The Current TB Drug Trial Landscape and the Need for Capacity Development

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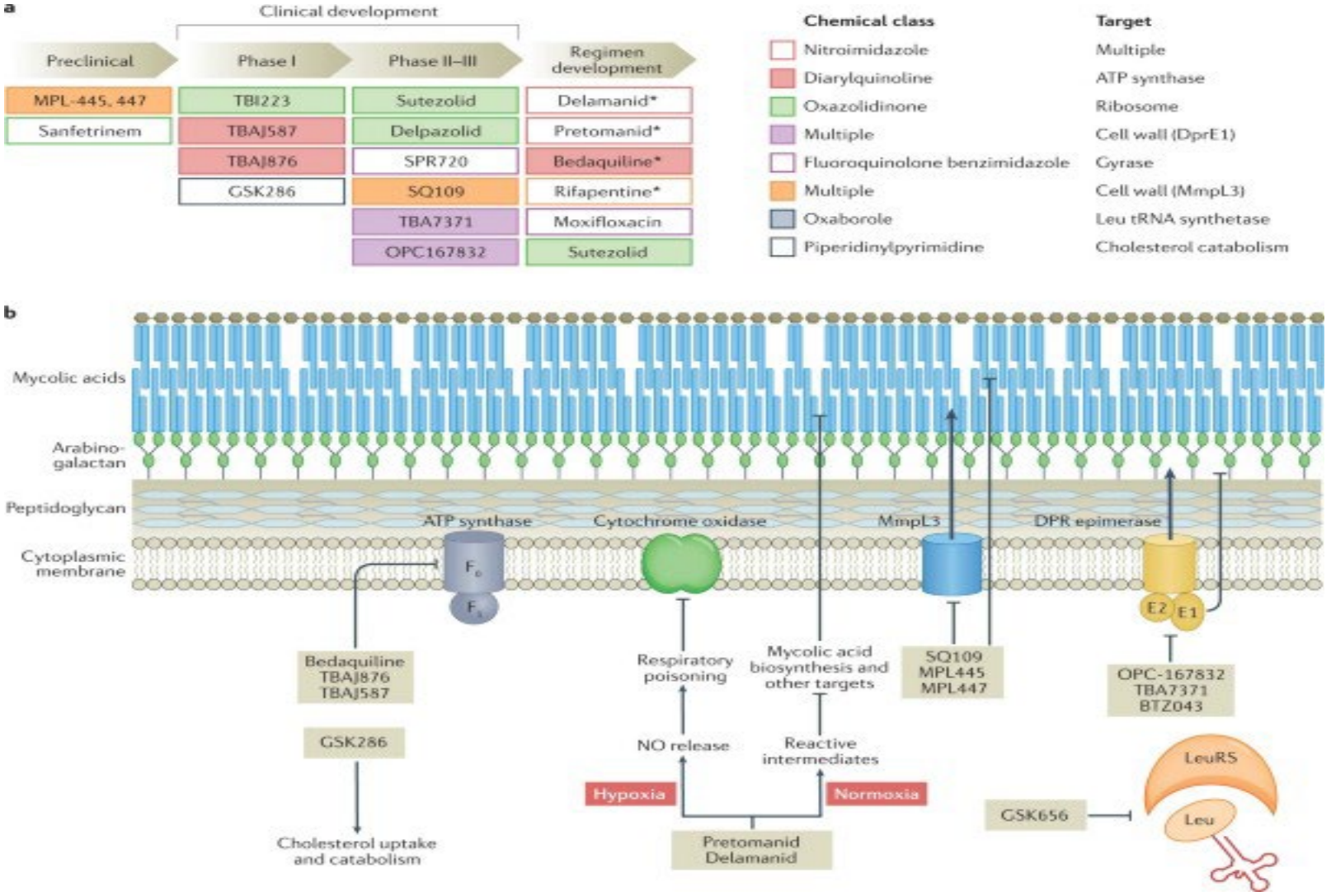
Director of TB Research Unit
National Center for Tuberculosis and Lung Diseases

Swiss TPH Hybrid Symposium The Tuberculosis Pandemic – a Call to Action Science, Application, Politics
21-22 March, 2023

TB drug development challenges:

- Curing TB takes considerably longer than any other bacterial infection of the lungs owing to a combination of drug, pathogen and host factors;
- Drug tolerance fuels and synergizes with drug resistance;
- Single drug and regimen development tested in sequence is inherently slow, while tools are emerging to rationally prioritize regimens early in the cascade;

Anti-tuberculosis drug pipeline and mechanism of drug action



Nature Reviews Microbiology (*Nat Rev Microbiol*) ISSN 1740-1534 (online)

2022 Global New TB Drug Pipeline[1] Updated 11/3/2022

Discovery | Preclinical Development | Clinical Development

Lead Optimization → Early Stage Development → GMP / GLP Tox. → Phase 1 → Phase 2 → Phase 3 → Regulatory Market Approvals

Indazole sulfonamides

Diarylthiazoles

DprE1 Inhibitors

Direct InhA Inhibitors

Mtb energy metabolism

Gyrase Inhibitors

Arylsulfonamides

Inhibitors of MmpL3, Translocase-1, ClpC1, PKS13, F-ATP synthase

Oxazolidinones

DnaE1 / Nargenicin analogs

TBD-09, TBD-10 (MK-7762, -3854)

MPL-447*

JSF-3285*

CPZEN-45*

NTB-3119*

MBX-4888A (1810)*

FNDR-10045*, FNDR-20364*

GSK-839*

OTB-658

BVL-GSK098*

GSK-286*

TBAJ-876

TBAJ-587

TBI-223

Macozinone* (PBTZ-169)

Sanfetrinem

Delpazolid

Sutezolid

Sudapyridine (WX-081)

BTZ-043*

TBA-7371*

OPC-167832*

GSK-656* (070)

Telacebec*

Pyrifazimine (TBI-166)

SPR720*

SQ-109*

Results Reported / Expected in 2022/23

TB Practecal

ZeNix

Bedaquiline*

Simplici TB

Delamanid*

(4-month regimen)

Pretomanid*

Truncate TB

(2-month regimens)

STREAM 2

Underline = updates since May 2022

*New chemical class. Known chemical classes for any indication are color coded: 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 identified: http://www.newtbdrugs.org/pipeline/discovery

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: November 2022

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Simplici TB

Delamanid*

(4-month regimen)

Pretomanid*

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(2-month regimens)

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Updated: November 2022

ZeNIX Trial – NC-007 Rationale

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

NIX-TB results

- **Patients with XDR-TB or failed MDR treatment**
- **Nix TB Trial (B-Pa-L) Phase III** (Phase II has been skipped)

Pretonamid 200mg qd

Bedaquiline 200mg tiw
After 2 week load:400 mg once daily for 2 weeks

Linezolid 1200mg qd
(before: 600mg bid)

6 months **oral** treatment
(option for 9 months for subjects who remain culture positive at month 4)

- Successful outcome in 95 of the first 107 patients (88,8%) after six months of treatment with BPaL and six months of post-treatment follow-up.

ZeNIX Trial – NC-007 Rationale

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Adverse events
- Optic and peripheral neuropathy
- Bone marrow suppression

Adverse events driven by linezolid often led to dose reductions, interruptions or discontinuation of linezolid:

Peripheral neuropathy (occurring in 81% of patients)

Myelosuppression (48%)

Source: Conradie et al. Bedaquiline, pretomanid and linezolid for treatment of extensively drug resistant, intolerant or non-responsive multidrug resistant pulmonary tuberculosis. *N Eng J Med* 2020;382:893-902.

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FDA

ZeNix Trial (B-Pa-L) NC-007

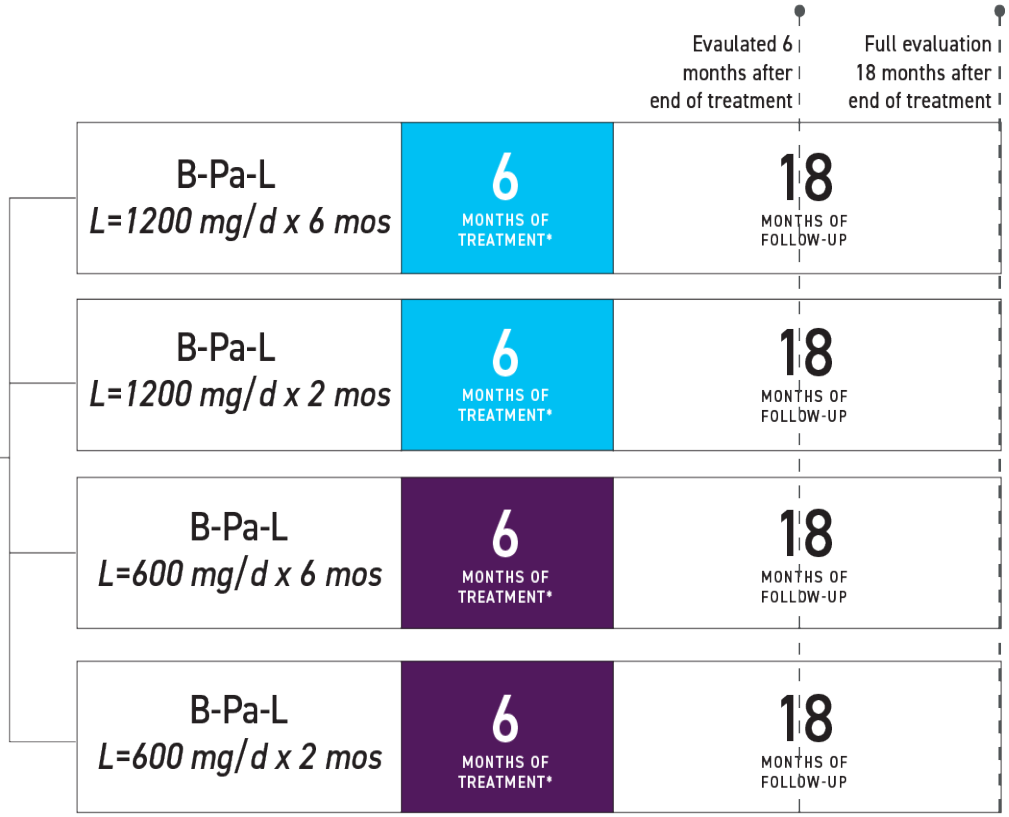
ZeNix Trial Design: Open label 4 arm

Extensively Drug-Resistant, Pre-Extensively Drug-Resistant

+

Treatment-Intolerant or Non-responsive Multidrug-Resistant TB Participants

randomized



*Additional 3 months if sputum culture positive between week 16 and week 26 treatment visits

Pa pretomanid dose = 200 mg daily

B bedaquiline dose = 200 mg x 8 weeks, then 100 mg x 18 weeks

Pre-2021 WHO Definitions of XDR-TB and Pre-XDR-TB

ZeNix Trial (B-Pa-L) NC-007

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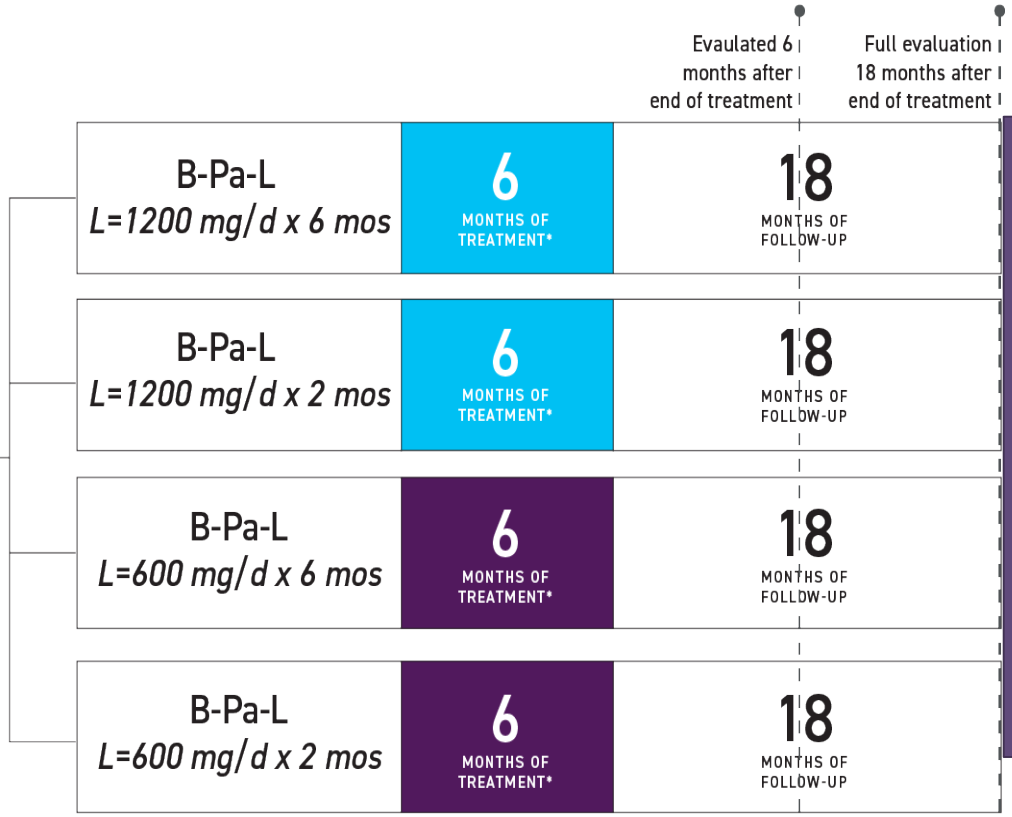

Primary endpoint the incidence of an unfavourable outcome, defined as treatment failure or disease relapse (clinical or bacteriologic) at 26 weeks after completion of treatment. In mITT population.

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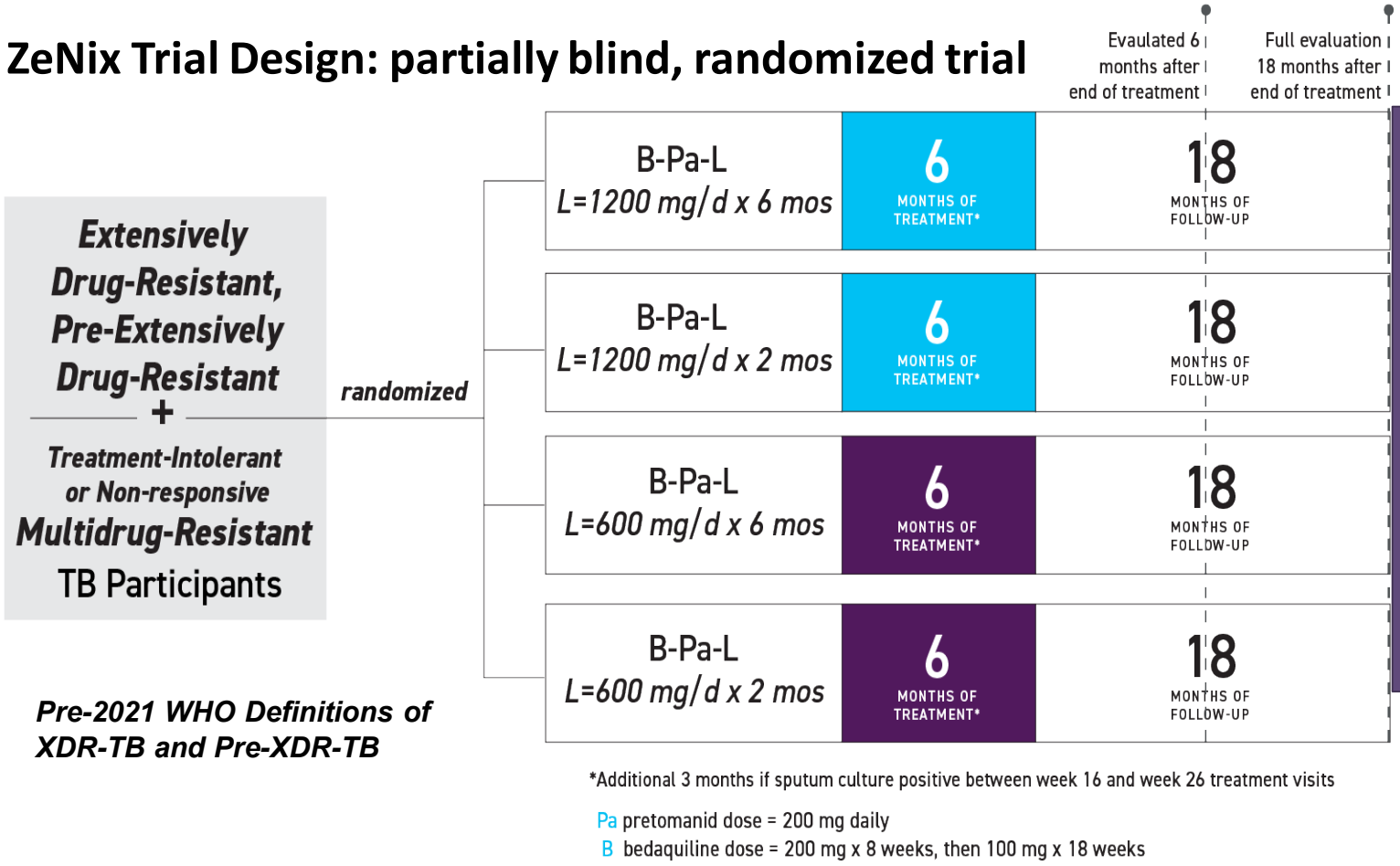
Pa pretomanid dose = 200 mg daily

B bedaquiline dose = 200 mg x 8 weeks, then 100 mg x 18 weeks

ZeNix Trial (B-Pa-L) NC-007

ZeNix Trial Design: partially blind, randomized trial



Primary endpoint the incidence of an unfavourable outcome, defined as treatment failure or disease relapse (clinical or bacteriologic) at 26 weeks after completion of treatment. In mITT population.

Total 11 Trial sites: Four in South Africa, one in the country of Georgia, one in Moldova, and five in Russia

ZeNix Trial (B-Pa-L) NC-007

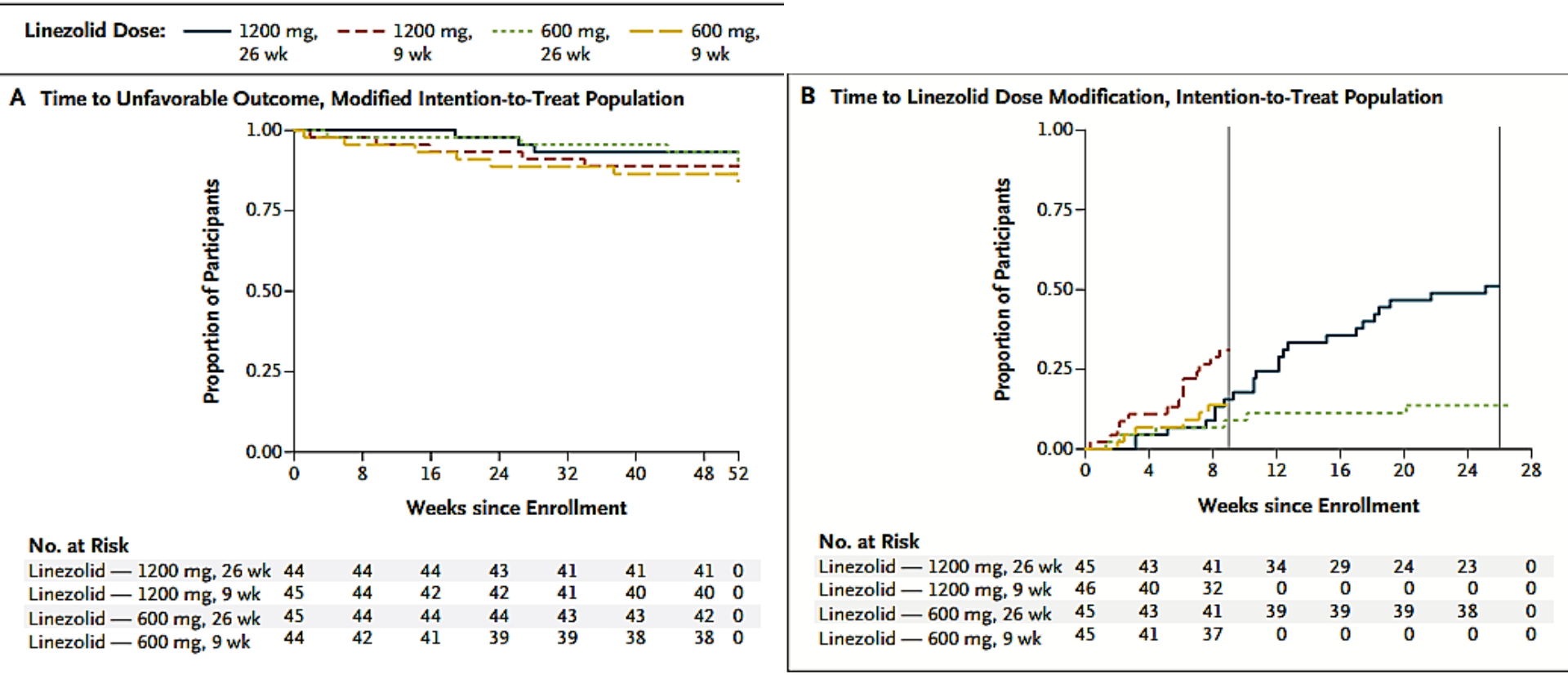
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis

F. Conradie, T.R. Bagdasaryan, S. Borisov, P. Howell, L. Mikiashvili, N. Ngubane, A. Samoilova, S. Skornykova, E. Tudor, E. Variava, P. Yablonskiy, D. Everitt, Wills, E. Sun, M. Olugbosi, E. Egizi, M. Li, A. Holsta, J. Timm, A. Bateson

N= 181 [75 (41.4%) XDR-TB, 85 (47.0%) pre-XDR 21 (11.6%) Ti/NR MDR.]



TB-PRACTECAL Trial for MDR-TB

Staged trial to evaluate BPaL-based regimens for all people with DR-TB (at least rifampicin-resistant), not just highly drug-resistant strains:

Stage 1

- Regimen 1 - BPaL + Moxifloxacin for 6 months (BPaLM)
- Regimen 2 - BPaL + Clofazimine for 6 months (BPaLC)
- Regimen 3 - BPaL for 6 months (BPaL)
- Local SOC: The local standard of care for MDR-TB was used as the internal control for both safety and efficacy

Stage 2

- Regimen 1 - BPaL + Moxifloxacin for 6 months
- Local SOC

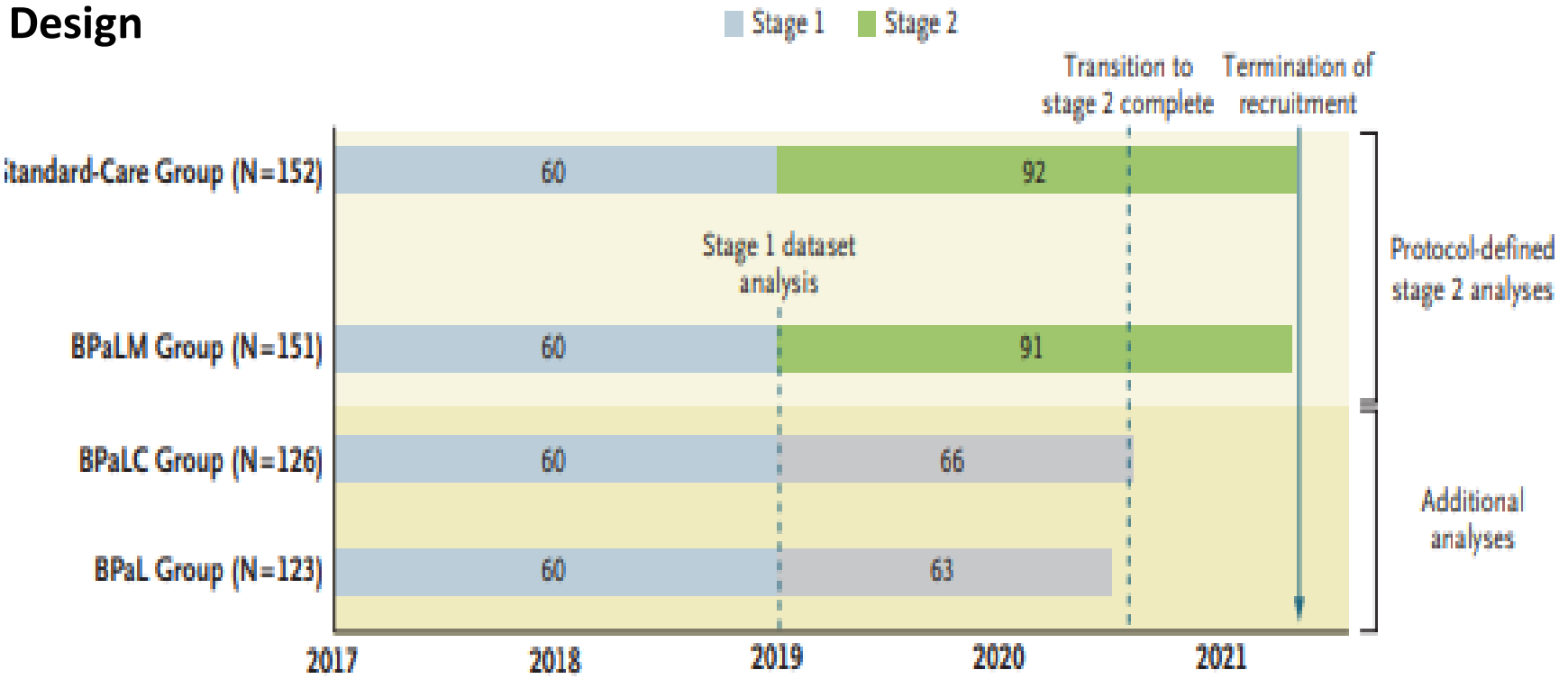
Bedaquiline administered at 400mg dly for 2 weeks then 200mg 3X for 22 weeks. Linezolid administered at 600mg daily for 16 weeks then 300mg daily for the remaining 8 weeks or earlier when moderately tolerated

Total seven trial sites across Belarus, South Africa and Uzbekistan.

MEDECINS SANS FRONTIERES

TB-PRACTECAL Trial for MDR-TB

TB-PRACTECAL Trial Design

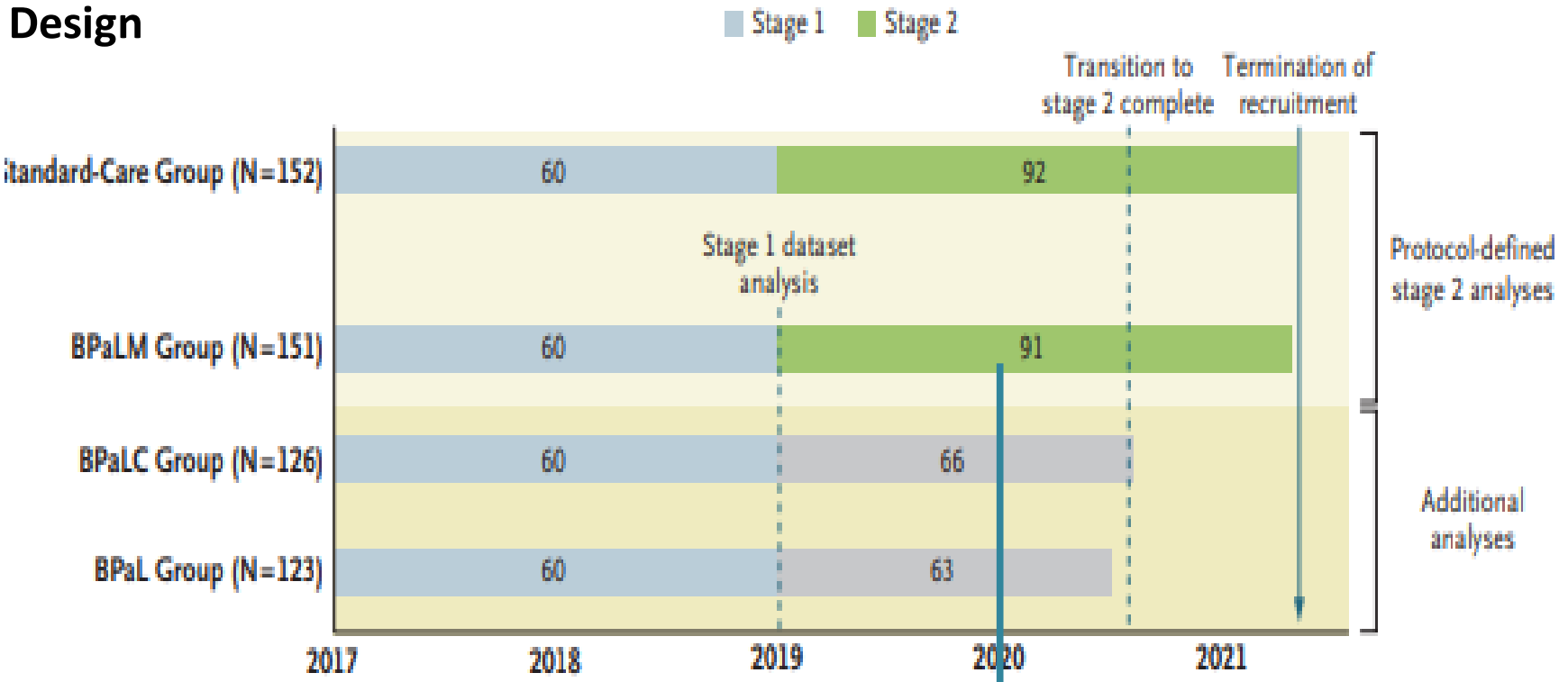


Primary endpoint: was an unfavorable status (a composite of death, treatment failure, treatment discontinuation, loss to follow-up, or recurrence of tuberculosis) at 72 weeks after randomization. The noninferiority margin was 12 percentage points

MEDECINS SANS FRONTIERES

TB-PRACTECAL Trial for MDR-TB

TB-PRACTECAL Trial Design



Primary endpoint: was an unfavorable status (a composite of death, treatment failure, treatment discontinuation, loss to follow-up, or recurrence of tuberculosis) at 72 weeks after randomization. The noninferiority margin was 12 percentage points

Steering committee elected to proceed with the BPaLM group only in Stage 2

TB-PRACTECAL Trial for MDR-TB

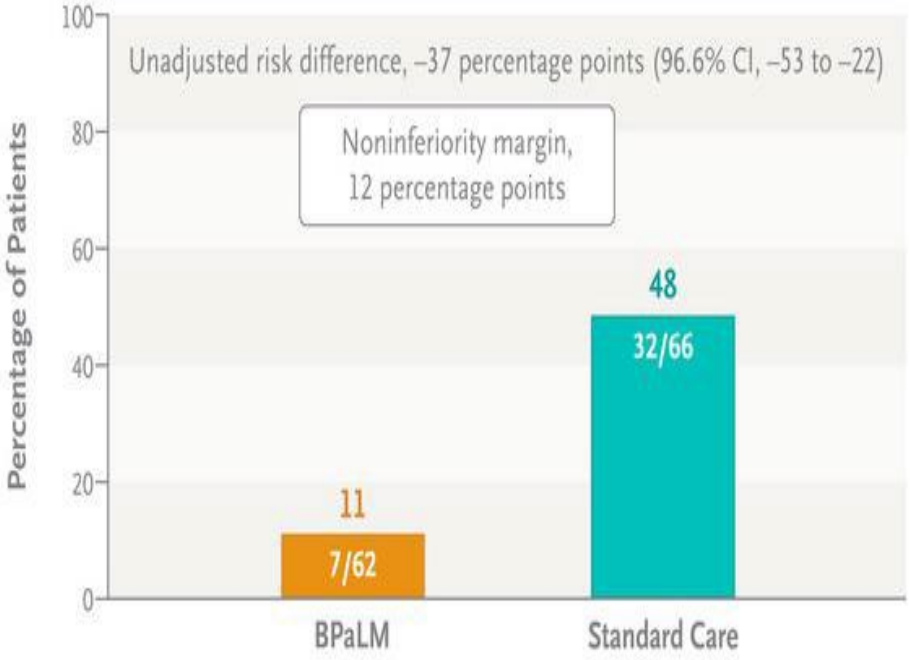
THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

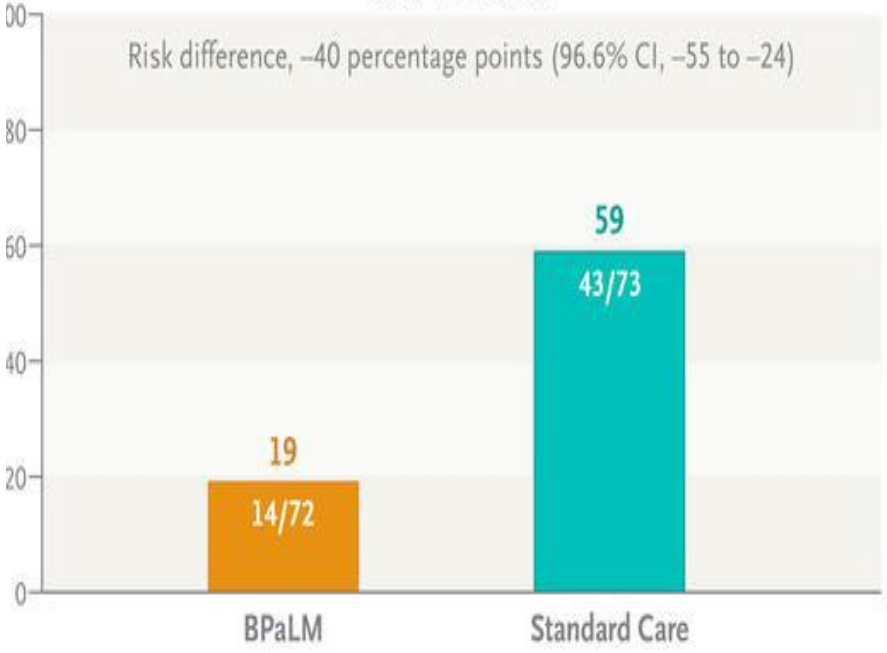
A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis

Bern-Thomas Nyang'wa, M.B., B.S., Catherine Berry, B.Med., Emil Kazounis, M.Med.Sci., Ilaria Motta, Ph.D., Nargiza Parpieva, Sc.D., Zinaida Tigay, M.D., Varvara Solodovnikova, M.D., Irina Liverko, Sc.D., Ronelle Moodliar, M.B., B.S., Matthew Dodd, M.Sc., Nosipho Ngubane, M.B., B.Ch., Mohammed Rassool, M.B., B.Ch.,

Unfavorable Outcome in Modified Intention-to-Treat Analysis



≥1 Serious Adverse Event or Adverse Event of Grade ≥3 over 72 Weeks



The Union
52ND WORLD CONFERENCE ON LUNG HEALTH
19—22 OCTOBER 2021

No adverse effects on male reproductive hormones in patients treated with pretomanid containing regimens

EP-14-228

K. Boekelheide, M. Olugbosi, D. Everitt, J. Nedelman, E. Sun, M. Spiegelman

Background

Toxicology studies of pretomanid observed testicular toxicity in rats, but not non-human primates.

Design Method

Levels of male hormones are summarized from 4 clinical studies (SimpliciTB, NC-002, NC-006 and STAND) where patients received 2–6 months of regimens containing 100 or 200 mg pretomanid in DS/DR patients, and HRZE, to assess potential impacts on male reproductive function.

Results

This analysis is based only on data from patients who provided samples at all visits. In SimpliciTB, 143 patients at baseline had median values for testosterone, inhibin-B, FSH, and LH within their reference ranges (albeit low within the range for testosterone) and similar across arms. After 4-6 months of treatment plus 3-5 months of recovery, all hormones remained within their reference ranges and were similar across arms with median testosterone and inhibin-B higher and median FSH and LH lower, indicating treatment-related amelioration of the relative hypogonadal state at baseline. In NC-002 (88 patients), NC005 (24 patients), and STAND (113 patients), hormone levels analyzed behaved similarly to SimpliciTB, across the HRZE and Pa-containing-regimens (100-and-200mg) arms.

Conclusions

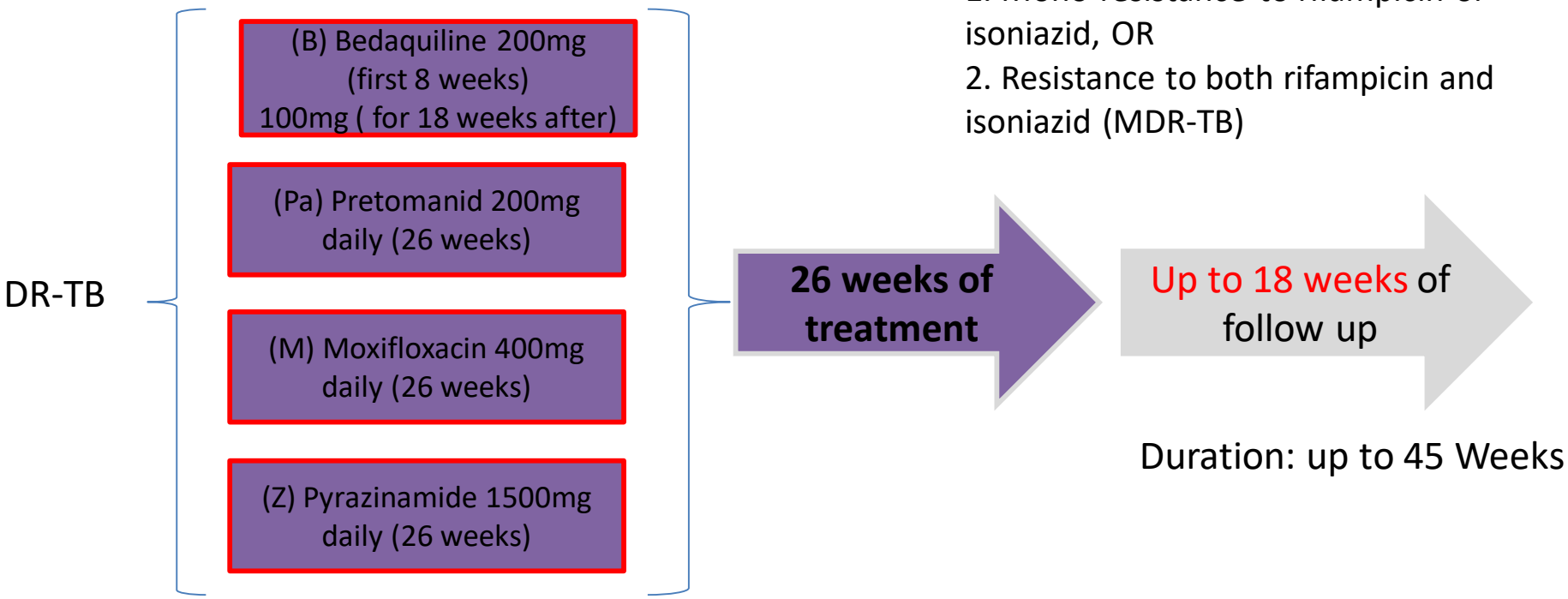
Treatment regimens with either 100 or 200 mg/d pretomanid administered for up to 6 months and standard of care (HRZE) similarly improved male hypogonadism present at baseline in DS- and DR-TB patients in four studies, indicating a lack of adverse effects of pretomanid on male reproductive function.

BPaMZ/SEM Study / Analysis pending

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Male Participants with DR-TB pulmonary TB

DR-TB participants defined as:
1. Mono-resistance to rifampicin or isoniazid, OR
2. Resistance to both rifampicin and isoniazid (MDR-TB)



Duration: up to 45 Weeks

(20 evaluable pts)
~ 25 subjects enrolled in the trial assuming a 20% participant drop out of the trial

BPaMZ/SEM

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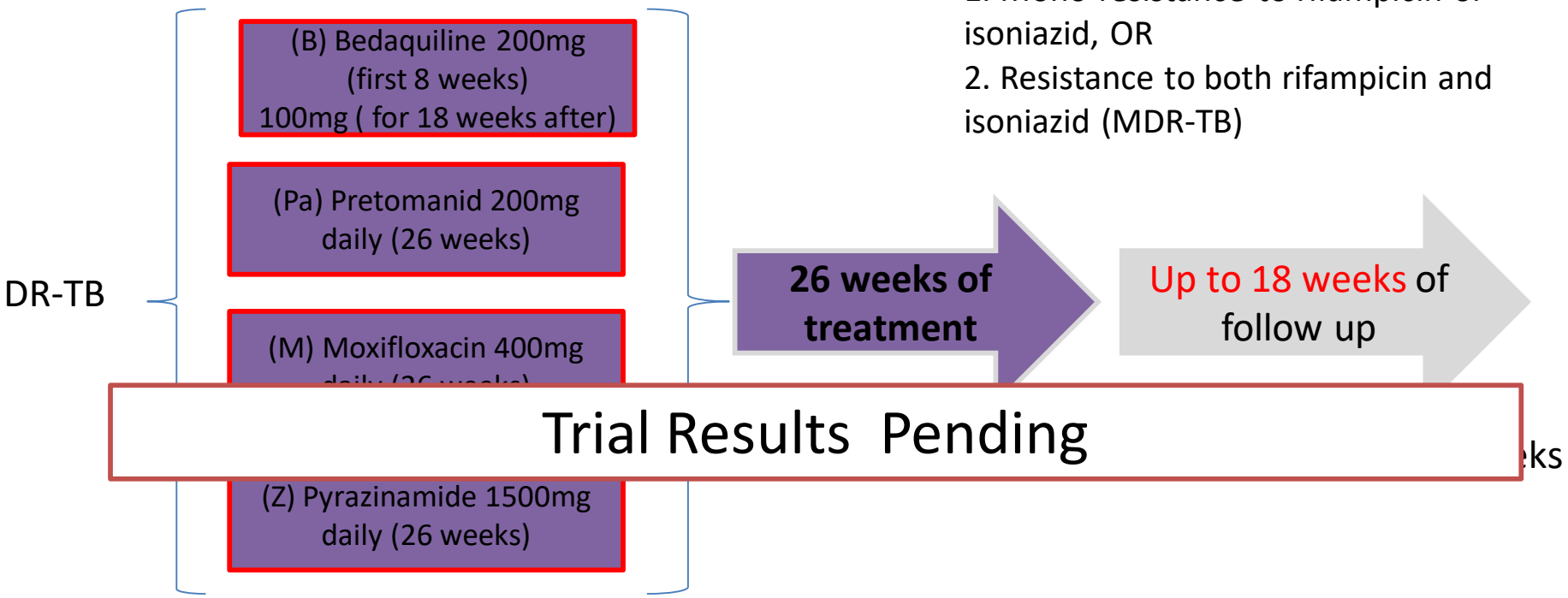

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Simplici TB (B-Pa-M-Z) NC-008 (Phase II c)

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Participants with newly diagnosed smear positive DS and MDR TB, 450 participants enrolled –data analysis pending

Screening		Treatment		Follow up	
-9	-1	1	57	till	104

DS →

BPaMZ:
Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 9 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily for 17 weeks (Total treatment duration 4 months

DS →

HRZE:
Isoniazid 75mg plus rifampicin 150mg plus pyrazinamide 400mg plus ethambutol 275mg combination tablets

MDR →

BPAMZ
Bedaquiline 200 mg daily for 8 weeks then 100 mg daily for 18 weeks, together with pretomanid 200 mg + moxifloxacin 400 mg + pyrazinamide 1500 mg daily for 26 weeks (Total treatment duration 6 months

Primary endpoint: Time to sputum culture conversion over 8 weeks

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HRZE:

Trial Results Pending

MDR →

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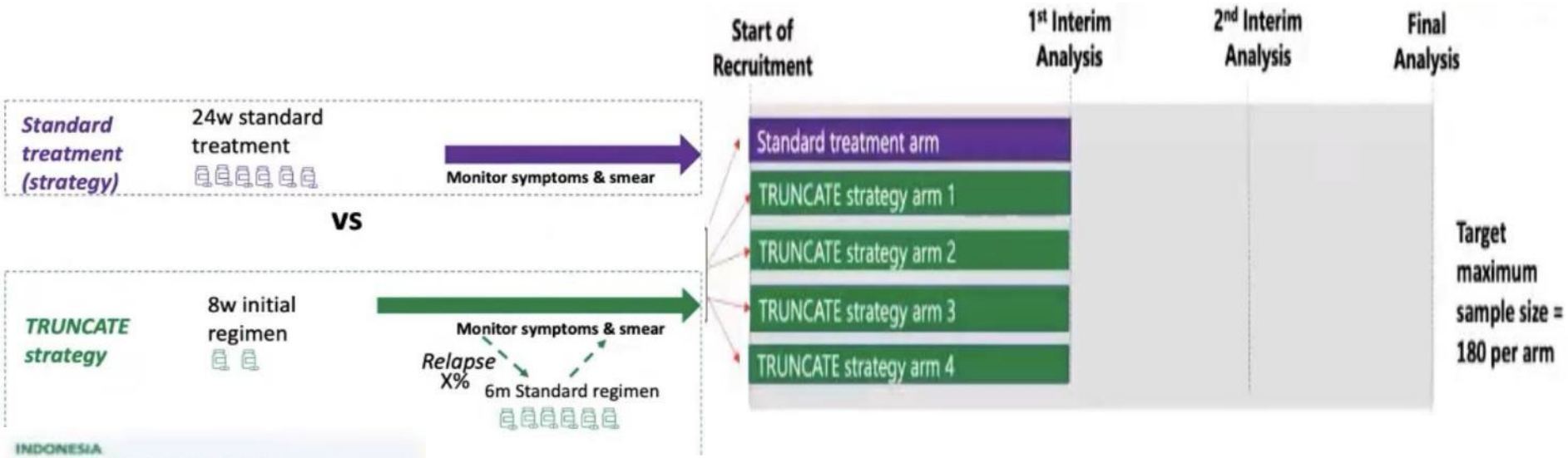
TRUNCATE-TB TRIAL

TRUNCATE-TB Trial Rationale

- Current Global standard regimen for DS-TB is 6m. HRZE (4HRZE/2HR)
- Established over 40 years ago
- Very good cure rate in Trials 95%
- Decreases to < 85% under programmatic conditions

TRUNCATE-TB TRIAL

TRUNCATE-TB Trial Design



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22 Universitas Hasanuddin, Makassar
23 Dr Soetomo Hospital, Surabaya
24 Universitas Indonesia, Jakarta
25 Dr Moewardi Hospital, Solo
26 Dr Saiful Anwar Hospital, Malang

THAILAND
31 King Chulalongkorn Memorial Hospital, Bangkok
32 Central Chest Institute of Thailand, Nonthaburi
33 Taksin Hospital, Bangkok

PHILIPPINES
41 Lung Center of Philippines, Quezon City
42 Quezon Institute, Quezon City
43 De La Salle Health Sciences Institute, Cavite
44 Perpetual Succour Hospital, Cebu
45 Tropical Disease Foundation, Makati City

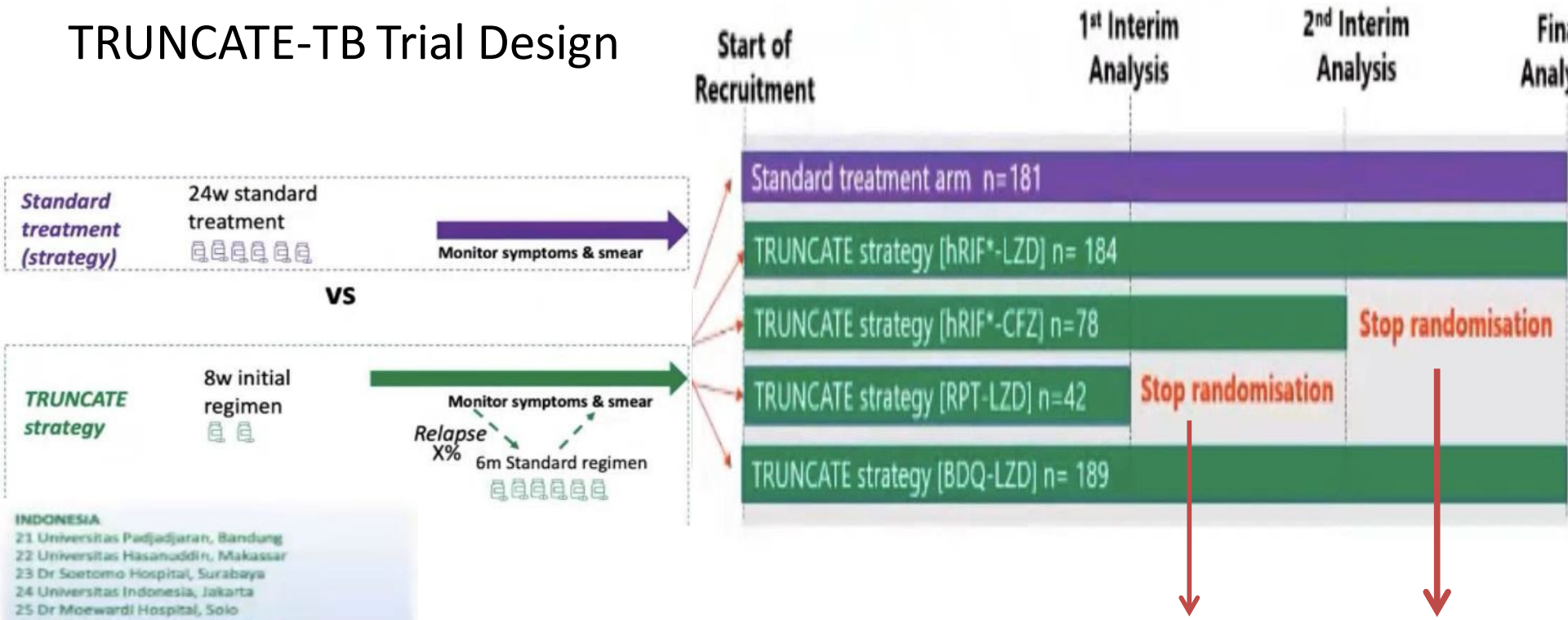
INDIA
51 NITRD, New Delhi

UGANDA
71 Infectious Diseases Institute, Kampala
72 Joint Clinical Research Centre, Lubowa
73 Joint Clinical Research Centre, Mbarara

Primary endpoint: % of unsatisfactory treatment outcome (death, active TB at w96, on treatment at w96) Non-inferiority declared if upper limit of 97,5 CI <12%

TRUNCATE-TB TRIAL

TRUNCATE-TB Trial Design



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73 Joint Clinical Research Centre, Mbarara

TSC Stopping decisions: High pill burden / regulatory refused CFZ importation

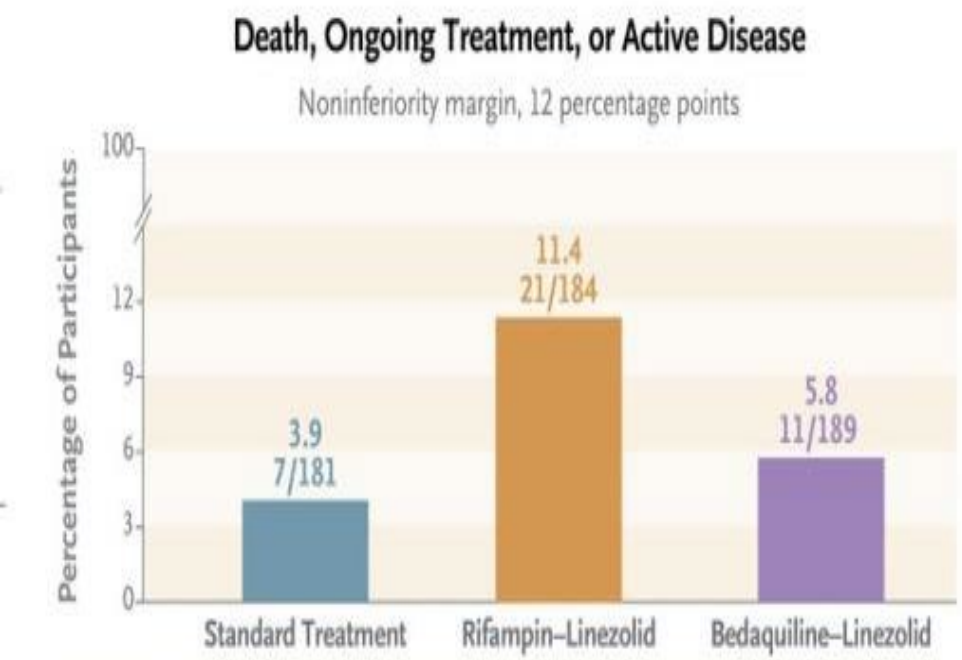
TRUNCATE-TB TRIAL

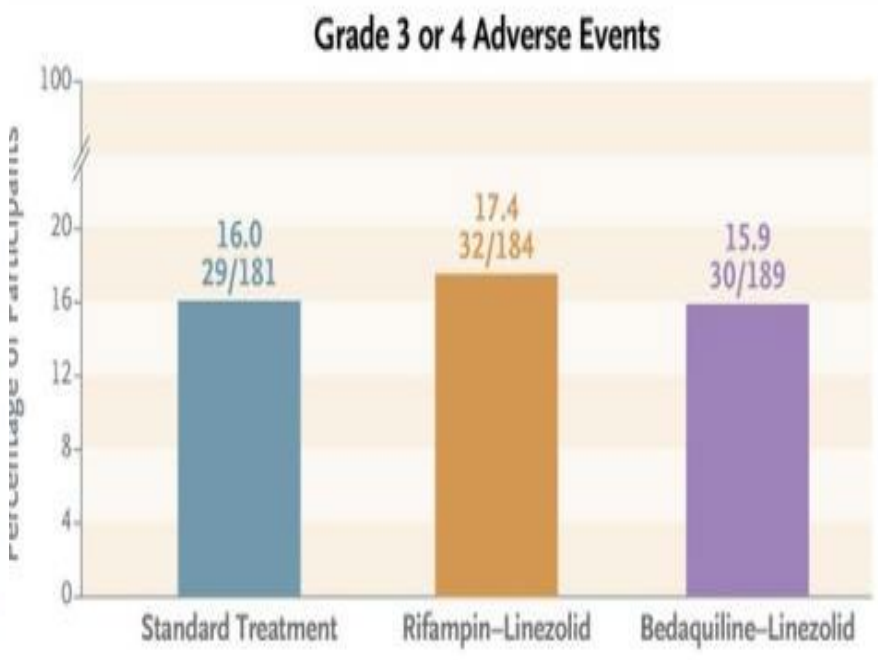
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Treatment Strategy for Rifampin-Susceptible Tuberculosis

Nicholas I. Paton, M.D., Christopher Cousins, M.B., Ch.B., Celina Suresh, B.Sc., Erlina Burhan, M.D., Ka Lip Chew, F.R.C.P.A., Victoria B. Dalay, M.D., Qingshu Lu, Ph.D., Tutik Kusmiati, M.D., Vincent M. Balanag, M.D., Shu Ling Lee, B.Sc., Rovina Ruslami, Ph.D., Yogesh Pokharkar, M.Sc., Irawaty Djaharuddin, M.D., Jani J.R. Sugiri, M.D., Rholine S. Veto, M.D.,





Noninferiority criterion met in the strategy group with an initial bedaquiline linezolid regimen (11 of the 189 participants (5.8 %) (adjusted difference, 0.8 percentage points; 97.5% CI, −3.4 to 5.1)

TRUNCATE-TB TRIAL

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Treatment Strategy for Rifampin-Susceptible Tuberculosis

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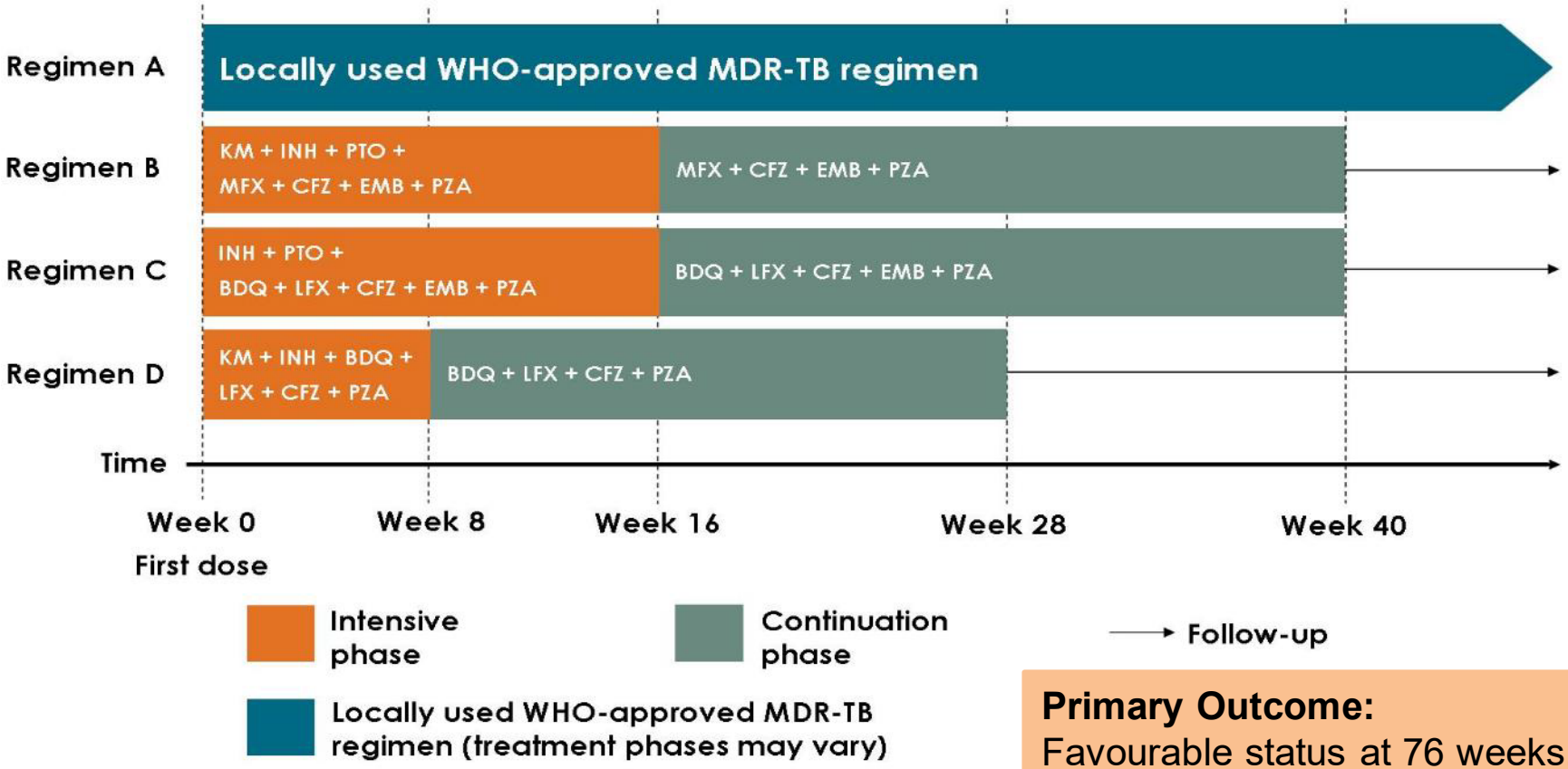
- Participant centered outcomes:
  - Safe: no excess severe/serious AEs, death, pulmonary disability
- Program centered outcomes:
  - Substantial reduction in overall treatment days (180 days vs 106/85days), increased motivation for adherence (score: 6 vs 8/8)
  - Low risk of drug resistance

STREAM Stage 2 – Trial Interventions



With Version 8.0 of the protocol:

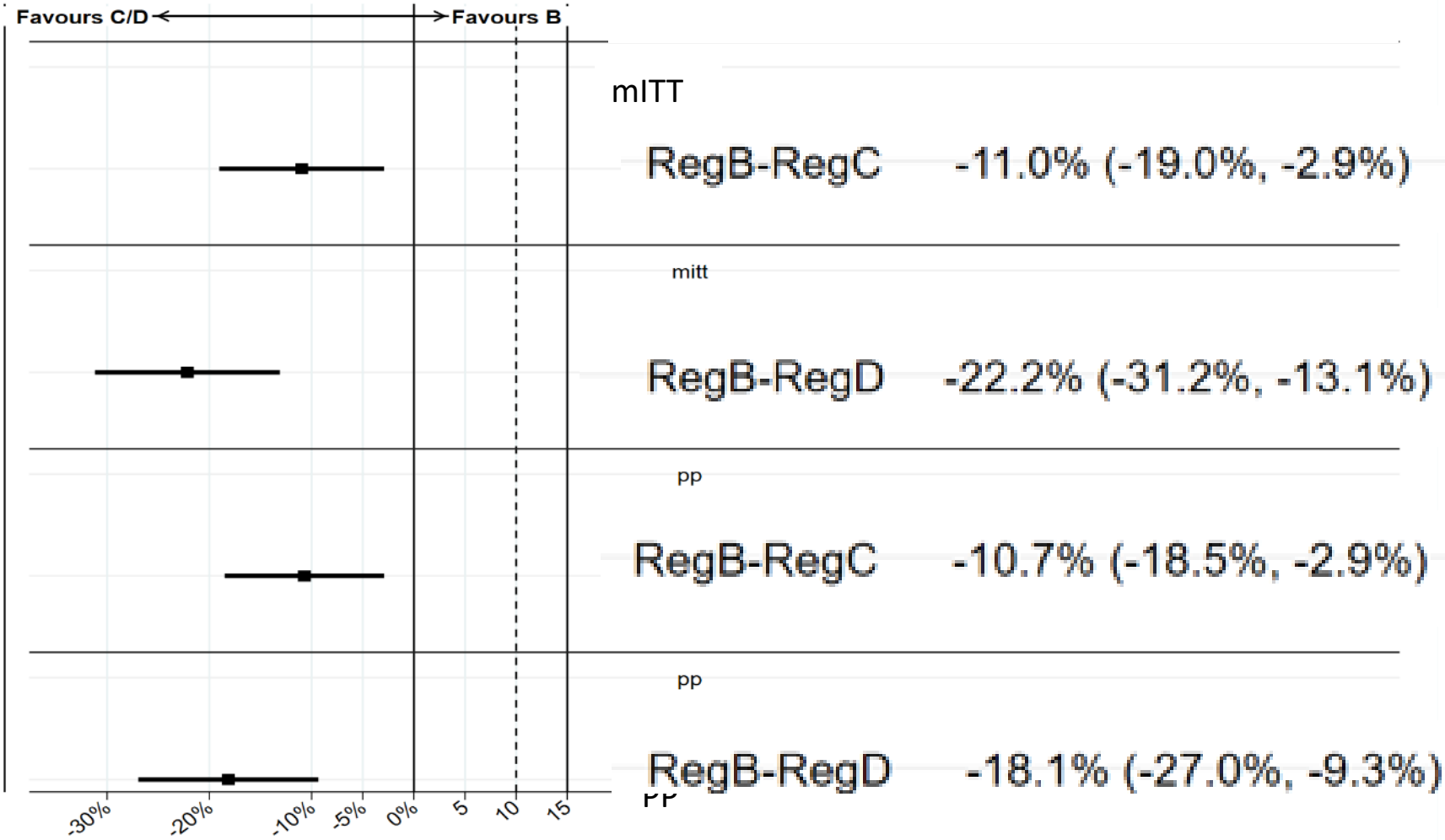
- Regimen B: replace moxifloxacin with levofloxacin
- Stop randomisations to Regimens A and D

Primary Outcome:
Favourable status at 76 weeks, defined as a negative culture for M tuberculosis at week 76 and on the preceding visit.

Thirteen Stage 2 sites were in Ethiopia, Georgia, India, Moldova, Mongolia, South Africa, and Uganda

Results: primary outcome, diff (95% CI)

Solid line for 0 difference, and the dashed line at a 10% difference which indicated the non-inferiority margin for the trial



The upper bound of both CIs is lower than 10% , they are also lower than zero, meaning that regimen C was non-inferior to regimen B, and is actually superior to regimen B.

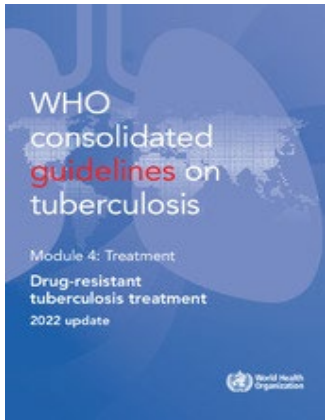
WHO Rapid communication / Key recommendations

1. **Shorter all-oral bedaquiline-containing regimen for multidrug- or rifampicin-resistant tuberculosis**
   - **With Eto/Pto or Lzd***
2. **The 6-month BPaL$_{(600mg)}$ regimen** with or without **Mfx** may be used programmatically in adults (≥15 years) with no known resistance/exposure to BPaL *
3. **Longer regimens for multidrug- or rifampicin-resistant tuberculosis**
4. **Modified shorter regimen under OR condition**

**Rapid communication: Key changes to the treatment of drug-resistant tuberculosis; May 2022*

Further needs …

- The efficacy, safety and tolerability of the regimens for subpopulations: children aged below 14 years, patients with extrapulmonary TB, PLHIV with CD4 counts below 100, and pregnant and lactating women....



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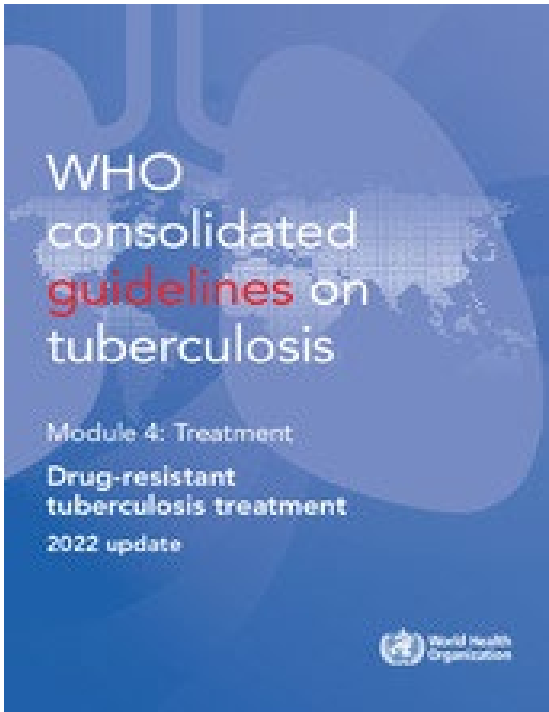
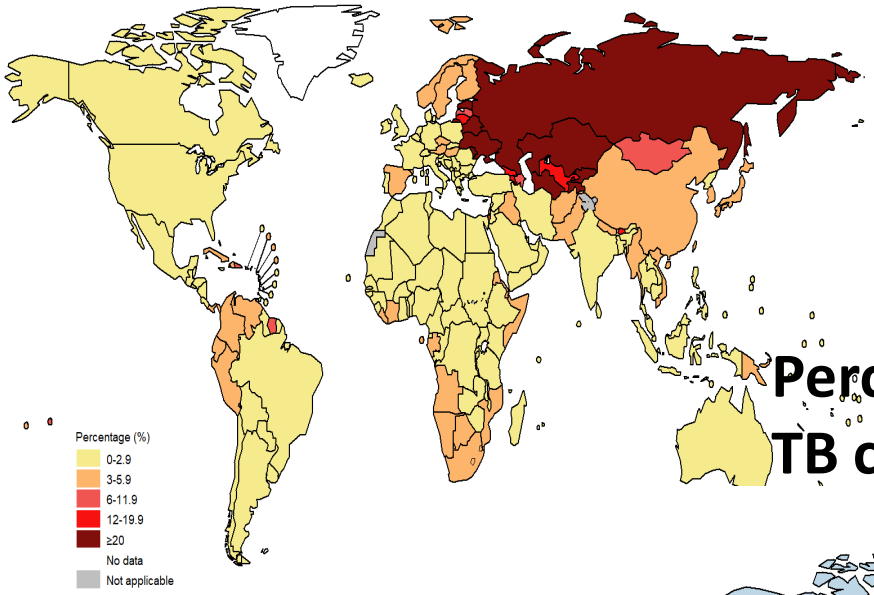
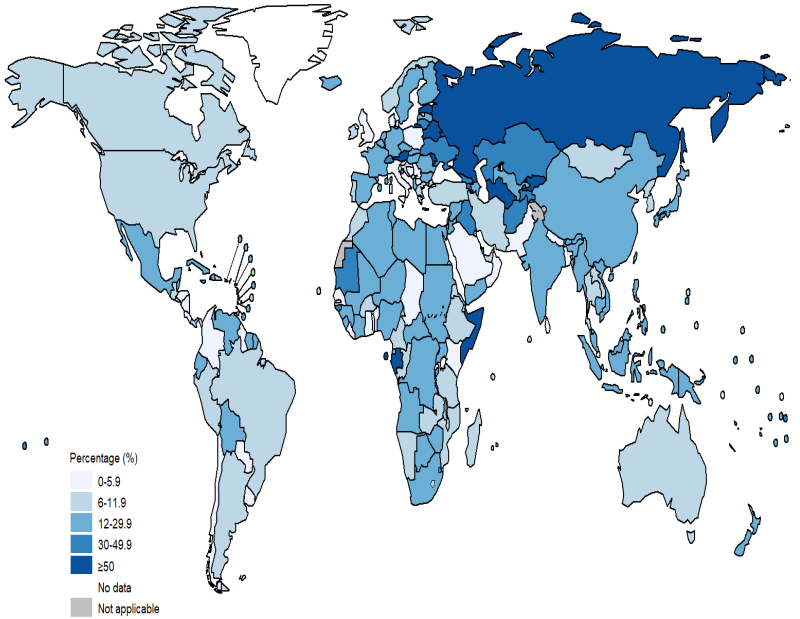


Percentage of new TB cases with MDR/RR-TB, 2021



Percentage of previously treated TB cases with MDR/RR-TB, 2021



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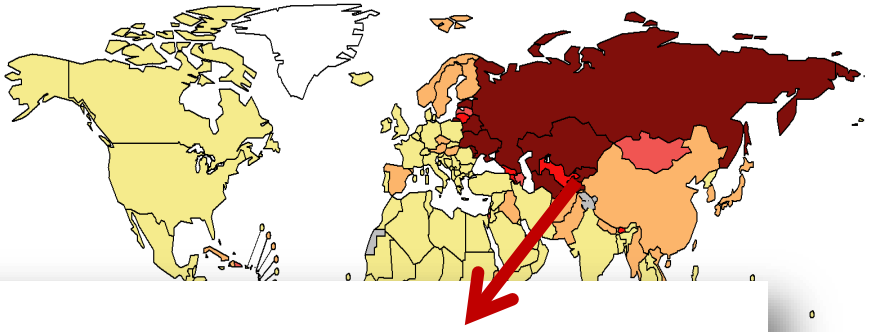


Tuberculosis profile: Kyrgyzstan

Population 2021: 6.5 million

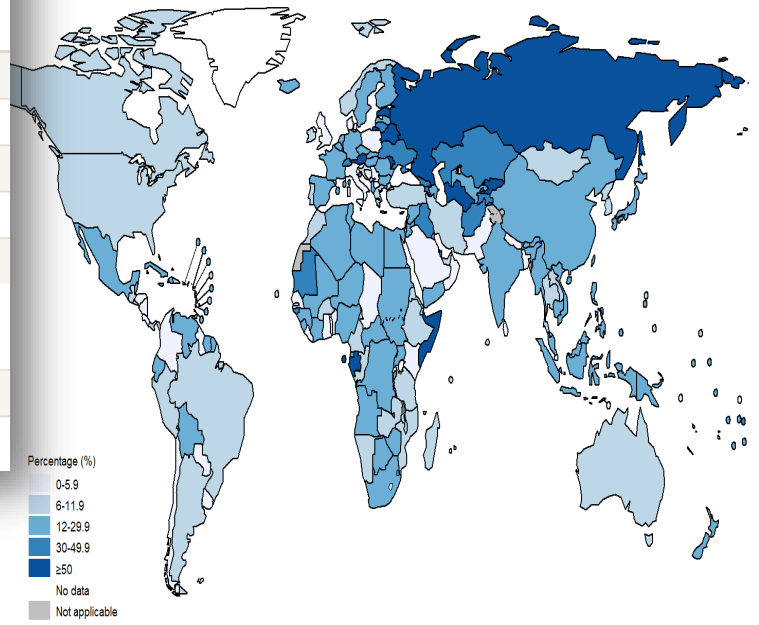
Estimates of TB burden*, 2021

	Number	(Rate per 100 000 population)
Total TB incidence	8 500 (7 000-10 000)	130 (108-155)
HIV-positive TB incidence	240 (190-310)	3.7 (2.9-4.7)
MDR/RR-TB incidence**	3 200 (2 500-3 800)	49 (39-58)
HIV-negative TB mortality	550 (460-650)	8.4 (7-9.9)
HIV-positive TB mortality	130 (110-160)	2.1 (1.7-2.4)

Estimated proportion of TB cases with MDR/RR-TB*, 2021

New cases	27% (26-29)
Previously treated cases	59% (57-62)

Percentage of previously treated TB cases with MDR/RR-TB, 2021



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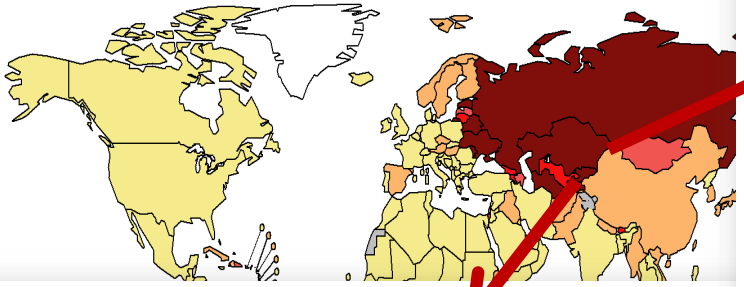

Tuberculosis profile: Uzbekistan

Population 2021: 34 million

Estimates of TB burden*, 2021

	Number	(Rate per 100 000 population)
Total TB incidence	21 000 (14 000-29 000)	62 (42-86)
HIV-positive TB incidence	600 (400-850)	1.8 (1.2-2.5)
MDR/RR-TB incidence**	4 200 (2 700-5 800)	12 (7.9-17)
HIV-negative TB mortality	1 100 (1 000-1 100)	3.2 (3-3.3)
HIV-positive TB mortality	250 (170-350)	0.73 (0.5-1)

Estimated proportion of TB cases with MDR/RR-TB*, 2021

New cases	17% (16-18)
Previously treated cases	29% (27-31)

Tuberculosis profile: Kyrgyzstan

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Estimates of TB burden*, 2021

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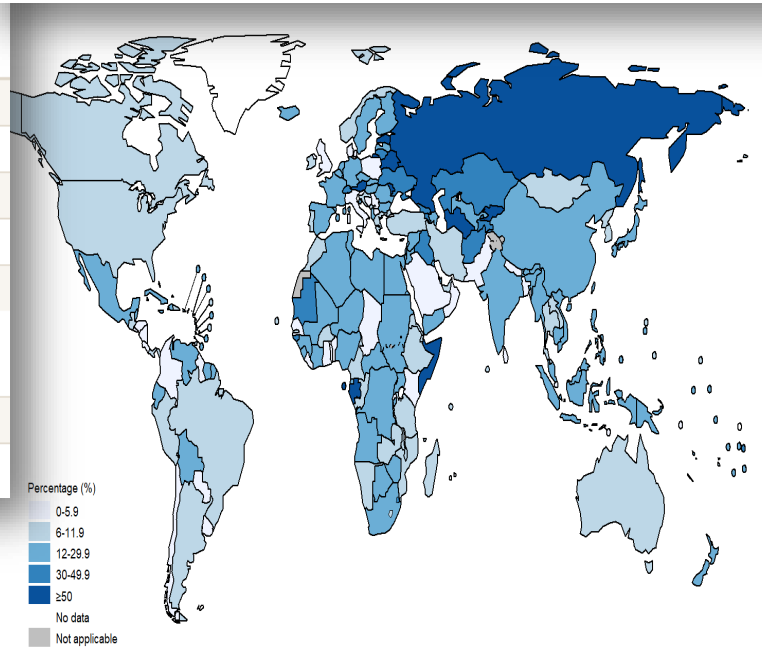

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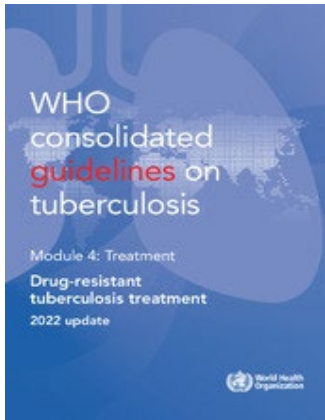
- Description of the mechanism and molecular markers of new drugs resistance (pretomanid), allowing development of the DST



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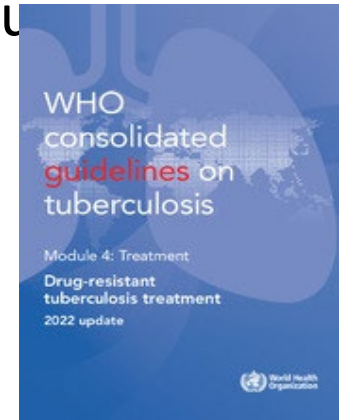
- Description of the mechanism and molecular markers of new drugs resistance (pretomanid), allowing development of the DST
- Documenting the full adverse event profile of pretomanid, and the frequency of relevant adverse events, with a focu hepatotoxicity and reproductive toxicity in humans



Conclusions:

- Compared to a decade ago, the anti-TB drug pipeline is well-shaped (Working Group on New TB Drugs).
- In 2019, the first 6-month regimen was approved for the treatment of M/ XDR-TB (BPaL)
- Shorter, better tolerated and more successful treatments are needed for all patient populations.
- To accomplish this both new antibiotics and new combinations of approved drugs and clinical candidates are required and most important research focus has become the prioritization of promising drug regimens.

Thank YOU!