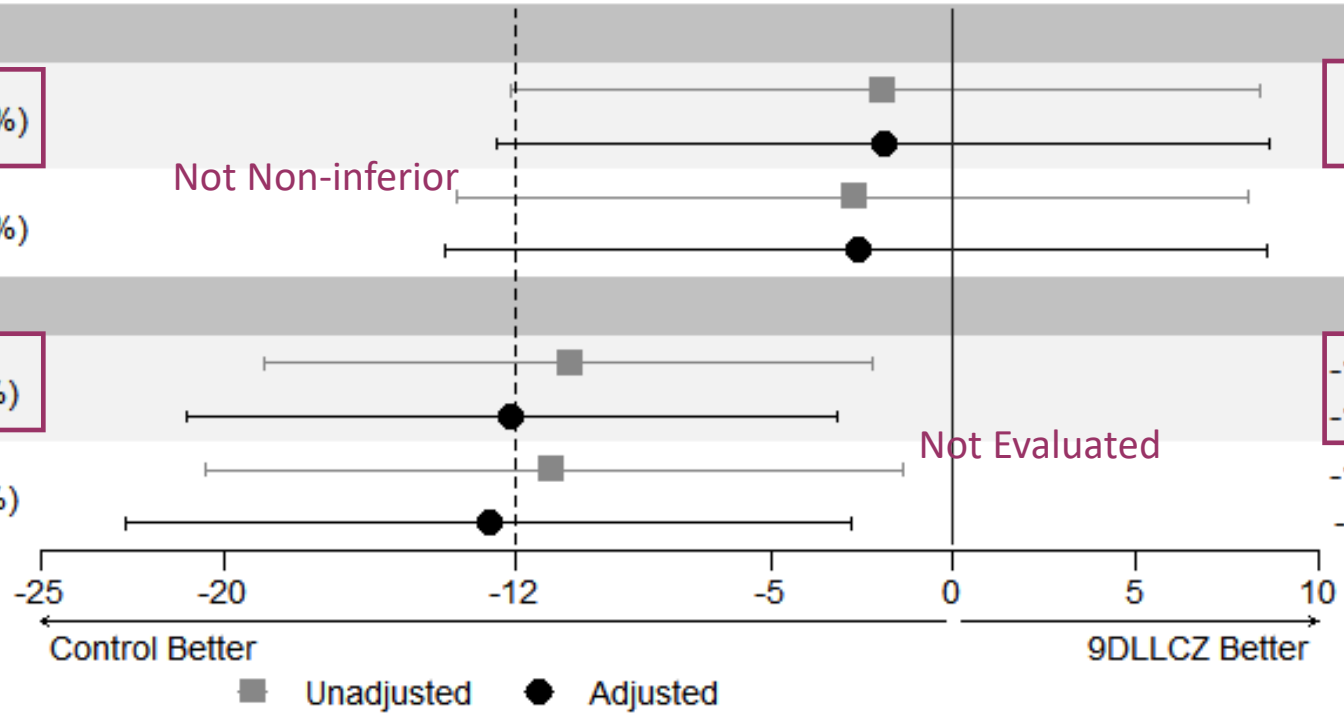
	endTB3 (9BDLLZ)	Control	RD (95% CI)
mITT			
W73	104/122 (85.2%)	96/119 (80.7%)	4.6% [-4.9%;14.1%] 3.9% [-5.8%;13.6%]
W104	103/122 (84.4%)	92/119 (77.3%)	7.1% [-2.8%;17.0%] 6.6% [-3.5%;16.7%]
Per Protocol			
W73	97/103 (94.2%)	71/74 (95.9%)	-1.8% [-8.1%;4.6%] -2.9% [-10.2%; 4.4%]
W104	97/103 (94.2%)	69/74 (93.2%)	0.9% [-6.4%;8.2%] -0.3% [-8.5%;7.8%]



All adjusted analyses yield similar results

Efficacy of endTB4 (DLLCZ) vs. SoC

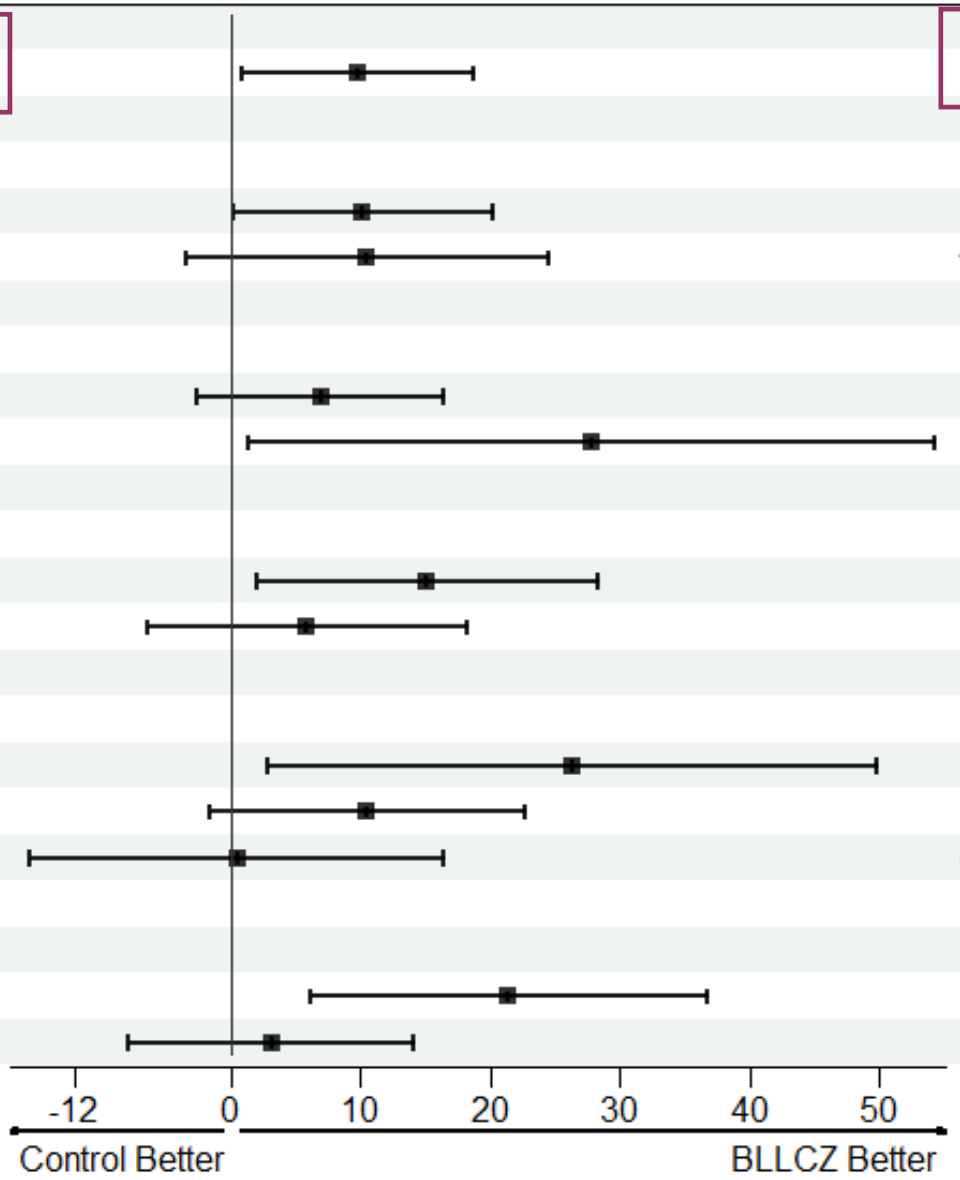
	endTB4 (9DLLCZ)	Control	RD (95% CI)
mITT			
W73	93/118 (78.8%)	96/119 (80.7%)	-1.9% [-12.1%;8.4%] -1.9% [-12.5%;8.7%]
W104	88/118 (74.6%)	92/119 (77.3%)	-2.7% [-13.6%;8.1%] -2.6% [-13.9%;8.6%]
Per Protocol			
W73	82/96 (85.4%)	71/74 (95.9%)	-10.5% [-18.9%;-2.2%] -12.1% [-21.0%; -3.2%]
W104	79/96 (82.3%)	69/74 (93.2%)	-11.0% [-20.5%;-1.4%] -12.7% [-22.7%;-2.8%]



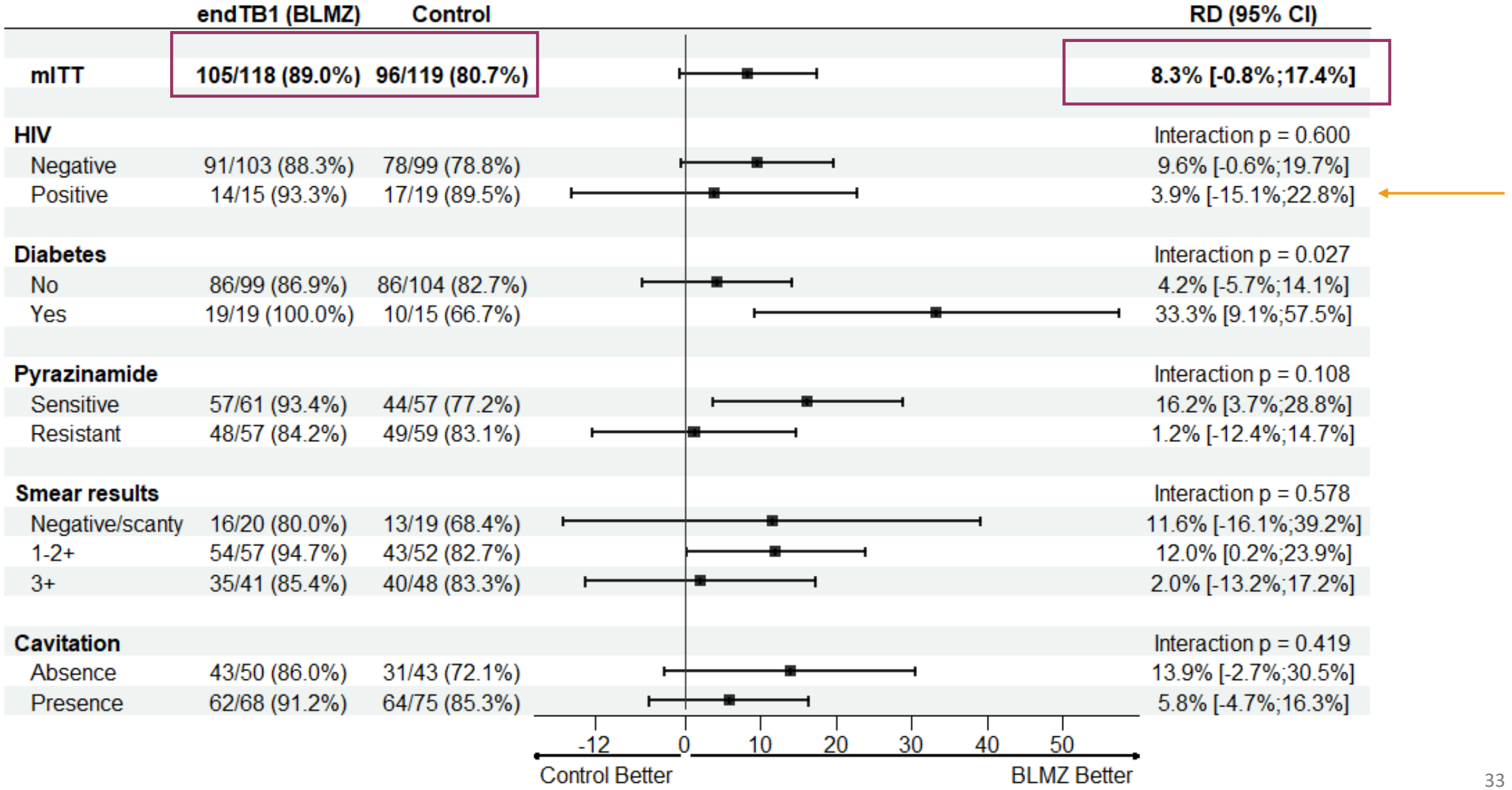
All adjusted analyses yield similar results

endTB2 (BLLCZ) Primary Efficacy by Key Subgroups - mITT population

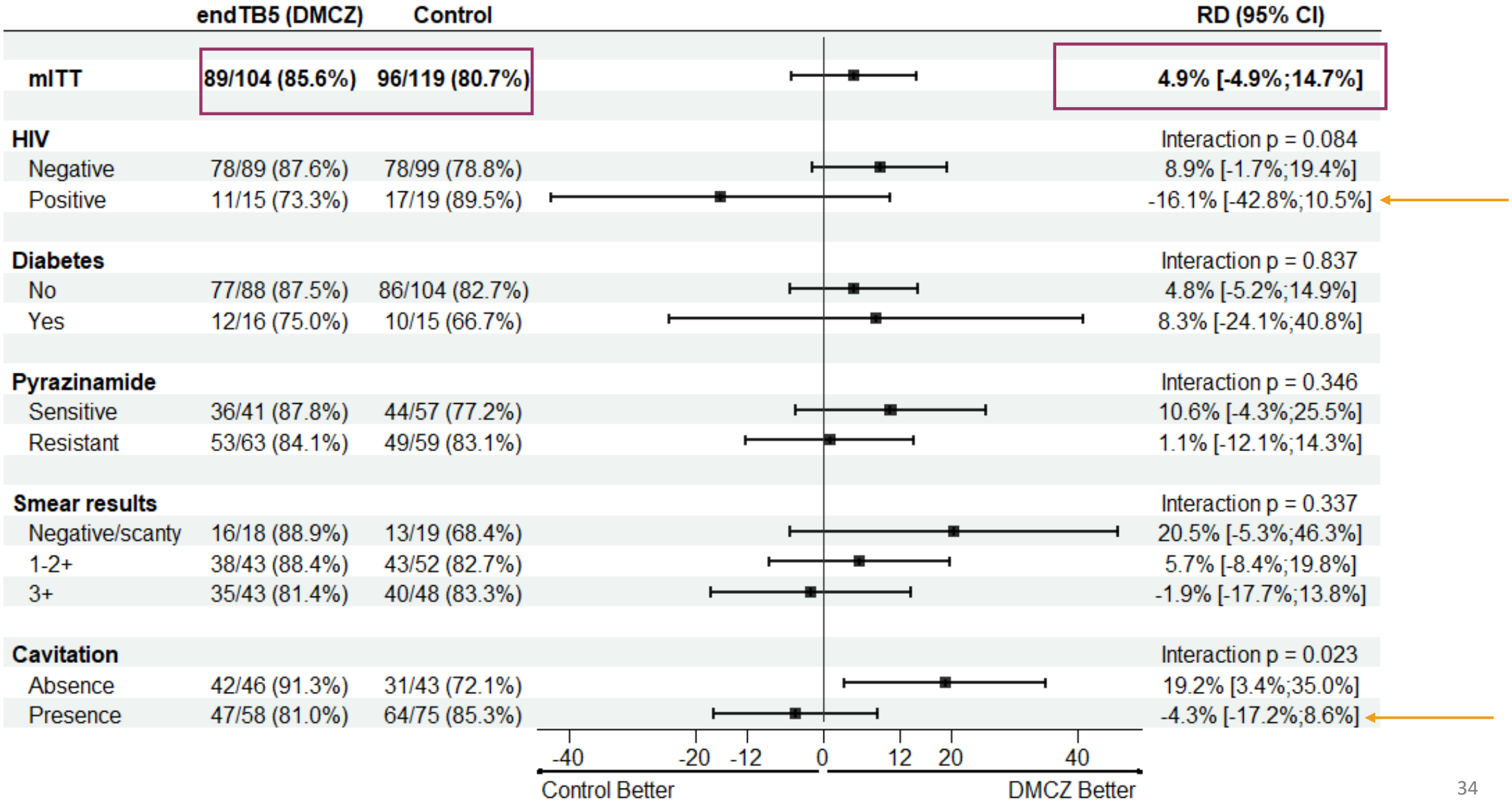
	endTB2 (BLLCZ)	Control	RD (95% CI)
mITT	**104/115 (90.4%)**	**96/119 (80.7%)**	**9.8% [0.9%;18.7%]**
HIV			Interaction p = 0.981
Negative	90/101 (89.1%)	78/99 (78.8%)	10.3% [0.2%;20.4%]
Positive	14/14 (100.0%)	17/19 (89.5%)	10.5% [-3.5%;24.5%]
Diabetes			Interaction p = 0.141
No	86/96 (89.6%)	86/104 (82.7%)	6.9% [-2.6%;16.4%]
Yes	17/18 (94.4%)	10/15 (66.7%)	27.8% [1.3%;54.3%]
Pyrazinamide			Interaction p = 0.312
Sensitive	48/52 (92.3%)	44/57 (77.2%)	15.1% [2.0%;28.3%]
Resistant	56/63 (88.9%)	49/59 (83.1%)	5.8% [-6.5%;18.2%]
Smear results			Interaction p = 0.193
Negative/scanty	18/19 (94.7%)	13/19 (68.4%)	26.3% [2.8%;49.8%]
1-2+	55/59 (93.2%)	43/52 (82.7%)	10.5% [-1.6%;22.7%]
3+	31/37 (83.8%)	40/48 (83.3%)	0.5% [-15.5%;16.4%]
Cavitation			Interaction p = 0.056
Absence	43/46 (93.5%)	31/43 (72.1%)	21.4% [6.1%;36.7%]
Presence	61/69 (88.4%)	64/75 (85.3%)	3.1% [-8.0%;14.1%]



endTB1 (BLMZ) Primary Efficacy by Subgroup - mITT population

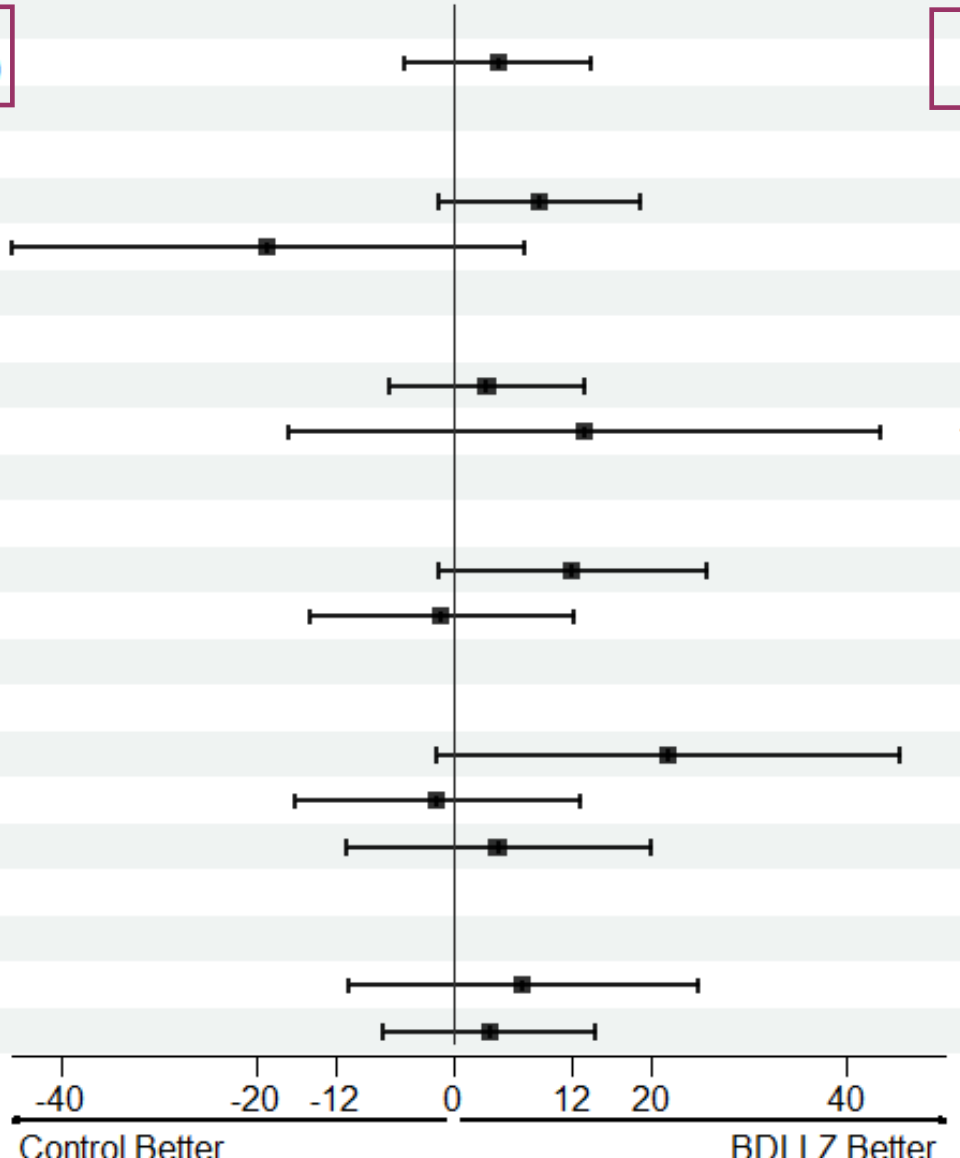


endTB5 (DMCZ) Primary Efficacy by Subgroup - mITT population

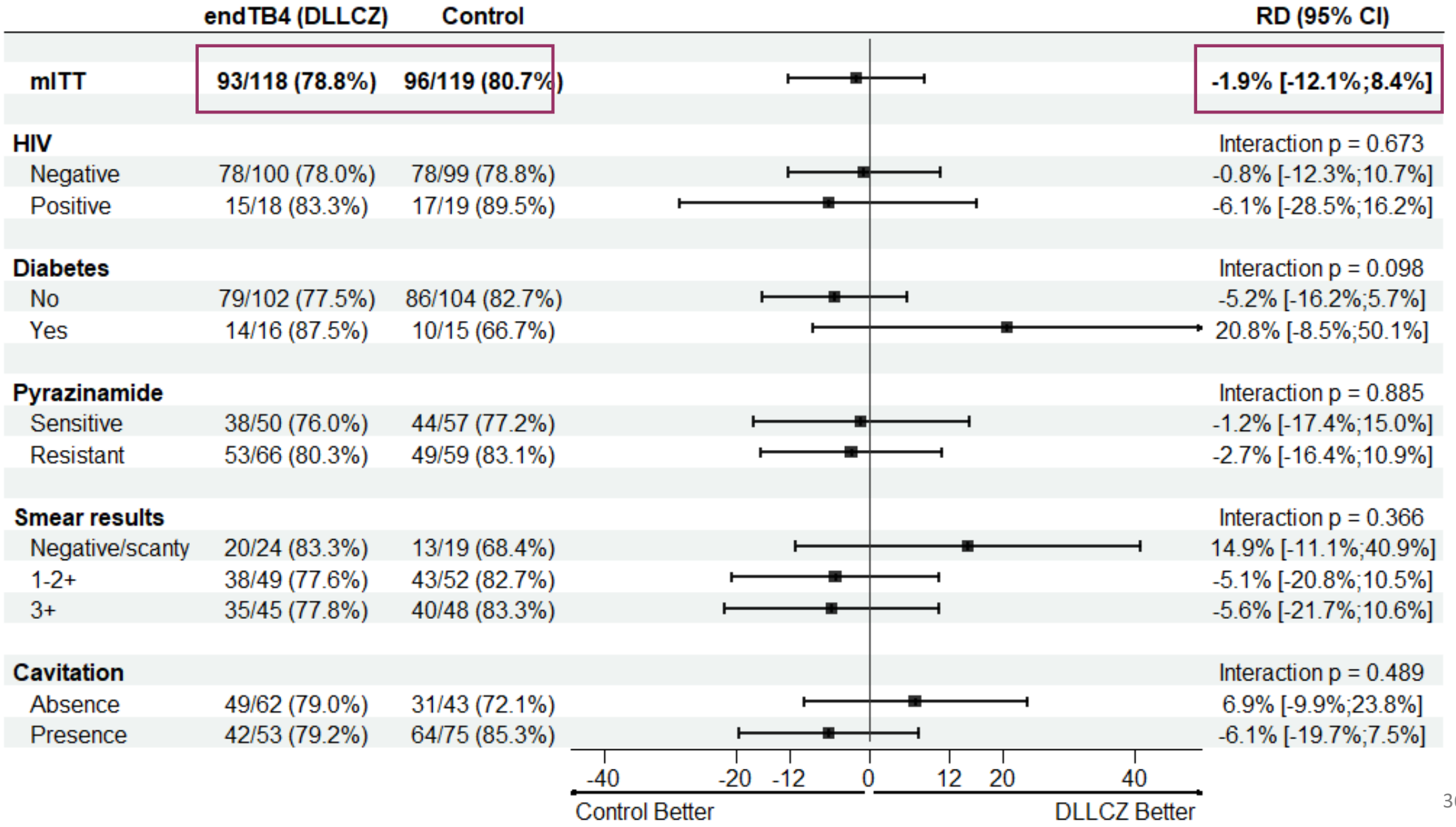


endTB3 (BDLLZ) Primary Efficacy by Subgroup - mITT population

	endTB3 (BDLLZ)	Control	RD (95% CI)
mITT	**104/122 (85.2%)**	**96/119 (80.7%)**	**4.6% [-4.9%;14.1%]**
HIV			Interaction p = 0.050
Negative	92/105 (87.6%)	78/99 (78.8%)	8.8% [-1.4%;19.1%]
Positive	12/17 (70.6%)	17/19 (89.5%)	-18.9% [-44.9%;7.2%]
Diabetes			Interaction p = 0.535
No	87/101 (86.1%)	86/104 (82.7%)	3.4% [-6.5%;13.4%]
Yes	16/20 (80.0%)	10/15 (66.7%)	13.3% [-16.7%;43.4%]
Pyrazinamide			Interaction p = 0.170
Sensitive	50/56 (89.3%)	44/57 (77.2%)	12.1% [-1.5%;25.7%]
Resistant	54/66 (81.8%)	49/59 (83.1%)	-1.2% [-14.6%;12.2%]
Smear results			Interaction p = 0.243
Negative/scanty	28/31 (90.3%)	13/19 (68.4%)	21.9% [-1.7%;45.5%]
1-2+	47/58 (81.0%)	43/52 (82.7%)	-1.7% [-16.1%;12.8%]
3+	29/33 (87.9%)	40/48 (83.3%)	4.5% [-10.9%;20.0%]
Cavitation			Interaction p = 0.585
Absence	38/48 (79.2%)	31/43 (72.1%)	7.1% [-10.7%;24.8%]
Presence	65/73 (89.0%)	64/75 (85.3%)	3.7% [-7.1%;14.5%]

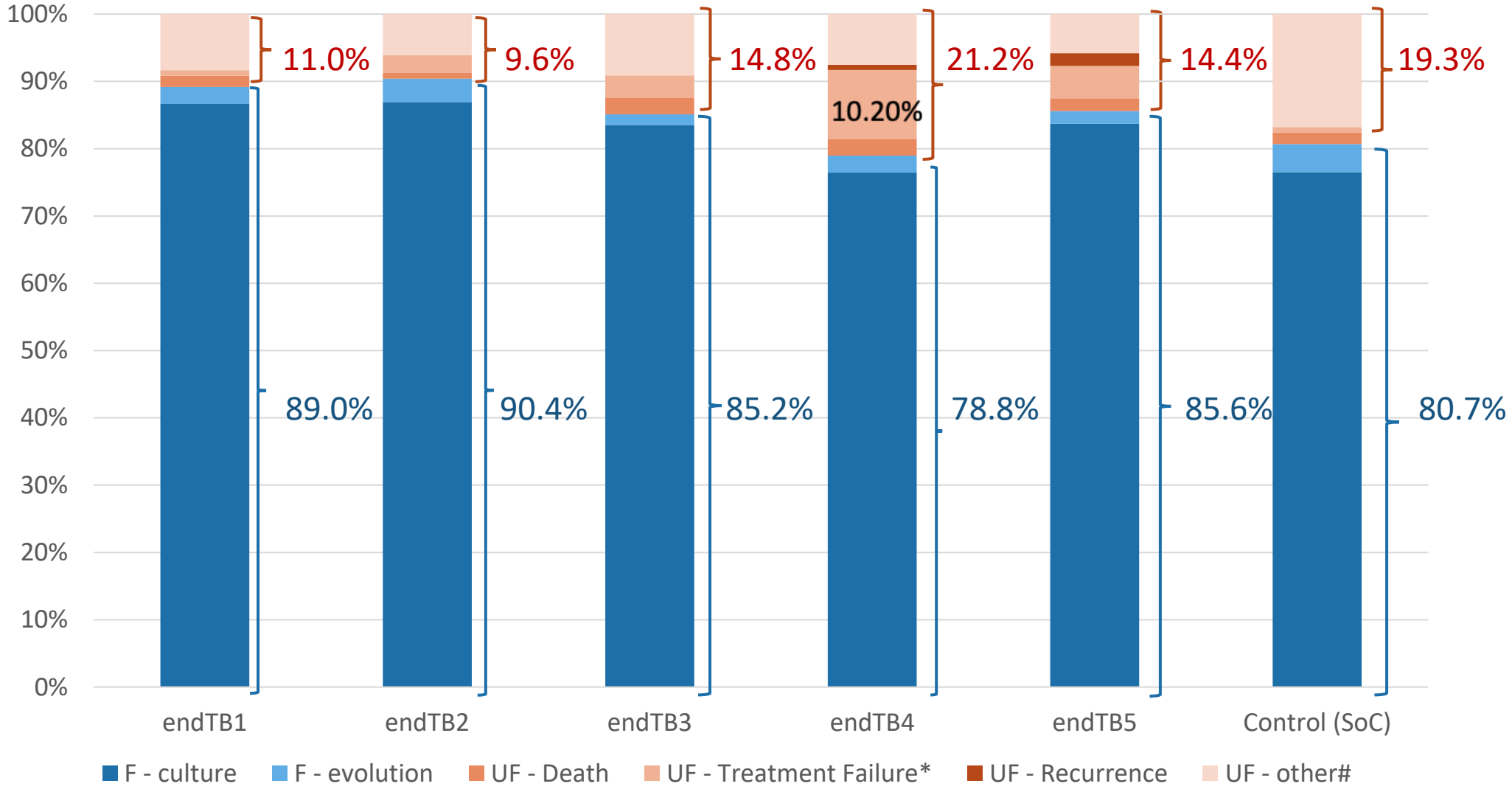


endTB4 (DLLCZ) Primary Efficacy by Subgroup - mITT population



Week 73 treatment outcomes, mITT (W73)

Rates of recurrence (3; 0.4%) & deaths (13; 1.9%)



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
  - **3 distinct, non-inferior (including one superior) regimens** can be composed with 7 different drugs that are already available for routine treatment of MDR-TB
  - 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

Safety methods

Adverse Event (AE)

Any **untoward** medical occurrence experienced by a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment,

- including any sign, symptom or lab abnormality (e.g. high liver enzymes following paracetamol intake)
- including aggravation or change to a pre-existing condition (e.g. worsening of pre-existing paraesthesia following fluconazole treatment).

Severity grading of AEs

- Severity = intensity
- Performed according to the MSF TB Severity Grading Scale (based on DMID grading system, complemented with a selection of terms from the CTCAE scale).

Example:

Condition term	Grade 1	Grade 2	Grade 3	Grade 4
Alanine Aminotransferase (ALT or SGPT) Increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN

Serious adverse event (SAEs)

Any unfavourable or unintended sign/ symptom/ disease (incl. lab abnormality) that at any dose is:

Fatal

Immediately life threatening

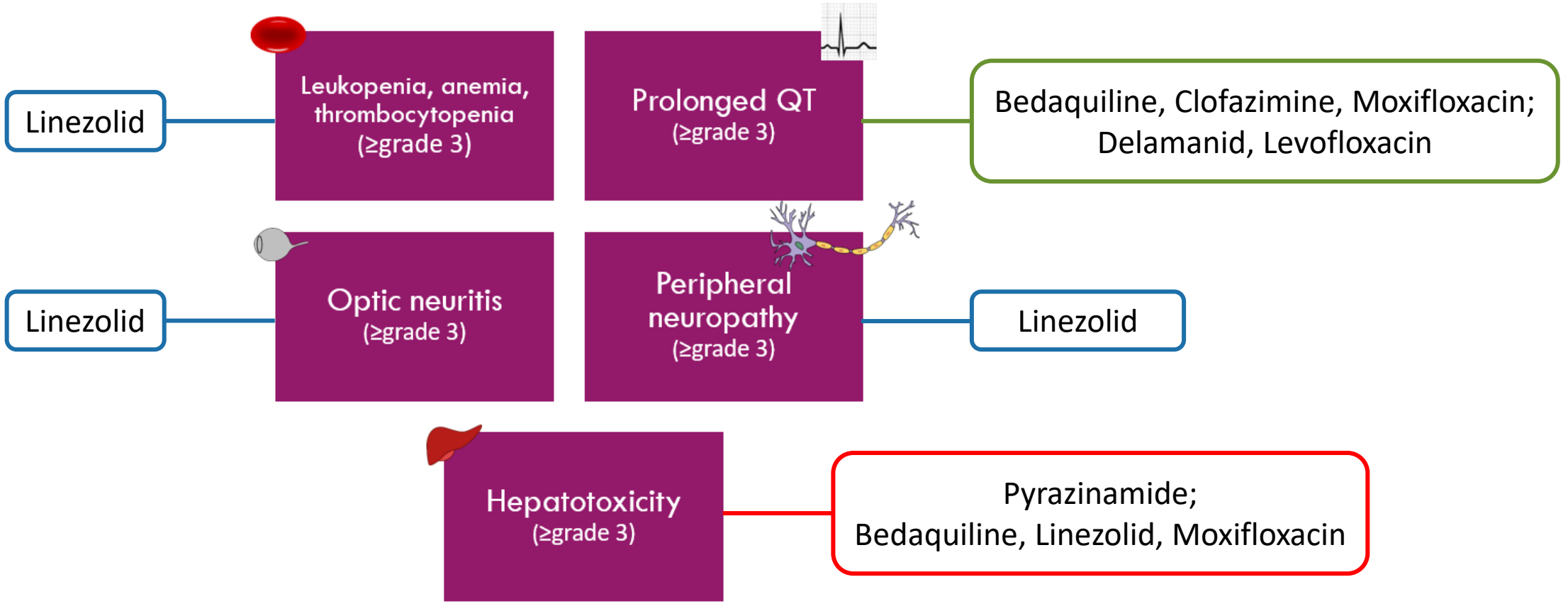

Leading to hospitalisation or prolongation of hospitalisation


Leading to a significant disability / incapacity

Birth defect or congenital anomaly


Otherwise medically important, necessitating an intervention to prevent one of the above listed outcomes

Adverse events of special interest (AESIs)



Safety objectives

To compare (each experimental arm to the control arm) the proportion of participants who, at Week 73:

- **Died of any cause;**
- Permanently stopped at least one drug due to AEs;
- Experienced **grade 3 or higher AEs** or **SAEs of any grade**;
- Experienced **AESIs**.

Caution 

- No formal statistical comparison
- Small numbers in some categories

Deaths and drug stops by arm by Week 73 – Safety population

Adverse events	endTB1 (BLMZ) (n = 126)	endTB2 (BLLCZ) (n = 122)	endTB3 (BDLLZ) (n = 127)	endTB4 (DLLCZ) (n = 124)	endTB5 (DMCZ) (n = 120)	endTB6 (Control) (n = 126)	Total (n = 745)
Deaths	3 (2.4%)	1 (0.8%)	3 (2.4%)	4 (3.2%)	2 (1.7%)	2 (1.6%)	15 (2.0%)
Related to study drugs	0	0	0	0	0	0	0

Deaths and drug stops by arm by Week 73 – Safety population

Adverse events	endTB1 (BLMZ) (n = 126)	endTB2 (BLLCZ) (n = 122)	endTB3 (BDLLZ) (n = 127)	endTB4 (DLLCZ) (n = 124)	endTB5 (DMCZ) (n = 120)	endTB6 (Control) (n = 126)	Total (n = 745)
Deaths	3 (2.4%)	1 (0.8%)	3 (2.4%)	4 (3.2%)	2 (1.7%)	2 (1.6%)	15 (2.0%)
Related to study drugs	0	0	0	0	0	0	0
Participants with ≥1 AE leading to permanent stop of ≥1 drug	29 (23.0%)	32 (26.2%)	41 (32.3%)	32 (25.8%)	22 (18.3%)	54 (42.9%)	210 (28.2%)

Most commonly stopped drugs (all arms):

- Pyrazinamide: 121 participants (16.2%); median 3.0 (IQR 1.7-6.2) months post-randomization
- Linezolid: 83 participants (11.1%); median 5.1 (IQR 2.6-7.4) months post-randomization

Grade ≥3 AEs and SAEs by arm by Week 73 – Safety population

Adverse events	endTB1 (BLMZ) (n = 126)	endTB2 (BLLCZ) (n = 122)	endTB3 (BDLLZ) (n = 127)	endTB4 (DLLCZ) (n = 124)	endTB5 (DMCZ) (n = 120)	endTB6 (Control) (n = 126)	Total (n = 745)
Grade ≥3 Aes							
Participants with ≥1 event	69 (54.8%)	68 (55.7%)	78 (61.4%)	75 (60.5%)	72 (60.0%)	79 (62.7%)	441 (59.2%)
Participants with ≥1 related event	38 (30.2%)	39 (32.0%)	42 (33.1%)	41 (33.1%)	21 (17.5%)	39 (31.0%)	220 (29.5%)
SAEs							
Participants with ≥1 event	18 (14.3%)	16 (13.1%)	20 (15.8%)	18 (14.5%)	20 (16.7%)	21 (16.7%)	113 (15.2%)
Participants with ≥1 related event	5 (4.0%)	9 (7.4%)	7 (5.5%)	9 (7.3%)	6 (5.0%)	5 (4.0%)	41 (5.5%)

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%)

Hematologic toxicity AESI 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%)

- Most common: Anemia, followed by decreased white blood cells, and decreased platelets
- Time to event: Median 2.7 (IQR 0.9-5.6) months post-randomization, all arms
- Outcome: 85% resolved
- Deaths: None

Definition: Hb <8 g/dL, white blood cells < 2000/mm3, platelets <50 000/mm3

Peripheral neuropathy AESI 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 peripheral neuropathy	4 (3.2%)	5 (4.1%)	9 (7.1%)	3 (2.4%)	3 (2.5%)	6 (4.8%)	30 (4.0%)

- Time to event: Median 5.3 (IQR 3.7-7.2) months post-randomization, all arms
- Outcome: 60% resolved, 23% sequelae/chronic
- Deaths: None

Definition: Concomitant paresthesia (burning, tingling, etc.) & neuro-sensory disorder (loss of sensation and/or vibration perception), at least one Grade 3

Optic neuropathy AESI 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 optic neuropathy	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	2 (1.6%)	4 (0.5%)

- Time to event: Median 2.8 (IQR 2.0-4.3) months post-randomization, all arms
- Outcome: 75% resolved, 25% sequelae
- Deaths: None

Definition: Vision loss, worse than 20/40 on Snellen chart/Tumbling E chart

QT prolongation AESI 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 QT prolongation	0 (0.0%)	4 (3.3%)	0 (0.0%)	0 (0.0%)	5 (4.2%)	0 (0.0%)	9 (1.2%)

- Time to event: Median 5.8 (IQR 4.8-7.3) months post-randomization, all arms
- Outcome: 100% resolved
- Deaths: None

Definition: Average QTcF ≥501 ms without signs/symptoms of serious arrhythmia; *or* average QTcF ≥501 or >60 ms change from baseline and proven ventricular arrhythmia or signs/symptoms of serious arrhythmia

Hepatotoxicity AESI 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 hepatotoxicity	23 (18.3%)	17 (13.9%)	8 (6.3%)	18 (14.5%)	12 (10.0%)	9 (7.1%)	87 (11.7%)

- Time to event: Median 1.9 [1.3-5.4] months post-randomization, all arms
- Outcome: 84% resolved, 2% sequelae/chronic
- Deaths: None

Definition: AST and/or ALT >5.0 - 20.0 x ULN

endTB trial – Safety Conclusions

- Low mortality (experimental and control)
- Permanent drug stoppage due to AEs more frequent in the control arm
  - Z the most commonly stopped drug, treatment efficacy still satisfactory
- 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
  - Regular monitoring permitted early detection and frequent resolution, e.g., linezolid-related toxicities, hepatotoxicity
  - ECG monitoring may be reduced and adapted according to individual risk level

endTB Trial – Linezolid dose reduction randomization

Background: Linezolid dose reduction

- Prolonged receipt of linezolid inhibits mitochondrial protein synthesis leading to myelosuppression, peripheral neuropathy, and optic neuropathy.[1]
- Linezolid toxicity has been reported in preclinical models and a single clinical study to be associated with elevated exposure ($AUC_{0\text{-}24h}$) and elevated trough concentrations (C_{min}).[2,3,4,5]
- Linezolid 300 mg daily has been used as a dose reduction strategy in several contemporary TB clinical trials after initial linezolid doses of 1200 mg or 600 mg daily (e.g., Nix-TB, ZeNix, TB-PRACTECAL, BEAT India).

1 Nuermberger E. Int J Tuberc Lung Dis. 2016;20:S48–S51. PMID: 28240573
2 Song T, et al. EBIOM. 2015 Nov;2(11):1627–33. PMCID: PMC4740314
3 Srivastava S, et al. Antimicrob Agents Chemother. 2017 Aug;61(8):e00751–17. PMCID: PMC5527615
4 Brown AN, et al. MBio. 2015 Nov 3;6(6):e01741–15. PMCID: PMC4631805
5 Deshpande D, et al. Clin Infect Dis. 2016 Nov 1;63(suppl 3):S80–7. PMCID: PMC5064157

Linezolid dose reduction randomization

- Participants initially randomized to endTB regimens 1-4 underwent a **secondary linezolid dose reduction randomization** (balanced, 1:1) to receive either linezolid 300 mg daily or linezolid 600 mg thrice weekly.
  - Prior to protocol v3.0, dose reduction was NOT randomized and choice of strategy was at the discretion of site investigators.
  - Beginning with protocol v3.0, randomization occurred at the Week 16 visit or after a linezolid-associated AE requiring dose reduction, whichever came first.
  - We prespecified exploratory objectives to evaluate the safety (*frequency of and time to severe linezolid-associated toxicity*) and efficacy (*Week 73 and Week 104 outcomes*) of the two linezolid dose reduction strategies.

Figure 1: Flow Diagram

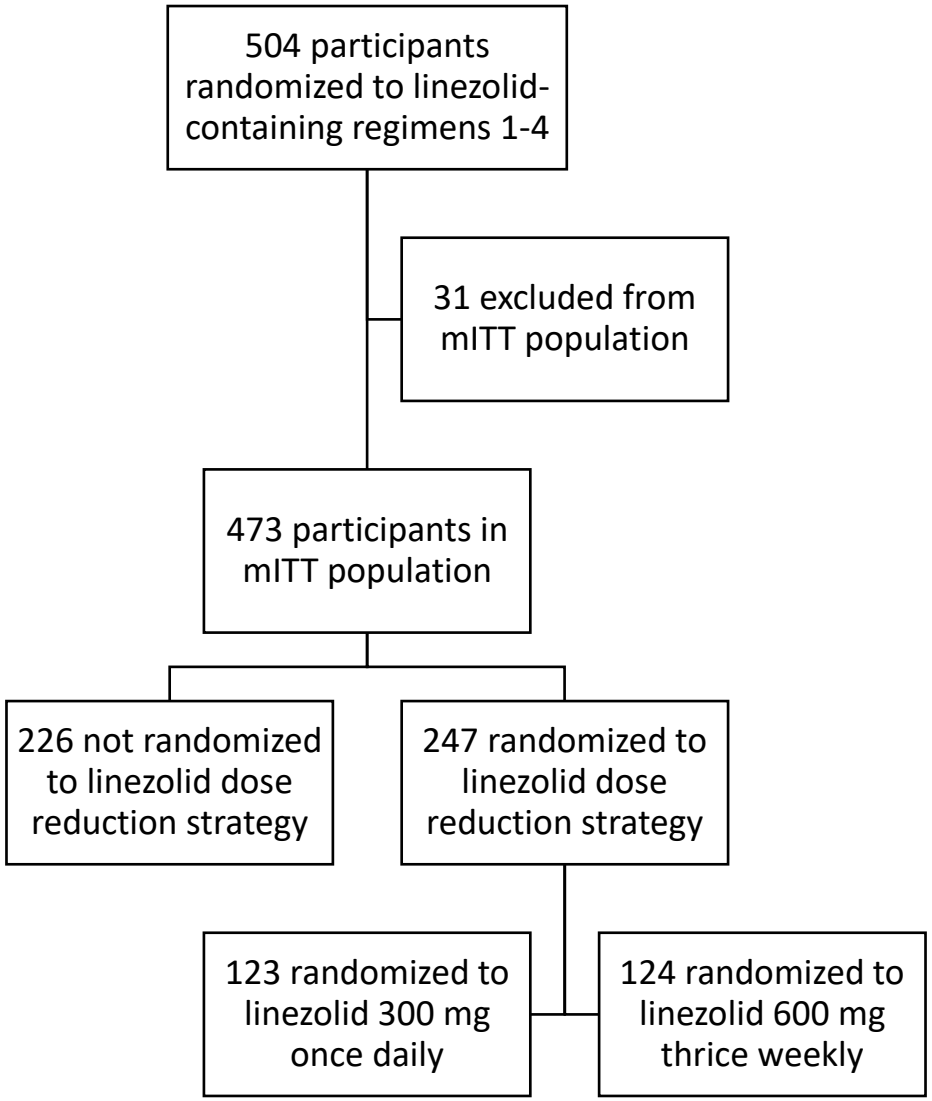


Table 1: Participant Characteristics (mITT) 1/2

Characteristic	300 mg daily (n=123)	600 mg 3x/week (n=124)	Total (N=247)
Age, median (IQR)	32.0 (25.0; 47.0)	33.0 (22.0; 45.0)	33.0 (23.0; 46.5)
Female sex	46 (37.4%)	44 (35.5%)	90 (36.4%)
BMI, median (IQR)	20.1 (17.6; 22.8)	20.6 (18.0; 23.3)	20.4 (17.8; 23.1)
Living with HIV	12 (9.8%)	12 (9.7%)	24 (9.7%)
CD4, median (IQR)	345 (170; 541), n=12	323 (80; 400), n=12	327 (98; 475), n=24
HBV or HCV	5 (4.1%)	6 (4.8%)	11 (4.5%)
Diabetes	23 (18.7%), n=122	21 (16.9%), n=123	44 (17.8%), n=245
Country			
IN	8 (6.5%)	8 (6.5%)	16 (6.5%)
KZ	21 (17.1%)	21 (16.9%)	42 (17.0%)
LS	12 (9.8%)	14 (11.3%)	26 (10.5%)
PE	53 (43.1%)	53 (42.7%)	106 (42.9%)
PK	29 (23.6%)	28 (22.6%)	57 (23.1%)

Table 1: Participant Characteristics (mITT) 2/2

Characteristic	300 mg daily (n=123)	600 mg 3x/week (n=124)	Total (N=247)
endTB Regimen			
endTB 1/BLMZ	38 (30.9%)	26 (21.0%)	64 (25.9%)
endTB 2/BCLLfxZ	32 (26.0%)	30 (24.2%)	62 (25.1%)
endTB 3/BDLLfxZ	27 (22.0%)	37 (29.8%)	64 (25.9%)
endTB 4/CDLLfxZ	26 (21.1%)	31 (25.0%)	57 (23.1%)
WBC, median (IQR)	8.84 (7.09; 11.0)	8.61 (6.82; 10.9)	8.68 (7.02; 11.0)
ANC, median (IQR)	6.32 (4.89; 8.30)	6.05 (4.69; 8.03)	6.21 (4.81; 8.12)
Hemoglobin, median (IQR)	12.2 (10.6; 13.6)	12.3 (10.7; 13.6)	12.2 (10.7; 13.6)
Platelets, median (IQR)	408 (320; 536)	410 (325; 493)	408 (324; 510)
Neuropathy grade, median (IQR)	0 (0; 1)	0 (0; 0)	0 (0; 1)

Severe linezolid-associated toxicity

We defined severe linezolid-associated toxicity as one of the following:

- Linezolid-associated Grade 3 or higher adverse events
  - Leukopenia
  - Anemia
  - Thrombocytopenia
  - Peripheral neuropathy
  - Optic neuropathy
- Linezolid-associated serious adverse events
- Linezolid-associated adverse events requiring linezolid discontinuation

Table 2: Severe Linezolid-Associated Toxicity

Population/Outcome	Total	300 mg daily	600 mg thrice weekly	Risk difference and HR [95% CI]	P-value
Total in safety population	260 (100%)	128 (100%)	132 (100%)		
Severe linezolid-related toxicity	46 (17.7%)	21 (16.4%)	25 (18.9%)	2.5% [-6.8%; 11.8%]	0.592
Time to severe linezolid-related toxicity, months, median (IQR)	3.0 (1.3; 5.9)	4.6 (2.6; 6.2)	2.5 (0.9; 3.6)	0.85 [0.47; 1.51]	0.570

Figure 2: Kaplan-Meier — Severe Linezolid Toxicity

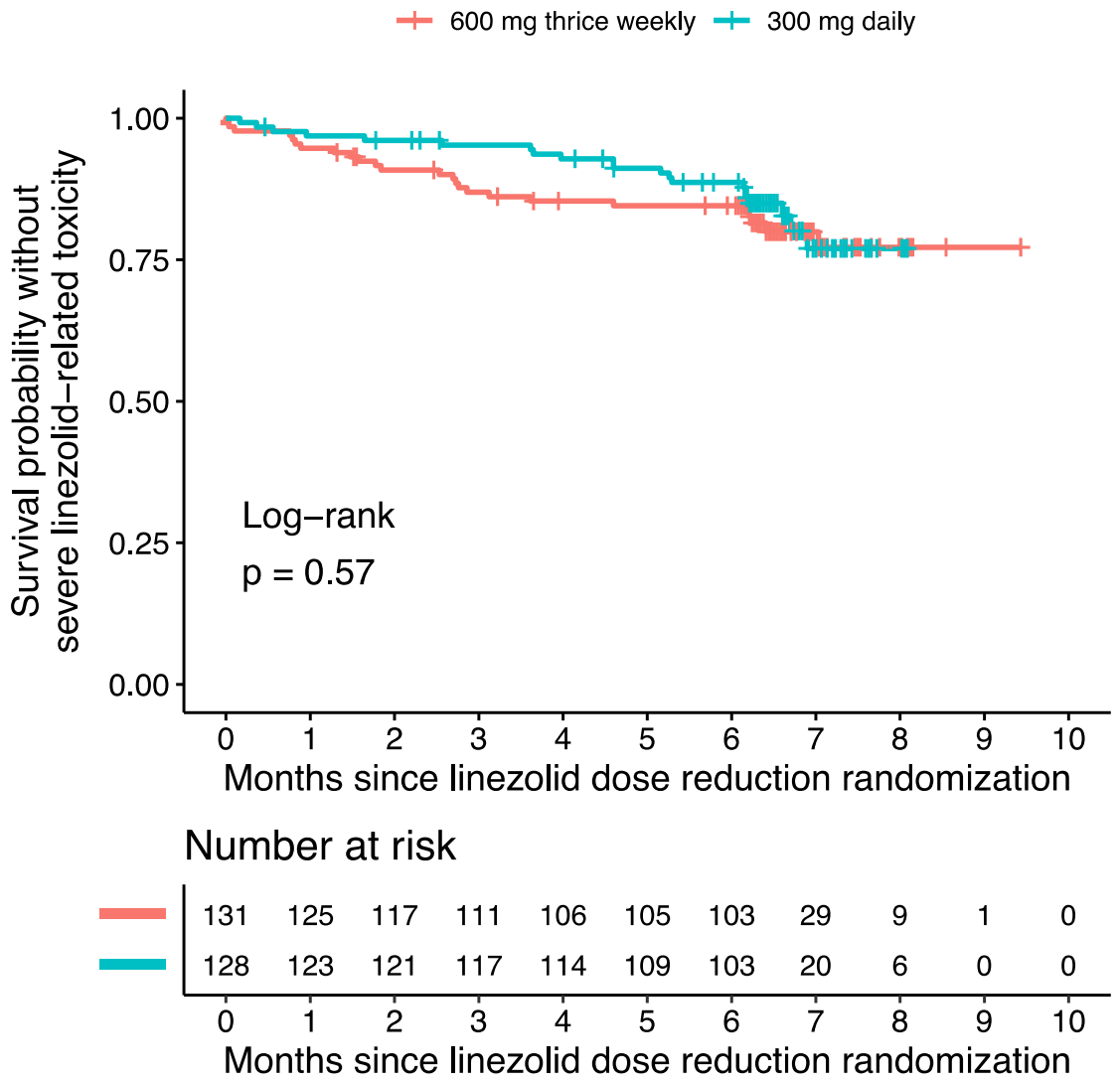


Table 3: Treatment Outcomes at W73 and W104

Population/Outcome	Total	300 mg daily	600 mg thrice weekly	Risk difference [95% CI]	P-value
Total in mITT population	247 (100%)	123 (100%)	124 (100%)		
Favorable outcome (W73)	224 (90.7%)	111 (90.2%)	113 (91.1%)	0.9% [-6.4%; 8.1%]	0.811
Favorable outcome (W104)	217 (87.9%)	107 (87.0%)	110 (88.7%)	1.7% [-6.4%; 9.9%]	0.679

Conclusions

- Two linezolid dose reduction strategies (300 mg daily or 600 mg thrice weekly) implemented at Week 16 or earlier due to AEs were similar with respect to severe linezolid-associated toxicity.
- The two strategies were also similar with respect to treatment efficacy.
- A limitation of this analysis was limited power due to delayed accrual (protocol amendment) and overestimation of events.
- Linezolid 300 mg daily is the most common dose reduction strategy in use — our findings support linezolid 600 mg thrice weekly as an alternative.

Thank you!

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:

Unitaid
SAVE LIVES FASTER










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








Innovation to guide practice in MDR/RR-TB treatment: efficacy and safety results of the endTB trial

Please share your questions

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