24-week regimens for treatment of rifampicin-resistant tuberculosis: four-arm randomised trial

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

Rifamipcin-resistant tuberculosis (RR-TB) affects around 465,000 people each year globally.

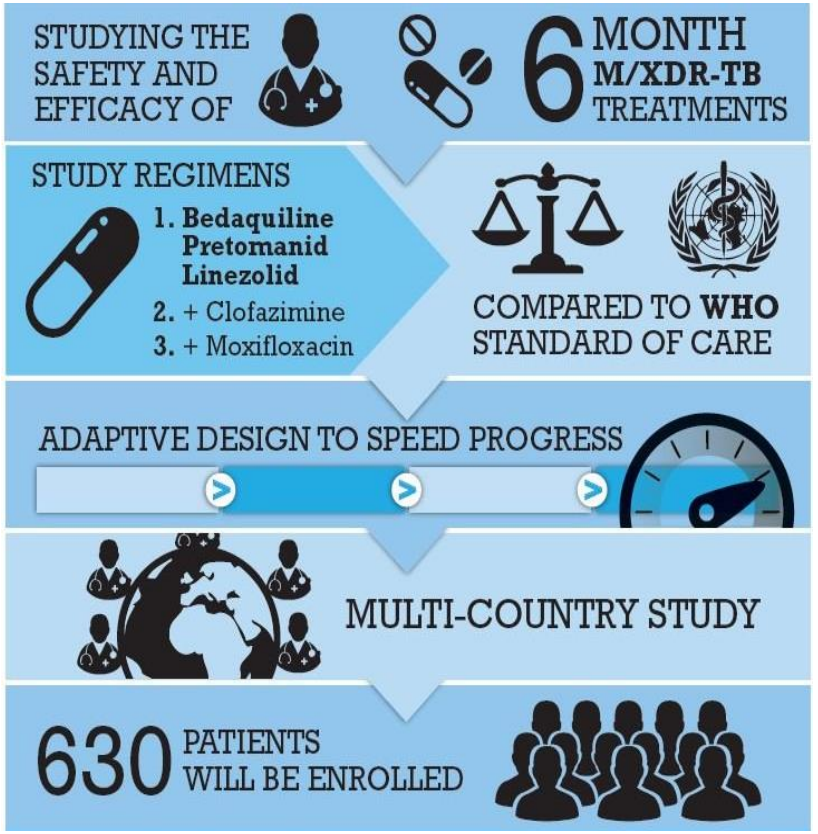
Current treatment is of 9-20 months' duration; is toxic and poorly efficacious.

TB-PRACTECAL IS:

- a regulatory-level,
- open-label,
- phase II/III,
- non-inferiority,
- randomised-controlled trial

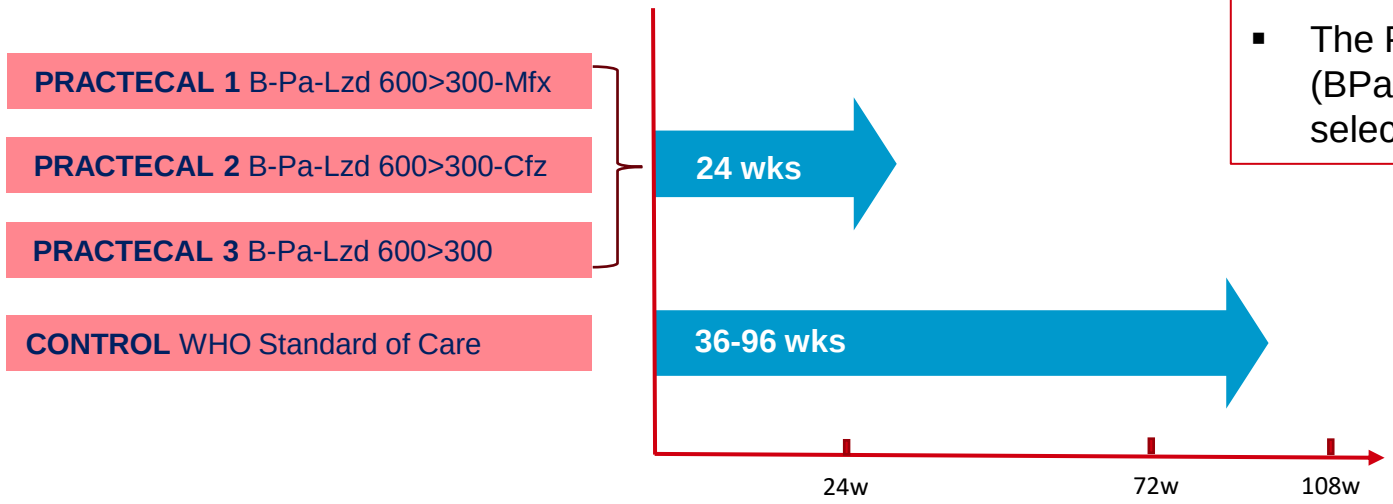
Current standard care

PRACTECAL Arm-1 (BPaLM)



TRIAL DESIGN

A randomised, controlled, open-label, phase II-III trial to evaluate the safety and efficacy of drug regimens containing bedaquiline and pretomanid for the treatment of patients with pulmonary rifampicin-resistant tuberculosis



STAGE 1 > STAGE 2

- All 3 investigational arms met criteria for stage 2 eligibility.
- No major safety signals were detected.
- The PRACTECAL arm1 (BPaLM) regimen was selected to continue to stage 2.

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SCIENTIFIC DAYS

STAGE 2 - PRIMARY OUTCOME

- Percentage of patients with an unfavourable outcome (treatment failure, death, treatment discontinuation, recurrence, loss to follow-up) at 72 weeks post-randomisation

STAGE 2 - SAFETY OUTCOMES

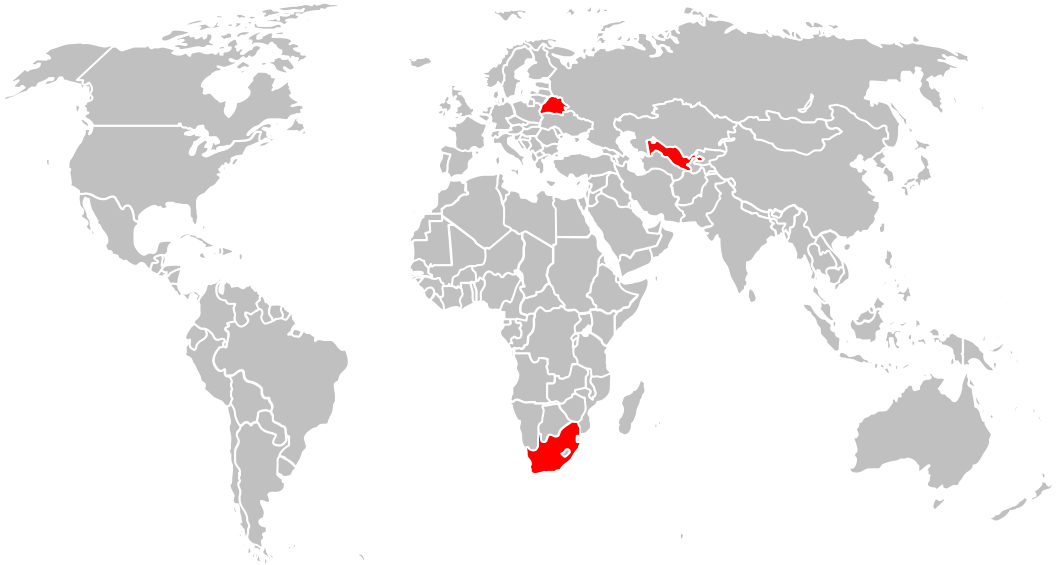
- Percentage of patients with an SAE or new grade ≥3 AE at 72/108 weeks and end of treatment (+30 days)

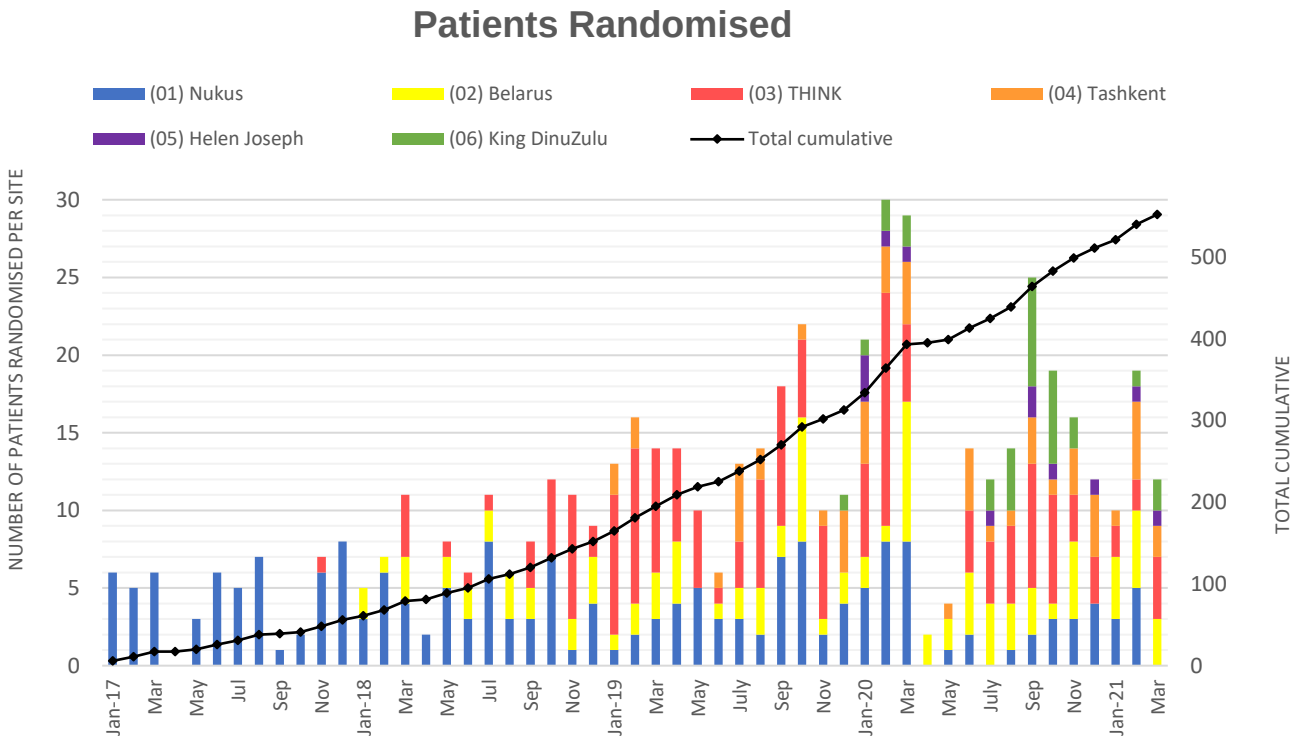
Sample size:

- Assumed unfavourable outcomes of:
  45% investigational arms
  50% in standard of care arms (SoC)
- Power = 85%
- Alpha = 1.7%
- Non-inferiority margin (delta) = 12%
- Not assessable in mITT population = 10%

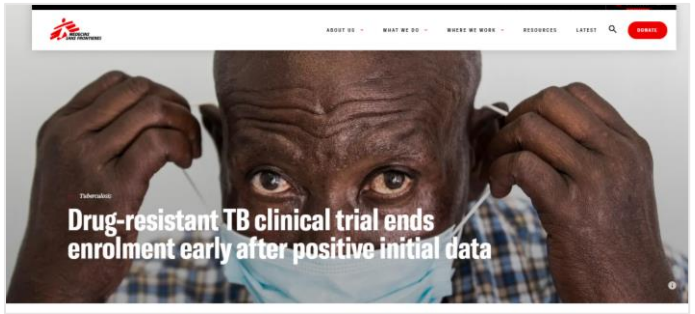
Final sample size = 201

TRIAL PROGRESS





- First patient Jan 2017
- 7 sites (UZB, BY, SA) contributed patients to the trial
- Stage 1 & 2 complete
- Randomisation stopped– due to benefit (DSMB recommendation, ~85% of target)
- Last patient March 2021 - **552 patients in total**



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Baseline characteristics of the mITT analysis cohort

	Control	PRACTECAL Arm 1 (BPaLM)	PRACTECAL Arm 2 (BPaLC)	PRACTECAL Arm 3 (BPaL)
mITT population 72 weeks	66	62	64	60
Age (years), median (range)	36 (19 to 71)	34 (18 to 61)	29 (19 to 63)	34 (18 to 62)
Female, n (%)	33 (50.0)	26 (41.9)	24 (37.5)	28 (46.7)
BMI (kg/m^2), median (IQR)	19.2 (17.3 to 22.0)	19.8 (18.1 to 22.1)	18.8 (17.4 to 22.0)	20.5 (18.2 to 22.8)
HIV positive, n (%)	15 (22.7)	14 (22.6)	14 (21.9)	14 (23.3)
CD4 count (cells/μL), median (IQR)	317 (154 to 383)	268 (182 to 364)	394 (112 to 511)	283 (153 to 424)
Smear positivity, n (%)	50 (75.8)	40 (64.5)	43 (67.2)	45 (75.0)
Cavity present, n (%)	47 (71.2)	33 (53.2)	39 (60.9)	41 (68.3)
Fluoroquinolone resistant*, n (%)	18 (27.7)	17 (28.3)	16 (25.8)	19 (33.9)
QTcF (ms), mean (SD)	398 (18)	396 (18)	393 (20)	398 (18)
ALT (IU/l), median (IQR)	20 (15 to 27)	18 (14 to 27)	18 (15 to 27)	19 (14 to 27)

* percentage of culture positive isolates

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SCIENTIFIC DAYS

Primary efficacy outcome (mITT)

	Control	PRACTECAL arm 1 (BPaLM)	PRACTECAL arm 2 (BPaLC)	PRACTECAL arm 3 (BPaL)
mITT population 72 weeks	66	62	64	60
Number with no unfavourable outcome	34 (51.5%)	55 (88.7%)	52 (81.3%)	46 (76.7%)
Number with an unfavourable outcome	32 (48.5%)	7 (11.3%)	12 (18.8%)	14 (23.3%)
Risk difference (one-sided 98.3% confidence interval)		-37.2% (-∞ to -21.6%)		
Risk difference (one-sided 97.5% confidence interval)			-29.7% (-∞ to -14.3%)	-25.2% (-∞ to -9%)
Non-inferiority p-value (non-inferiority margin of +12%)		p<0.0001		
Superiority p-value		p<0.0001		
Risk ratio (one-sided 98.3% CI)		0.23 (-∞ to 0.52)		
Risk ratio (one-sided 97.5% CI)			0.39 (-∞ to 0.68)	0.48 (-∞ to 0.81)

Safety Results (ITT)

	Control	PRACTECAL arm 1 BPaLM	PRACTECAL arm 2 BPaLC	PRACTECAL arm 3 BPaL
ITT population 72 weeks	73	72	72	69
Number of individuals with SAE* or new grade ≥3 AE (%)	43 (58.9)	14 (19.4)	23 (31.9)	15 (21.7)
Number of events	69	16	32	24
Risk difference**	0	-39.9%	-26.9%	-36.5%
98.3%CI upper bound	0	-24.1%	-10.0%	-20.3%

* Fatal/Immediately life-threatening, Hospitalization/prolonged hospitalization, Disability/incapacity, Birth defect/congenital anomaly, Medically important

** risk difference not adjusted for site as model failed to converge

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Conclusions

- **24 week all oral regimens containing a backbone of bedaquiline, pretomanid and tapered dose linezolid are both safe and efficacious in the treatment of rifampicin resistant tuberculosis**
- Efficacy appears to be BPaLM > BPaLC > BPaL >>SOC
- Patients taking investigational arms had fewer grade 3 and above AEs and SAEs as compared to SoC at week 72 (BPaLM> BPaL > BPaLC >> SOC)

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“When patients were started on the trial on day one, they would be assigned to either the new treatment arm or the standard of care arm. It was randomised by a computer program, so at the click of a button you'd instantly get to see that the patient got the new treatment arm and it felt like they were winning the lottery. It was really so exciting because you just know how much better it is and I would give this internal little whoop of joy.

You could see the relief and the happiness because they were told they would only need to take four different drugs for only six months, and they were much less likely to have side effects. Which is huge, it makes a massive difference to them.

To be able to give our patients hope is honestly the most wonderful, wonderful thing as a doctor.”

Dr. Susan Ford

TB PRACTECAL Sub-Investigator,

Tuberculosis and HIV Investigative Network (THINK), South Africa

A Global Collaboration

- Médecins Sans Frontières
- Swiss Tropical & Public Health Institute
- London School of Hygiene and Tropical Medicine
- University College London
- Global Alliance for TB Drug Development
- Drugs for Neglected Diseases Initiative
- eResearch Technology, Inc.;
- Ministry of Health, Republic of Uzbekistan
- Ministry of Health, Belarus
- Republican Specialised Scientific Practical Medical Centre of Tuberculosis and Pulmonology (TBI)
- Republican Scientific and Practical Centre for Pulmonology and Tuberculosis (RSPCPT)
- TB & HIV Investigative Network (THINK)
- Clinical HIV Research Unit, Wits Health Consortium
- TDR, Special Programme for Research and Training in Tropical Diseases

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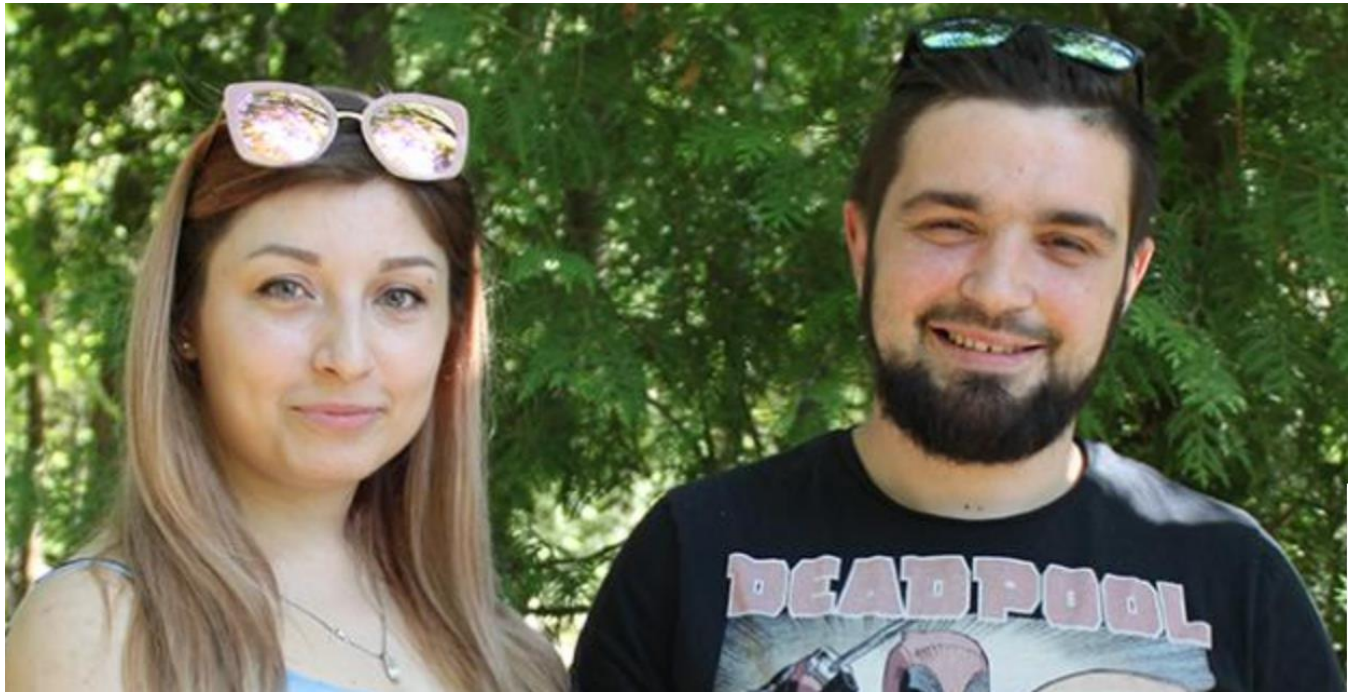
TB Practecal
Innovating MDR-TB Treatment



With special acknowledgement of our participants

Questions / comments
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