

Targeting Tuberculosis: A Clinical Trials Update

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Disclaimer

- ▶ Dr. Horsburgh has no conflicts of interest to disclose

Outline

- ▶ Background
- ▶ Trials for Drug-sensitive TB
- ▶ Trials for MDR-TB
- ▶ Trials for “Pan-TB”
- ▶ Trials for Latent TB Infection
- ▶ New directions in TB clinical trials

Background

▶ Recent Successes:

- ▶ 4 months HRZE/HR for DS-TB in children with less severe disease
- ▶ 4 months HPMZ for DS-TB in adults
- ▶ 6 months BPaLM for MDR-TB and BPaL for XDR-TB
- ▶ 6 months Levo for MDR-LTBI
- ▶ 1 month INH+Rifapentine for LTBI?

Trials for DS-TB

WHO recommended Regimens for DS-TB

- ▶ Daily 2HRZE/4HR (with Fixed Dose Combinations when possible)
- ▶ 2HPMZ/2HPM for those aged 12+
- ▶ 2HRZE/2HR for those aged 0-16 with non-severe TB and no suspicion of MDR-TB

Frequency of nausea and/vomiting in two clinical cohorts on HPZM

Study	AE reported	Grade 1-2	Grade 3-4	HPZM discontinued
San Francisco	Nausea and/or vomiting	9/22 (41%)	0	7 (32%)
New York City *	Nausea	9/30 (47%)	0	
	Vomiting	5/30 (26%)	0	

- ▶ Overall outcomes of HPZM treatment:
 - San Francisco: 11/22 (50%) stopped due to AEs
 - New York City: 15/36 (42%) stopped due to AEs

- Louie J, et al. *Open Forum Inf Dis* 2024 Mar 26;11(4):ofae178
- Galvis M, et al. *Int J Tuberc Lung Dis* 2025; 29: 318-24

Phase 3 DS-TB trials underway

- ▶ PORT - 6 months of **high-dose RIF**+HZE
- ▶ OptiRiMoxTB- 4 months of **high-dose RIF**+HZE or HZM
- ▶ STEP2C - 3/4 months **high-dose RIF** +/- **high-dose PZA**
- ▶ ORIENT - 4 months HPMZ with **high-dose Rifapentine**
- ▶ RIFAstrat - 4 months **high-dose RIF**
- ▶ RADIO-TB - HRZE of varying durations for TB on CXR, not microbiologically confirmed
- ▶ NIRT Trial - 4 months HRZE+Moxi (single arm)
- ▶ SMILE-TB - Randomized trial of 2HPZM for uncomplicated TB in children; open for enrollment

Phase 2 DS-TB trials currently underway

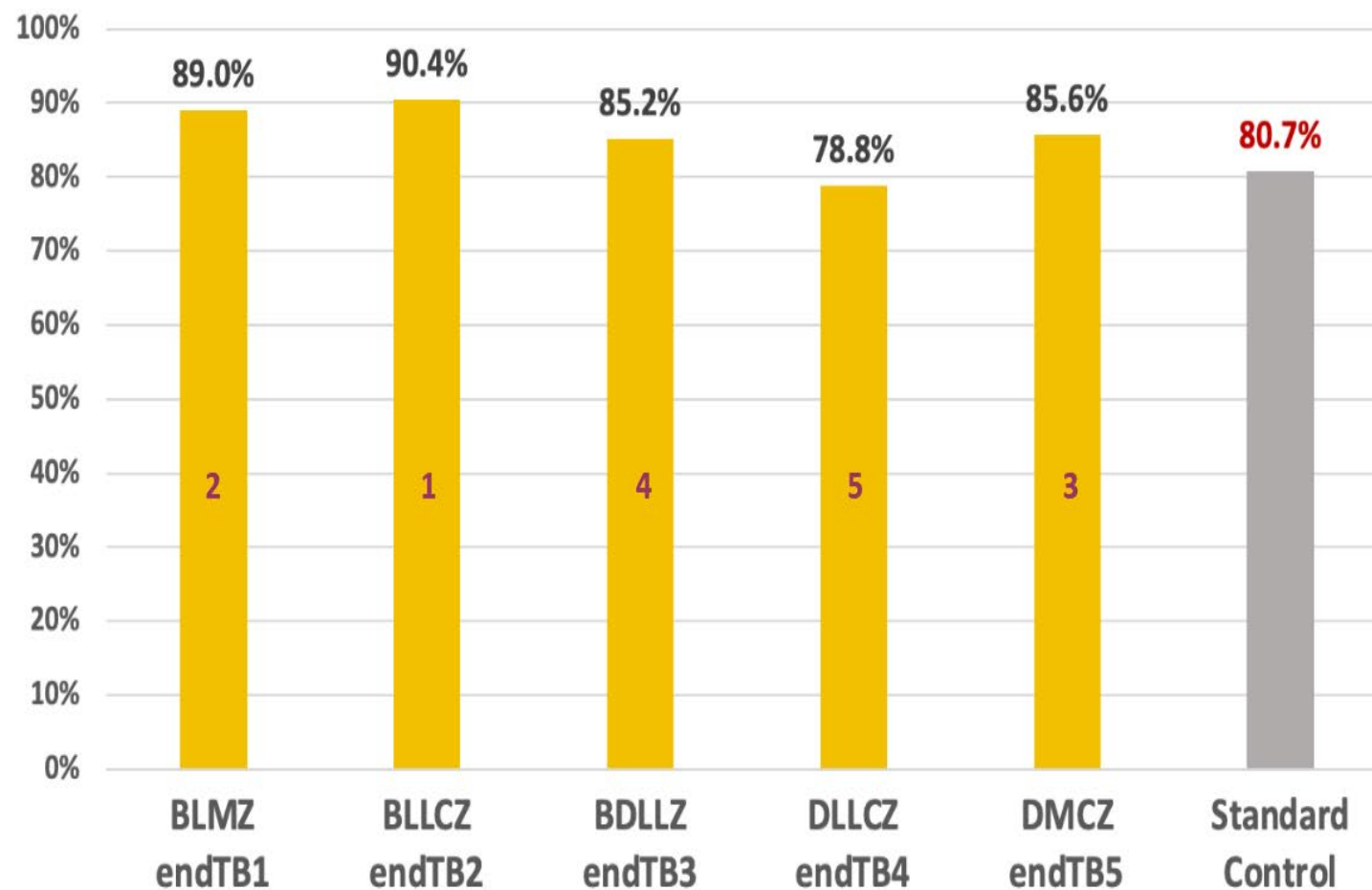
- ▶ CRUSH-TB - 17 weeks of BMZ+Rifabutin or BMZ+Delamanid, fully enrolled, with 292 participants
- ▶ STEP2C - RHZ + BTZ-043

Trials for MDR-TB

Recently completed trials of MDR-TB

- ▶ End TB (MDR)
- ▶ EndTB-Q (MDR with FQ resistance)
- ▶ BEAT-Tuberculosis (MDR with or without FQ-R)

endTB Regimens | Primary Efficacy Endpoint, mITT (W73)



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



Adverse events	endTB1 (BLMZ) (n = 126)	endTB2 (BLICZ) (n = 122)	endTB3 (BDLLZ) (n = 127)	endTB4 (DLICZ) (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%)
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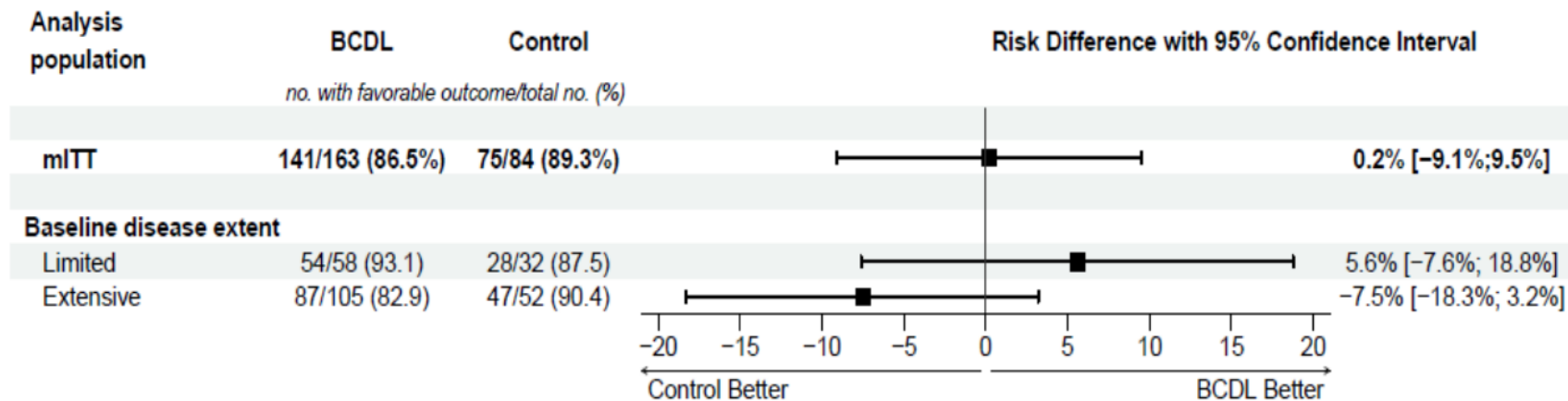
Most commonly stopped drugs (all arms):

- **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

EndTB-Q

- ▶ Bedaquiline + Clofazimine + Delamanid + Linezolid for 6 months in people with limited disease and for 9 months in people with extensive disease
- ▶ Option to extend treatment from 6 to 9 months if response not satisfactory at 6 months

endTB-Q | Adjusted* forest plots: mITT & PP efficacy at Week 73, stratified by baseline disease extent



*adjusted for randomization stratification variables: country & baseline extent of disease

endTB-Q | Adverse Events: Total, Grade ≥ 3 & SAE at treatment end + 4 weeks[#] (Safety population)



	Experimental N=213	Control N=105	Total N=318
Participants with any Grade ≥ 3 AE*	136 (63.8%)	80 (76.2%)	216 (67.9%)
Participants with any SAE**	31 (14.5%)	23 (21.9%)	54 (17.0%)
Permanent discontinuation of ≥ 1 drug(s) for AEs	30 (14.1%)	57 (54.3%)	87 (27.4%)
Death[#]	9 (4.2%)	2 (1.9%)	11 (3.5%)

[#] Includes all follow-up period; 5 deaths were not included in the efficacy analyses: 3 in people excluded from mITT and 2 that occurred after end of study participation; 2 were TB-related; 2 were TB-drug related

[#] Post hoc analysis; primary safety analysis is at Week 73; * 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 medically important.

EndTB-Q Conclusions

- ▶ BCDL for 6 or 9 months produced high rates of good outcomes (87% cure), although slightly lower than the long regimen (89% cure).
- ▶ BCDL started at 6 months—and extended to 9 months in case of delayed treatment response—achieved excellent results in people without severe TB disease at treatment start (93% cure).
- ▶ In people with severe TB disease, BCDL for 9 months was not sufficient to prevent relapse compared to the long regimen.

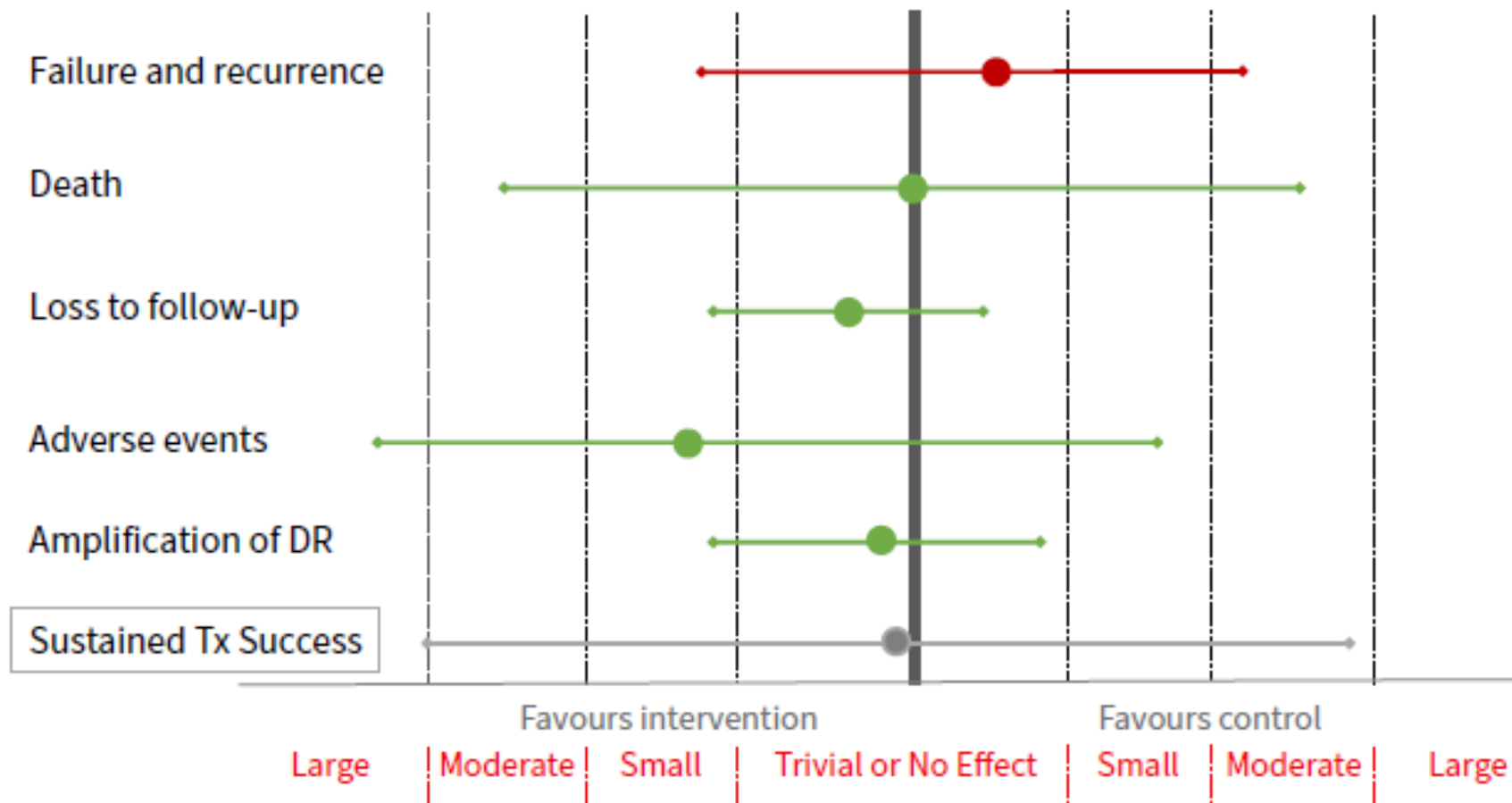
BEAT-Tuberculosis Trial

For MDR-TB when FQ Susceptibility unknown

- ▶ Bedaquiline + Clofazimine + Delamanid + Linezolid + Levofloxacin, until baseline FQ susceptibility obtained
- ▶ Discontinue either Clofazimine or Levofloxacin when baseline FQ susceptibility obtained

BEAT-Tuberculosis Trial

BEAT TB – 6-month regimen BDLLfxC



WHO-recommended Regimens for MDR-TB: updated April 2025

- ▶ 6BPaLM for FQ-susceptible MDR
- ▶ 6BDL(Lfx)C for MDR when FQ-resistant or unknown
- ▶ 9 month all-oral regimen (BLMZ recommended) for FQ-susceptible MDR-TB
- ▶ Individualized longer regimens also OK

Phase 3 trials underway for MDR-TB

- ▶ PRISM - for FQ-S MDR-TB; stratified treatment with BPaLM
- ▶ INSPIRE - 6 months BD + Contezolid + Lfx or other (if FQ-R)
- ▶ WISH - 6 months Sudapyrine + OBT

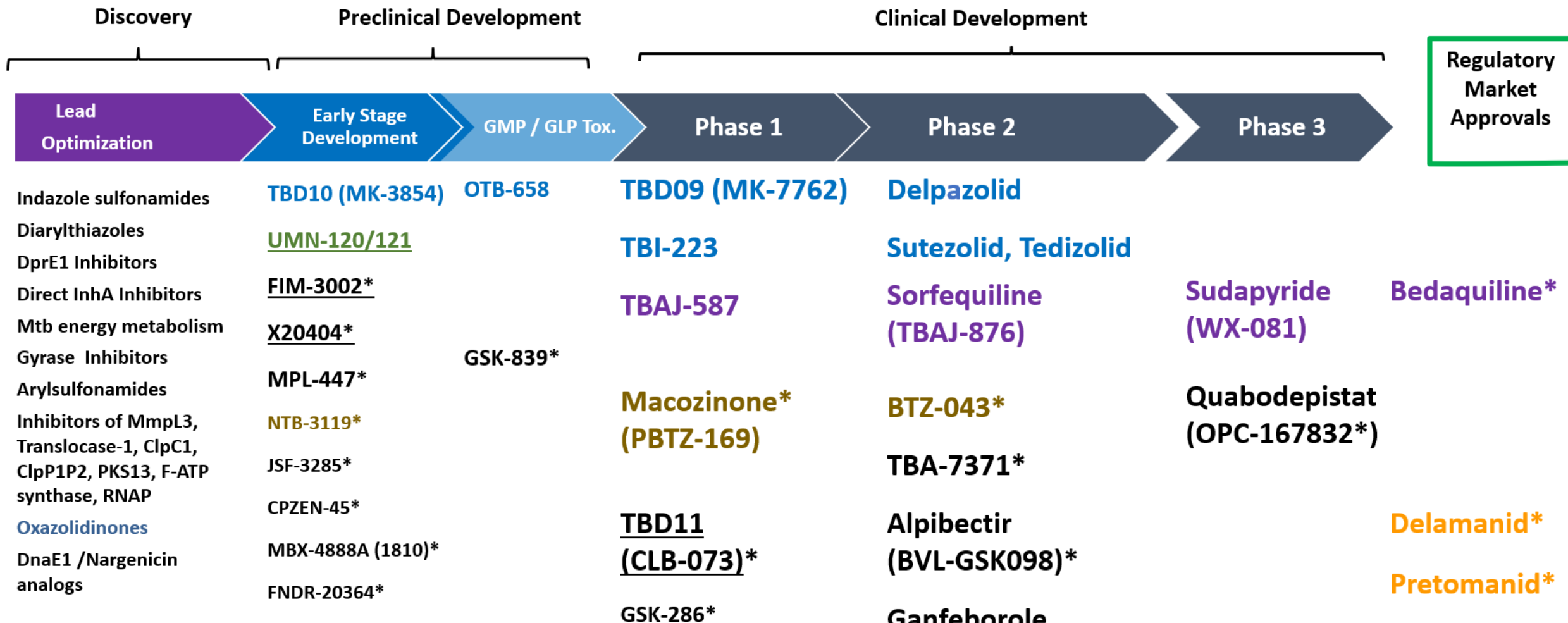
Phase 2 MDR-TB trials currently underway

- ▶ **DRAMATIC** - BDLLxC for FQ-S MDR, 16, 24, 32 or 40 weeks, fully enrolled

The Holy Grail

- ▶ A regimen that will treat TB without the need for drug susceptibility testing
- ▶ So-called “Pan-TB” regimen

2025 Global New TB Drug Pipeline¹



*New chemical class. Known chemical classes for any indication are color coded: Rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam. Smaller type indicates candidates requiring additional research/support to advance.

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>

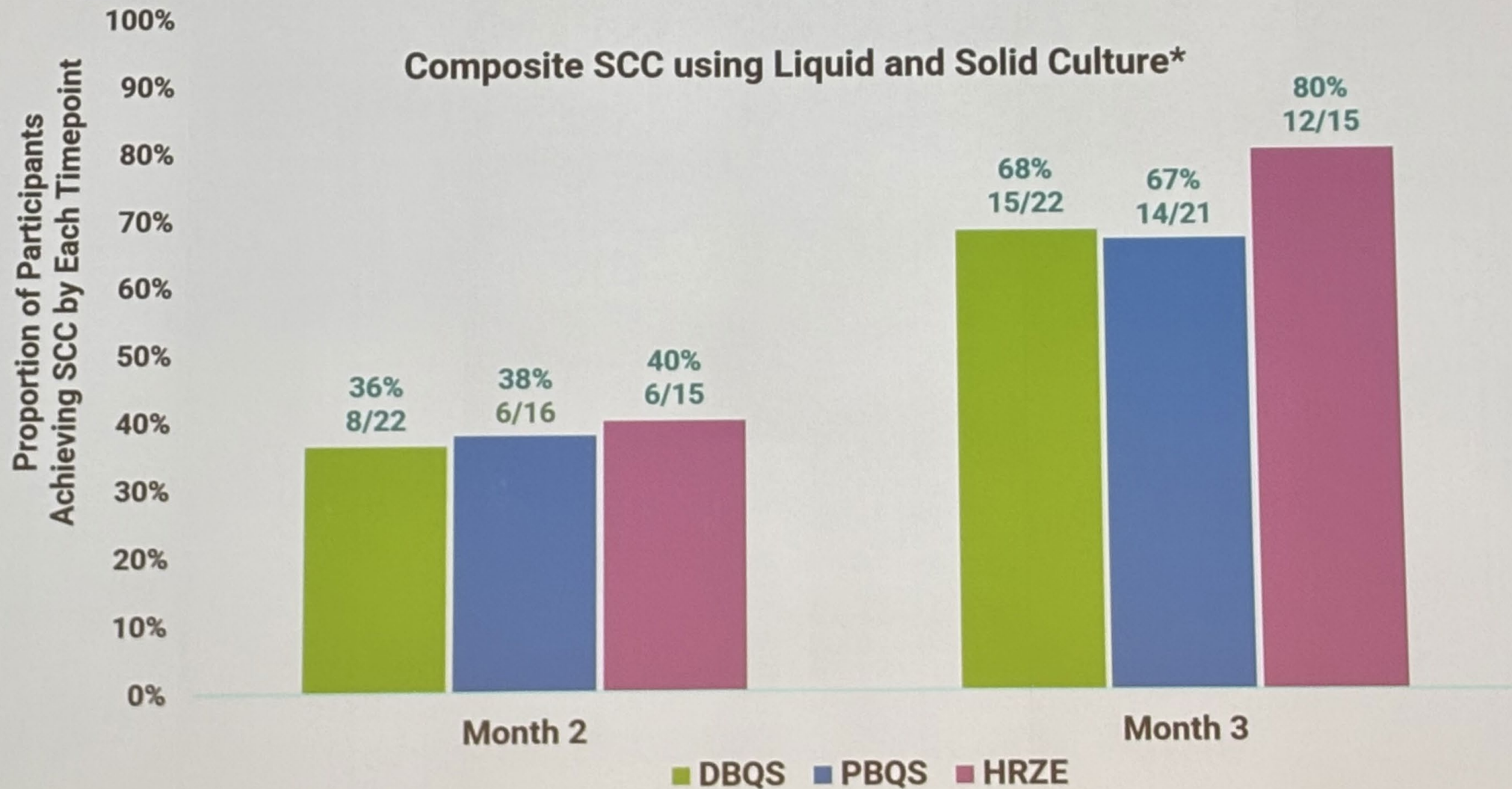
Phase 2 PAN-TB trials recently completed

- ▶ PAN-TB
- ▶ Quantum-TB Trial

PAN-TB Trial (GMRI)

- ▶ Bedaquiline, Pretomanid, Sutezolid and Quabodepistat
- ▶ Bedaquiline, Delamanid, Sutezolid and Quabodepistat
- ▶ 4 months duration, followed for 1 year
- ▶ Plan to take best arm into Phase 3 duration-randomized trial

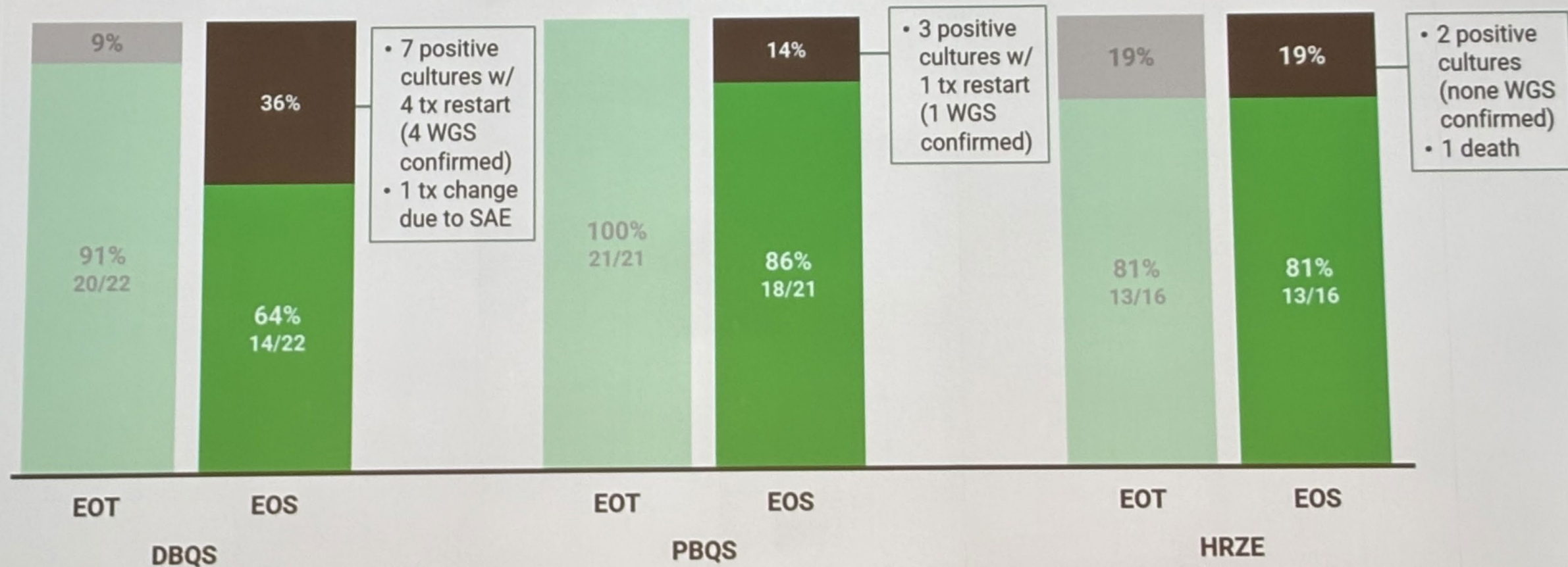
XBQS Sputum Culture Conversion at 2 and 3 Months is Insufficient for Identifying Pathway to a 3-Month Regimen



* Modified Per Protocol Population

Positive Cultures Observed During Follow-up for 4-Month XBQS Regimens

Favorable vs Unfavorable Outcome at EOT and End of Study (EOS)†



No resistance to HRZE, B, or D identified on phenotypic drug susceptibility testing; MIC testing for P, Q, and S pending

† Participants in Modified Per Protocol population were followed through Month 12 **or** a minimum of 6 months after treatment completion

Quantum-TB Trial

- ▶ Quabodepistat, Bedaquiline, and Delamanid for 17 weeks vs. HRZE for 24 weeks

Phase 2 PAN-TB trials currently underway

- ▶ DECISION - B + D + BTZ-043
- ▶ RAD-TB - B + Pa + Sutezolid or TBI-223
- ▶ NC-009 - TBAJ-876 + Pa + LZD
- ▶ PARADIGM4TB - Ganfeborole, BTZ-043, Quabodepistat, Delpazolid

Trials for LTBI

WHO recommended Regimens for LTBI

- ▶ 6 months INH for presumed DS-TB
- ▶ 4 months RIF for presumed DS-TB
- ▶ 3 months Rifapentine plus Isoniazid for presumed DS-TB
- ▶ 6 months Levofloxacin for presumed MDR-TB

Recently completed trials of LTBI

- ▶ 2R2 Trial (LTBI, DS)

2R2 Trial for LTBI

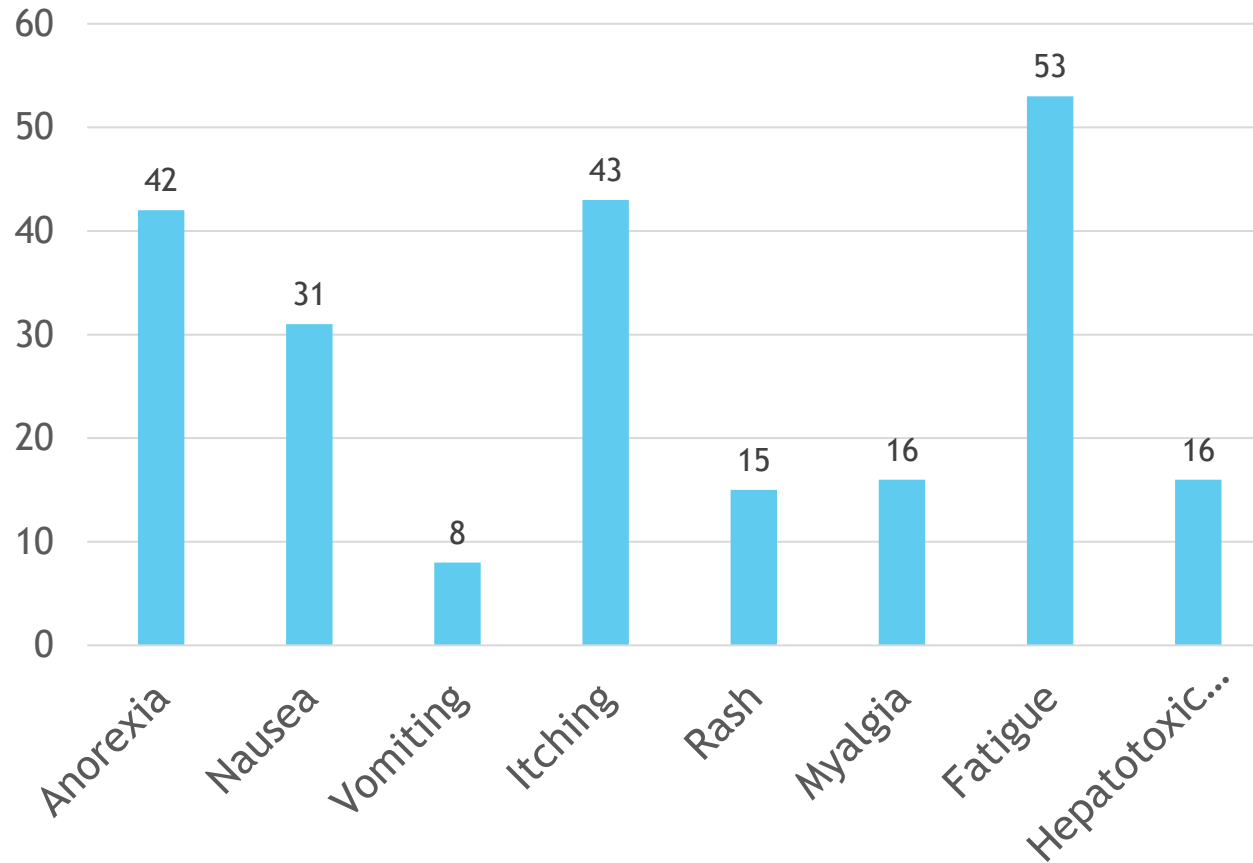
- ▶ 2 months of 30 mg/kg RIF vs
- ▶ 2 months of 20 mg/kg RIF vs.
- ▶ 4 months of 10 mg/kg RIF for LTBI
- ▶ 2-month regimens had significantly worse completion than 4-month regimen, and 2 months of 30/mg/kg had worse safety

Phase 3 trials underway for LTBI

- ▶ ASTERIOD - 6 weeks Rifapentine for DS LTBI, ~1200/ 3400 enrolled
- ▶ PHOENiX - Delamanid for MDR LTBI; fully enrolled
- ▶ BREACH-TB - Bedaquiline for LTBI, under development
- ▶ Brazil 1HP

New Directions in TB Trials

High rates of side effects with HRZE in prospective cohort



- **68% $\geq$ grade 2 AE**
- **10% changed therapy due to adverse events**

High rates of Adverse events in large retrospective cohorts

- ▶ Retrospective cohort of 2953 participants in Malaysia
 - 475 had a treatment interruption
 - 53% of interruptions were due to adverse events
 - Treatment interruptions associated with
 - Changes in treatment
 - Prolonged treatment
 - Lower treatment success

Refocus on patient experience

- ▶ Superiority trials focusing on tolerability/safety
- ▶ Study participants represent the global TB pandemic
- ▶ Primary endpoint: on-time treatment completion of the original prescribed regimen

Potential trials to increase tolerability

- ▶ Ondansetron prophylaxis to decrease nausea
- ▶ Substitution of FQ for H or Z in HRZE
- ▶ PZA-free regimens for people with less extensive disease
- ▶ Treatment initiation by dose-escalation
- ▶ Hepatoprotective agents?

Conclusions

- ▶ We have made real progress in the last decade, especially with MDR-TB
- ▶ Shorter is better...but only if also better tolerated
- ▶ Many new drugs in the pipeline...with as yet poorly defined safety and tolerability
- ▶ Pessimism about ever getting a “Pan-TB” regimen
- ▶ Optimism that we can do better than HRZE!