

Shorter TB Treatment

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Some Framing Concepts

- “Shorter” is a relative term
 - Shorter than what?
 - What is short enough?
 - Is there a tradeoff (efficacy, safety, number of drugs)?
- Individualized vs Standardized
- Availability of DST

Lessons from Drug-Sensitive TB Treatment

- MRC Trials 1940's – 1980's
 - Streptomycin + Bedrest → → → HRZE 6-month regimen
- Introduction of new drugs
- Understanding of disease and drug mechanisms
- Directly observed therapy

ORIGINAL ARTICLE

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

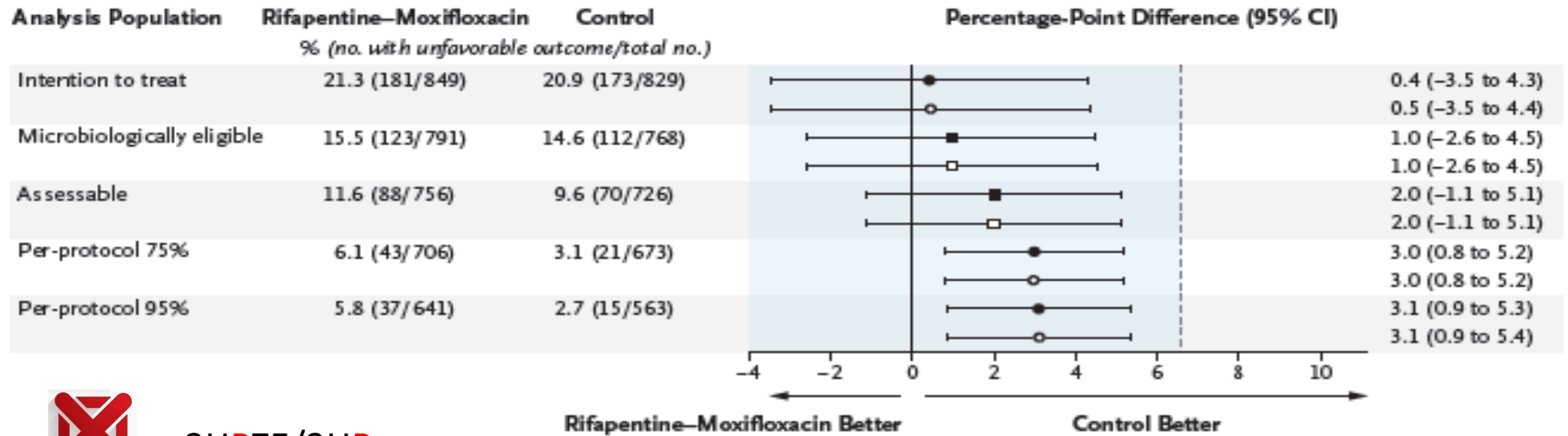
S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott, J. Shenje, E. Sizemore, A. Vernon, Z. Waja, M. Weiner, S. Swindells, and R.E. Chaisson, for the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium

A

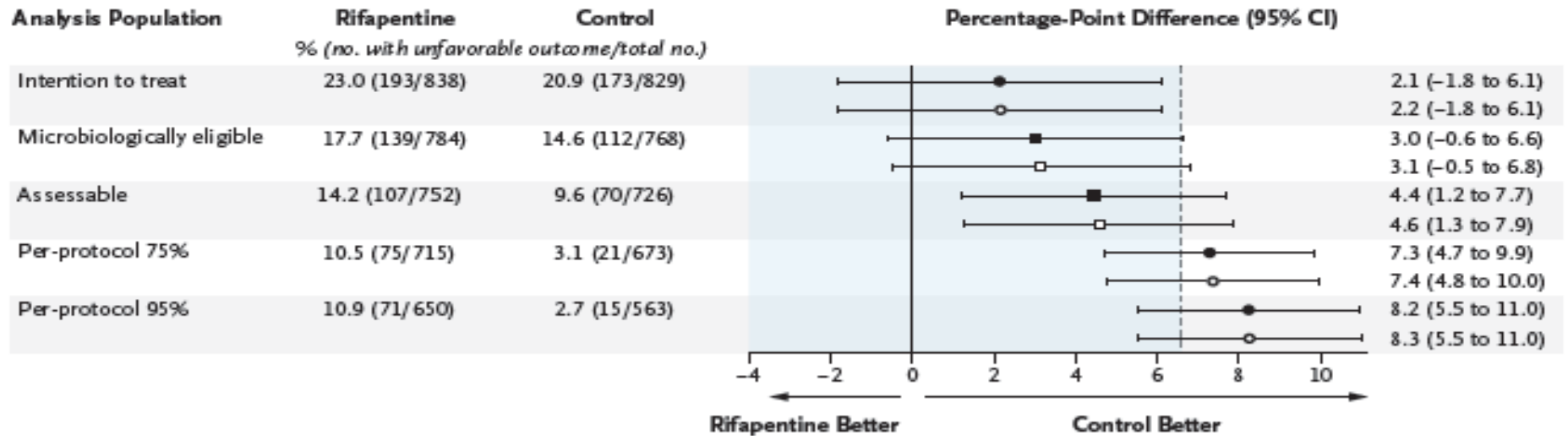


2HPZM/2HPM

■ Primary: adjusted for HIV and cavitation □ Primary: unadjusted
 ● Secondary: adjusted for HIV and cavitation ○ Secondary: unadjusted



2HPZE/2HP



Shorter Treatment Trials for DS-TB

- TRUNCATE
 - HRZE vs (4) 5-drug regimens for 8 weeks → 12 weeks if needed
 - HRZE + Cfz or Lzd; HPZ-Lzd-Levo; HZE-Lzd-Bdq
 - Monitor for relapse → 6-month HRZE
 - Outcome is status at 96 weeks
- RIFASHORT
 - 6-mo HR(600)ZE vs 4-mo HR(1200)ZE vs 4-mo HR(1800)ZE
- SimplificiTB
 - HRZE vs 4-mo BPaMZ

Results of a standardised regimen for multidrug-resistant tuberculosis in Bangladesh (IJTLD, 2004)

| | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|
| K | K | K | | | | | | | | | | | | | | | | | | |
| C | C | C | | | | | | | | | | | | | | | | | | |
| O | O | O | O | O | O | O | O | O | O | O | O | O | O | O | | | | | | |
| H | H | H | H | H | H | H | H | H | H | H | H | H | H | H | | | | | | |
| Z | Z | Z | Z | Z | Z | Z | Z | Z | Z | Z | Z | Z | Z | Z | | | | | | |
| E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E |
| P | P | P | P | P | P | P | P | P | P | P | P | P | P | P | P | P | P | P | P | P |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |

Kanamycin
 Clofazimine
 Ofloxacin
 Isoniazid
 Pyrazinamide
 Ethambutol
 Prothionamide

| | | |
|----------------------------|----------------------------|-----------------------------|
| Compulsory hospitalization | | |
| PHASE I 7 drugs | PHASE II 5 drugs | PHASE III 2 drugs |

69% cured (40/58)

Shorter Treatment Trials for Drug-Resistant TB

- **STREAM (1 and 2)**
 - CFZ, EMB, Moxi/Levo, PZA for 40 weeks, plus INH, KAN, and Pth in the first 16 weeks
 - CFZ, EMB, Levo, PZA, BDQ for 40 weeks, plus INH, Pth for the first 16 weeks.
 - CFZ, Levo, PZA, BDQ for 28 weeks, plus INH, KAN for the first 8 weeks.
- **EndTB**
 - (5) 9-month regimens of 4-5 drugs from among: BDQ, DLM, CFZ, Levo/Moxi, LIN, PZA
- **NEXT**
 - BDQ, LIN, Levo, PZA, plus: high-dose INH/Eth/Trd for 6-9 months
- **MDR-END**
 - DLM, LIN, Levo, PZA for 9-12 months
- **TB Practecal**
 - BDQ, Pa, LIN +/- CFZ or Moxi for 6 months
- **Nix-TB and ZeNix**
 - BDQ, Pa, LIN for 6 months (BPaL)
- **...and others**

Nix-TB: 6-month BPaL Study in Highly Drug-Resistant TB

New England Journal of Medicine, March 2020

PARTICIPANTS

109 enrolled

71 with XDR-TB

65%

38 with TI/NR* MDR-TB

34%

RESULTS

90% had favorable outcomes

XDR-TB

89%

79-95 (95% CI)

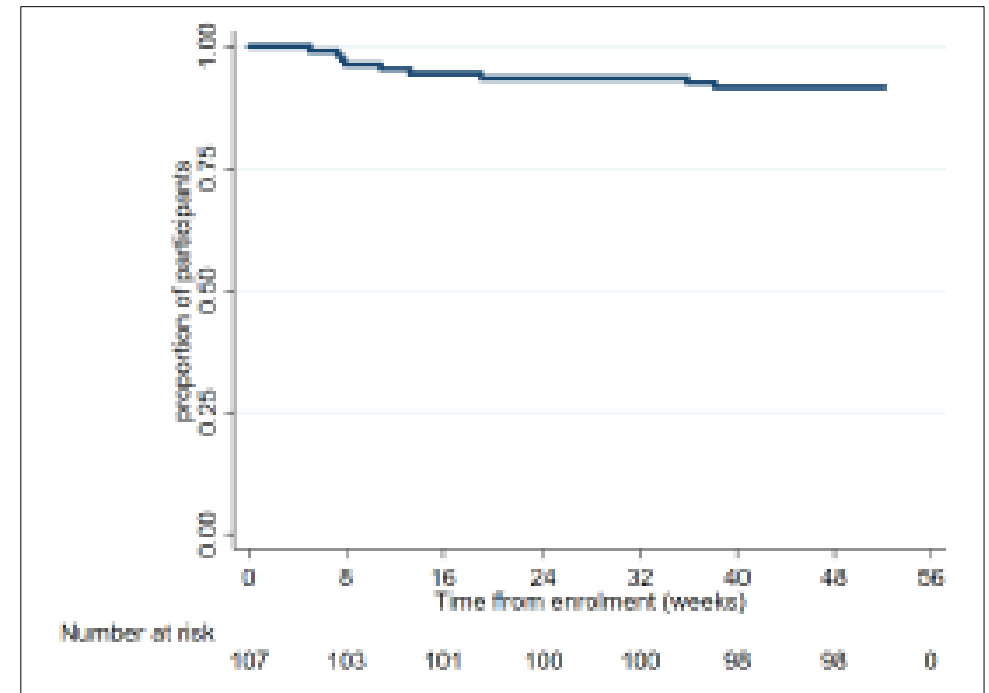
TI/NR* MDR-TB

92%

79-98 (95% CI)

Nix-TB EFFICACY:

Time to Unfavorable Outcome



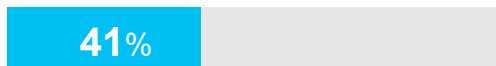
*Treatment intolerant or non-responsive MDR-TB

ZeNix: Optimizing Linezolid in the BPaL regimen

PARTICIPANTS

181 participants with confirmed TB

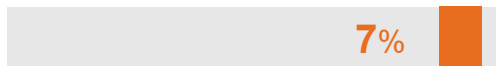
75 with XDR-TB



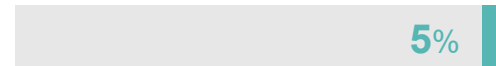
85 with pre-XDR-TB



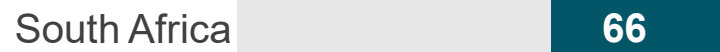
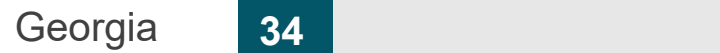
12 with NR MDR-TB



9 with TI MDR-TB



Country



LINEZOLID DOSING

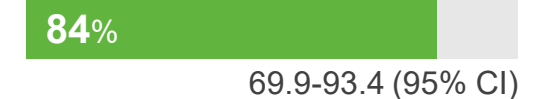
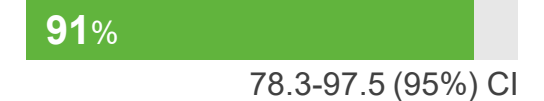
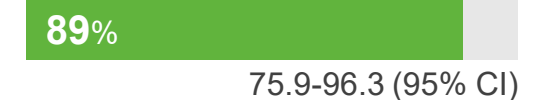
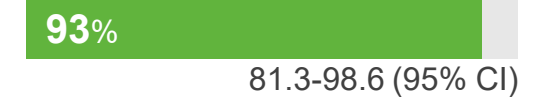
1200 mg x 6 mo

1200 mg x 2 mo

600 mg x 6 mo

600 mg x 2 mo

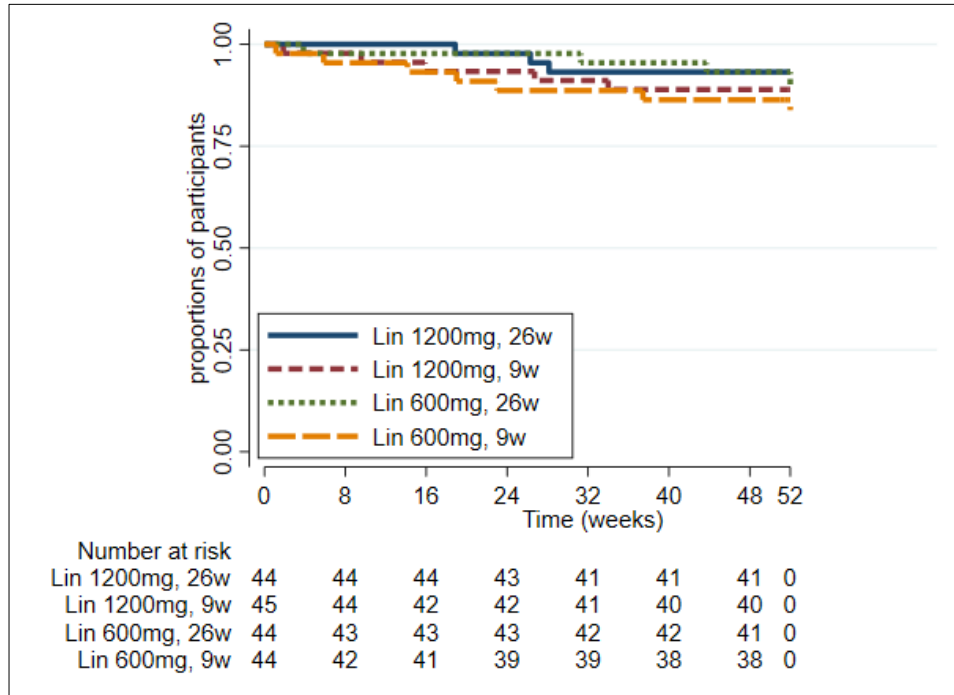
FAVORABLE OUTCOMES



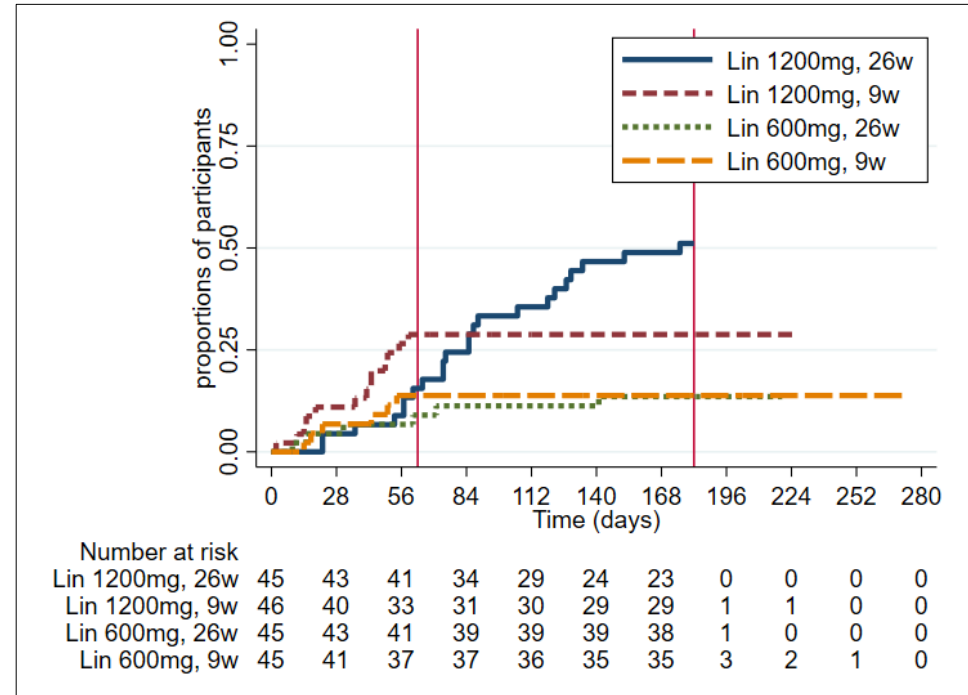
*Treatment-intolerant or non-responsive MDR-TB
Using definition of XDR-TB prior to 2020

ZeNix Results at Primary Endpoint

ZeNix Efficacy: Time to Unfavorable Outcome



ZeNix Safety: Time to First LIN Dose Modification



- High success rate of Nix-TB replicated
- Lower and/or shorter linezolid dosing had improved safety and tolerability
- Extends Nix-TB results to broader patient populations

Progress in the Treatment of Highly Drug-Resistant TB

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|
| K | K | K | | | | | | | | | | | | | | | | | |
| C | C | C | | | | | | | | | | | | | | | | | |
| O | O | O | O | O | O | O | O | O | O | O | O | O | O | O | | | | | |
| H | H | H | H | H | H | H | H | H | H | H | H | H | H | H | | | | | |
| Z | Z | Z | Z | Z | Z | Z | Z | Z | Z | Z | Z | Z | Z | Z | | | | | |
| E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E |
| P | P | P | P | P | P | P | P | P | P | P | P | P | P | P | P | P | P | P | P |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |

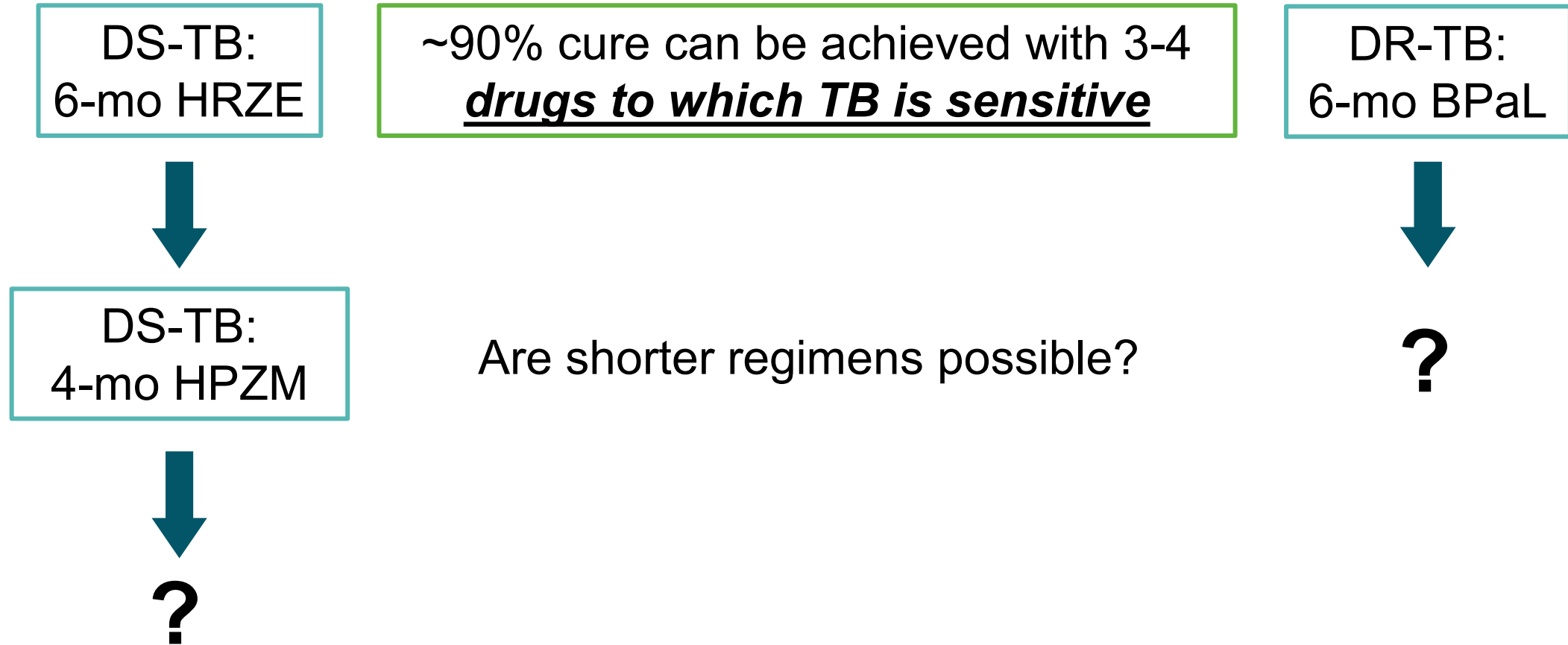
**7 drugs
21 months
69% cured**



| | | | | | |
|----|----|----|----|----|----|
| B | B | B | B | B | B |
| Pa | Pa | Pa | Pa | Pa | Pa |
| L | L | L | L | L | L |
| 1 | 2 | 3 | 4 | 5 | 6 |

**3 drugs
6 months
90% cured**

Convergence of DS- and DR-TB Treatment



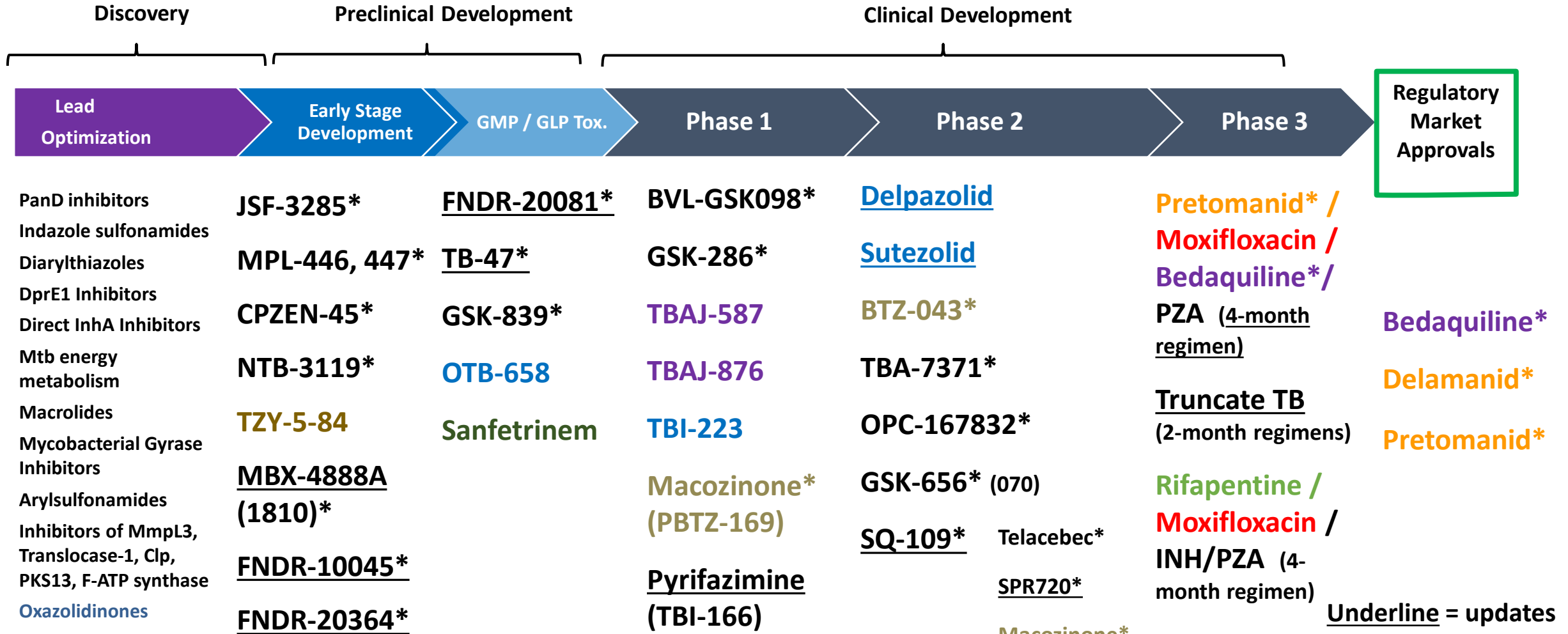
Towards a Universal, Shortened Regimen

- Invest in new drugs, new drug classes, and new mechanisms
- Construct regimens of drugs without pre-existing resistance
- Optimize safety and adherence (dosing, drug interactions, FDC)
- Methodically interrogate optimal duration
- Monitor for resistance emergence

| | Discovery | | Early Development | | Late Development | | |
|--|--|---|--|---|--|--|---|
| | Lead Identification | Lead Optimization | Preclinical Development | Phase 1 | Phase 2A/2B | Phase 3 | Marketed Products |
| | ClpP1P2 Lead ID Programs <ul style="list-style-type: none"> • CETR • Harvard • Texas A&M • UIC | Anti-TB Natural Products Evotec ClpC1 <ul style="list-style-type: none"> • CETR • Harvard • UIC | Preclinical TB Regimen Development JHU | TBAJ-876 / Diarylquinoline TBAJ-587 / Diarylquinoline ERA4TB TBI-223 / Oxazolidinone IMM | BPaMZ/SEM UoSA Sutezolid / Oxazolidinone Gates MRI TBA-7371 / DprE1 Inhibitor <ul style="list-style-type: none"> • FNDR • Gates MRI | NixTB Bedaquiline / Pretomanid / Linezolid (BPaL) Viatriis ZeNix Bedaquiline / Pretomanid / Linezolid (BPaL) Viatriis SIMPLICITB Bedaquiline / Pretomanid / Moxifloxacin / Pyrazinamide (BPaMZ) <ul style="list-style-type: none"> • PanACEA • Radboud • Viatriis | Optimized Pediatric Formulations Ethambutol Macleods Isoniazid Macleods Pyrazinamide Macleods Rifampicin/Isoniazid Macleods Rifampicin/Isoniazid / Pyrazinamide Macleods Pediatric Formulation Development Pretomanid Viatriis Pretomanid for use in BPaL Pretomanid for use in BPaL Regimen <ul style="list-style-type: none"> • Hongqi • ITRC • KNCV • Lupin • Macleods • Viatriis |
| | GHIT Hit ID Programs <ul style="list-style-type: none"> • Daiichi Sankyo RD Novare • Texas A&M • UIC | InhA Inhibitors GHDDI Intracellular Active Series GSK KasA GSK MmpL3 Inhibitors <ul style="list-style-type: none"> • AbbVie • ERA4TB | | | | | |
| | GHIT Hit-to-Lead Programs <ul style="list-style-type: none"> • Astellas • Chugai • Daiichi Sankyo RD Novare • Takeda • UIC | | | | | | |
| | Intracellular Active Series Evotec Malate Synthetase Inhibitors Texas A&M Pantothenamide <ul style="list-style-type: none"> • TropiQ • WCM | | | | | | |
| | PknB <ul style="list-style-type: none"> • Schrödinger • UoA | | | | | | |
| | RNA Polymerase Inhibitors CETR Whole Cell Hit-to-Lead Program GSK | | | | | | |
| | TB Alliance Portfolio Partners | | | | | | |
| | AbbVie Astellas Bill & Melinda Gates Medical Research Institute (Gates MRI) Center for Excellence in Translational Research (CETR) Chugai Daiichi Sankyo RD Novare ERA4TB Consortium EU-Pearl Consortium Evotec Foundation for Neglected Disease Research (FNDR) GlaxoSmithKline (GSK) | Global Health Drug Discovery Institute (GHDDI) Harvard University Hongqi Pharmaceutical Institute of Materia Medica (IMM) IMPAACT International Tuberculosis Research Center (ITRC) Johns Hopkins University (JHU) KNCV Tuberculosefonds Lupin Pharmaceuticals Macleods Pharmaceuticals Medical Research Council (MRC) at UCL Médecins Sans Frontières (MSF) National Institutes of Health (NIH) PanACEA | PAN-TB Consortium Schrödinger Stellenbosch University Takeda Pharmaceuticals TB Drug Accelerator (TBDA) Texas A&M University TropiQ UNITE4TB Consortium University College London (UCL) University of Auckland (UoA) University of Illinois at Chicago (UIC) University of St. Andrews (UoSA) Viatriis Weill Cornell Medical (WCM) Yonsei University | | | | |

* Phase 3 clinical trials are added to the pipeline after enrollment of the first patient and are removed after publication of trial results. This document is updated on a quarterly basis.

2021 Global New TB Drug Pipeline ¹



*New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

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 series identified: <http://www.newtbdrugs.org/pipeline/discovery>



Underline = updates since March 2021

Updated: October 2021