Improving treatment of MDR-TB: results of the endTB clinical trial

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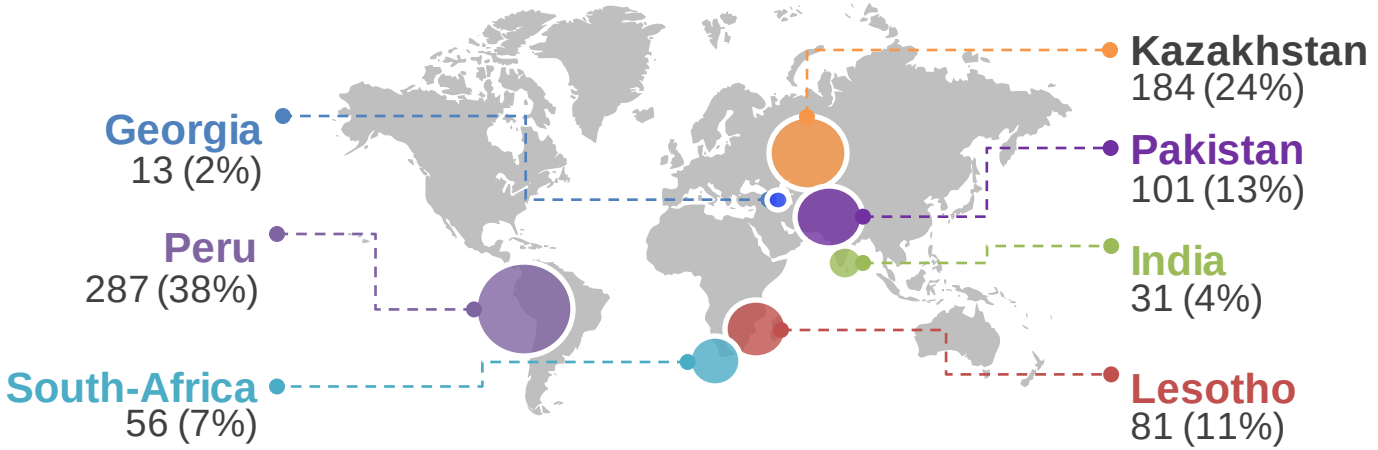
Conflict of Interest:
The author has declared no conflict of interest.

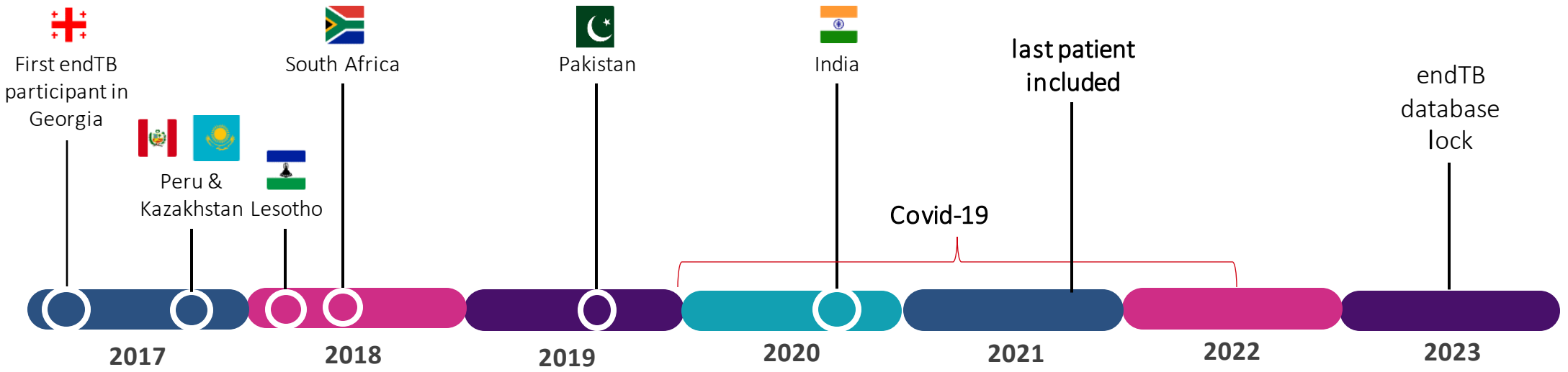
The endTB Project

The endTB clinical trial

7 countries | **12 sites** | **754 participants** | **More than 18,000 visits conducted**

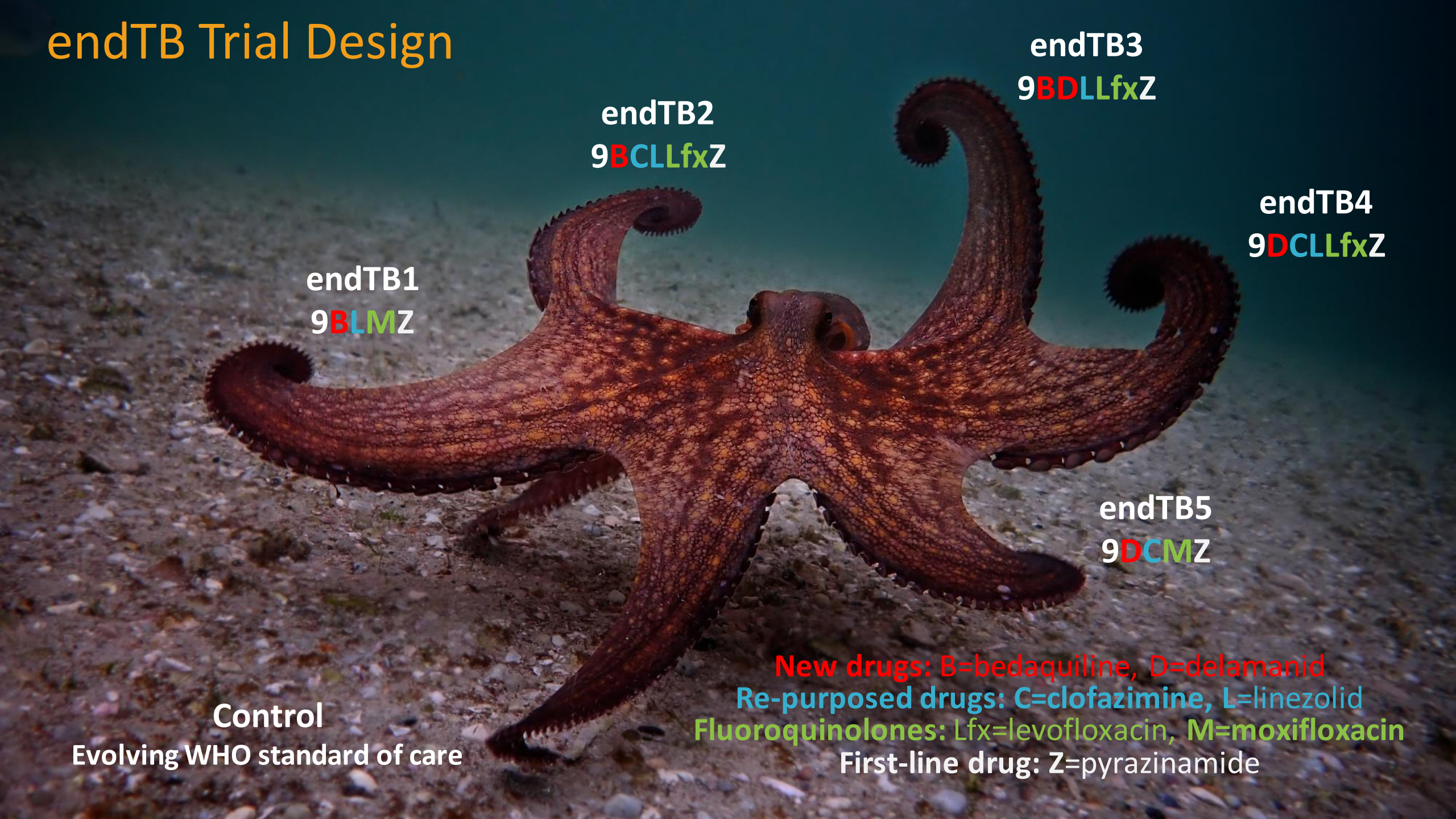
- **Open label, Phase III, non-inferiority clinical trial**
- **Pulmonary tuberculosis (TB)** with **resistance to rifampicin** and **susceptibility to fluoroquinolones**
  - Participants aged **≥15 years**
- No pregnancy, allergy or resistance to study drugs, severe lab abnormalities or cardiac risk factors





endTB clinical trial
Design

endTB Trial Design



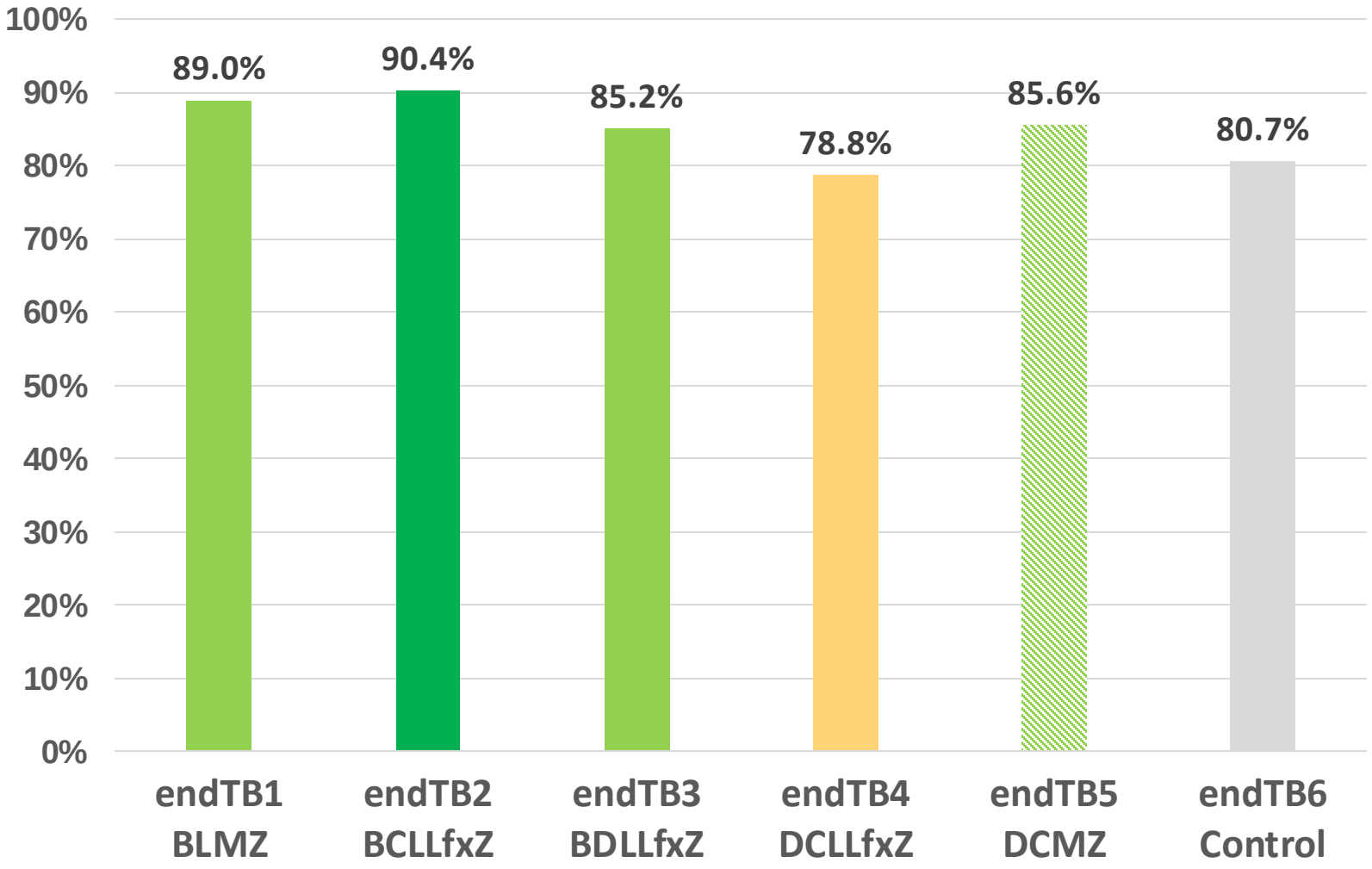
endTB clinical trial
Results

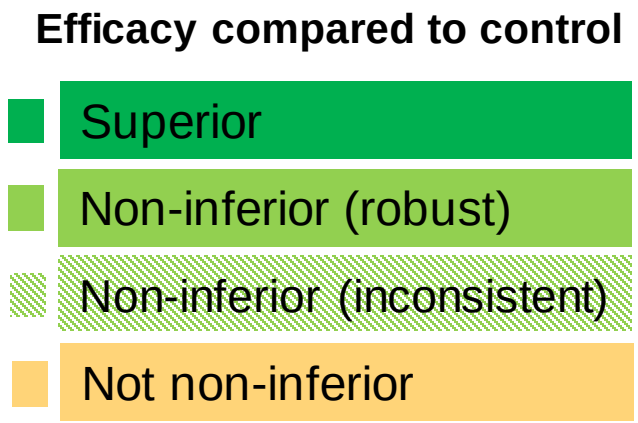
Selected baseline characteristics

Baseline characteristic	Total (N = 696)
Age (years), median (range)	32.0 [15.0;71.0]
Sex, female	264 (37.9%)
BMI (kg/m²), 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%)

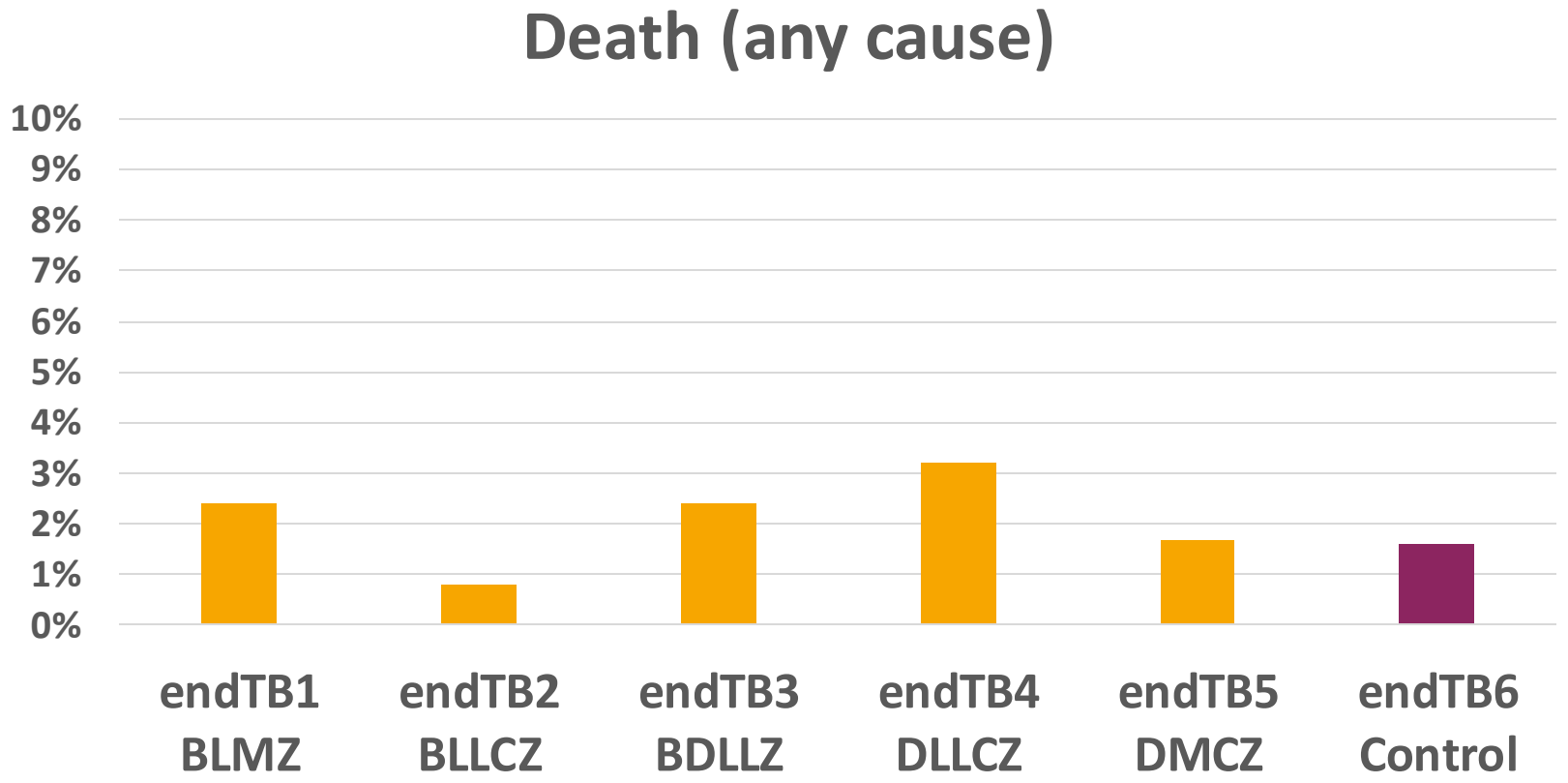
* Prior history, new diagnosis during trial screening/baseline visits, new diagnosis while in trial

Efficacy of endTB regimens (Week 73 favourable outcome, N=696)





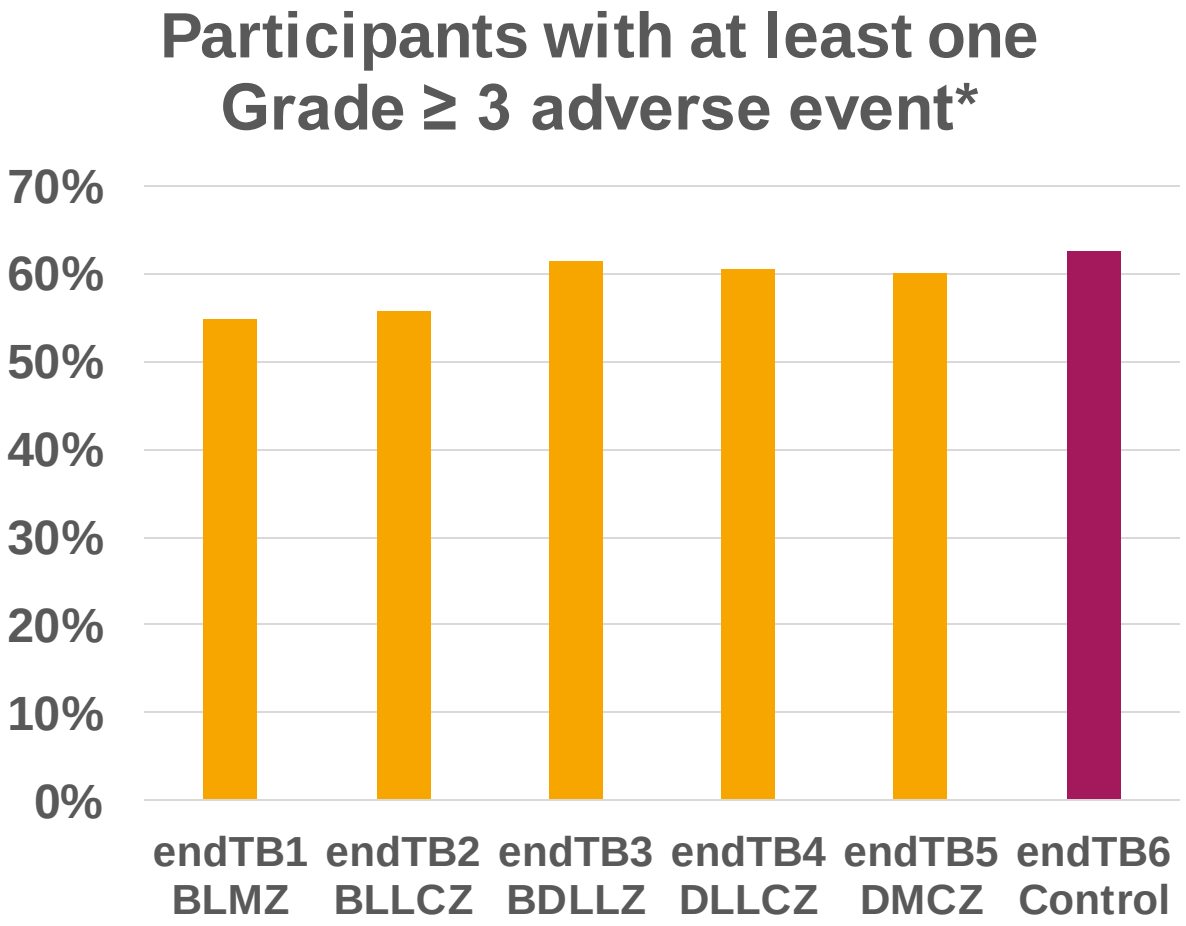
Safety results: Deaths - Week 73 (N=745)

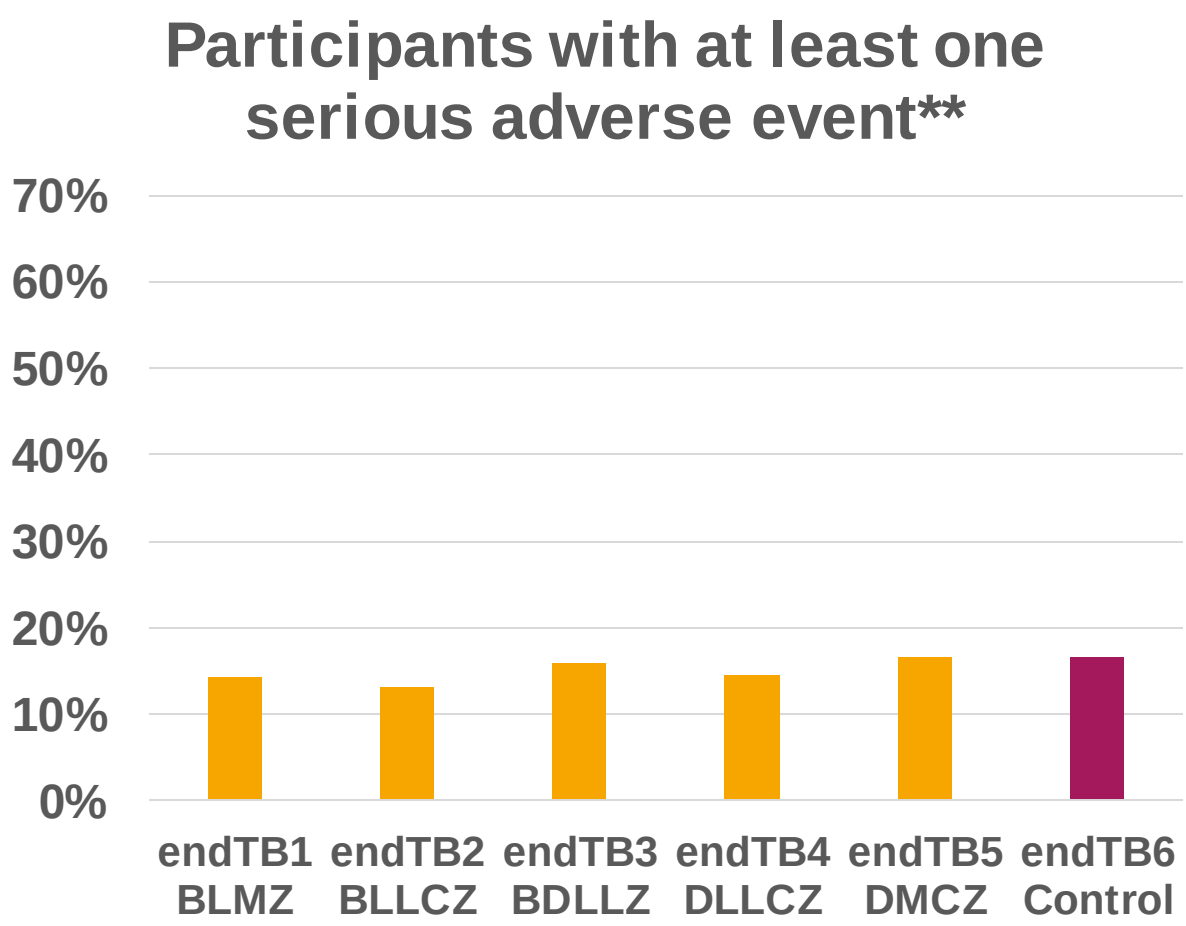


Total N= 15 (2%)

No death was considered to be related to study drugs.

Safety results: Grade ≥3 AEs and SAEs - Week 73 (N=745)





* 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.

endTB trial – conclusions

Provides robust evidence for 3 regimens that are NI to a contemporaneous, modern, control regimen (endTB1=9BLMZ, endTB2=9BCLLfxZ, endTB3=9BDLLfxZ)

- Offers **patient-centered treatment options** for all age groups: **adults, adolescents, children** (all drugs have pediatric formulations, endorsements for use in kids), and **pregnant people**

endTB5 (9DCMZ) offers possible, shortened, all-oral alternative for patients unable to take linezolid or bedaquiline

Low mortality & similar frequency of important AEs in experimental and control arms

- Higher than expected in all arms: reflects comprehensive pharmacovigilance in the trial

Confirms importance of appropriate, risk-based AE monitoring and management

endTB clinical trial
Quality of care and quality management

Quality of care and quality management

Good patient management	Person-centered patient adherence support and study retention	Enhanced centralized oversight, staff engagement and quality management
31 planned clinic visits per patient, from weekly to every 6-8 weeks	Holistic health approach including **easy access to medical teams** via telephone, medical referrals incl. hospitalization, pain management, psychological support, insurance	**Clinical trial coordination**, including with TB Lab
Set of **defined procedures** to be carried out at particular visits*		**Stringent regulatory framework**
Additional **unscheduled visits** as needed	**Non-monetary support** (travel, clothes, food), **teleconsultations** during the COVID-19 pandemic	Robust **centralized quality-assurance management systems**
Coordination of care by trial team		**Data management**, data reviews
Drug quality by centralized procurement, pharmacy monitoring		Regular on-site and remote **quality control** by Sponsor and trained independent trial monitors
Directly observed treatment, **treatment supporters**, counsellors		Regular **structured trainings** for staff and **clear delegation of tasks**
Report of all adverse events, **pharmacovigilance system**		
Possible **patient referral** to the national TB program (in case of poor treatment response, AE, withdrawal of consent, lost to follow or other)		

*clinical, biochemical, hematologic, bacteriologic, adherence, neurologic, optic, audiometric, radiographic, cardiac monitoring

Quality indicators and implications

Good patient management

96.5% of visits carried out as planned

Higher success rates (**78.8%-90.4%**) in all 6 arms vs previously reported programmatic global success rates (63%)

Person-centered adherence support

80.0% participants took the drugs for the expected duration and completed treatment

77.4% participants took >80% of the drugs as prescribed

Enhanced centralized oversight, staff engagement and quality management

50% important visits and **100%** major adverse events reviewed by trial monitors

<u>Hypothesis</u>
Quality of care has an impact on patient experience and outcomes

<u>Suggestion #1</u>
Routine implementation of this approach could be transformative

<u>Suggestion #2</u>
Perform qualitative and implementation studies in real life conditions

What’s next?

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- **Dissemination of endTB results** in countries where we work (and beyond)
- **Share endTB trial data with WHO** (guideline review in 2024, 2nd quarter)
- **Accelerate the uptake of new regimens** (endTB and BPaLM)
  - Routine care or observational research, before new WHO guidelines
  - **arcTB** project, submitted for Unitaid funding (MSF OCP and OCA + endTB partners PIH and IRD + Stellenbosch and ITM)
- **endTB-Q trial (RR, FQ-R TB):** participant follow-up ongoing, results at Union conference (Nov 2024)?

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!



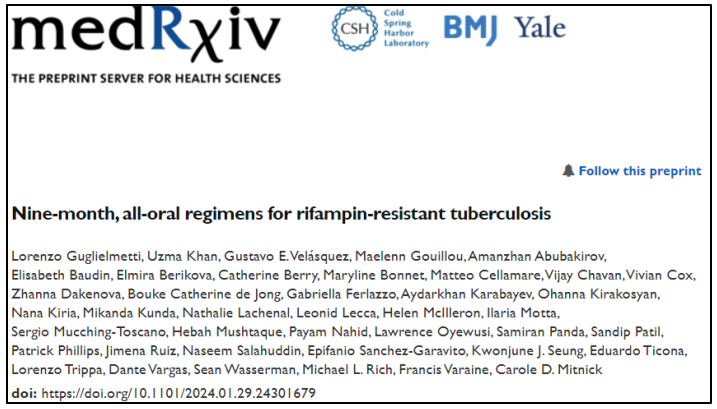





Questions?

1. Available on https://endtb.org/
   - endTB video on results
   - videos of the Union symposium and community connect session
   - results in a leaflet
   - ppt slides of the Union conference

2. Pre-print manuscript



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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

EXTRA SLIDES

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, 754 participants
Rifampicin-resistant and FQ-susceptible pulmonary TB (FQ-S)

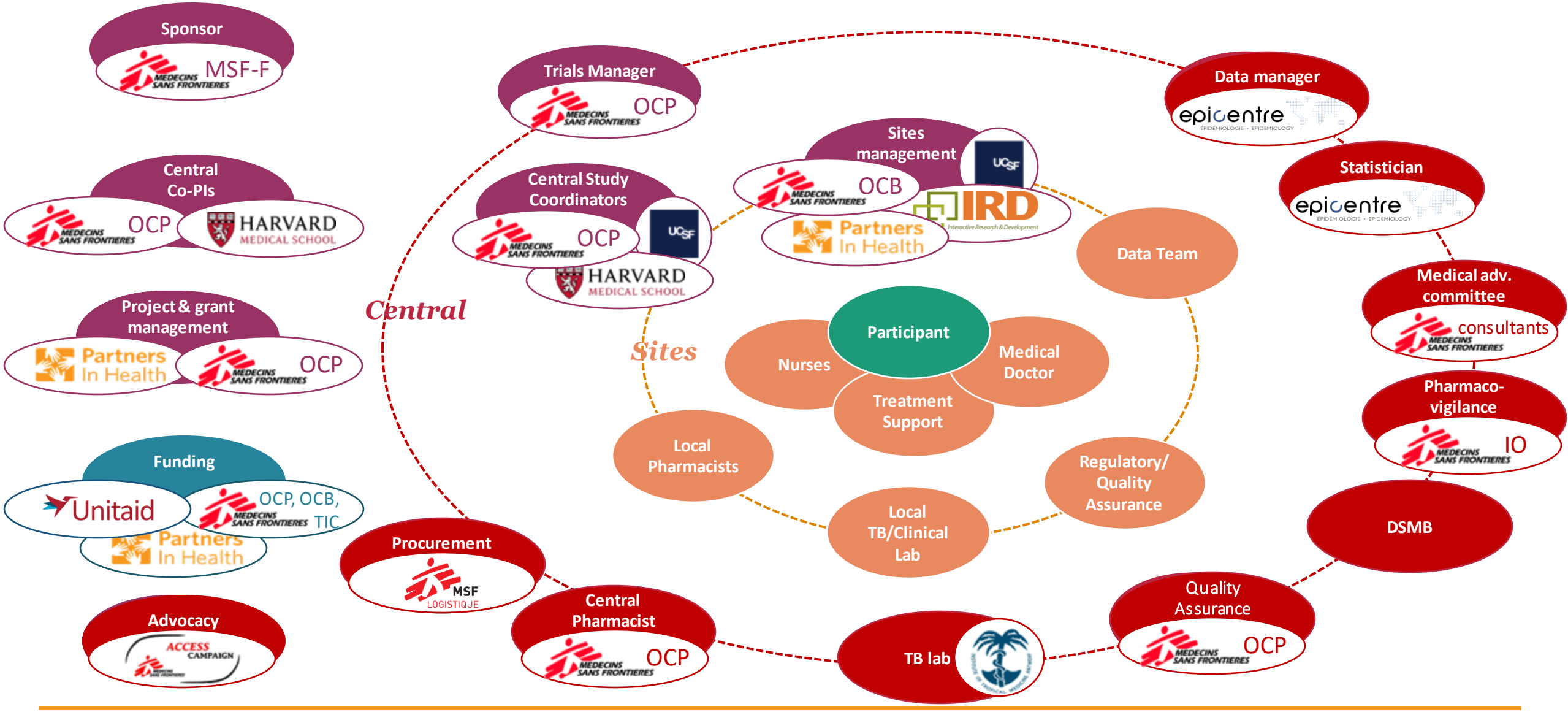
endTB-Q trial (follow-up) 6 Countries, 324 participants
Rifampicin- and FQ-resistant pulmonary TB (FQ-R)

Randomized, controlled, open-label, non-inferiority Phase III trials

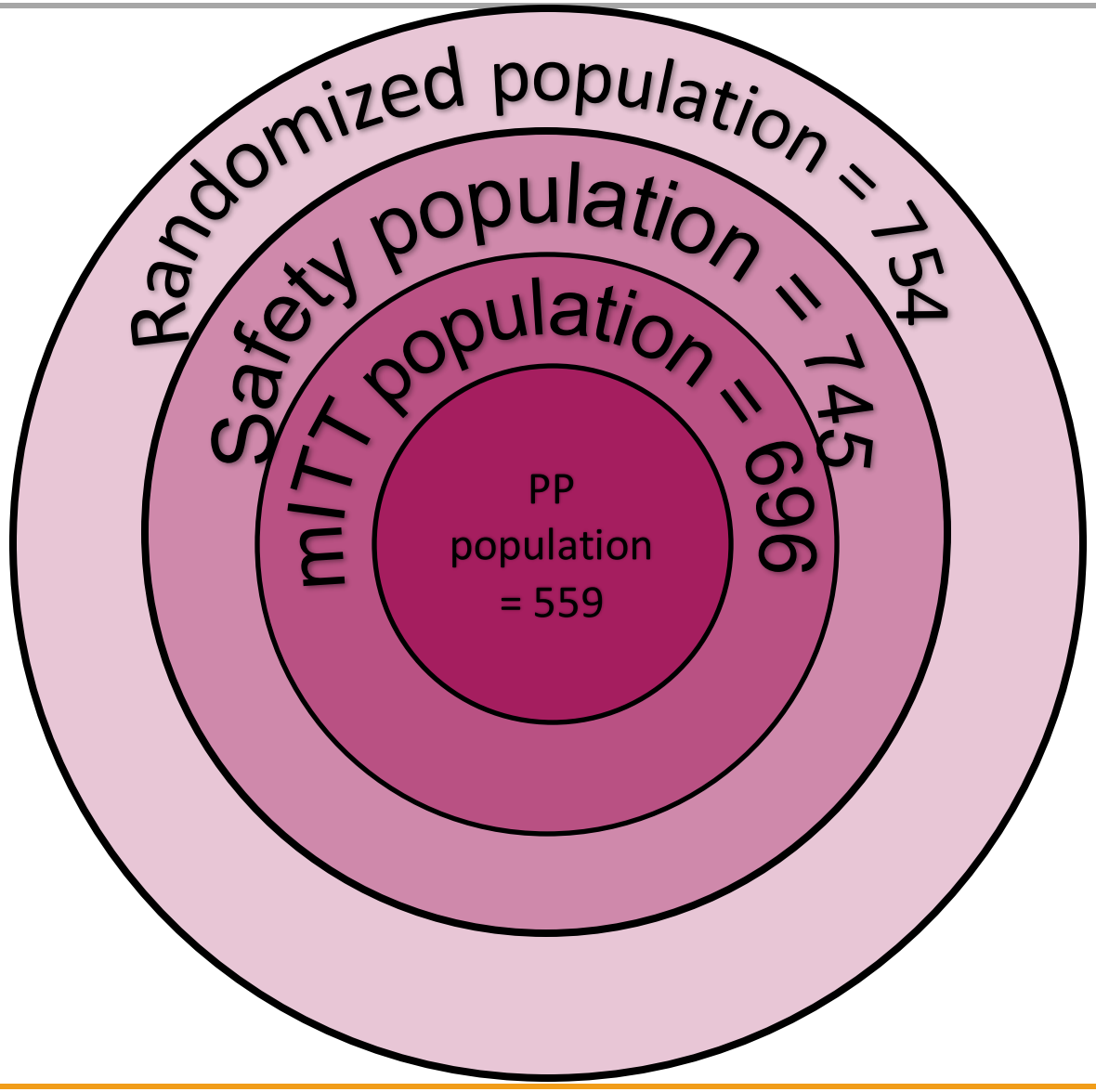
Primary endpoint: 73-week favorable outcome

Follow-up: 73 to 104 weeks post randomization

The endTB complementary partnership



Main analysis populations



Randomized population: all randomized participants

Safety population: all randomized pts who received ≥ 1 dose of study treatment

Modified intention-to-treat (mITT) population: all randomized pts that met eligibility criteria with some exclusions

Per protocol (PP) population: randomized pts who followed study protocol